国立病院機構鹿児島医療センター

研究業績集　第21号

令和2年4月～令和3年3月(2020 年 4 月～2021 年 3 月)

国立病院機構鹿児島医療センター

臨床研究部

はじめに

鹿児島医療センター研究業績集第 21 号の発刊にあたって

令和 2 年度（2020 年度）研究業績集第 21 号を発刊する運びとなりました。平成 11 年（1999 年）に始まり、21 冊目となります。今回の論文数は再掲載を含めて 73 編（英文 50 編、和文 23 編）、学会報告 80 件（国際 5 件、国内 75 件）でした。論文数はかなり増加していましたが、一方、学会発表は減少していました。長期にわたるコロナ禍の影響もあると感じます。ご一読いただけましたら幸いです。

コロナ感染症の流行が始まり、2 年が経過しようとしています。様々な学会や研究会も Web 形式となり、対面形式が激減しています。移動もなく、いつでもどこでも参加できる利点は有りますが、独特の会場の雰囲気や臨場感を肌で感じる事が難しくなってしまいました。特に対面式を知らない世代（若手）は今後経験不足による影響が出ないものかと危惧しております。また、当院に限らず、日本中、世界中が新型コロナ感染症一色になり、様々な Data が薬品会社などからの一方通行になっている印象も受けます。もう一度足を地につけ、様々な視点から活発な意見や指摘が出るようにしたいものです。明けない夜は無いと言われていますのでコロナ禍後に期待しています。

現行のシステムでは、資金や制度面で研究の継続が難しくなってきています。研修医や専門医制度の中ではポイントを獲得しなくてはならず、集中して深く検討するより、広く浅く早く結果を出さざるを得ないシステムです。技術は学びやすいですが、考える力を養うには適さないかも知れません。研究も可能な限り若くて順応性の高い時期から始めてもらいたいものですが、現行では難しいようです。おそらく、今後制度の見直しがあるなら、少し改善してもらいたいものです。研究費の少なさは言及するまでも有りません。

コロナ感染症もまだまだ続いておりますが、どのような状況になろうとも研究が継続できるシステムが重要と考えています。そしてできるだけ若い人たちが研究に携わり、厚みのある医療を提供していきたいものです。臨床が中心の施設では有りますが、引き続き研究にも関われる施設を目指して参ります。ご指導、ご鞭撻のほど宜しくお願いいたします。各施設で素晴らしい研究が創作されますことを祈念いたします。

令和 3 年 12 月

独立行政法人国立病院機構鹿児島医療センター

田 中 康 博

目次

1. 臨床研究部の組織概要

1. 名称・所在地

独立行政法人国立病院機構鹿児島医療センター臨床研究部

鹿児島県鹿児島市城山町８－１

2. 沿革

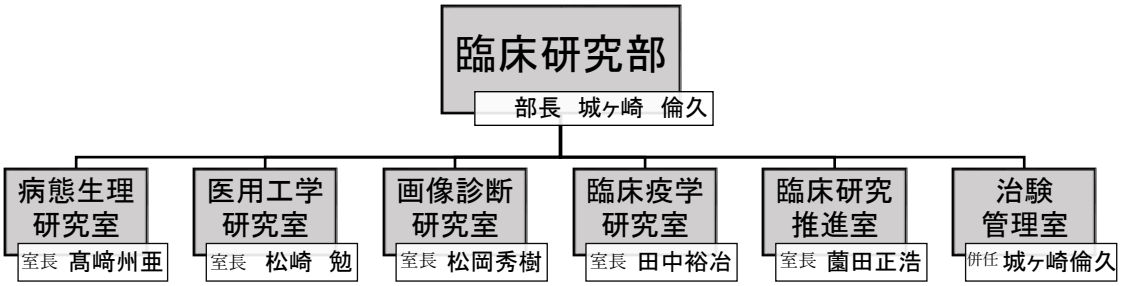
臨床研究部は平成 11 年 10 月に設置されました。当初は病態生理研究室、医用工学研究室、画像診断研究室、臨床疫学研究室、治療評価研究室の 5 室で運営されていました。平成 19 年に治療評価研究室を臨床研究推進室と名称変更を行い、さらに平成 25 年からは治験管理室を加え、現在 1 部 6 室で活動しています。臨床研究部は平成 18 年より東病棟 8 階で活動していましたが、平成 30 年 4 月の逓信病院機能移転に伴い、平成 29 年 11 月に東病棟 8 階から旧看護学生更衣棟に移転しました。

3. 組織構成

臨床研究部長の総括のもとに以下の研究室を設置しています。

1. 病態生理研究室
2. 医用工学研究室
3. 画像診断研究室
4. 臨床疫学研究室
5. 臨床研究推進室
6. 治験管理室

令和2年度の臨床研究部の各室の体制は以下に示す通りです。



4. 鹿児島大学大学院医歯学総合研究科

当院は平成 21 年より、鹿児島大学の連携大学院となっており、先進医療学講座（連携講座）生理活性物質制御学を開講しています。

これまでに 5 人の学生が臨床研究部で研究を行い、鹿児島大学大学院医歯学総合研究科の大学院博士号を取得しました。

5. 臨床研究部の活動

1）臨床研究

NHO 指定臨床研究として「新型コロナワクチンの投与開始初期の重点的調査（コホート調査）」に参加し、日本で初めての新型コロナワクチン先行接種に 252 名登録しました。その後 PMS 研究(コミナティ筋注一般使用成績調査)として 222 名を 1 年間追跡調査しています。

NHO 共同研究として自己免疫性疾患特異的 iPS 細胞を国立病院機構弘前病院に提供し、共同研究を行っています。

本部主導大規模臨床研究（EBM 研究）としては 5 件の課題に参加しています。内訳としては外科 2 件、血液内科 1 件、糖尿病・内分泌内科 1 件、循環器内科 1 件でした。

NHO ネットワーク研究にも積極的に参加しており、現在 11 件の課題があります。内訳としては臨床研究部主導が 3 件、血液内科が 3 件、糖尿病・内分泌内科が 2 件、外科が 1 件、脳血管内科が 1 件、病理診断科が 1 件でした。

NHO が主導する研究以外でも、各診療科、コメディカル、看護部、看護学校で独自の研究が行われており、研究課題数は全部で 97 課題ありました。

2）競争的研究費

競争的研究費は、厚生労働省科学研究費を小児科が 1 件、日本医療開発研究機構研究費を皮膚腫瘍科・皮膚科が 1 件、日本学術振興会科学研究費補助金の基盤研究（C）を歯科口腔外科と腫瘍内科が各 1 件ずつ獲得しています。いずれも分担研究です。

民間セクターからの寄付金は 18 件あり、心臓血管外科が 4 件、消化器内科、外科が各 3 件、皮膚腫瘍科・皮膚科と放射線室が各 2 件、第 1 循環器内科、第 2 循環器内科、不整脈治療科、麻酔科が各 1 件でした。

3）治験・製造販売後調査

2020 年度（令和 2 年度）は残念ながら新規治験はありませんでした。継続契約の治験は第Ⅱ相が 2 件、第Ⅲ相が 6 件でした。そのうち医薬品の治験が 6 件、医療機器の治験が 1 件、再生医療の治験が 1 件ありました。診療科の内訳としては血液内科が 3 件、脳血管内科、循環器内科が各々2 件、婦人科が 1 件でした。

2020 年度に終了した治験としては契約件数が 3 件であり、契約症例 20 件のうち実施症例が 13 件であり実施率としては 65%でした。

製造販売後調査については、今年度新規登録のあった課題が 12 件ありました。内訳としては血液内科が 4 件、循環器内科が 3 件、皮膚腫瘍科・皮膚科が 2 件、心臓血管外科、消化器内科、腫瘍内科が各々1 件でした。

2020 年度の受託研究請求額は 2,007 万円でした。

4）学会発表・論文発表 （当院所属として発表されたもの）

学会発表については、国内学会が 72 題、国際学会が 5 題でした。論文については、英語論文は 36 編、そのうち当院職員が筆頭者になっているものは 12 編でした。和文原著・総説は 12 編、そのうち当院職員が筆頭者になっているものは 11 編でした。

5）倫理審査委員会・治験審査委員会・研究倫理教育の推進

倫理審査委員会・治験審査委員会は 2020 年度に各々12 回開催しました。

今年度途中まで当院の倫理審査委員会および治験審査委員会の外部委員としてお世話になっておりました大野達郎先生がご逝去されました。謹んでお悔やみ申し上げます。外部委員の後任として元南日本新聞の有川賢司先生にお願いしました。元小学校校長の江口惠子先生には引き続き外部委員としてご協力いただいています。

臨床研究を行う上で倫理教育が必須です。国立病院機構では臨床研究に関わる全ての職員に研究倫理教育 e ラーニングプログラムである eAPRIN の受講を行っています。臨床研究部では鹿児島医療センターの eAPRIN の受講登録・管理・受講支援を行っています。今年度は 380 名が受講修了しました。

2020 年 7 月 15 日には看護部を対象とした「研究倫理」の研修を行いました。

6）日本学術振興会科学研究費申請

日本学術振興会科学研究費の申請にあたって「研究機関における公的研究費の管理・監査のガイドライン（実施基準）」に基づく「体制整備等自己評価チェックリスト」および、「研究活動における不正行為への対応等に関するガイドラインに基づく取組状況に係るチェックリスト」を提出する必要があります。臨床研究部では、毎年この 2 つのチェックリストを文部科学省に提出しています。また「体制整備等自己評価チェックリスト」については厚生労働省にも提出しています。

7）鹿児島市医報学術への寄稿

当院は毎年 2 回春と秋に鹿児島市医報の「学術」コーナーに寄稿しています。

今年度は第 59 巻 9 号に消化器内科の櫻井先生の「KM-CART による癌性腹水治療の現状」が、第 60 巻 3 号には脳神経内科の谷口先生の「当院における頚部内頚動脈狭窄症に対する外科治療」が掲載されました。

2. 臨床研究と治験

① 臨床研究

（ア） NHO 指定臨床研究

種別	研究責任医師	研究課題名
厚生労働科学研究 （指定研究）20HA2013	城ヶ崎倫久	新型コロナワクチンの投与開始初期の重点的調査（コホート調査）
NHO 共同研究	城ヶ崎倫久	自己炎症性疾患特異的 iPSC 細胞の培養ストックの作成及び分化誘導

（イ） EBM 研究

領域・課題番号	研究責任医師	研究課題名
特定臨床研究 H26-EBM(介入)-03	菰方輝夫	膵がん切除後の補助化学療法における S-1 単独療法と S-1 とメトホルミンの併用療法の非盲検ランダム化第Ⅱ相比較試験（ASMET 研究）
H26-遺伝子-02	大塚眞紀	未治療多発性骨髄腫における遺伝子解析による治療感受性・予後予測因子の探索的研究(NGSMM 研究）
H26-遺伝子-03	郡山暢之	日本人の肥満症の発症と治療効果・抵抗性に関連する遺伝素因の探索 -オーダーメイド医療の確立-（G-FORCE 研究）
特定臨床研究 H27-EBM(介入)-01	菰方輝夫	免疫抑制患者に対する 13 価蛋白結合型肺炎球菌ワクチンと 23 価莢膜多糖体型肺炎球菌ワクチンの連続摂取と 23 価莢膜多糖体型肺炎球菌ワクチン単独摂取の有効性の比較 -二重盲検無作為化比較試験-（CPI Study）
H29-EBM(観察)-02	中島 均	我が国における左冠動脈主幹部インターベンションに対するコホート研究(LM-JANHO)

（ウ） NHO ネットワーク共同研究

領域	研究責任医師	研究課題名
H27-NHO(糖尿)-01	郡山暢之	多面的管理達成者の糖尿病腎症予後改善効果を予測できる非侵襲的指標の確立（DNrem研究）
H29-NHO(脳卒中)-01	松岡秀樹	虚血性脳卒中患者における脳微小出血進展への抗血栓薬の関与に関する研究
H29-NHO（循環）-01	城ヶ崎倫久	経皮的心肺補助離脱のデイリー予測スコア作成に関する研究（NHOC-PCPS）
H30-NHO(血液)-01	大塚眞紀	高齢者移植非適応再発・難治末梢性 T 細胞リンパ腫に対するゲムシタビン、デキサメサゾン、シスプラチン（GDP）療法＋ロミデプシン療法の第Ⅱ相試験(PTCL-GDPR)

領域	研究責任医師	研究課題名
H30-NHO(外科)-01	菰方輝夫	本邦における成人鼠経ヘルニア術後慢性疼痛の実態調査とそのリスク因子解析 -多施設共同前向きコホート研究-(ヘルニアスタディ)
H30-NHO(糖尿病)-01	郡山暢之	多面的管理達成者の糖尿病性腎臓病(DKD)予後改善効果評価法の確立と、効果予測のための非侵襲的指標の確立(DKDrem-2 研究)
H30-NHO(循環)-01	城ヶ崎倫久	真の心房細動発症リスク同定のための新規バイオマーカー CA-125 の検討(CA125-AF)
H31-NHO(血液)-01	大塚眞紀	未治療濾胞性リンパ腫における Obinutuzumab の治療成績、QOL、費用対効果、予後に関する多施設前向きコホート研究(PEACE-FL)
H31-NHO(血液)-02	大塚眞紀	B 細胞性急性リンパ性白血病におけるターゲットキャプチャー RNA-seq を用いたサブタイプ診断の実行可能性に関する研究
H31-NHO(多共)-02	野元三治	メトトレキサート(MTX)関連リンパ増殖性疾患の遺伝子変異プロファイルの解析
R2ー NHO(心脳)-04	城ヶ崎倫久	がん化学療法関連心筋症の予測、早期発見、早期治療 ～心臓超音波検査 speckle tracking 法、タイチン truncating 変異の検出、尿中タイチン N フラグメント測定、血中心筋トロポニン I 高感度測定の比較検討～

(エ) 競争的研究費等

I. 公費臨床試験

財源	課題名	研究者名	金額(円)
厚生労働省 厚生労働科学研究費補助金	特発性心筋症に関する調査研究(20FC0201)	分担研究者 吉永正夫	500,000
日本医療研究開発機構研究費	爪部悪性黒色腫への指趾骨温存切除による新たな低侵襲標準治療の開発	分担研究者 松下茂人	260,000
科学研究費助成事業 基盤研究(C)	摂食機能評価に基づいた栄養食事指導の有効性と体組成改善への影響の検討	分担研究者 中村康典	65,000
科学研究費助成事業 基盤研究(C)	生体内ゲノム編集を利用した HTLV-1 を標的にする新規抗ウイルス療法	分担研究者 魚住公治	130,000

II. 民間セクターからの寄付金

課題名	研究者名	金額(円)
弁膜症疾患における低侵襲治療の研究のため	片岡哲郎	500,000
弁膜症疾患における低侵襲治療の研究のため	東 健作	500,000
肝細胞がんに対する肝動脈塞栓療法に関する研究	櫻井一宏	100,000
大血管領域に対する治療戦略の研究助成	金城玉洋	600,000

課題名	研究者名	金額(円)
弁膜症術後評価に関する臨床研究	金城玉洋	300,000
心臓血管外科手術手技の研究のため	金城玉洋	100,000
弁膜症術後評価に関する臨床研究	金城玉洋	300,000
肝細胞がんに対する肝動脈塞栓療法に関する研究	櫻井一宏	100,000
肝細胞がんに対する肝動脈塞栓療法に関する研究	櫻井一宏	100,000
肝細胞がんに対する肝動脈塞栓療法に関する研究	櫻井一宏	100,000
外科・消化器外科治療の研究のため	菰方輝夫	200,000
安全な消化器外科手術に対する研究助成のため	菰方輝夫	200,000
外科手術の安全性に関する臨床研究のため	菰方輝夫	100,000
安全な麻酔管理の研究のため	佐保尚三	300,000
皮膚潰瘍でのアクアセル Ag フォームを用いたバイオフィルム形成阻止能と筋繊維芽細胞形成の動態についての解析に関する研究	松下茂人	100,000
慢性皮膚潰瘍での細菌負荷・バイオフィルム形成と筋線維芽細胞の形態構築動態の解析に対する研究助成のため	松下茂人	300,000
心房細動のカテーテルアブレーションの安全性に関する研究	塗木徳人	200,000
放射線(核医学)領域に関する研究	杉尾　浩	500,000
核医学画像診断技術の研究(核医学的手法を用いた画像診断に関する研究)	杉尾　浩	400,000

(オ) 臨床研究課題

	研究内容・課題名	部署・研究者名
1	非弁膜症性心房細動を有する後期高齢患者を対象とした前向き観察研究(ANAFIE Registry)	第 1 循環器内科 片岡哲郎
2	安定型冠動脈疾患を合併する非弁膜症心房細動患者におけるリバーロキサバン単剤療法に関する臨床研究(AFIRE study)	第 1 循環器内科 中島　均
3	深部静脈血栓症及び肺血栓塞栓症の治療及び再発抑制に対するリバーロキサバンの有効性及び安全性に関する登録観察研究(J'xactly Study)	第 1 循環器内科 中島　均
4	大動脈瘤/大動脈解離患者の実態調査および予後に関する前向き観察研究	第 1 循環器内科 中島　均
5	動脈硬化を基盤とした虚血性心臓病における新規血液マーカーの確立	第 1 循環器内科 中島　均
6	2 管球 CT を用いた冠動脈狭窄、心筋虚血、心筋線維化の総合的評価に関する多施設研究(AMPLIFiED)	第 1 循環器内科 中島　均

	研究内容・課題名	部署・研究者名
7	エベロリムス溶出性コバルトクロムステント（CoCr-EES[XIENCE]）留置後のDAPT 投与期間を 1 か月に短縮することの安全性を評価する多施設前向きオープンラベル無作為化比較試験（ShorT and OPtimal duration of Dual AntiPlatelet Therapy study-2(STOPDAPT-2)	第 1 循環器内科 中島　均
8	実施臨床におけるエベロリムス溶出性ステント（XIENCE V™）とシロリムス溶出性ステント（CYPHER SELECTTM+ステント）の有効性および安全性についての多施設前向き無作為化オープンラベル比較試験：長期追跡試験（RESET Extended Follow-up Study）	第 1 循環器内科 中島　均
9	高尿酸血症に対するキサンチンオキシダーゼ阻害剤フェブキソスタットの血管障害予防効果に関する多施設共同ランダム化比較試験（PRIZE study）	第 1 循環器内科 中島　均
10	SGLT2 阻害薬による動脈硬化予防の多施設共同ランダム化比較試験（PROTECT）	第 1 循環器内科 中島　均
11	実地臨床におけるバイオリムス溶出性ステント（BES）とエベロリムス溶出性ステント（EES）の有効性及び安全性についての多施設前向き無作為化オープンラベル比較試験（NEXT）	第 1 循環器内科 中島　均
12	至適な血管内超音波ガイド経皮的冠動脈インターベンションの複雑性病変における臨床経過を評価する 前向き観察研究（OPTIVUS）	第 1 循環器内科 中島　均
13	破裂性腹部大動脈瘤に対する開腹手術とステントグラフト内挿術の治療選択に関する全国多施設観察研究	心臓血管外科 向原公介
14	自己心膜による大動脈弁再健術の多施設共同研究体制とデータベースの確立	心臓血管外科 向原公介
15	非弁膜症性心房細動とアテローム血栓症を合併する脳梗塞例の二次予防における最適な抗血栓療法に関する多施設共同ランダム化比較試験 （Optimal Antithrombotic Therapy in Ischemic Stroke Patients with Non-Valvular Atrial Fibrillation and Atherothrombosis：ATIS-NVAF）	脳血管内科 松岡秀樹
16	脳卒中研究者新ネットワークを活用した脳・心血管疾患における抗血栓療法の実態と安全性の解明（The Bleeding with Antithrombotic Therapy Study 2：BAT2）	脳血管内科 松岡秀樹
17	INVOS の値と MRI や血管造影所見との関連性についての研究	脳血管内科 松岡秀樹
18	虚血性脳卒中患者における脳微小出血進展への抗血栓薬関与に関する研究	脳血管内科 松岡秀樹
19	K-RESOLVE Network 研究	脳血管内科 松岡秀樹
20	機械的血栓回収療法による再開通後の脳循環時間と再潅流障害との関連についての研究	脳血管内科 濵田祐樹
21	くも膜下出血アウトカム評価ツールの日本語版開発（SAHOT-J）	脳神経外科 谷口　歩
22	脳卒中患者の長期予後追跡のための QOL データ収集システムの開発 （PROP-J）	脳神経外科 谷口　歩
23	高齢者の出血性脳卒中に対する外科治療の有用性について	脳神経外科 谷口　歩
24	特発性正常圧水頭症の治療	脳神経外科 谷口　歩
25	破裂脳動脈瘤に対する外科治療	脳神経外科 谷口　歩

	研究内容・課題名	部署・研究者名
26	特発性心筋症に関する調査研究	小児科 吉永正夫
27	高齢者移植非適応再発・難治末梢性 T 細胞リンパ腫に対するゲムシタビン、デキサメサゾン、シスプラチン（GDP）療法＋ロミデプシン療法の第 II 相試験	血液内科 大塚眞紀
28	未治療 CCR4 陽性高齢者 ATL に対するモガムリズマブ併用 CHOP-14 の第 II 相試験	血液内科
29	骨髄増殖性腫瘍の実態と遺伝子変異検索	血液内科
30	未治療濾胞性リンパ腫における Obinutuzumab の治療成績、QOL、費用対効果、予後に関する多施設前向きコホート研究	血液内科 大塚眞紀
31	B 細胞性急性リンパ性白血病におけるターゲットキャプチャーRNA-seq を用いたサブタイプ診断の実行可能性に関する研究	血液内科 大塚眞紀
32	成人 T 細胞白血病リンパ腫における CCR4 遺伝子変異と予後の検討	血液内科
33	血小板減少を呈する患者における酵素測定法によるゴーシェ病スクリーニング	血液内科 大塚眞紀
34	切除不能肝細胞癌に対するレンバチニブ早期投与効果についての多施設共同研究	消化器内科 櫻井一宏
35	膵がん切除後の補助化学療法における S-1 単独療法と S-1 とメトホルミンの併用療法の非盲検ランダム化第 II 相比較試験	外科 菰方輝夫
36	免疫抑制患者を対象とした PCV13/PPSV23 と PPSV23 の予防効果の比較試験	外科 菰方輝夫
37	本邦における成人鼠径ヘルニア術後慢性疼痛の実態調査とそのリスク因子解析－多施設共同前向きコホート研究－	外科 菰方輝夫
38	アバスチン点滴静注用　特定使用成績調査「進行又は再発の子宮頸癌」	婦人科
39	ヘパリン Na 注 1 万単位/10mL「モチダ」 副作用調査 「ヘパリンナトリウムの投与によって発現した腹腔内出血に対する副作用調査」	婦人科
40	GOTIC-002　局所進行子宮頸癌根治放射線療法施行例に対する UFT による補助化学療法のランダム化第Ⅲ相比較試験	婦人科
41	放射線治療の治療効果評価法・合併症低減法	放射線科
42	オクトレオスキャン症例の解析	放射線科
43	骨転移のある前立腺癌に対する塩化ラジウム治療	放射線科
44	塩化ラジウム治療における MRI の評価	放射線科
45	脊髄クモ膜下麻酔効果に体位、腹圧が及ぼす影響に関する研究	麻酔科 佐保尚三
46	RST の当院での介入状況の検討	麻酔科 佐保尚三

	研究内容・課題名	部署・研究者名
47	早期リハ介入の効果の検討	麻酔科 佐保尚三
48	血管エラストーシス(Vascular elastosis)の症例収集および組織学的研究	病理診断科 後藤正道
49	ブルーリ潰瘍(M.ulcerans 感染症)における無痛性病態メカニズムの解明	病理診断科 後藤正道
50	メトトレキサート(MTX)関連リンパ増殖性疾患の病態解明のための多施設共同研究(H28-NHO(多共)-02)	病理診断科 野元三治
51	造血幹細胞移植療法における口腔合併症に対する系統的口腔管理の構築	歯科口腔外科 中村康典
52	骨吸収抑制薬関連顎骨壊死に対する口腔管理に関する研究	歯科口腔外科 中村康典
53	当院における周術期口腔機能管理も対する理解度と満足度に関する検討	歯科口腔外科 下田平佳純 鞍掛奈津希
54	JCOG1602: 爪部悪性黒色腫への指趾骨温存切除による新たな低侵襲標準治療の開発	皮膚腫瘍科・皮膚科 松下茂人
55	JCOG1309 病期Ⅱ期およびⅢ期皮膚悪性黒色腫に対するインターフェロンβ局所投与による術後補助療法のランダム化比較第Ⅲ相試験	皮膚腫瘍科・皮膚科 松下茂人
56	皮膚腫瘍における免疫応答解析に基づくがん免疫療法予測診断法の確立	皮膚腫瘍科・皮膚科 松下茂人
57	JCOG1605:パクリタキセル既治療原発性皮膚血管肉腫に対するパゾパニブ療法の非ランダム化検証的試験	皮膚腫瘍科・皮膚科 松下茂人
58	ニボルマブ+イピリムマブで治療される悪性黒色腫患者における腸内細菌代謝産物の臨床的意義に関する前向き観察研究	皮膚腫瘍科・皮膚科 松下茂人
59	進行期悪性黒色腫疾患に対する術後補助療法後に関する観察研究	皮膚腫瘍科・皮膚科 松下茂人
60	粘膜型/末端黒子型メラノーマにおけるニボルマブ＋イピリムマブ併用療法の一次治療と抗 PD-1 抗体単剤療法の一次治療(無効後ニボルマブ＋イピリムマブを含む)の効果に関する多施設共同後ろ向き研究	皮膚腫瘍科・皮膚科 松下茂人
61	結合組織性皮膚疾患における病態解明	皮膚腫瘍科・皮膚科 松下茂人
62	悪性黒色腫における免疫チェックポイント阻害薬効果に対する HLA CLASS Ⅱの影響	皮膚腫瘍科・皮膚科 松下茂人
63	メラノサイト系の悪性腫瘍に関する角層解析の有用性	皮膚腫瘍科・皮膚科 松下茂人
64	完全奏効(CR)患者における抗 PD-1 抗体治療中止後の効果持続についての後方視的研究	皮膚腫瘍科・皮膚科 松下茂人
65	HTLV-1 感染症の発症リスクの解明に関する研究	腫瘍内科 魚住公治
66	甲状腺癌の分子標的薬による治療	腫瘍内科 魚住公治
67	ANAFIE Registry(非弁膜症性心房細動を有する後期高齢者を対象とした前向き観察試験)	不整脈治療科

	研究内容・課題名	部署・研究者名
68	RYOMA Registry（カテーテルアブレーションを施術した非弁膜症性心房細動症例の抗凝固療法の実態とその予後に関する観察研究）	不整脈治療科
69	ラムシルマブとパクリタキセル併用療法における投与中の血圧上昇の実態調査	薬剤部 鳥山陽子
70	末期心不全患者に対するモルヒネの使用状況調査	薬剤部 髙城沙也香
71	irAE マネジメント向上を目的とした施設間連携への取り組み“鹿児島がん免疫療法サポートネットワーク（KISNet）”の評価及び有用性の検討	薬剤部 松尾圭祐
72	院外処方箋への臨床検査値記載による有用性の検討	薬剤部 吉永光辰
73	経胸壁心エコー図にて指摘しえた経カテーテル大動脈弁留置術後に生じた血栓弁 6 症例	臨床検査科 宮﨑明信
74	骨シンチグラフィ解析ソフトウェアの研究・開発・評価等に関する研究	放射線室 杉尾　浩
75	心臓リハビリテーションにおける多職種での包括的介入について	リハビリテーション科 口石智秀
76	心臓リハビリテーションの内容改善と管理体制について	リハビリテーション科 口石智秀
77	吸湿性繊維保護具を使用した場合のドレープ内の湿度温度および蒸れ感の変化	東 2 病院 田中　康
78	急性期病院の混合病棟で勤務する看護師の勤務継続につながる職務満足度因子の傾向	東 3 病棟 折田紋奈
79	看護師のリハビリテーションに対する認識とその影響因子	東 5 病棟 橋口未由紀
80	循環器疾患患者のアドバンス・ケア・プランニング（ACP)の必要性に関する病棟看護師の認識	東 6 病棟 溝口　準
81	経カテーテル的大動脈弁置換術を受ける患者のフレイルに影響する要因分析	東 7 病棟 厚地美穂
82	難治性腹水で KM－CART を実施した患者の身体症状に及ぼす苦痛や効果	東 8 病棟 井手口和絵
83	骨髄異形成症候群の患者とエンド・オブ・ライフ・ディスカッションを行う看護師の構え	西 4 病棟 榊　詩織
84	外回り看護師が手術中に個人防護具着用を徹底できない要因	手術室 砂坂志織
85	循環器外来における未受診患者の要因と分析	外来 井出之上涼子
86	ファシリテーター育成によるケースカンファレンスへの効果	副看護師長 尾辻真由美
87	A 病院のベテラン看護師が副看護師長に求める役割	副看護師長 久保田詳子
88	看護師が働き続けられる職場環境の検討～看護職のワークライフバランスインデックス調査を使用して～第 2 報	看護師長 加藤崇志

	研究内容・課題名	部署・研究者名
89	九州管内の国立病院機構病院 28 施設に勤務する卒後 1～5 年目看護職の属性と看護実践能力との関連	看護学校 山田　巧
90	学内で実施した精神看護学実習における看護学生の学び	看護学校 石原史絵
91	実習指導者会議における臨床判断モデルとリフレクションを活用した学習会の効果	看護学校 西元智子
92	看護専門学校を卒業した新人看護師が抱く困難感	看護学校 髙木雅弘
93	看護学生の認知症高齢者に抱くイメージ	看護学校 星野睦美
94	看護学生の「子ども理解」に関する学年比較	看護学校 谷川仁美
95	精神看護学の講義「看護師の感情労働」理解促進のための映画教材の効果	看護学校 西元智子
96	学生が認識する意味のあるカンファレンスと意味のあるカンファレンスの成立要因	看護学校 西園里美

② 治験実績

以下に 2020 年度の治験の実績を示す。

2020 年度（令和 2 年度）治験内容　　2020.4～2021.3

	医薬品		医療機器		再生医療		合計
	新規契約	継続契約	新規契約	継続契約	新規契約	継続契約	
治験　第Ⅱ相	0(0)	1(1)	0(0)	0(0)	0(0)	1(1)	2(2)
治験　第Ⅲ相	0(1)	5(5)	0(0)	1(1)	0(0)	0(0)	6(7)
治験　第Ⅳ相	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
合計	0(1)	6(6)	0(0)	1(1)	0(0)	1(1)	8(9)

（ ）内は昨年の実数

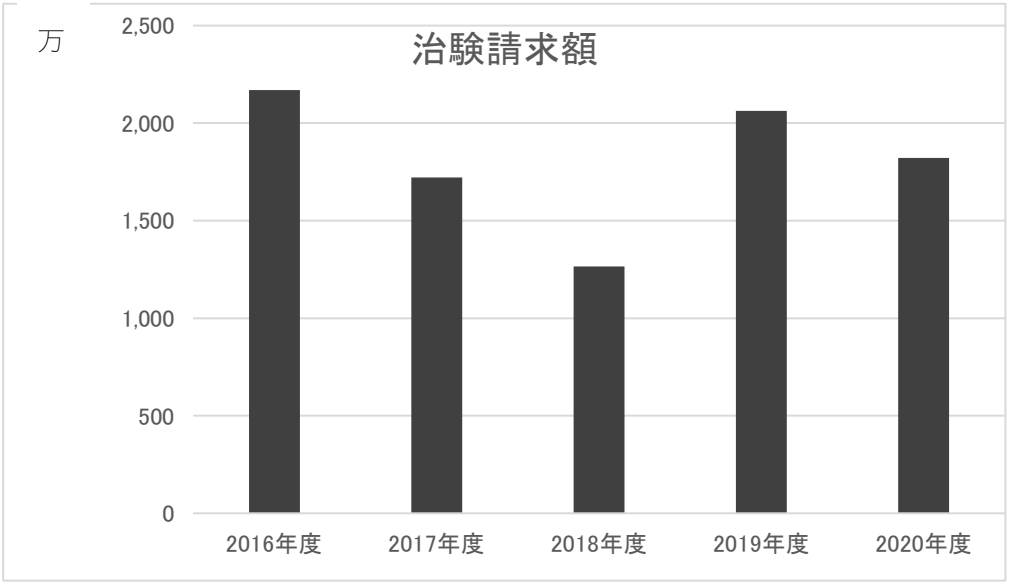
Ⅱ/Ⅲ相試験はⅡ相の項目に記載

実施率（2020 年度に終了した治験）

	契約件数（件）	契約症例・調査数	実施症例・調査票	実施率（%）
治験	3(1)	20(3)	13(1)	65(33.3)

（ ）内は昨年の実数

治験請求額推移



（ア） 治験の細目

研究課題名	研究依頼者	責任医師
未治療の多発性骨髄腫患者を対象とした BMS-901608 の国内第 2 相臨床試験	ブリストル・マイヤーズ スクイブ株式会社	大塚眞紀
（再生医療等製品） 株式会社ヘリオスの依頼による脳梗塞患者を対象とした HLCM051 の第 II/III 相試験	株式会社ヘリオス	松岡秀樹
ゼリア新薬工業株式会社の依頼による子宮頸癌患者を対象としたZ-100 の第Ⅲ相試験	ゼリア新薬工業株式会社	大田俊一郎
（医療機器） 虚血性心疾患患者に対する OMKK02 の医療機器治験	オーバスネイチメディカル株式会社	中島　均
第一三共株式会社の依頼による急性骨髄性白血病患者を対象としたキザルチニブ(AC220)の第Ⅲ相試験	第一三共株式会社	大塚眞紀
第一三共株式会社の依頼による血栓性脳梗塞患者を対象とした CS-747S の第Ⅲ相試験	第一三共株式会社	松岡秀樹
大塚製薬の依頼によるうっ血性心不全患者を対象とした OPC-61815 の第Ⅲ相試験	大塚製薬株式会社	薗田正浩
R788 の慢性特発性血小板減少性紫斑病患者を対象とした第 III 相臨床試験	キッセイ薬品工業株式会社	大塚眞紀

（イ） 製造販売後調査

研究課題名	研究依頼者	責任医師
アデムパス錠　使用成績調査	バイエル薬品株式会社	蔡　榮鴻
オプジーボ点滴静注　使用成績調査「根治切除不能な悪性黒色腫」	小野薬品工業株式会社	松下茂人
フォシーガ錠　長期使用に関する特定使用成績調査	アストラゼネカ株式会社	郡山暢之
ゼルボラフ錠 240mg　特定使用成績調査	中外製薬株式会社	松下茂人
ゼルボラフ錠 240mg　特定使用成績調査	中外製薬株式会社	魚住公治
ジャカビ錠 5 mg　特定使用成績調査（骨髄線維症）	ノバルティスファーマ株式会社	花田修一
献血グロベニン-I静注用　使用成績調査（再審査用）「スティーブンス・ジョンソン症候群及び中毒性表皮壊死症」	日本製薬株式会社	松下茂人
ｵﾌﾟｽﾐｯﾄ錠 10mg 特定使用成績調査(長期使用)	ヤンセンファーマ株式会社	塗木徳人
ビプリブ®点滴静注用4OO単位　使用成績調査	武田薬品工業株式会社	花田修一
ジャカビ®錠　5mg　特定使用成績調査	ノバルティスファーマ株式会社	大塚眞紀
ヤーボイ点滴静注液 50 mg　特定使用成績調査 「根治切除不能な悪性黒色腫に対する全例調査」	小野薬品工業株式会社	松下茂人
オプジーボ点滴静注 20 mg・100 mg特定使用成績調査「切除不能な進行・再発の非小細胞肺癌に対する全例調査」	小野薬品工業株式会社	魚住公治
マリゼブ®錠 12.5mg、25mg　特定使用成績調査（長期使用に関する調査）	MSD 株式会社	郡山暢之
レブラミド®カプセル 5mg, 2.5mg　特定使用成績調査 「未治療の多発性骨髄腫に対する有効性・安全性調査」	ブリストル・マイヤーズ スクイブ株式会社	大塚眞紀

研究課題名	研究依頼者	責任医師
ジャカビ®錠　5mg 特定使用成績調査（真性多血症）	ノバルティスファーマ株式会社	魚住公治
ｵﾌﾟｽﾐｯﾄ錠 10mg 特定使用成績調査(長期使用)	ヤンセンファーマ株式会社	田中裕治
ファリーダック®カプセル 10・15mg 特定使用成績調査	ノバルティスファーマ株式会社	花田修一
アイノフロー吸入用 800ppm 使用成績調査	エア・ウォーター株式会社	金城玉洋
オプジーボ特定使用成績調査〔根治切除不能又は転移性の腎細胞癌〕	小野薬品工業株式会社	魚住公治
オプジーボ特定使用成績調査 〔根治切除不能又は転移性の腎細胞癌」	小野薬品工業株式会社	宮元一隆
デュラグルチド（トルリシティ皮下注 0.75 mg アテオス）特定使用成績調査	日本イーライリリー株式会社	郡山暢之
カイプロリス点滴静注用 10 ㎎,40 ㎎　使用成績調査 「再発又は難治性の多発性骨髄腫に対する全例調査」	小野薬品工業株式会社	花田修一
カイプロリス点滴静注用 10 ㎎,40 ㎎　使用成績調査 「再発又は難治性の多発性骨髄腫に対する全例調査」	小野薬品工業株式会社	魚住公治
タフィンラーカプセル 50 ㎎、75 ㎎/メキニスト錠 0.5 ㎎、2 ㎎ 特定使用成績調査「BRAF 遺伝子変異を有する根治切除不能な悪性黒色腫」	ノバルティスファーマ株式会社	松下茂人
エムプリシティ点滴静注 300mg・400mg 特定使用成績調査	ブリストル・マイヤーズスクイブ株式会社	花田修一
キイトルーダ®点滴静注使用成績調査（悪性黒色腫）	MSD株式会社	松下茂人
ベンテイビス使用成績調査（PAH）	バイエル薬品株式会社	蔡　榮鴻
オプジーボ特定使用成績調査〔再発又は難治性の古典的ホジキンリンパ腫〕	小野薬品工業株式会社	花田修一
ファリーダック®カプセル 10・15mg 特定使用成績調査	ノバルティスファーマ株式会社	魚住公治
オプジーボ使用成績調査〔再発又は遠隔転移を有する頭頸部癌〕	小野薬品工業株式会社	松崎　勉
ニンラーロカプセル使用成績調査（全例調査）「再発又は難治性の多発性骨髄腫」	武田薬品工業株式会社	大塚眞紀
ムンデシンカプセル 100mg 特定使用成績調査	ムンディファーマ株式会社	大塚眞紀
レブラミド®カプセル　使用成績調査「再発又は難治性の成人 T 細胞白血病リンパ腫」	ブリストル・マイヤーズスクイブ株式会社	大塚眞紀
アイクルシグ錠15mg 使用成績調査	大塚製薬株式会社	大塚眞紀
自家培養表皮ジェイスの先天性巨大色素性母斑に対する使用成績調査	株式会社ジャパン・ティッシュ・エンジニアリング	松下茂人
サデルガカプセル 100mg 特定使用成績調査	サノフィ株式会社	大塚眞紀
バベンチオ点滴静注200mg　特定使用成績調査 （根治切除不能なメルケル細胞癌）	メルクバイオファーマ株式会社(IQVIA サービシーズジャパン株式会社)	松下茂人
スインプロイク錠 使用成績調査	塩野義製薬株式会社	松崎　勉
ウプトラビ錠 0.2mg・0.4mg　特定使用成績調査 「長期使用に関する調査」	日本新薬株式会社	田中裕治
リムパーザ錠 100mg、150mg 使用成績調査　白金系抗悪性腫瘍剤感受性の再発　卵巣癌患者を対象とした全例調査	アストラゼネカ株式会社	大田俊一郎
ダラザレックス点滴静注 100mg、400mg　特定使用成績調査（再発又は難治性の多発性骨髄腫）＜ﾌﾟﾛﾄｺｰﾙ No.DZX1L＞	ヤンセンファーマ株式会社	大塚眞紀

研究課題名	研究依頼者	責任医師
サビーン®点滴静注用 500mg 使用成績調査（全例調査）	キッセイ薬品工業株式会社	魚住公治
ベスポンサ®点滴静注用 1mg 特定使用成績調査	ファイザー株式会社	原口浩一
ラパリムスゲル 0.2%一般使用成績調査(全例調査)-結節性硬化症に伴う皮膚病変-	ノーベルファーマ株式会社	松下茂人
レボレード錠 特定使用成績調査 （再生不良性貧血）	ノバルティスファーマ株式会社	大塚眞紀
献血ノンスロン500注射用・献血ノンスロン1500注射用 アンチトロンビンⅢ低下を伴う門脈血栓症 使用成績調査	日本製薬株式会社	菰方輝夫
献血ノンスロン500注射用・献血ノンスロン1500注射用 アンチトロンビンⅢ低下を伴う門脈血栓症 使用成績調査	日本製薬株式会社	櫻井一宏
トラクリア小児用分散錠 32mg 特定使用成績調査（長期使用）	ヤンセンファーマ株式会社	田中裕治
イストダックス®点滴静注用 10mg 使用成績調査「再発又は難治性の末梢性 T 細胞リンパ腫」	ブリストル・マイヤーズスクイブ株式会社	大塚眞紀
トラディアンス配合錠 特定使用成績調査 （長期使用に関する調査）	日本ベーリンガーインゲルハイム株式会社	郡山暢之
ビラフトビ®・メクトビ®併用療法特定使用成績調査〔BRAF 遺伝子変異を有する根治切除不能な悪性黒色腫〕	小野薬品工業株式会社	松下茂人
ゾスパタ錠 一般使用成績調査〔プロトコル No.XSP001〕	アステラス製薬株式会社	大塚眞紀
ヴァンフリタ錠一般使用成績調査	第一三共株式会社	大塚眞紀
レパーサ皮下注 特定使用成績調査（長期使用）	アムジェン株式会社	片岡哲郎
レパーサ皮下注 特定使用成績調査（長期使用）	アムジェン株式会社	東 健作
デファイテリオ静注 200mg 一般使用成績調査	日本新薬株式会社	大塚眞紀
キイトルーダ®点滴静注 副作用・感染症・有害事象詳細調査	MSD 株式会社	魚住公治
オプジーボ点滴静注 20mg・100mg・240mg、ヤーボイ点滴静注液 50mg 副作用・感染症詳細調査	小野薬品工業株式会社	小森崇矢
ジフォルタ®注射液 20 ㎎使用成績調査	ムンディファーマ株式会社	大塚眞紀
ベレキシブル®錠 特定使用成績調査 再発又は難治性の中枢神経系原発リンパ腫（PCNSL）	小野薬品工業株式会社	魚住公治
サピエン 3（TAV in SAV）使用成績調査	エドワーズライフサイエンス株式会社	片岡哲郎
サピエン 3（TAV in SAV）使用成績調査	エドワーズライフサイエンス株式会社	平峯聖久
コララン®特定使用成績調査（洞調律かつ投与開始時の安静時心拍数が 75 回/分以上の慢性心不全：ただし、β遮断薬を含む慢性心不全の標準的な治療を受けている患者に限る。）	小野薬品工業株式会社	中島 均
コララン®特定使用成績調査（洞調律かつ投与開始時の安静時心拍数が 75 回/分以上の慢性心不全：ただし、β遮断薬を含む慢性心不全の標準的な治療を受けている患者に限る。）	小野薬品工業株式会社	東 健作
「メマリーOD 錠」に関する副作用詳細調査	第一三共株式会社	森内昭博
ビンダケルカプセル特定使用成績調査－トランスサイレチン型心アミロイドーシス患者に対する調査－（プロトコール№B3461064）	ファイザー株式会社	薗田正浩

3. 業績報告

① 英文原著論文等

※2020 年度中に Epub(online で公開)された論文も含みます。また、実際に印刷された年度に再掲載しています。鹿児島医療センター以外の所属で発表された論文も掲載しました。

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■脳血管内科

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■小児科

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内科治療抵抗性の腕頭動脈可動性プラークを塞栓源とした再発性脳梗塞の1例
第 46 回日本脳卒中学会学術総会、Web 開催、2021 年 3 月 11 日～13 日

7. 吉永正夫
トピックス「学校心臓検診を活かす:小児突然死予防に果たす役割」. 学校心臓検診の歴史と将来展望
第 84 回日本循環器学会学術集会、Web 開催、2020 年 7 月 27 日～10 月 30 日

8. 中﨑奈穂
離島在住の食物アレルギー患者への対応と問題点
第 57 回日本小児アレルギー学会学術大会、Web 開催、2020 年 10 月 31 日～11 月 30 日

9. 吉永正夫、小澤淳一、吉田葉子、今村知彦
パネルディスカッション「不整脈」最新の遺伝性不整脈の臨床. QT 延長症候群 (LQT1～3)
第 56 回日本小児循環器学会総会学術集会、Web 開催、2020 年 11 月 22 日

10. 田中裕治
Rastelli 術後の感染性心内膜炎で手術適応と判断したが、手術を回避できた 2 症例
第 56 回日本小児循環器学会総会・学術集会、Web 開催、2020 年 11 月 22 日

11. 中別府聖一郎、大渡五月、藤野聡司、原口浩一、大塚眞紀
ホジキンリンパ腫の病気診断にあたり PET-CT で連続していない集積箇所から濾胞性リンパ腫を診断した症例
第 11 回血液学会九州地方会、Web 開催、2021 年 3 月 13 日

12. 菰方輝夫、多田宣裕、吉川弘太、海江田衛、塗木健介
肝門部胆管内発育を伴った cStage IVc 大腸癌に対する外科治療
第 120 回日本外科学会定期学術集会、Web 開催、2020 年 8 月 14 日

13. 夛田宣裕、吉川弘太、海江田衛、塗木健介、菰方輝夫
Tokyo Gudelines 2018 における急性胆嚢炎ハイリスク患者に対する PTGBD 至適導入時期の検討
第 120 回日本外科学会定期学術集会、東京（リモート学会）、2020 年 8 月 14 日

14. 古川恵瑞、今田　亮、夛田宣裕、塗木健介、實　操二、菰方輝夫
上部消化管造影検査後バリウム貯留による大腸穿孔を来した 1 例
第 80 回鹿児島県臨床外科学会医学会、鹿児島、2020 年 8 月 22 日

15. 夛田宣裕、吉川弘太、塗木健介、菰方輝夫、野元三治
バウヒン弁を先進部とする成人特発性腸重積症の一切除例
第 56 回日本腹部救急医学会総会、名古屋（リモート学会）、2020 年 10 月 8 日～11 月 2 日

16. 菰方輝夫、夛田宣裕、吉川弘太、海江田衛、塗木健介
抗血栓薬服用者に対する膵頭十二指腸切除術の出血および血栓塞栓症を含む周術期成績
第 75 回日本消化器外科学会総会、Web 開催、2020 年 12 月 15 日

17. 夛田宣裕、古川恵瑞、海江田衛、塗木健介、實　操二、菰方輝夫
交通外傷による外傷性左横隔膜単独損傷の一例
第 57 回日本腹部救急医学会総会、Web 開催、2021 年 3 月 11 日～31 日

18. 夛田宣裕、古川恵瑞、塗木健介、實　操二、菰方輝夫
術前に重症大動脈弁狭窄症に対して経カテーテル的大動脈弁置換術を行った高齢者結腸癌の3例
第 81 回鹿児島県臨床外科学会医学会、鹿児島、2021 年 3 月 20 日

19. 濵島雅代
DOAC での抗凝固療法中に脳梗塞を再発した Trousseau 症候群の一例
第 143 回鹿児島産科婦人科学会学術集会、鹿児島、2020 年 9 月 26 日

20. 松崎尚寛、西元謙吾、松崎　勉、久徳貴之、伊東小都子
副甲状腺癌の血管内転移症例
第 82 回耳鼻咽喉科臨床学会、Web 開催、2020 年 12 月 25 日

21. 後藤正道、野元三治、夛田宣裕
静脈エラストーシスによる虚血性回腸炎の一例
第 108 回日本病理学会オンライン総会、福岡、2020 年 7 月 1 日～31 日

22. 野元三治
骨髄病変
第 376 回九州・沖縄スライドコンファレンス、Web 開催、2020 年 7 月 18 日

23. 中村康典、木村奈美子、下田平佳純、横山千鶴、江口洋子、吉村卓也、手塚征宏、西　恭宏
造血幹細胞移植療法に対する周術期口腔機能管理とその効果
第 17 回日本口腔ケア学会総会・学術大会、長崎、2020 年 9 月 3 日

24. 下田平佳純、中村康典、木村菜美子、横山千鶴、江口洋子、堂園文子、西　恭宏
鹿児島医療センターにおける口腔ケアチーム活動に関する臨床統計学的検討
第 17 回日本口腔ケア学会総会・学術大会、長崎、2020 年 9 月 3 日

25. 中村康典、木村菜美子、下田平佳純、横山千鶴、鞍掛奈津希、江口洋子、田場　要、池田智子
鹿児島医療センターにおける口腔ケアチーム活動と現状
第 74 回国立病院総合医学会、Web 開催、2020 年 10 月 17 日～11 月 14 日

26. 灰床裕介、前田拓郎、板山雄亮、小吉尚裕、森内昭博、桜井一宏、魚住公治、井戸章雄
胃内に脱落した食道ステントを経内視鏡的に摘出し得た噴門悪性黒色腫の1例
第 116 回日本消化器病学会九州支部例会、Web 開催、2020 年 12 月 4 日～5 日

27. 青木恵美、松下茂人、山村健太郎 、坂本翔一、蓑川葉子
当科で経験した腋窩部皮膚皮下腫瘍
第 63 回日本形成外科学会総会・学術集会、Web 開催、 2020 年 8 月 26 日～8 月 28 日

28. 坂本翔一、松下茂人、青木恵美、山村健太郎、簔川葉子、前田拓郎、塗木健介、島岡俊治、北薗正樹
内視鏡的粘膜下層剥離術を併用した肛囲乳房外パジェット病の治療経験
第 35 回日本皮膚外科学会総会・学術集会、Web 開催、2020 年 10 月 17 日～18 日

29. 青木恵美、山村健太郎、簔川葉子、坂本翔一、松下茂人
当科で経験した頭頸部有棘細胞癌の病期分類と予後～AJCC 第 7 版と第 8 版の比較～
第 72 回日本皮膚科学会西部支部学術大会、Web 開催、2020 年 10 月 25 日

30. 蓑川葉子、松下茂人、青木恵美、山村健太郎、坂本翔一
上眼瞼瞼板結膜を用いた後葉再建の 3 例
第 72 回日本皮膚科学会西部支部学術大会、Web 開催、2020 年 10 月 25 日

31. 青木恵美、山村健太郎、蓑川葉子、坂本翔一、平野　唯、小森崇矢、杉野仁美、松下茂人
当科における有棘細胞癌治療の検討
第 186 回日本皮膚科学会鹿児島地方会、鹿児島、2020 年 12 月 6 日

32. 青木恵美、松下茂人、小森崇矢、杉野仁美、坂本翔一、山村健太郎、吉岡　学、井上明葉
皮膚有棘細胞癌再発例に対する治療の検討
第 36 回日本皮膚悪性腫瘍学会学術大会、Web 開催、2021 年 1 月 8 日

33. 松下茂人、中村泰大、田中亮多、荒木隆一郎、山村健太郎、吉岡　学、井上明葉、小森崇矢、齋藤晋太郎、寺本由紀子、中村貴之、藤澤康弘、青木恵美
当施設主導の多施設臨床研究―顔面基底細胞癌の浸潤レベルに関する 718 例の解析
第 186 回日本皮膚科学会鹿児島地方会、鹿児島、2020 年 12 月 6 日

34. 松下茂人
皮膚科医の立場での「皮膚外科学」と皮膚がんへの取り組み
第 72 回日本皮膚科学会西部支部学術大会、Web 開催、2020 年 10 月 25 日

35. 小森崇矢、松下茂人、青木恵美、杉野仁美
免疫療法中に生じた重症光線過敏症の 1 例とその予後に対する検討
第 36 回日本皮膚悪性腫瘍学会学術大会、2021 年 1 月 8 日

36. 上山未紗
高度難聴を合併した肺炎球菌性髄膜炎の一例
第 331 回 日本内科学会九州地方会、Web 配信、2020 年 11 月 29 日

37. 山下悠亮
スネアでの牽引により右室中隔乳頭筋の断裂を起こし、重症三尖弁閉鎖不全を合併したリード抜去症例
第 12 回植込デバイス関連冬期大会、愛知、2021 年 2 月 7 日

38. 馬場華奈、谷口 潤、尾之江剛樹
婦人科 TC 療法における末梢神経障害に対するミロガバリンの有効性と安全性の検討
第 30 回日本医療薬学会年会、Web 開催、2020 年 10 月 24 日～11 月 1 日

39. 森田真樹子、鳥山陽子、松尾圭祐、江崎 瞳、谷口 潤、尾之江剛樹
ラムシルマブ・パクリタキセル併用療法における 投与中の血圧推移と治療効果の関連性
第 30 回日本医療薬学会年会、Web 開催、2020 年 10 月 24 日～11 月 1 日

40. 高城沙也香、鳥山陽子、永石浩貴、松尾圭祐、江崎 瞳、谷口 潤、尾之江剛樹
末期心不全患者に対するモルヒネの使用状況調査
第 30 回日本医療薬学会年会、Web 開催、2020 年 10 月 24 日～11 月 1 日

41. 吉永光辰、迫田英樹、谷口 潤、尾之江剛樹
院外処方箋への臨床検査値記載による有用性の検討
第 30 回日本医療薬学会年会、Web 開催、2020 年 10 月 24 日～11 月 1 日

42. 谷口 潤、松尾圭祐、尾之江剛樹、櫻井一宏
悪性リンパ腫治療による B 型肝炎ウイルス再活性化に対するテノホビルアラフェナミドの有効性と安全性の検討
第 30 回日本医療薬学会年会、Web 開催、2020 年 10 月 24 日～11 月 1 日

43. 谷本憲哉、尾之江剛樹、谷口 潤、松尾圭祐、迫田英樹、永石浩貴
頭頚部がん患者における Cetuximab 投与時の PPI が低 Mg 血症に及ぼす影響の検討
第 30 回日本医療薬学会年会、Web 開催、2020 年 10 月 24 日～11 月 1 日

44. 松尾圭祐、谷口 潤、尾之江剛樹、松下茂人
irAE マネジメント強化に向けた施設間連携への取り組み～KISNet(鹿児島がん免疫療法サポートネットワーク)活動報告～
第 74 回国立病院総合医学会、Web 開催、2020 年 10 月 17 日～11 月 14 日

45. 松尾圭祐、鳥山陽子、森田真樹子、馬場華菜、永石浩貴、谷口 潤、尾之江剛樹
頭頚部癌 CCRT における CDDP 投与状況調査と投与量に関する検討
第 30 回日本医療薬学会年会、Web 開催、2020 年 10 月 24 日～11 月 1 日

46. 迫田英樹、馬場華菜、栗脇千春、山下正治、山口　俊
セファゾリン供給停止による微生物の薬剤感受性率および心臓血管外科の手術部位感染への影響
第 30 回日本医療薬学会年会、Web 開催、2020 年 10 月 24 日～11 月 1 日

47. 今村聖奈、尾之江剛樹、谷口　潤
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第 74 回国立病院総合医学会、Web 開催、2020 年 10 月 17 日～11 月 14 日

48. 宮﨑明信、宮崎いずみ、山本理絵、岡村優樹、梅橋功征、古野　浩
経胸壁心エコーにて指摘した TAVI 後血栓弁の 3 症例
第 69 回日本医学検査学会、Web 開催、2020 年 10 月 1 日～31 日

49. 宮﨑明信、山本理絵、岡村優樹、宮崎いずみ、原田美里、時吉恵美、是枝和子、中釜美乃里、
梅橋功征、古野　浩
経カテーテル大動脈弁留置術後血栓弁 6 症例における心エコー評価についての検討
日本超音波医学会第 30 回九州地方会学術集会、誌上発表、2020 年 10 月 4 日

50. 宮﨑明信、岡村優樹、山本理絵、宮崎いずみ、原田美里、時吉恵美、大迫亮子、是枝和子、
梅橋功征、野崎加代子、古野　浩
一過性脳虚血発作の塞栓源が経カテーテル大動脈弁留置術後血栓弁と疑われた 1 症例
第 39 回日本脳神経超音波学会総会、誌上発表 2020 年 12 月 8 日～9 日

51. 宮﨑明信、大迫亮子、是枝和子、時吉恵美、岡村優樹、山本理絵、原田美里、宮崎いずみ、
梅橋功征、野崎佳代子、馬場善政、古野　浩
心膜血腫による心タンポナーデの診断に TEE が有用であった症例
第 45 回日本超音波検査学会学術集会、2020 年 12 月 19 日～2021 年 1 月 31 日

52. 日野出勇次、花木祐介、大隈理恵、渡口貴美子、外園宗徳、清家奈保子
FileMaker Pro を用いた臨床検査技師と看護師間における情報共有システムの構築
第 74 回国立病院総合医学会、Web 開催、2020 年 10 月 17 日～11 月 14 日

53. 波野真伍、波野史典、小濱祐行、古城　剛、前之園隆一、政元いずみ、山口宗一、橋口照人
心房細動アブレーション治療における長期予後予測バイオマーカーの検討～血管内皮機能関連マーカーの可能性～
第 21 回日本検査血液学会学術集会、Web 開催、2020 年 7 月 11 日

54. 原田美里、宮﨑明信、梅橋功征、宮﨑いずみ、山本理絵、是枝和子、野﨑加代子、古野　浩
心嚢液貯留を契機に発見された心臓血管肉腫の 1 症例
第 69 回日本医学検査学会、Web 開催、2020 年 10 月 1 日～31 日

55. 原田美里、宮﨑明信、岡村優樹、是枝和子、山本理絵、時吉恵美、中釜美乃里、日野出勇次、
渡辺秀明、古野　浩
心嚢液貯留を契機に発見された心臓腫瘍の 3 症例
日本超音波医学会第 30 回九州地方会学術集会、誌上発表、2020 年 10 月 4 日

56. 山本理絵、宮﨑明信、原田美里、時吉恵美、岡村優樹、是枝和子、中釜美乃里、日野出勇次、
野﨑加代子、古野　浩
心室中隔穿孔術後再度穿孔を認めた一症例
第 30 回日本超音波医学会九州地方会学術集会、Web 開催、2020 年 10 月 4 日

57. 山本理絵、原田美里、岡村優樹、時吉恵美、是枝和子、宮崎明信、日野出勇次、古野　浩
心エコー検査で指摘し得た上行大動脈仮性瘤-肺動脈穿破
第 45 回日本超音波検査学会学術集会、2020 年 12 月 19 日～2021 年 1 月 31 日

58. 是枝和子、宮﨑明信、岡村優樹、原田美里、山本理絵、時吉恵美、中釜美乃里、日野出勇次、渡辺秀明、古野　浩
上行大動脈置換術後に仮性瘤を形成した 2 症例
日本超音波医学会第 30 回九州地方会学術集会、2020 年 10 月 4 日

59. 城戸隆宏、野﨑加代子、大迫亮子、宮下恵美、宮崎明信、梅橋功征、古野　浩
当院で経験したワイル病の 1 例
第 69 回日本医学検査学会、Web 開催、2020 年 10 月 1 日～31 日

60. 城戸隆宏、野﨑加代子、宮下恵美、宮崎明信、梅橋功征、古野　浩
多発性転移性肝癌を起こした原発性虫垂癌の一例
第 45 回日本超音波検査学会学術集会、Web 開催、2020 年 12 月 19 日～2021 年 1 月 31 日

61. 田場　要、森山海帆、木之瀬晴香、池田智子、口石智秀、中村康典
当院の急性期脳梗塞患者に対する口腔管理の現状
第 74 回国立病院総合医学会、Web 開催、2020 年 10 月 17 日～11 月 14 日

62. 尾上諒介、蔡　榮鴻、石神えり、口石智秀、黒岩剛成、西濱佑斗、薗田正浩
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4. 論文

当院所属で筆頭者として発表された論文を掲載します。

PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2020) **0**, 1–9 doi: 10.1111/ped.14253

Original Article

Promoting physical activity through walking to treat childhood obesity, mainly for mild to moderate obesity

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Abstract ***Background*:** There are no randomized controlled trials examining the effect of walking on childhood obesity.

***Methods*:** A randomized controlled trial was conducted between August 2014 and April 2015 in Japan. Elementary school children aged 6 to 12 years with a percentage overweight (%OW) of ≥20% were recruited. One hundred and ninety children wanted to participate in the program, and all were accepted. After viewing a video that promoted physical activity through walking, participants were randomly assigned to three groups: walking (≥10 000 steps on school holidays), limiting screen time (<90 min on weekdays and <150 min on school holidays), and a control group (no intervention). The primary outcome was a decrease in %OW after 3 months' intervention. Per protocol analysis was performed using 156 participants who fulfilled the inclusion criteria of a %OW ≥20%.

***Results*:** The mean %OW was 35 ± 7% before intervention. The mean reduction in %OW after intervention in the walking (n = 59), limiting ST (n = 46), and control (n = 51) groups were −4.06 ± 4.84, −1.97 ± 4.62, and −1.81 ± 3.64 percentage points, respectively. Reduction in %OW was significantly larger in the walking group than in the control group: adjusted mean difference, −2.18 percentage points (95% confidence interval, −3.85 to −0.52), P = 0.002. The intervention in children also had favorable effects on the lifestyles of their parents. The intention-to-treat analysis of all 190 participants showed comparable results.

***Conclusion*:** Promoting physical activity through walking on school holidays may be an additional strategy for treating elementary school children with obesity.

Key words child, exercise, obesity, television, walking.

The worldwide prevalence of overweight and obesity in children and adults has increased considerably during the past three decades in developed and developing countries.[1] Prevalence may be reaching a plateau in several developed countries; however, it remains historically high.[2] Nationwide studies indicate that obesity still represents a major public health concern worldwide for children and adults.[3–5]

Common strategies for preventing or treating obesity in children and adolescents are promoting daily physical activity (PA),[6–8] modifying dietary intake,[8,9] limiting screen time (ST),[10,11] ensuring sufficient sleep duration,[11] providing parental and / or social supports,[7] and a combination of these strategies.[12] Participating in daily moderate to vigorous PA (MVPA) for at least 60 min has been recommended for children and adolescents in many countries, and this is still a standard strategy.[13] On the other hand, light to moderate intensity PA has been also introduced to promote health and prevent cardiovascular (CV) diseases because it presents fewer potential barriers and is more convenient than achieving MVPA.[14,15] Walking is a recommended activity for increasing the energy expenditure of obese participants and has been adopted as an intervention for treating obesity in adults.[16] However, there are limited data on the effectiveness of walking for treating childhood obesity.[14] In addition, many studies were undertaken in a school setting,[14] and few studies

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The trial registration number was UMIN000014896.

Received 29 November 2019; revised 18 February 2020; accepted 27 March 2020.

examined the effectiveness of walking interventions outside of the school setting.[16,17]

An important issue in Japan is an abrupt increase in the prevalence of obesity during elementary school years.[18] A general decrease in PA and increase in sedentary lifestyle is another concern in Japanese children, particularly on school holidays, and this is exaggerated in children with obesity.[19] One fourth of children decrease the number of steps by more than 50% on school holidays compared with school days (weekdays).[19] Our hypothesis was that promoting PA through walking on school holidays was an additional way to treat childhood obesity in children with obesity. The aim of the present study was therefore to determine the effectiveness of promoting PA through walking during school holidays in elementary school children with obesity, using a randomized controlled trial.

Methods

Participants

A multi-center randomized controlled trial was conducted between August 2014 and April 2015 in seven areas in Japan: Hokkaido, Toyama, Ibaraki, Aichi, Hyogo, Fukuoka, and Kagoshima. Subjects were recruited for registration to the study with an announcement by school officials, the regional education board, and the websites of the affiliated hospitals of the authors.

Eligibility criteria for the per protocol analysis were elementary school children with obesity aged 6–12 years. Obesity was defined as percentage overweight (%OW) ≥20%, which is the consensus recommendation as the definition for childhood obesity in Japan.[19] The %OW is calculated from Ikuo *et al.*[20] as

$$[(\text{individual body weight})/(\text{age } -\text{, sex } -\text{, and height specific reference body weight}) - 1^{t}] \times 100$$

In cases where multiple children in a family met eligibility criteria, one child per family was accepted. Participants were excluded if they had been previously or were currently involved in a weight-management program or were using appetite- or weight-affecting medications. Children who did not meet the obesity criterion of %OW ≥20% but who wanted to participate in the program were also accepted to participate; however, the data of these children who did not meet the criterion were excluded in the per protocol analysis. The design was not changed after trial commencement.

Written informed consent was obtained on the first day of the intervention from parents or guardians. The study was approved by the ethics committee of the National Hospital Organization of Kagoshima Medical Center.

Interventions

A three-arn intervention was implemented for 3 months. Groups 1 and 2 were intervention groups; Group 1 represented promoting PA through walking and Group 2 represented avoiding sedentary lifestyle. Group 1 (walking group) walked ≥10 000 steps on school holidays. Group 2 (limiting ST group) engaged in <90 min of ST on weekdays, and <150 min of ST on school holidays. Group 3 (control group) received no intervention. Parents (mother and / or father, or care givers) were asked to walk together with their children and help them enjoy walking. Screen time included the time spent watching television and playing electronic games on television, computers, cell phones, or other devices. The targets for walking and limiting ST groups were based on the mean values established in a preliminary study conducted in 2013 and 2014 with elementary school children who had a % OW <20% (Tables S1 and S2). A walking intervention on school holidays was chosen because physical activity levels fell dramatically on school holidays in a previous study[19] and our preliminary study (Table S1). In Japan, "school holidays" usually mean Saturdays and Sundays.

Participants and their parents were asked to watch a 14 min procedural video. The video was made exclusively for the present study, to encourage lifestyle modifications and to provide the same explanation to participants in all geographical areas. The video emphasized the effectiveness of walking, limiting ST, diet modifications, and increasing the number of chews before swallowing.[21] After showing the procedural video, the authors again explained the aim, methods of intervention, and measures to the participants and their parents. Energy intake restriction was not included in the present study to focus on the effectiveness of walking and limiting ST.

All participants, irrespective of their assigned group, were also asked to perform the following activities, with parental support: (i) write down daily behaviors on prepared forms: (a) the number of walking steps on school holidays, and (b) ST on school holidays, and on Fridays as a reference for school days; (ii) return some of the forms at the midpoint of the intervention, after approximately 1.5 months, using a self-addressed, stamped envelope; and (iii) bring the remaining forms with them to the prescribed meeting place at the end of the intervention. A pedometer with a memory facility for 7 days (HJ-325; Omron Healthcare Co., Kyoto, Japan) was given to all participants to record the number of steps.

Assessment of daily activity of participants and their parents at baseline and at the end of intervention

At baseline and at the end of the intervention, participants and their parents were asked about mean exercise time and mean ST per day on weekdays and school holidays. Participants were also asked about participation in extracurricular or club sports activities. Exercise time included time spent walking, jogging, bicycling, doing gymnastics, swimming, and engaging in extracurricular or club sports activities. Parents' height and weight were based on self-reported data.

Outcomes

The primary outcome was a decrease in %OW after 3 months of intervention. Secondary outcomes were changes in CV risk

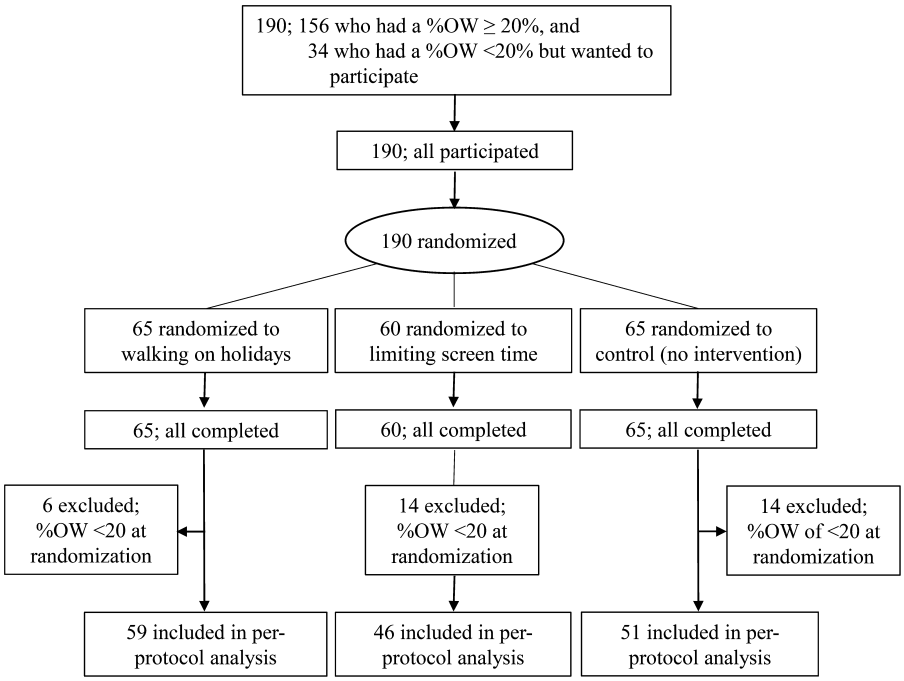

Fig. 1 Participation, randomization, and intervention flow. Abbreviation: %OW, percent overweight

factor values. Trial outcomes were not changed after the trial commenced. For the readers' convenience in interpreting information, body mass index (BMI) Z-scores based on the references of Japan,[22] the International Obesity Task Force (IOTF),[23] and the Centers for Disease Control and Prevention in the USA[24] have also been added in this manuscript. Body mass index was calculated as (weight in kg)/(height in m)^2.

Randomization and allocation concealment mechanism

After providing informed consent, participants were assigned randomly to three groups at a ratio of 1:1:1. The allocation sequence was concealed from the researchers at each enrolment location and was controlled with the use of computerized sequentially numbered containers generated by a statistician (H.O.).

Measurements

Measurements were conducted at baseline and at the end of the intervention in each location. Assessors were blind to group allocation at each measurement.

Height was measured to the nearest 0.1 cm, and weight was measured to the nearest 0.1 kg at each hospital, clinic, or health-care center. Blood pressure was measured three times using an automated oscillatory system (TM-2571, A&D Co. Ltd., Tokyo, Japan) after participants had rested for 10 min in a seated position; the mean value of the second and third measurements was used. Waist circumference was measured at the umbilical level to the nearest 0.1 cm.

Blood samples were collected in the morning on the first day and at the end of the intervention, after an overnight fast. High-density lipoprotein (HDL) cholesterol levels were determined by a direct quantitative assay, and levels of triglycerides, total cholesterol, and alanine aminotransferase (ALT) were determined by enzymatic assays using an automated analyzer (JCA-BM8060; JEOL Ltd., Tokyo, Japan). Levels of fasting plasma glucose (FPG) were determined by the hexokinase method using an automated analyzer (JCA-BM9000 series, JEOL Ltd). Insulin levels were measured using a chemiluminescence immunological assay and an automated analyzer (Lumipulse Presto II; Fujirebio Inc., Tokyo, Japan). All assays were performed by SRL, Inc. (Tokyo, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR) was used as a surrogate marker for insulin resistance,[25] and was calculated as fasting insulin (μIU/mL) × fasting glucose (mmol/L)/22.5.

Statistical methods

The per protocol analysis excluding those who did not meet the obesity criterion was applied. Differences in the mean values of baseline characteristics among the groups were examined using the Kruskal–Wallis test followed by multiple pairwise comparisons of groups. Changes in the variables of participants between baseline and postintervention within each group were examined using the Wilcoxon signed-ranks test.

The mean difference in primary outcome was adjusted to the geographic area, the baseline data of each variable at the pre-intervention, age, and sex in an analysis of covariance

Table 1 Baseline characteristics of participants

Intervention groups	Walking	Limiting ST	Control
Number of participants	59	46	51
Age (year)	9.7 ± 1.3	10.0 ± 1.5	9.9 ± 1.5
Sex (male/female)	38/21	28/18	31/20
Height (cm)	138.7 ± 9.1	140.9 ± 11.5	139.1 ± 8.6
Weight (kg)	46.8 ± 9.8	47.8 ± 11.5	46.2 ± 9.8
Percentage overweight (%)	37.5 ± 12.9	34.4 ± 9.2	34.5 ± 12.4
Classification of obesity (mild / moderate / high)†	19/28/12	16/27/3	24/19/8
Body mass index (kg/m^2)	24.0 ± 2.7	23.7 ± 2.2	23.6 ± 2.7
BMI z-score			
Japanese reference	1.86 ± 0.35	1.79 ± 0.29	1.76 ± 0.35
IOTF reference	2.36 ± 0.44	2.25 ± 0.37	2.21 ± 0.45
CDC reference	1.90 ± 0.30	1.82 ± 0.27	1.79 ± 0.32
Waist circumference (cm)	79.3 ± 8.9	78.1 ± 7.5	77.6 ± 8.4
Systolic blood pressure (mmHg)	107 ± 10	104 ± 11	104 ± 11
Diastolic blood pressure (mmHg)	59 ± 8	59 ± 8	58 ± 10
Triglycerides (mg/dL)	89 (60/122)	68 (47/111)	76 (51/103)
HDL cholesterol (mg/dL)	56 ± 13	55 ± 10	58 ± 12
Non-HDL cholesterol (mg/dL)	126 ± 27	125 ± 27	124 ± 33
Fasting plasma glucose (mg/dL)	89 ± 6	89 ± 6	91 ± 5
Insulin (μU/mL)	10.2 (7.1/12.1)	8.7 (6.2/11.6)	8.8 (5.7/14.0)
Homeostasis assessment of Insulin resistance	2.3 (1.6/2.7)	2.0 (1.3/2.5)	2.0 (1.3/3.1)
Alanine aminotransferase (U/L)	20 (16/34)	18 (15/25)	18 (14/26)

Data are expressed as means ± standard deviations. The data with skewed distribution are expressed as the median with 25th/75th percentiles in parentheses.

There were no significant differences among groups. Statistical analysis was performed using the Kruskal–Wallis test and *post hoc* test between groups.

Abbreviations: CDC, Centers for Disease Control and Prevention; HDL, high-density lipoprotein; IOTF, International Obesity Task Force.

†Classification of obesity was based on the Japanese criteria.

(ANCOVA). Statistical analysis was performed using SPSS Statistics version 21.0 (IBM Japan, Ltd, Tokyo, Japan). A two-tailed probability value of <0.05 was considered statistically significant.

Results

Subjects

The participant flow is presented in Figure 1. We randomized 190 children into the walking (n = 65), limiting ST (n = 60), and control (n = 65) groups. Randomization was performed in each local area, which contributed to the differences in group size. All participants completed the interventions. After excluding participants who did not fulfil the inclusion criterion at the start of the intervention, the per-protocol analysis was performed using a total of 156 children, with 59 in the walking group, 46 in the limiting ST group, and 51 in the control group. There were no difference in the indices of obesity (% OW, BMI, and BMI z-score), blood pressures, and blood sample data among the groups (Table 1).

Interventions

The mean duration of intervention was 3.2 ± 0.2 months in all three groups. The walking group achieved a significantly higher number of walking steps on school holidays than did the limiting ST and control groups (Table 2). By contrast, the limiting ST group evidenced significantly less ST on both weekdays and school holidays than did the walking and control groups. In the walking group, 86% of the participants were successful in achieving the intervention goal of ≥10 000 steps on school holidays.

Changes in CV variables from baseline to postintervention by group

The %OW, BMI Z-scores, and waist circumference significantly decreased, not only in the intervention (walking or limiting ST) groups but also in the control group (Table 3). The ALT level also significantly decreased in the intervention groups. The walking group showed a significant decrease in diastolic blood pressure and levels of triglyceride and non-HDL cholesterol after the intervention. Sex-specific differences in changes in these CV variables were not present from baseline to postintervention in each group. In the intention-to-

Table 2 Mean number of steps and screen time in each group during the intervention

Per-protocol analysis	Walking (A)	Limiting ST (B)	Control (C)	A vs C	B vs C	A vs B
Number of subjects	59	46	51			
Mean steps (School holiday)	11 899 ± 2,296	9,119 ± 2,736	9,503 ± 3,345	<0.001		<0.001
Mean ST (Weekday, min)	149 ± 77	98 ± 31	141 ± 66		0.002	<0.001
Mean ST (School holiday, min)	184 ± 77	134 ± 35	204 ± 106		<0.001	0.005

Abbreviation: ST, screen time.

Table 3 Changes in variables between baseline and postintervention

Intervention group	Walking group (n = 59)			Limiting ST group (n = 46)			Control group (n = 51)		
	Baseline	Postintervention	P	Baseline	Postintervention	P	Baseline	Postintervention	P
Height (cm)	138.7 ± 9.1	140.4 ± 9.1	<0.001	140.9 ± 11.5	142.6 ± 11.5	<0.001	139.1 ± 8.6	140.7 ± 8.6	<0.001
Weight (kg)	46.8 ± 9.8	47.0 ± 10.1	0.13	47.8 ± 11.5	48.7 ± 11.5	<0.001	46.2 ± 9.8	47.0 ± 10.1	<0.001
Percent overweight (%)	37.5 ± 12.9	33.5 ± 13.3	<0.001	34.4 ± 9.2	32.4 ± 8.6	<0.001	34.5 ± 12.4	32.7 ± 13.0	<0.001
Body mass index (BMI) (kg/m^2)	24.0 ± 2.7	23.6 ± 2.8	<0.001	23.7 ± 2.2	23.5 ± 2.1	0.32	23.6 ± 2.7	23.5 ± 2.8	0.40
BMI Z-score									
Japanese reference	1.86 ± 0.34	1.75 ± 0.38	<0.001	1.80 ± 0.29	1.73 ± 0.28	0.003	1.76 ± 0.35	1.69 ± 0.39	<0.001
IOTF reference	2.36 ± 0.44	2.20 ± 0.47	<0.001	2.25 ± 0.37	2.16 ± 0.34	0.001	2.21 ± 0.45	2.13 ± 0.47	<0.001
CDC reference	1.90 ± 0.30	1.78 ± 0.35	<0.001	1.82 ± 0.27	1.76 ± 0.27	0.001	1.79 ± 0.36	1.73 ± 0.36	<0.001
Waist circumference (cm)	79.3 ± 8.9	78.2 ± 9.3	0.002	78.1 ± 7.5	77.2 ± 8.2	0.03	77.6 ± 8.4	77.0 ± 8.8	0.047
Systolic blood pressure (mmHg)	107 ± 10	106 ± 11	0.47	104 ± 11	104 ± 12	0.98	104 ± 11	105 ± 10	0.66
Diastolic blood pressure (mmHg)	59 ± 8	56 ± 8	0.006	59 ± 8	57 ± 6	0.02	58 ± 10	57 ± 7	0.61
Triglycerides (mg/dL)	89 (60/122)	67 (53/90)	0.02	68 (47/111)	69 (42/91)	0.07	76 (51/103)	60 (42/87)	0.24
HDL cholesterol (mg/dL)	56 ± 13	56 ± 14	0.91	55 ± 10	56 ± 8	0.46	58 ± 12	58 ± 12	0.42
Non-HDL cholesterol (mg/dL)	126 ± 27	119 ± 26	<0.001	125 ± 27	121 ± 24	0.11	124 ± 33	121 ± 32	0.14
Fasting plasma glucose (mg/dL)	89 ± 6	92 ± 7	0.02	89 ± 6	92 ± 6	0.001	91 ± 5	92 ± 6	0.34
Insulin (μU/mL)	10.2 (7.1/12.1)	11.5 (6.9/14.9)	0.03	8.7 (6.2/11.6)	9.3 (7.3/12.2)	0.016	8.8 (5.7/14.0)	9.4 (7.5/17.2)	0.06
HOMA-IR	2.3 (1.6/2.7)	2.6 (1.6/3.5)	0.01	2.0 (1.3/2.5)	2.1 (1.6/3.1)	0.11	2.0 (1.3/3.1)	2.0 (1.7/4.2)	0.07
Alanine aminotransferase (U/L)	20 (16/34)	17 (14/24)	<0.001	18 (15/25)	17 (13/26)	0.04	18 (14/26)	18 (15/26)	0.63

Data are expressed as means ± standard deviation. Data with skewed distributions are expressed as the median, with 25th/75th percentiles in parentheses.

Abbreviations: HDL, high-density lipoprotein; HOMA-IR, homeostasis assessment of insulin resistance; ST, screen time.

treat analysis, all three groups also showed similar changes (data not shown).

Adjusted mean differences in outcomes by group for primary and secondary outcomes

The adjusted mean differences in the decrease in the %OW, the primary outcome, BMI, and BMI Z-score were significantly larger in the walking group compared with those in the control group in the per-protocol analysis (Table 4 and Fig. 2). The differences in changes between intervention groups (walking and limiting ST) and between the limiting ST group and the control group were not significant. The walking group also showed a significantly larger mean difference in change in ALT levels than did the control group. The intention-to-treat analysis showed similar results (data not shown).

Effects of the intervention in children on lifestyles of their parents

Table 5 shows changes in the lifestyle variables of participants and their parents, from baseline to the end of intervention, based on questionnaire data. In all three groups, not only participants but both parents significantly increased their exercise time on school holidays. In the correlation analysis of overall groups, changes in exercise time on holidays from baseline to postintervention among participants, their fathers, and their mothers were significantly correlated with each other (participants versus fathers, correlation coefficient 0.376, $P < 0.001$; participants versus mothers, correlation coefficient 0.396, $P < 0.001$; fathers and mothers, correlation coefficient 0.336, $P < 0.001$), and fathers had significantly decreased BMI from baseline to postintervention.

Table 4 Mean differences in change from baseline to postintervention by group and adjusted mean differences in change between the walking and control groups in the per protocol analysis

Groups	Mean difference (95% CI)			Adjusted mean difference	
	Walking	Limiting ST	Control	Walking vs control[†]	*P*
Number of subjects	59	46	51		
Weight (kg)	0.26 (–0.11/0.62)	0.80 (0.33/1.28)	0.88 (0.51/1.24)	−0.67 (−1.2/−0.14)	0.01
Percent overweight (%)	−4.06 (–5.32/−2.80)	−1.97 (−3.34/−0.60)	−1.81 (−2.84/−0.79)	−2.18 (−3.85/−0.52)	0.01
Body mass index (BMI) (kg/m^2)	−0.46 (–0.67/–0.26)	−0.16 (–0.39/0.08)	−0.10 (−0.27/−0.08)	−0.37 (−0.65/−0.09)	0.009
BMI Z-score					
Japanese reference	−0.12 (−0.15/-0.08)	−0.06 (−0.10/−0.03)	−0.06 (−0.09/-0.03)	–0.06 (−0.11/−0.01)	0.01
IOTF reference	−−0.16 (−0.21/−0.11)	−0.09 (−0.13/−0.04)	−0.08 (−0.12/−0.04)	−0.08 (−0.14/−0.02)	0.01
CDC reference	−0.12 (−0.15/−0.08)	−0.07 (−0.10/−0.03)	-0.07 (−0.09/−0.04)	−0.06 (−0.10/−0.01)	0.01
Alanine aminotransferase (U/L)[‡]	−0.19 (−0.29/-0.10)	−0.08 (−0.16/0.00)	−0.03 (−0.12/0.05)	−0.16 (−0.26/−0.06)	0.002

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; IOTF, International Obesity Task Force; ST, screen time.

[†]The mean difference between the walking and control groups from baseline to postintervention is adjusted for geographic area, baseline data, age, and sex.

[‡]Among the cardiovascular risk factors except for obesity indices, only the mean difference in alanine aminotransferase level showed significance between walking and control groups. The data for alanine aminotransferase are shown after log transformation because of skewed distribution.

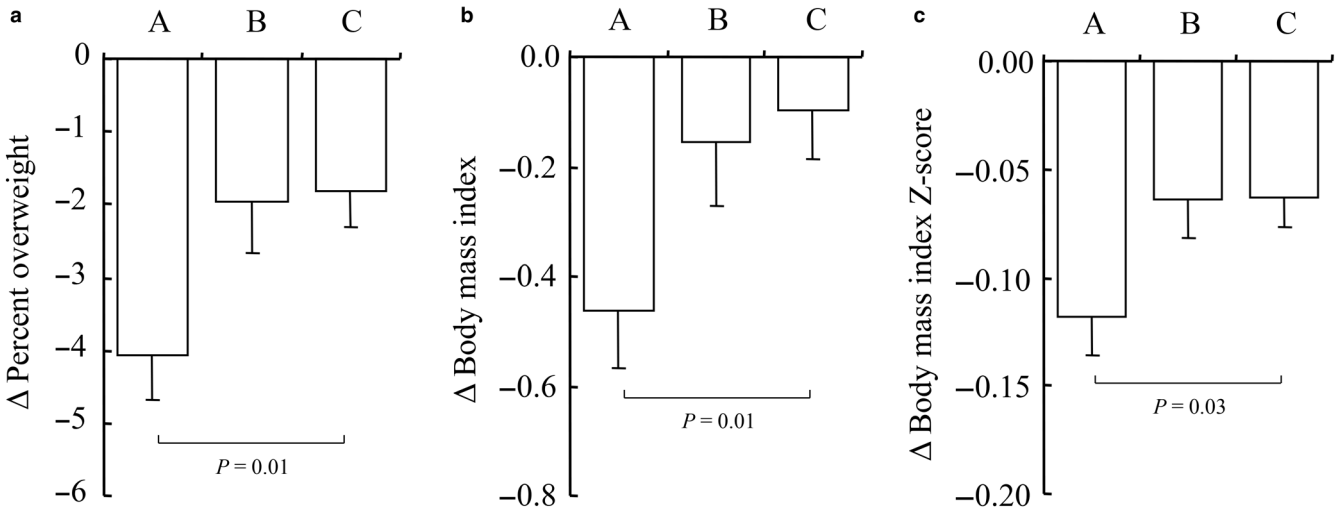

Fig. 2 Effect of intervention. Per protocol analysis revealed that reduction in percentage overweight (a), body mass index (b), and Z-score (c) in the walking group (A) was significantly larger than in the control group (C), although no difference was present between the walking and the screen-time-limiting (B) groups. Each bar shows the mean; whiskers represent the standard error of the mean.

No data on adverse events are reported in the present study and no participants withdrew from the study due to such events.

Discussion

The present randomized, controlled trial showed that participants in the walking group obtained a significantly larger adjusted mean decrease in %OW, BMI, and BMI Z-scores than did the control group, indicating that walking is an additional effective strategy for treating obesity in elementary school children.

Walking has been used in randomized controlled trials as an effective strategy for adults to lose weight or to improve their CV risk levels.[16] Walking guidelines for children are just being developed;[26] however, few data are available on whether walking is effective in treating childhood obesity.[14] In the present study, none of the participants newly started or stopped participating in extracurricular or club sports activities during the intervention period (Table 5); however, according to the data from the lifestyle questionnaires, median exercise times significantly increased in all three groups on school holidays, suggesting that the effects in the present study resulted from an increase in the time spent walking. Morgan *et al.* performed a randomized controlled trial that included 93 overweight / obese fathers and their 132 primary school children of any weight status.[16] A 7 week intervention with dietary

Table 5 Changes in lifestyle variables of participants and their parents from baseline to postintervention (at the end of intervention) based on the data of questionnaires

Intervention group	Walking (n = 59)		Limiting ST (n = 46)		Control (n = 51)		Total (n = 156)	
	Baseline	Postintervention	Baseline	Postintervention	Baseline	Postintervention	Baseline	Postintervention
Participants' daily activity								
Participation in sports activity[†]	32/59	32/59	21/46	21/46	32/51	32/51	85/156	85/156
Exercise time (weekday, min)[‡]	60 (20/90)	60 (27/93)	20 (0/60)	40 (10/60)	30 (0/60)	60 (14/90)*	30 (0/60)	60 (15/90)*
Exercise time (holiday, min)[‡]	30 (0/90)	90 (60/120)***	30 (0/60)	60 (30/120)**	30 (060)	60 (30/120)**	30 (0/60)	60 (30/120)***
Screen time (weekday, min)	140 ± 67	126 ± 58*	151 ± 81	96 ± 35***	146 ± 65	131 ± 61	145 ± 71	119 ± 55***
Screen time (holiday, min)	236 ± 103	216 ± 112	240 ± 121	153 ± 39***	258 ± 133	222 ± 109*	244 ± 119	199 ± 100***
Paternal profile								
BMI	27.4 ± 5.1	27.2 ± 5.1	24.8 ± 2.2	24.6 ± 2.1	26.8 ± 4.7	26.7 ± 5.0	26.5 ± 4.4	26.2 ± 4.5**
Exercise time (weekday, min)[‡]	0 (0/30)	0 (0/60)*	0 (0/20)	0 (0/30)	0 (0/60)	0 (0/60)	0 (0/30)	0 (0/60)
Exercise time (holiday, min)[‡]	0 (0/60)	30 (0/90)***	0 (0/30)	30 (0/83)*	0 (0/60)	30 (0/90)*	0 (0/60)	30 (0/90)**
Screen time (weekday, min)	99 ± 62	96 ± 60	117 ± 66	127 ± 70	131 ± 92	117 ± 55	115 ± 75	112 ± 63
Screen time (holiday, min)	208 ± 144	187 ± 122	226 ± 125	227 ± 105	231 ± 139	207 ± 122	221 ± 137	205 ± 117
Maternal profile								
BMI	24.1 ± 4.5	24.1 ± 4.7	22.6 ± 3.4	22.7 ± 3.4	24.0 ± 5.1	24.1 ± 5.0	23.6 ± 4.4	23.6 ± 4.5
Exercise time (weekday, min)[‡]	0 (0/30)	10 (0/60)[†]	0 (0/30)	15 (0/30)	18 (0/58)	30 (0/60)*	0 (0/30)	20 (0/60)**
Exercise time (holiday, min)[‡]	0 (0/40)	60 (0/60)***	0 (0/30)	30 (0/60)**	20 (0/60)	45 (0/60)*	0 (0/30)	30 (0/60)***
Screen time (weekday, min)	119 ± 96	110 ± 81	143 ± 151	122 ± 135	130 ± 935	126 ± 93	130 ± 114	119 ± 103
Screen time (holiday, min)	162 ± 103	152 ± 81	163 ± 152	170 ± 158	184 ± 112	162 ± 121	170 ± 122	161 ± 121

Data are expressed as mean ± standard deviation. The data with skewed distributions are expressed as the median with 25th/75th percentiles in parentheses.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.
[†]Participation in extracurricular or club sports activities. The data were expressed as (number of participants)/(total number).
[‡]Exercise time included the times for walking, jogging, bicycle, gymnastics, swimming, and extracurricular or club sports activities.

modifications and PA promotion using pedometers brought about a significant decrease in the BMI of both fathers and children in the intervention group, compared with those in the control group.[16] Tanaka *et al*. reported that modification of eating behaviors and walking more than 10 000 steps per day on school holidays for 1 year resulted in reductions in BMI and %OW of 53 obese elementary school children in a non-randomized clinical setting.[27] These data suggest that walking interventions have the potential to improve obesity.

The matters of concern are the efficacy and feasibility of the walking intervention strategy. In terms of efficacy, MVPA had been reported as having remarkable efficacy. Sacker *et al*., for example, found that obese children obtained an adjusted mean change in Z-score of −0.24 (vs the control group) using a combination of interventions (including 1 h of exercise, twice a week) in a 6 month randomized controlled trial.[7] Davis *et al*. reported that obese children achieved an adjusted mean change in Z-score of −0.10 through high-dose (40 min/day, 5 days/week) aerobic exercise in their 10- to 15-week randomized controlled trial.[6] The efficacy of walking of the present study (adjusted mean difference of −0.06 by Japanese reference) was similar to that of a low-dose (20 min/day, 5 days/week) aerobic exercise (−0.04 vs the control group)[6] and a 1-year, cluster-randomized clinical trial by Taveras *et al*. (−0.06 vs the control group).[12] These data suggest that walking is an effective intervention in children with obesity. Concerning feasibility, an MVPA intervention showed a low retention rate of 62%,[8] while low-dose exercise interventions have shown rates as high as 94%–95%.[6,7] In the present study, all participants completed the intervention, and 88% and 86% (data not shown) of the walking group in the intention-to-treat and in the per protocol analyses, respectively, were successful in achieving the mean number of ≥10 000 steps on school holidays, suggesting that walking is a feasible intervention.

Important findings in the present study were that all three groups showed the increase in exercise time and decrease in ST on holidays and that all three groups achieved significant decreases in %OW, BMI Z-score, and waist circumferences. All participants listened to information about the effectiveness of lifestyle change at the start of the intervention. We think that the participants and their parents understood that lifestyle changes on holiday might be effective in treating obesity. The significant improvement in CV variables in the control group may result in no significant difference in efficacy between the limiting ST and control groups, although research shows that limiting ST is a promising way to treat childhood obesity.[10] Nevertheless, the walking group showed significantly more walking steps on holiday and the walking group, but not the limiting ST group, obtained a significantly larger adjusted mean decrease in obesity indices than the control group, indicating that walking on holiday is an additional effective strategy to treat childhood obesity.

The present study also showed that the intervention in children had a favorable effect on the lifestyles of their parents; in addition, paternal BMI decreased from baseline to postintervention. Trier *et al*. reported that a family-based childhood obesity treatment program focusing on the child had positive effects on parental BMI, with both mothers and fathers losing weight during their child's intervention for obesity.[28] The parental anthropometric data of that study and the present study were based on parental self-reports. In future work, objectively measured anthropometric measurement should be implemented with parents throughout the intervention.

This study has limitations. First, the present study did not include the intervention arms of MVPA and diet, although we had intended to implement simple and minimum intervention arms. Future studies are needed that include MVPA and / or diet interventions. Second, we did not measure the number of walking steps during holidays at baseline (before starting the interventions). Instead, we assessed daily activity at baseline and at the end of the intervention; however, the walking steps at baseline would have given us the exact relationship between changes in the number of walking steps and changes in the indices of obesity or CV risk factor levels. In future studies, the number of walking steps should also be collected using a telemetric system instead of using self-reported information. Finally, the present study examined the short-term efficacy of a walking intervention, and further randomized controlled trials are needed to determine the long-term effects of walking. For that purpose, it is important to ask children and parents to incorporate walking on holidays into their routine. It may be necessary to keep regular visits to clinics or hospitals and provide multidisciplinary medical supports by doctors, nurses, and dieticians to maintain the effect in the long-term intervention.[29,30]

In conclusion, walking is one strategy that can be adopted for the treatment of obesity in elementary school children, because walking is both efficacious and feasible; however, there is still ample need to clarify the efficacy of walking to promote childhood health.

Acknowledgment

The present study was supported by a Health and Labor Sciences Research Grant from the Ministry of Health, Labor and Welfare of Japan (H24-014) (to MY).

Disclosure

The authors declare no conflict of interest.

Author contributions

All of the authors designed the study. M.A., A.M., M.A., Y.I., T.H., M.T., L.L., H.H., and M.N. collected the data. M.Y., H.O, and H.T. analyzed the data. M.Y. wrote the manuscript. All of the authors read and approved the final manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Mean number of steps per day of elementary school children in the preliminary study.

Table S2. Mean screen time of elementary school children in the preliminary study.

Supporting Table 1. Mean number of steps per day of elementary school children in the preliminary study

	Boys		Girls	
Percent overweight	< 20%	≥ 20%	< 20%	≥ 20%
No. of participants	479	60	522	52
Age	9.5 ± 1.7	9.8 ± 1.4	9.5 ± 1.7	9.6 ± 1.7
School holiday	**9896 ± 4776**	9004 ± 5009	8475 ± 3692	8150 ± 3396
Weekday	12,256 ± 3986	11,948 ± 4169	10,520 ± 3365	10,501 ± 3209

The data were obtained from a preliminary study performed between 2013 and 2014 in eight areas in Japan. The study was supported by a Health and Labour Sciences Research grant from the Ministry of Health, Labour and Welfare of Japan (H24-014). The target value for walking per day was based primarily on data obtained from boys that are shown in bold.

Supporting Table 2. Mean screen time of elementary school children in the preliminary study

	Boys		Girls	
Relative body weight	< 20%	≥ 20%	< 20%	≥ 20%
No. of participants	179	20	188	25
Age	9.5 ± 1.7	9.8 ± 1.4	9.5 ± 1.7	9.9 ± 1.5
School holiday	**153 ± 100**	183 ± 92	**153 ± 86**	186 ± 98
Weekday	**107 ± 72**	136 ± 87	**100 ±69**	140 ± 90

The data were obtained from a preliminary study performed in 2014 in eight areas in Japan. The study was supported by a Health and Labour Sciences Research grant from the Ministry of Health, Labour and Welfare of Japan (H24-014). The target value for limiting screen time on weekdays was determined as 90 min, and not 100 min, because the duration of screen time of “an hour and a half on weekdays and two and a half hours on holidays” was easier to recall.

Arch Clin Med Case Rep 2020; 4 (2): 292-301 *DOI: 10.26502/acmcr.96550199*

Case Report

Long-Term Observation of Improvement in Liver Fibrosis Index by A Glucagon-Like Peptide-1 Receptor Agonist in A Patient with Type 2 Diabetes: A Case Report

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Received: 04 March 2020; **Accepted:** 16 March 2020; **Published:** 10 April 2020

Abstract

We describe a 51-year-old man with type 2 diabetes and hepatic dysfunction with suspected nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH). No liver biopsy was performed. His blood test showed a decrease in platelet count (PLT) of 6.3 × 104/μL. Serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were increased, and the AST/ALT ratio (AAR) exceeded 1. FIB4 index, an index of liver fibrosis, was remarkably high at 7.65. On abdominal computed tomography (CT), hepatic parenchyma was visualized as a low absorption area (CT value: 36 HU, L/S ratio <1), suggesting fat accumulation. HbA1c was 8.0%. Treatment was started with liraglutide 0.9 mg/day and changed to exenatide sustained-release formulation 2 mg/week about 1 year later. HbA1c remained around 6%. Both AST and ALT improved to the upper normal limit level, and AAR also decreased in about 2 years. Five years later, PLT increased to 13 × 104/μL and the FIB4 index decreased to 3.30.

In the future, we hope that long-term and prospective studies including histological evaluation and imaging findings of NAFLD/NASH will be conducted, and that the multi-faceted, potential effects of GLP-1RA will be further clarified.

Keywords: Glucagon-like peptide-1 receptor agonist; Nonalcoholic fatty liver disease (NAFLD); Nonalcoholic steatohepatitis (NASH); Type 2 diabetes mellitus; FIB4 index

1. Introduction

The prevalence of nonalcoholic fatty liver disease (NAFLD) is increasing in Japan, along with an increase in obesity and metabolic syndrome [1]. In NAFLD, ectopic fat accumulated in the liver and skeletal muscle leads to insulin resistance, resulting in impaired glucose tolerance and an increase in free fatty acids in the blood, both of which further promote hepatic steatosis [2]. Patients with NAFLD are 3.51 times more likely to develop type 2 diabetes compared to a control group [3], while 50-60% of patients with type 2 diabetes have a complication of NAFLD [4]. Furthermore, NAFLD associated with type 2 diabetes tends to progress to nonalcoholic steatohepatitis (NASH) [5]. Therefore, NAFLD complications must always be kept in mind in patients with type 2 diabetes.

The primary treatment of NAFLD is weight loss via diet and exercise, but noncompliance to this regimen is high. Therefore, the effects of various drugs on improving NAFLD have been examined, although no established drug treatment has been identified. Multiple large randomized controlled trials (RCTs) have shown that pioglitazone (Pio), an insulin sensitizer, improves liver function and histology of NAFLD within 6 months after administration [6-8]. On the other hand, only about 40-60% of patients experience a therapeutic response, and long-term administration is associated with obesity, edema, heart failure, fracture, and bladder cancer [9]. Recently, the usefulness of glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 inhibitors for the treatment of NAFLD has been reported [10]. In clinical practice, these 2 additional treatment options increase the number of drugs available for NAFLD, but the effect of these agents on the improvement of liver fibrosis and long-term prognosis are unknown. Few reports show improvements in NAFLD using a once-weekly GLP-1 receptor agonist (GLP-1RA) [11, 12].

This case report describes a patient treated with a once-weekly GLP-1RA who showed continuous improvement in liver function and liver fibrosis, indices of NAFLD or NASH associated with type 2 diabetes. Although liver biopsy was not performed, this case suggests a potential hepatoprotective effect of a GLP-1RA over a long period.

2. Case Report

A 51-year-old man with a family history of type 2 diabetes, occasional drinking, and smoking 20 cigarettes a day underwent surgery for lung cancer at age 47. He was diagnosed with type 2 diabetes and suspected NAFLD/NASH at a gastroenterology department he visited before presenting to our hospital. No liver biopsy was performed. Multiple oral hypoglycemic agents (OHA) were started, and at age 48 years, basal insulin supporting oral therapy (BOT) was introduced. However, HbA1c was >8%. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were gradually increased, and it was recommended that he see a specialist to help with blood glucose control. In June 2012, he was referred to our outpatient clinic.

The patient was 174.0 cm tall and weighed 90.4 kg (body mass index, 29.8 kg/m^2). Blood pressure was 108/71 mmHg, and heart rate was regular at 71 beats/min. His cardiopulmonary examination showed normal results, and no abnormal abdominal findings were identified. A blood test showed a clear decrease in platelet count (PLT) of 6.3 × 10^4/μL, and a coagulation test showed a slight prolongation of prothrombin time. Serum levels of both AST and ALT were increased, and the AST/ALT ratio (AAR) exceeded 1. Cholinesterase (ChE) and serum protein levels were also low, and FIB4 index (age × AST [IU/L]/PLT [10^9/L] × √ALT [IU/L]) [13], an index of liver fibrosis, was remarkably high at 7.65 [<1.3]. Both hepatitis B virus antigen and hepatitis C virus antibody were negative (Table 1). Abdominal ultrasonography and abdominal computed tomography (CT) (Figure 1) obtained by the previous physician showed that the liver surface was slightly irregular and the margins were dull, suggesting chronic hepatitis. Hepatic parenchyma was visualized as a low absorption area (CT value: 36 HU, L/S ratio <1), suggesting fat accumulation. Splenomegaly was mild, and no ascites was noted (Figure 1). HbA1c was 8.0%, but fasting serum C-peptide immunoreactivity was 3.4 ng/mL, C-peptide immunoreactivity index was 1.92, and endogenous insulin secretion ability was maintained (Table 1). No microangiopathy was observed.

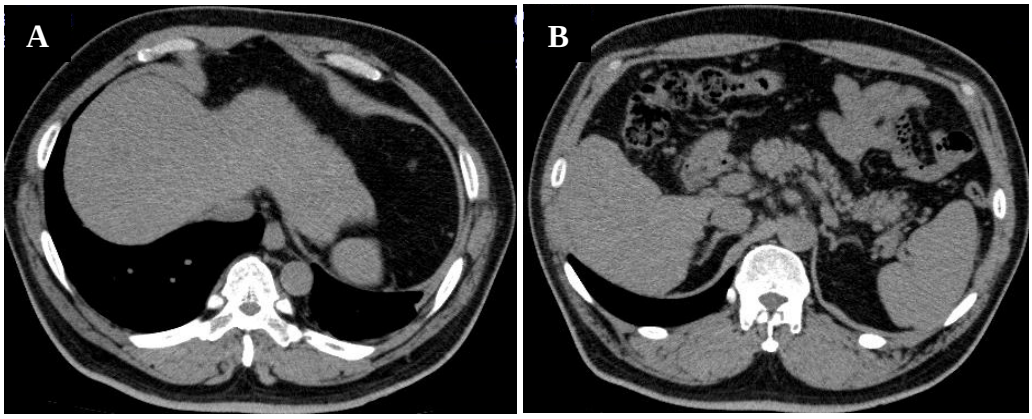

Figure 1: Abdominal computed tomography. The surface of the liver is slightly irregular and the margin is dulled, and the liver parenchyma is depicted as a low-absorption zone (CT value: 36 HU, Liver / Spleen (L / S) ratio <1).

Peripheral blood		**Biochemistry**			
WBC	3550 / μL	TP	6.2g/dL	Na	137 mEq/L
RBC	399 × 10^4 / μL	Alb	3.1g/dL	K	4.2 mEq/L
Hb	13.6 g/dL	TTT	6.9MU	Cl	108 mEq/L
Ht	40.9%	ZTT	18.0KU	T-chol	229 mg/dL
PLT	6.3 × 10^4 / μL	T-Bil	1.8mg/dL	LDL-chol	112 mg/dL
		AST	72IU/L	HDL-chol	40 mg/dL
Coagulation-related		ALT	58IU/L	TG	277 mg/dL
PT	14.1 sec	LDH	229IU/L	Ferritin	291 ng/mL

PT-%	75.4%	ChE	189IU/L		
PT-INR	1.17	ALP	410IU/L	Glucose metabolism-related	
		γGTP	274IU/L	FPG	177 mg/dL
Infection-related		Amy	90IU/L	HbA1c	8.0%
HBsAg	(-)	BUN	11.1mg/dL	F-sCPR	3.4 ng/mL
HBcAb	(-)	Cre	0.67mg/dL	2hr-sCPR	5.3 ng/mL

WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Ht, hematocrit; PLT, platelets; PT, prothrombin time; INR, international normalized ratio; HBsAg, hepatitis B virus antigen; HBcAb, hepatitis B virus antibody; TP, total protein; Alb, albumin; TTT, thymol turbidity test; ZTT, zinc sulfate turbidity test; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ChE, cholinesterase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyltransferase; Amy, amylase; BUN, blood urea nitrogen; Cr, creatinine; T-chol, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; F-sCPR, fasting serum C-peptide immunoreactivity; 2hr-sCPR, 2 hours postprandial serum C-peptide immunoreactivity.

Table 1: Laboratory data on admission.

The clinical course of the patient is shown in Figure 2. In a previous BOT, 20 units insulin glargine (Gla) was subcutaneously administered once daily in the morning and 3 OHA used together: glimepiride (Glim) 6 mg, metformin (Met) 500 mg, and sitagliptin (Sita) 50 mg. Gla was discontinued and Glim was reduced from 6 mg to 3 mg because he was obese and had sufficient endogenous insulin secretion. Pio was started at 7.5 mg and was increased to 15 mg two months later, and Sita was changed to a once-daily GLP-1RA, liraglutide (Lira) 0.9 mg/day. Glycemic control improved steadily, and after about 1 year, Glim was gradually reduced and discontinued, and the GLP-1RA was changed to a once-weekly exenatide sustained-release formulation (ExLA) 2 mg/week at the wish of the patient. Since then, blood glucose control was good, and HbA1c remained around 6%. His body weight temporarily increased after the treatment change, but after stopping Pio in 2014, it decreased to around 90 kg, the same as before starting the GLP-1RA, and stabilized. In terms of liver function, Both AST and ALT improved to the upper normal limit level, and AAR also decreased in about 2 years. PLT and ChE showed a time-dependent recovery trend up to 5 years after the start of treatment. In particular, PLT increased from $6.3 \times 10^4/\mu L$ before the treatment change to $10 \times 10^4/\mu L$ in 2015 and increased to $13 \times 10^{4/}\mu L$ in 2017. As a result, the FIB4 index decreased continuously and markedly, from 7.65 before treatment to 3.30 after 5 years. No adverse events due to the GLP-1RA were observed during the treatment period.

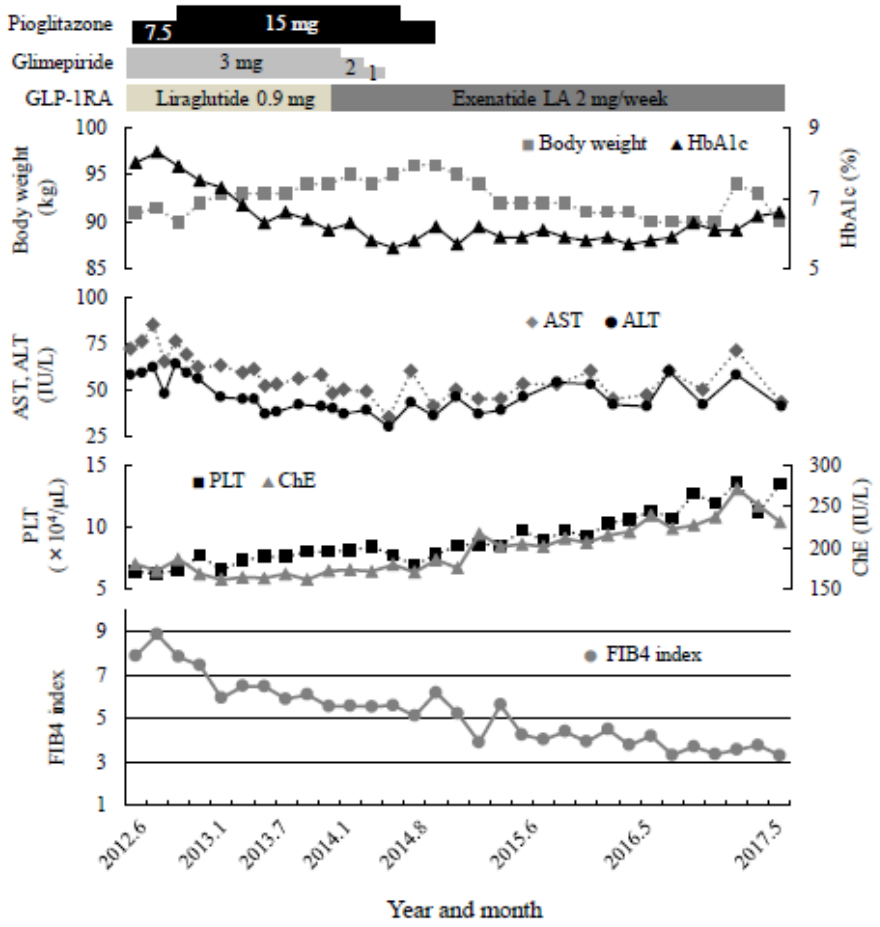

Figure 2: Clinical course of the patient. GLP-1RA, Glucagon-like peptide-1 receptor agonist; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PLT, platelet count; ChE, cholinesterase.

3. Discussion

Administration of long-acting GLP-1RAs (Lira, ExLA) to improve blood glucose control in this patient with type 2 diabetes and hepatic dysfunction resulted in continuous improvement of liver function and liver fibrosis index over about 5 years. This patient was obese at age 45 at the start of therapy with no history of excessive alcohol consumption. Viral hepatitis was ruled out, and blood sampling data showed AAR > 1, marked PLT reduction, hypoproteinemia, and high serum ferritin. Furthermore, the FIB4 index significantly exceeded the cutoff value of 3.25 (specificity 95%), which strongly suggests hepatic fibrosis [14]. Abdominal ultrasound and CT revealed a chronic hepatitis pattern and intrahepatic fat accumulation. These findings suggest that the cause of liver dysfunction in this case was likely NAFLD/NASH. Although liver biopsy is considered the gold standard for histological diagnosis of NAFLD/NASH, it was not performed in this patient. Notably, it is not realistic to perform a liver biopsy in all NAFLD cases. In addition, objectivity regarding liver biopsy findings is poor due to differences in diagnosis between pathologists and sampling errors [15]. In recent years, nonalcoholic fatty liver (NAFL), which is equivalent to conventional simple fatty liver, and NASH have come to be regarded as representing different stages of the same disease rather than different diseases. Therefore, attention has been paid to the evaluation of hepatic fibrosis using a

serum marker, a scoring system, or a diagnostic image, which are noninvasive procedures and can be performed repeatedly. Among these assessments, FIB4 index, NAFLD fibrous score, and BARD score [an easily calculated composite score based on the results of forced entry logistic regression analysis (BMI >28=1 point, AAR of >0.8=2 points, DM=1 point)] [16] use specific scoring systems, and their usefulness has been verified [17]. Kakuta et al. examined the usefulness of 7 scoring methods in 576 Japanese patients with NAFLD diagnosed by liver biopsy and found that the FIB4 index was the most reliable index of liver fibrosis [14]. It was reported that a cutoff of 1.45 could detect severe fibrosis cases (stage 3 and 4) with a sensitivity of 90% and a specificity of 64% (specificity increased to 95% at a cutoff of 3.25) [14]. In this case, combination therapy with Pio was successful for the treatment of NAFLD/NASH at first, but was discontinued after 19 months due to weight gain. After discontinuation of Pio, body weight stabilized at just over 90 kg, as was seen at the first consultation. About 1 year after the start of the GLP-1RA, the glycemic control status improved to HbA1c 6%, and remained stable even after the change to the once-weekly sustained-release GLP-1RA. On the other hand, PLT, ChE, and FIB4 index continued to improve even after weight and glycemic control stabilized. One of the hepatoprotective effects of GLP-1RA that does not depend on body weight or blood glucose may be an improvement in insulin resistance. Miki et al. demonstrated that the GLP-1 receptor (GLP-1R) is expressed on adipocytes and muscle cells, and that GLP-1 enhances glucose uptake by insulin into rat adipocytes [18]. If insulin resistance is improved, lipolysis from fat cells is suppressed. As a result, blood fatty acids and fat supply and accumulation in the liver are also reduced. In addition, Gupta et al. reported that Exendin-4 has an inhibitory effect on hepatic steatosis by directly activating 3-phosphoinositide-dependent protein kinase-1 (PDK-1), protein kinase B (AKT), and protein kinase C (PKC) –ζ of the insulin signaling system via the GLP-1R in the fated human hepatoma cell line, HuH-7 [19]. On the other hand, various direct effects of GLP-1 on the liver, including suppression of inflammation and oxidative stress, reduction of hepatic fatty acid synthesis and β-oxidation, reduction of intrahepatic fat accumulation by enhancement of autophagy, or suppression of hepatic cell death (apoptosis/necrosis) through reduction of endoplasmic reticulum *stress* have been reported in experimental studies (Figure 3) [20, 21]. These mechanisms may contribute to the improvement on NAFLD/NASH seen with a GLP-1RA.

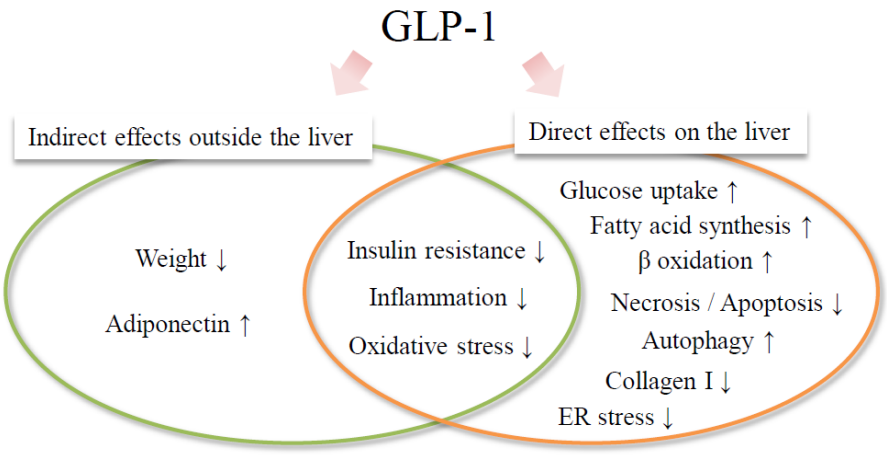

Figure 3: Various mechanisms of action of GLP-1 receptor agonists on NAFLD / NASH. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis NASH; ER, endoplasmic reticulum.

This patient received both Lira and ExLA, long-acting GLP-1RAs. GLP-1RAs have a variety of extrapancreatic effects such as weight loss via appetite suppression, as well as blood glucose-dependent insulin secretion, glucagon suppression, and blood glucose improvement through a delay in gastric emptying. [22]. Recently, it has been reported that some GLP-1RAs suppress cardiovascular events and renal function deterioration [23-26]. Many clinical studies have suggested the usefulness for liver protection in NAFLD/NASH [27]. In the LEAN-J study conducted in Japan, 0.9 mg of Lira was administered to 10 patients with type 2 diabetes with NAFLD/NASH who had not received any drug treatment for 96 weeks, and liver tissue findings before and after administration were compared. Seven patients showed improvement in inflammatory findings, and 6 patients showed a reduction in liver fibrosis [28]. In the first multicenter RCT, the LEAN study, obese NASH patients were randomly assigned to Lira 1.8 mg or a control group and observed for 48 weeks [29]. Liver tissue findings associated with NASH were significantly improved in the Lira group compared to the control group (relative risk 4.3, P = 0.019), and this improvement in tissue findings was independent of changes in body weight and HbA1c [29]. Multiple meta-analyses have also concluded that GLP-1RAs significantly improve liver tissue findings and liver function in NAFLD/NASH patients with or without diabetic complications [30, 31]. However, the mechanism of the hepatoprotective effect of GLP-1RAs has not yet been fully elucidated, and there are no reports on long-term prognosis.

There is no evidence assessing long-term drug effects on NAFLD or effects on endpoints such as progression to cirrhosis and improved prognosis. In terms of Pio, the only hypoglycemic drug recommended in Japan for treatment of NAFLD/NASH, 3 large-scale RCTs have been published [6-8], but all reported that the therapeutic effect lasted at most for 2 years. There are also reports that there was no additional effect after 3 years of extended administration [32]. In this case, long-term administration of a GLP-1RA continuously improved the FIB4 index for at least 5 years. Mesquita et al. performed in vitro experiments using human and rat hepatic stellate cells (HSCs) and in vivo experiments using cirrhosis model rats, and clarified the antifibrotic effect of Lira. That is, HSCs were inactivated by Lira, decreasing nuclear factor-kappa B/sex-determining region Y-box 9 activity in a GLP-1R–independent manner. As a result, liver fibrosis was improved by suppressing collagen I production, and portal vein pressure was also reduced by improving microvascular function [33]. Although further clinical validation is needed, it is expected that GLP-1RAs may have a long-term antifibrotic effect even in cases where liver fibrosis has already progressed. It is also possible that these agents may improve prognosis.

In this case, treatment was started with Lira 0.9 mg/day, a once-daily GLP-1RA, and changed to once-weekly ExLA 2 mg/week about 1 year later. ChE and the FIB4 index continuously improved. To date, few reports have verified the clinical effect of a once-weekly GLP-1RA on NAFLD/NASH. Seko et al. revealed an improvement in liver function and liver hardness evaluated using elastography by retrospectively examining 15 NAFLD patients with type 2 diabetes who received the once-weekly drug duraglutide (Dura) 0.75 mg/week for 12 weeks [11]. Post-hoc testing of the recently reported Phase 3 AWARD trial of Dura also suggests that administration of Dura for 6 months may improve liver dysfunction associated with NAFLD [12]. However, it should be noted that the administration period was short in each case, and that HbA1c and body weight were simultaneously improved with liver function.

The limitation of this case report is that liver biopsy was not performed. In addition, as it was a retrospective observation, only AST, ALT, PLT, ChE, and FIB4 index findings were available. Therefore, no changes in hyaluronic acid, type IV collagen 7s, ferritin, high sensitive C-reactive protein, or coagulation factors could be confirmed. This is a topic for further study, including follow-up diagnostic imaging. In addition, the involvement of diet and exercise therapy in hepatoprotection during the observation period cannot be ruled out, although there were no significant changes in these lifestyle factors during the observation period, based on patient interviews and changes in body weight. Similarly, there were no changes in blood pressure or lipid management.

A GLP-1RA, and in particular, a once-weekly, long-acting GLP-1RA, is convenient and tolerable, and may be important factors in terms of patient quality of life. In the future, we hope that long-term and prospective studies including histological evaluation and imaging findings of NAFLD/NASH will be conducted, and that the multi-faceted potential effects of GLP-1RAs will be further clarified.

4. Conclusion

We reported a case of NAFLD or NASH associated with type 2 diabetes, in which a continuous improvement in liver function and liver fibrosis index with a once-weekly GLP-1RA was observed for at least 5 years.

Acknowledgments

The authors thank the patient for permission to publish this manuscript. The authors also thank Dr. Hidetaka Moriya of Moriya Hospital who referred this patient to our hospital.

Conflicts of Interest

Dr. Yoshihiko Nishio received a personal lecture fee from Novo Nordisk Pharma Ltd.

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Citation: Akinori Tokito, Nobuyuki Koriyama, Yoshihiko Nishio. Long-Term Observation of Improvement in Liver Fibrosis Index by A Glucagon-Like Peptide-1 Receptor Agonist in A Patient with Type 2 Diabetes: A Case Report. Archives of Clinical and Medical Case Reports 4 (2020): 292-301.

BMC Endocrine Disorders

CASE REPORT Open Access

Growth hormone deficiency with late-onset hypothalamic hypoadrenocorticism associated with respiratory and renal dysfunction: a case report

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Abstract

Background: The prevalence of childhood-onset growth hormone (GH) deficiency (GHD) is estimated to be approximately 1 in 5000 or more, with the cause unknown in most cases (idiopathic isolated GHD). However, additional disorders of secretion of other pituitary hormones reportedly develop over time, with a frequency of 2–94% (median, 16%). Furthermore, median times to development of other anterior pituitary hormone deficiencies have been reported to be 6.4–9.4 years. On the other hand, adult patients affected by childhood-onset GHD reportedly develop impaired ventilation function due to reduced lung volumes and respiratory pressures, probably due to reductions in respiratory muscle strength. In addition, GH is known to play a role in stimulating the glomerular filtration rate (GFR), and the estimated GFR (eGFR) is decreased in patients with GHD.

Case presentation: This case involved a 65-year-old woman. Her short stature had been identified at around 3 years of age, but no effective treatments had been provided. The patient was mostly amenorrheic, and hair loss became apparent in her late 30s. She developed hyperuricemia, dyslipidemia, and hypertension at 45 years of age. In addition, the patient was diagnosed with hypothyroidism at 50 years of age. At 58 years of age, endocrinological examination showed impaired secretion of thyroid-stimulating hormone, luteinizing hormone/follicle-stimulating hormone, and growth hormone, and magnetic resonance imaging showed an empty sella turcica. However, secretion ability of adrenocorticotropic hormone was retained. At 63 years of age, respiratory function tests confirmed a markedly restricted ventilation disorder (vital capacity, 0.54 L; percentage predicted vital capacity, 26.9%). Renal function had also decreased (eGFR, 25.0 mL/min/1.73 m^2). Furthermore, she was diagnosed with hypothalamic secondary hypoadrenocorticism. The patient developed CO_2 narcosis at 65 years of age, and noninvasive positive pressure ventilation was started.

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Conclusions: The rare case of a 65-year-old woman with childhood-onset GHD with panhypopituitarism, including late-onset secondary hypoadrenocorticism in her 60s, associated with severely impaired respiratory function and renal dysfunction, was reported. In GHD patients with risk factors for progression from isolated GHD to combined pituitary hormone deficiency, such as empty sella turcica, lifelong endocrinological monitoring may be important.

Keywords: Growth hormone (GH), Childhood-onset growth hormone deficiency (GHD), Empty Sella turcica, Late-onset secondary hypoadrenocorticism, Panhypopituitarism, Restricted ventilation disorder, Estimated glomerular filtration rate (eGFR)

Background

The prevalence of childhood-onset growth hormone (GH) deficiency (GHD) is estimated to be approximately 1 in 5000 or more, with the cause unknown in most cases (idiopathic isolated GHD) [1]. However, additional disorders of secretion of other pituitary hormones reportedly develop over time, with a frequency of 2–94% (median, 16%) [2]. Furthermore, median times to development of luteinizing hormone (LH)/follicle-stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), and thyroid-stimulating hormone (TSH) deficiencies have been reported to be 6.4–9.4 years [2].

On the other hand, hormones are well known to regulate and/or affect skeletal muscle contractility, energy supply and metabolic pathways, membrane permeability, and protein turnover due to a combination of different mechanisms. Respiratory muscle has the physiological and biochemical characteristics of skeletal muscle. Various hormone disturbances are therefore associated with impairment of respiratory muscle function [3]. For example, adult patients affected by childhood-onset GHD reportedly develop impaired ventilatory function due to reduced lung volumes and respiratory pressures, probably due to reductions in respiratory muscle strength [4]. In addition, GH is known to play a role in stimulating the glomerular filtration rate (GFR) [5, 6], and GFR is decreased in patients with GHD [7].

The rare case of a 65-year-old woman with childhood-onset GHD with panhypopituitarism, including late-onset secondary hypoadrenocorticism appearing in her 60s, is presented. The patient showed impairment of both respiratory and renal functions.

Case presentation

The patient was a 65-year-old woman with no relevant family history. She was born without any perinatal anomalies, although short stature was identified at around 3 years of age, but she never received effective treatments. Withdrawal bleeding occurred from around the age of 16 years after hormone-replacement therapy was started to address the absence of secondary sexual characteristics and primary amenorrhea. However, treatment was self-interrupted 1 year later, and she remained amenorrheic thereafter. The patient noticed hair loss in her late 30s. She visited a medical practitioner due to gout at 45 years of age and was subsequently treated for hyperuricemia, dyslipidemia, and hypertension at the clinic. In addition, the patient was diagnosed with hypothyroidism at 50 years of age, and thyroid hormone-replacement therapy was started (levothyroxine sodium hydrate, 50 μg/day). In 2013, at 58 years of age, the patient was referred to our department for endocrinological examination of short stature. The results of this examination showed impaired secretion of TSH on the thyrotropin-releasing hormone (TRH) stimulation test, impaired secretion of LH/FSH on the luteinizing hormone-releasing hormone (LH-RH) stimulation test, impaired secretion of GH on both arginine and GH-releasing peptide-**2** (GHRP-2) stimulation tests (Fig. 1), and an empty sella turcica with atrophy of the anterior pituitary gland on magnetic resonance imaging (MRI) (Fig. 2), but secretion of ACTH was retained on the corticotropin-releasing hormone (CRH) stimulation test (Fig. 3a). For this reason, GH-replacement therapy (0.075 mg/day of somatropin; genetic recombinant) was started. In addition, chronic kidney disease of unknown cause was identified (estimated glomerular filtration rate [eGFR], 31.9 mL/min/1.73 m^2) (Table 1). At 63 years of age, hypoxia and hypercapnia were identified (partial pressure of carbon dioxide [pCO_2], 59.6 mmHg; partial pressure of oxygen [pO_2], 48.7 mmHg), and respiratory function testing confirmed a markedly restricted ventilation disorder, and both vital capacity (VC) and forced vital capacity (FVC) were significantly reduced (VC, 0.54 L; percentage predicted VC (%VC), 26.9%; FVC, 0.50 L), but percentage predicted forced expiratory volume in 1 s (%$FEV_{1.0}$) was within normal limits (80.0%). Because the patient did not wish to receive home oxygen therapy (HOT) or respiratory rehabilitation, she was followed-up. However, HOT (0.5 L/min by nasal cannula) was started about 6 months later as her exertional dyspnea gradually worsened, and renal function also

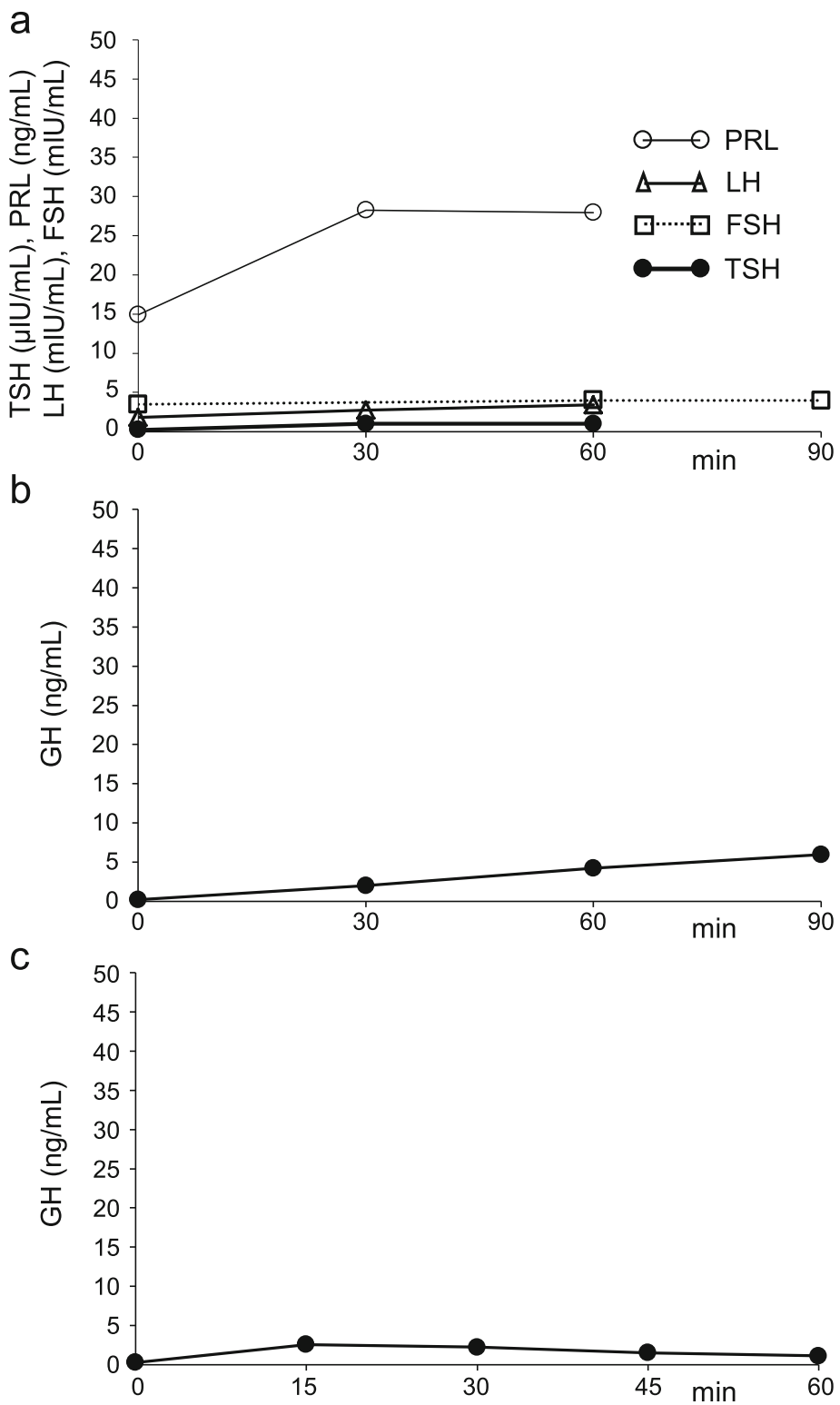

Fig. 1 Findings of endocrine function tests 1. Findings at 58 years of age. TSH (closed circles, thick solid line) and PRL (open circles, thin solid line) responses to TRH (500 μg, i.v.), and LH (open triangles, thick solid line) and FSH (open squares, dashed line) responses to LH-RH (100 μg, i.v.) (**a**). GH response to arginine (0.5 g/kg, d.i.v.) (**b**). GH response to GHRP-2 (100 μg, i.v.) (**c**). TSH, thyroid-stimulating hormone; PRL, prolactin; TRH, thyrotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; LH-RH, luteinizing hormone-releasing hormone; GH, growth hormone; GHRP-2, GH-releasing peptide-2; i.v., intravenous infusion; d.i.v., drip intravenous infusion

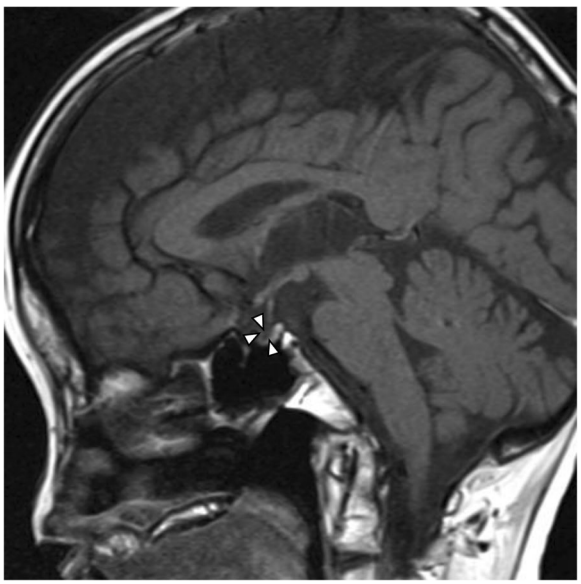

Fig. 2 Hypothalamic-pituitary MRI image. A sagittal T1-weighted image is shown, confirming an empty sella turcica. No abnormality in the hypothalamus-pituitary stalk is evident, and a high-intensity signal is present in the posterior lobe. The anterior lobe is atrophic. Arrowheads indicate an empty sella turcica

slowly decreased (eGFR, 25.0 mL/min/1.73 m^2). Since there was no bronchiectasis or emphysema, pulmonary embolism and shunt disease were ruled out by the lung perfusion scan (technetium-99 m-labeled macro-aggregated albumin scintigraphy), and since there was weakness of proximal muscle without abnormal neurological findings, the patient was diagnosed with endocrine myopathy by both a respiratory physician and a neurologist. Furthermore, a nephrologist noted that there was no glomerulonephritis or hereditary kidney disease, and that there was unexplained renal atrophy. Around this time, frequent episodes of hypoglycemia occurred, and a low basal level of serum cortisol (6.38 μg/dL), a relatively low basal level of plasma ACTH (34.2 pg/dL), and a low 24-h urinary cortisol level (5.5 μg/day) were confirmed (Table 1). Delayed overreaction of plasma ACTH and failure of serum cortisol on the CRH stimulation test were confirmed (Fig. 3a, b), and a failure of plasma ACTH on the insulin tolerance test was confirmed (Fig. 3c). Furthermore, the cortisol response on the rapid ACTH stimulation test was slightly delayed and attenuated (Fig. 3d), and the prolonged ACTH stimulation test showed a sufficient increase in urinary free-cortisol levels (Fig. 3e). The patient was therefore diagnosed with hypothalamic secondary hypoadrenocorticism, and replacement therapy was started (prednisolone at 2.5 mg/day). At 65 years of age, the patient developed CO_2 narcosis (pCO_2, 80.1 mmHg, pO_2, 76.0 mmHg) during bronchopneumonia treatment, and ventilatory function was: VC, 0.48 L; %VC, 27.1%; and FVC, 0.49 L. Noninvasive positive-pressure ventilation (NPPV) (2.0 L/min by mask) was started and continued at home.

The patient was 129.4 cm tall and weighed 21.8 kg (body mass index, 13.2 kg/m^2). Blood pressure was 110/57 mmHg, and heart rate was regular at 93 beats/min. She showed no mental retardation, and no pigmentation on the skin and oral mucosa. Her hair was thin, and no underarm or pubic hair was present. The Turner classification for the breasts was stage 1. Mild scoliosis was evident. Cardiopulmonary examination showed normal results, and no abnormal abdominal findings were identified.

Discussion and conclusions

Patients with GHD can present with either an isolated deficiency or a combination of deficiencies of pituitary hormones [combined pituitary hormone deficiency (CPHD)] at any time from the neonatal period to adulthood. Additional endocrinopathies may develop in varying numbers and at various times [8]. It has been reported that additional hormone deficiencies were more frequent in the order of TSH, LH/FSH, ADH, and ACTH, and the median time interval from GHD diagnosis to the onset of other hormone deficiencies ranged from 1.9 years for TSH, to 2.4 years for ADH and ACTH, and 3.3 years for LH/FSH [9]. On the other hand, Otto et al. [2] reported that the most common deficiencies were LH/FSH deficiencies (38%), followed by TSH (31%), ACTH (12%), and ADH deficiencies (5%). In addition, they also reported that patients with various deficiencies presented at different times during follow-up: ADH deficiency at 3.1 ± 1 years; TSH deficiency at 7.5 ± 5.6 years; LH/FSH deficiencies at 8.3 ± 4 years; and ACTH deficiency at 9.3 ± 3.5 years [2]. Though these differences could be the result of differences in the age or follow-up period of the population studied, they may also be due to the variable endocrine phenotypes of CPHD patients [8]. In the majority of studies, the most frequent additional deficit was TSH deficiency, with the least frequent one being diabetes insipidus (DI); the prevalences of LH/FSH and ACTH deficiencies varied [8]. In addition, the following have been shown to be risk factors for progression from isolated GHD to CPHD: 1) severe GHD; 2) female sex; 3) organic GHD etiology; 4) longer follow-up; 5) genetic defects; 6) structural abnormalities of the forebrain and hypothalamo-pituitary region (ectopic posterior pituitary, absent pituitary stalk, small anterior pituitary, abnormal corpus callosum, septo-optic dysplasia, empty sella turcica, optic nerve hypoplasia, holoprosencephaly, etc.); 7) presence of extrapituitary malformations; and 8) delivery complications, breech delivery, and perinatal/neonatal adverse events [8]. This patient had an empty sella turcica, a 62-year period of follow-up,

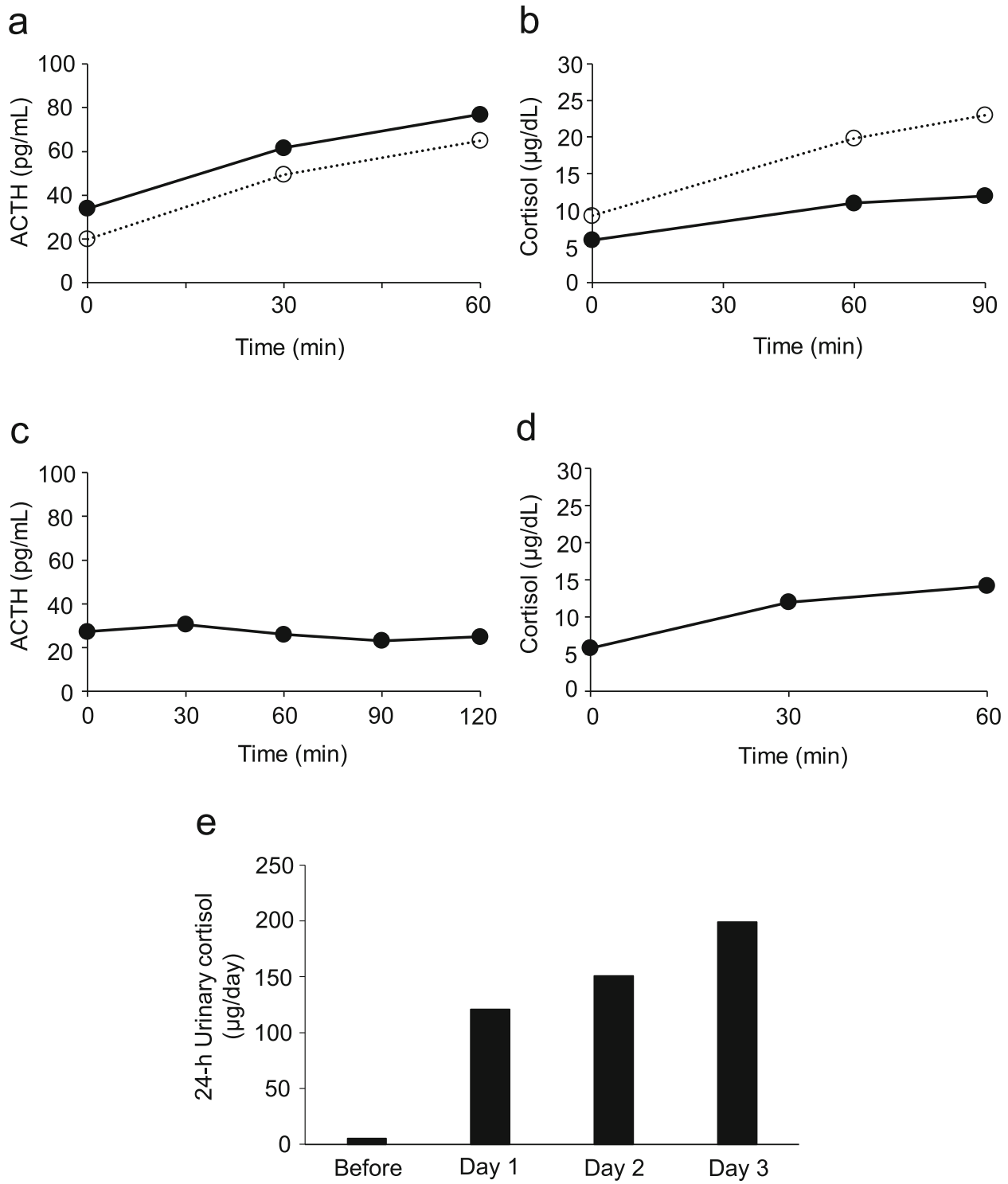

Fig. 3 Findings of endocrine function tests 2. (**a**) ACTH and (**b**) cortisol responses to a CRH (100 μg, i.v.**)** stimulation test. In both cases, a closed circle (solid line) indicates the value at 63 years of age, compared to results at 58 years of age (open circles and dashed lines). (**c**) Insulin tolerance test. ACTH response to insulin (0.05 units/kg bodyweight, i.v.). (**d**) Rapid ACTH stimulation test. Cortisol response to ACTH **(**tetracosactide acetate 0.28 mg, i.v.**)**. (**e**) Prolonged ACTH simulation test. Cortisol response to ACTH **(**tetracosactide acetate, 0.56 mg, i.m.**)**. **c**, **d**, and **e** all show data at 63 years of age. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; i.v., intravenous; i.m., intramuscular

Table 1 Laboratory findings

	At 58 years	At 63 years		
Biochemistry				
Alb	4.1	3.9	g/dL	[4.10–5.10]
Na	139	135	mmol/L	[138–145]
K	5.3	4.8	mmol/L	[3.6–4.8]
Cl	104	94	mmol/L	[101–108]
Ca	8.8	9.2	mg/dL	[8.8–10.1]
IP	5.0	3.0	mg/dL	[2.7–4.6]
CK	209	119	U/L	[41–153]
BUN	45.5	50.5	mg/dL	[8.0–20.0]
Cr	1.36	1.56	mg/dL	[0.46–0.79]
eGFR	31.9	26.8	mL/min/1.73 m^2	
UA	5.0	7.9	mg/dL	[2.6–5.5]
CRP	0.26	0.06	mg/dL	[0.00–0.14]
Endocrinology				
FT3	2.8	NR	pg/mL	[2.48–4.14]
FT4	0.90	0.97	ng/dL	[0.76–1.65]
TSH	0.473	0.303	μU/mL	[0.541–4.261]
PRL	10.7	17.9	ng/mL	[3.12–15.39]
GH	0.13	1.07	ng/mL	[0.13–9.88]
IGF-1	28.0	19.0	ng/mL	[66.0–205.0]
LH	1.89	1.00	mIU/mL	[5.72–64.31]
FSH	4.05	2.69	mIU/mL	[≤ 157.79]
E2	≤ 10.0	≤ 5.0	pg/mL	[6.2–37.0]
ACTH 06:00	35.5	34.2	pg/mL	[7.2–63.3]
12:00	22.1	NR		
16:00	13.9	NR		
CORT 06:00	12.9	6.4	μg/dL	[6.2–18.0]
12:00	10.8	NR		
16:00	4.9	NR		
U-CORT	4.1	5.5	μg/day	[11.2–80.3]

Reference ranges are shown in brackets. *Alb* albumin, *IP* inorganic phospohorus, *CK* creatine kinase, *BUN* blood urea nitrogen, *Cr* creatinine, *eGFR* estimated glomerular filtration rate, *UA* uric acid, *CRP* C-reactive protein, *FT3* free triiodothyronine, *FT4* free thyroxine, *TSH* thyroid-stimulating hormone, *PRL* prolactin; *GH* growth hormone, *IGF-1* insulin-like growth factor 1, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *E2* estradiol, *ACTH* adrenocorticotropic hormone, *CORT* cortisol, *U-CORT* urinary cortisol, *NR* no result

severe GHD, and female sex as risk factors. The interval from diagnosis of GHD to additional pituitary hormone deficiency was about 13 years for LH/FSH, about 47 years for TSH, and about 60 years for ACTH, although no DI was present. According to previous reports, the greatest age at onset of ACTH deficiency was in the 40s [10]; onset in the 60s is thus extremely rare.

The present patient also developed hypoxia and hypercapnia due to the markedly decreased VC. Adult patients with CPHD have been reported to show impairment of ventilatory function, and GH-replacement therapy can help restore it [4, 11, 12]. It has also been reported that GH-replacement therapy for GHD in adults results in increased maximal oxygen uptake, presumably due to increased respiratory muscle strength [13] and increased mean frequency of the surface electromyogram of the muscle fiber area in quadriceps [14]. However, only one report appears to have described severe respiratory failure requiring use of NPPV [12]. Furthermore, this patient had chronic kidney disease of unknown cause. In children with GHD, insulin growth factor (IGF)-1 activity has been reported to be significantly positively correlated with GFR [15]. Sohmiya et al. reported that chronic GH replacement improved progressive renal dysfunction in a patient with Sheehan's syndrome associated with chronic renal failure [16]. On the other hand, since the action of IGF-1 is suppressed by an increase in IGF binding proteins, it has been reported that combined therapy with GH and IGF-1 is a reasonable treatment in chronic renal failure [17]. Checking GH secretion capacity may be important when the cause of respiratory or renal dysfunction is unclear. In the present case, the reason why GH replacement therapy did not improve the respiratory or renal disorder is considered to be because a sufficient amount of GH could not be administered due to the patient reporting a poor mood and the appearance of edema caused by increasing somatotropin. The prognosis of CPHD remains unclear due to very few reports with a long follow-up period. In particular, cases of CPHD that do not receive sufficient GH replacement therapy may have organ damage, as in the present case, and close attention is thus required.

One limitation of the present report was that genetic mutations in pituitary transcription factors (HESX1, PROP1, POU1F1, LHX3, LHX4, GLI2, and SOX3) were not confirmed [18]. Why progression of hypoadrenalism due to ACTH deficiency took so long also remains unclear, and further evaluations of this issue should be conducted in the future.

In conclusion, a rare case of a 65-year-old woman with childhood-onset GHD with panhypopituitarism, including late-onset secondary hypoadrenocorticism in her 60s, and severely impaired respiratory function and renal dysfunction, was presented. In GHD patients with risk factors for progression from isolated GHD to CPHD, lifelong endocrinological monitoring may be important.

Abbreviations

GH: Growth hormone; GHD: Growth hormone deficiency; GFR: Glomerular filtration rate; eGFR: Estimated glomerular filtration rate; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone; ACTH: Adrenocorticotropic hormone; TSH: Thyroid-stimulating hormone; TRH: Thyrotropin-releasing hormone; LH-RH: Luteinizing hormone-releasing hormone; GHRP-2: Growth hormone-releasing peptide-2; MRI: Magnetic resonance imaging; CRH: Corticotropin-releasing hormone; pCO_2: Partial pressure of carbon

dioxide; pO_2: Partial pressure of oxygen; VC: Vital capacity; FVC: Forced vital capacity; %VC: Percentage predicted vital capacity; $\%FEV_{1.0}$: Percentage predicted forced expiratory volume in 1 s; HOT: Home oxygen therapy; NPPV: Noninvasive positive-pressure ventilation; CPHD: Combined pituitary hormone deficiency; ADH: Antidiuretic hormone; DI: Diabetes insipidus

Acknowledgements
The authors wish to thank the patient and her family for their permission to publish this manuscript. Furthermore, the authors would like to thank Forte Science Communications (Tokyo, Japan) for providing medical editorial services.

Authors' contributions
N.Koji., A.T., K.K., S.K., and K.O. attended the patient; N.Koji. and N.Kori. wrote the manuscript; A.T., K.O., and Y.N. gave conceptual advice. N.Kori. supervised management of the case and contributed to writing and editing the manuscript. All authors have read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written, informed consent was obtained from the patient for publication of this case report and all accompanying images.

Competing interests
The authors declare that there are no competing interests regarding the publication of this article.

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Received: 8 January 2020 Accepted: 12 April 2020
Published online: 16 April 2020

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Publisher's Note

Journal of Medical Case Reports

CASE REPORT Open Access

Neurofibromatosis type 1 associated with hypophosphatemic osteomalacia due to hypersecretion of fibroblast growth factor 23: a case report

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Abstract

Background: Neurofibromatosis type 1 is characterized by multiple café au lait spots and cutaneous and plexiform neurofibromas, and is one of the most common autosomal dominant hereditary disorders caused by mutations of the neurofibromatosis type 1 tumor suppressor gene. Osteomalacia in neurofibromatosis type 1 is very rare and is characterized by later onset in adulthood. In humans, fibroblast growth factor 23, which is a causative factor of tumor-induced osteomalacia, is not only a paracrine and autocrine factor, but is also a physiological regulator of phosphate balance in normal serum.

Case presentation: Our patient was a 65-year-old Japanese woman whose neurofibromas began to appear when she was in elementary school. At age 28, she was diagnosed as having neurofibromatosis type 1. A spinal compression fracture and multiple rib fractures were identified in 2012 and 2017, respectively. Her laboratory findings revealed hypophosphatemia due to renal phosphate wasting and a high serum level of fibroblast growth factor 23. Neurofibromas located on the surface of her right forearm and left upper arm, in which a slight abnormal accumulation of tracers was observed on ^{111}indium-pentetreotide scintigraphy, were surgically removed, but there was no improvement in hypophosphatemia or serum fibroblast growth factor 23 after surgery. Therefore, we administered eldecalcitol, which also failed to produce improvement in abnormal data. Subsequent combination with dibasic calcium phosphate hydrate led to improvement in some of the abnormalities, including hypophosphatemia. Immunohistochemical staining using anti-human fibroblast growth factor 23 antibody revealed slightly positive results, however, only one out of three amplifications of the fibroblast growth factor 23 gene was observed by real-time polymerase chain reaction, and no clear fibroblast growth factor 23 gene expression in the resected neurofibromas could be confirmed.

Conclusions: We here describe a first rare case of a 65-year-old woman with neurofibromatosis type 1 associated with hypophosphatemic osteomalacia in which a high serum fibroblast growth factor 23 level was confirmed.

Keywords: Fibroblast growth factor 23, Tumor-induced osteomalacia, Neurofibromatosis type 1, Hypophosphatemia, 25-hydroxyvitamin D_3

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Background

Neurofibromatosis type 1 (NF1) is characterized by multiple café au lait spots and cutaneous and plexiform neurofibromas (NFomas), and is one of the most common autosomal dominant hereditary disorders caused by mutations of the NF1 tumor suppressor gene (*NF1*) on chromosome 17 [1–3]. In addition, generalized skeletal abnormalities, such as mild short stature [4] and decreased bone mineral density (BMD) [5], are frequent in NF1. Osteomalacia in NF1, however, is very rare and is characterized by later onset in adulthood [6].

In humans, fibroblast growth factor 23 (FGF23), which is a causative factor of tumor-induced osteomalacia (TIO), is a 251 amino acid polypeptide hormone (32.5 kDa) belonging to the fibroblast growth factor (FGF) family [7]. FGF23 can be amplified from the human heart, liver, thyroid/parathyroid, intestine, lymph node, thymus, and skeletal muscle and bone by the reverse transcription-polymerase chain reaction technique [7–9]. Furthermore, it was reported that FGF23 acts on sodium–phosphorus co-transporter in the renal tubule and inhibits 1α-hydroxylation of 25-hydroxyvitamin D_3 ($25(OH)D_3$); thus, leading to renal phosphate leakage, hypophosphatemia, inappropriately normal or low 1α25-dihydroxyvitamin D_3 ($1\alpha25(OH)_2D_3$) levels, and decreased bone mineralization [10]. Hence, FGF23 is not only a paracrine and autocrine factor, but is also a physiological regulator of phosphate balance in normal serum [11].

Here, we report a rare case of a 65-year old woman with hypophosphatemic osteomalacia associated with NF1. Her serum FGF23 levels were elevated but no clear expression of FGF23 was confirmed in her surgically resected NFomas by immunohistochemical and molecular analysis.

Case presentation

Our patient was a 65-year-old Japanese woman whose NFomas began to appear when she was in elementary school. She was born without any perinatal anomalies. At age 28, she was diagnosed as having NF1. In 2012, a spinal compression fracture was identified during a visit to a local orthopedic surgeon for lumbago. In 2017, she visited a local orthopedic surgeon with a chief complaint of lateral chest pain, and multiple rib fractures were identified. Hence, she was referred to our department for endocrinological examination. Pregabalin 50 mg was administered daily, and loxoprofen sodium hydrate 60 mg was used at the time of pain.

She was 147.1 cm tall, weighed 47.5 kg, body mass index was 22.0 kg/m^2, body temperature was 36.6 °C, blood pressure was 105/72 mmHg, and pulse was 72 beats/minute and regular. She showed no mental retardation, and no pigmentation on her skin and oral mucosa. Her cardiopulmonary examination was normal. She had no abnormal abdominal and neurological findings or skeletal abnormalities. Soft NFomas of various sizes were scattered all over her body, and relatively large masses approximately 4 cm in diameter were present on the surface of her right forearm and left upper arm (Fig. 1). Her eldest daughter has also been diagnosed as having NF1. She was a caregiver; our patient drank alcohol occasionally but did not smoke tobacco. Her serum levels of inorganic phosphorus (IP), $25(OH)D_3$, and maximum transport of phosphorus in the renal proximal tubules (TmP/GFR) were inappropriately low (Table 1). Serum alkaline phosphatase (ALP), intact parathyroid hormone (intact PTH), bone-specific alkaline phosphatase (BAP), tartrate-resistant acid phosphatase 5b (TRACP 5b), and undercarboxylated osteocalcin (ucOC) levels were all elevated. Her serum level of FGF23 was high. The results of total blood cell count and other biochemical parameters were almost within normal limits (Table 1). BMD using dual-energy X-ray absorptiometry of the second to fourth lumbar vertebrae (L2–4, total) and left femoral neck were 0.764 g/cm^2 and 0.504 g/cm^2, with a young adult mean (YAM) of 64% and 54%, respectively. Computed tomography displayed no space occupying lesions other than NFomas on the body surface. Multiple areas

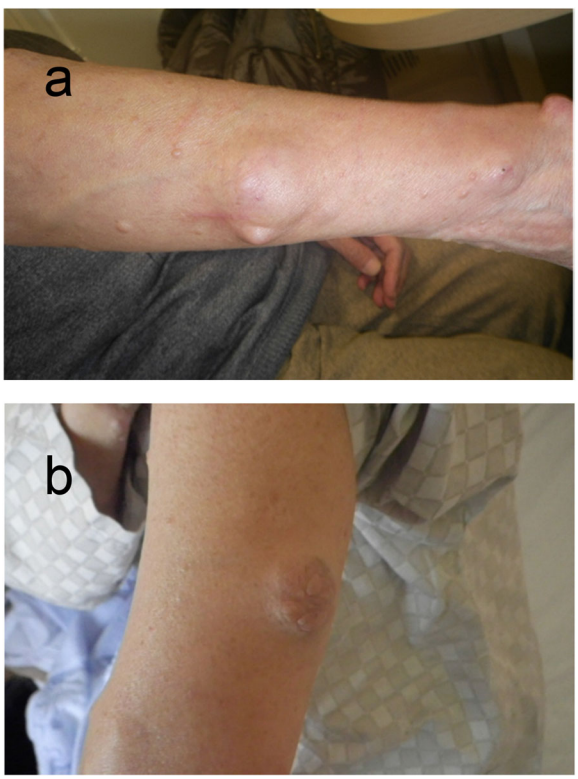

Fig. 1 Photograph of the patient's neurofibromas. Two neurofibromas were present: one on the surface of her right forearm (**a**) and one on the surface of her left upper arm (**b**)

Table 1 Laboratory findings

Inspection Item				Reference range
Urine analysis	Protein	(–)		
	Glucose	(–)		
	Occult blood	(–)		
Urine biochemistry	TmP/GFR	1.77		22–40
Peripheral blood	WBC	3270	/μL	
	RBC	409×10^4	/μL	
	Hb	11.5	g/dL	
	PLT	24.6×10^4	/μL	
Biochemistry	AST	14	IU/L	
	ALT	11	IU/L	
	LDH	168	IU/L	
	ALP	641	IU/L	106–322
	γ-GTP	26	IU/L	
	T. Bil	0.95	mg/dL	
	Alb	4.24	g/dL	
	Na	144	mmol/L	
	K	3.4	mmol/L	3.6–4.8
	Cl	106	mmol/L	
	Ca	8.8	mg/dL	
	IP	1.9	mg/dL	2.7–4.6
	Mg	2.0	mg/dL	
	BUN	12.1	mg/dL	
	Cr	0.51	mg/dL	
	eGFR	90.4	mL/minute/1.73m^2	
	FBG	97	mg/dL	
	HbA_{1c}	5.2	%	
Endocrinology	Intact PTH	123	pg/mL	10–65
	$25(OH)D_3$	14.0	ng/mL	20–60
	$1α25(OH)2D_3$	57.2	pg/mL	20–60
	FGF23	57.0	pg/mL	< 30
	BAP	55.1	μg/L	3.8–22.6
	TRACP 5b	996	mU/dL	120–420
	ucOC	19.0	ng/mL	< 4.5

Alb albumin, *ALP* alkaline phosphatase, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BAP* bone-specific alkaline phosphatase, *BUN* blood urea nitrogen, *Cr* creatinine, *eGFR* estimated glomerular filtration rate, *FBG* fasting blood glucose, *FGF23* fibroblast growth factor 23, *γ-GTP* γ-glutamyltransferase, *Hb* hemoglobin, HbA_{1c} glycosylated hemoglobin, *IP* inorganic phosphorus, *LDH* lactate dehydrogenase, *PLT* platelets, *PTH* parathyroid hormone, *RBC* red blood cells, *T. Bil* total bilirubin, *TmP/GFR* maximum transport of phosphate in the renal proximal tubules, *TRACP 5b* tartrate-resistant acid phosphatase 5b, *ucOC* undercarboxylated osteocalcin, *WBC* white blood cells, *1α25(OH)2D3* 1α25-dihydroxyvitamin D_3, *25(OH)D3* 25-hydroxyvitamin D_3

of abnormal tracer uptake were seen in her rib on ^{99}technetium (Tc)-methylene diphosphonate bone (MDPB) scintigraphy. Slight abnormal accumulation of tracers was observed in the NFomas located on the surface of her right forearm and left upper arm on ^{111}indium-pentetreotide scintigraphy (Octreoscan) (Fig. 2). She did not agree with venous sampling because of difficulty in maintaining her supine position for prolonged periods because of systemic pain. Since she strongly desired resection of the NFomas on her right forearm and left upper arm, we respected her wish and excised them in February 2018. Pathology evaluation demonstrated benign NFomas. Unfortunately, there was no improvement in serum IP levels after surgery. Therefore, we administered eldecalcitol (active vitamin D_3 analogue) 0.75 μg per day, which also failed to produce improvement in hypophosphatemia and other abnormal data. Subsequent combination with dibasic calcium phosphate hydrate (3.0 g/day) led to improvement in some of the abnormalities, including hypophosphatemia: IP, 3.1 mg/dL (2.7–4.6); ALP, 209 U/L (106–322); intact PTH, 46 pg/mL (10–65); BAP, 12.4 μg/L (3.8–22.6); and TRACP-5b, 309 mU/dL (120–420) (data not shown). After 6 months, serum calcium, IP, intact PTH, and BAP were 9.1 mg/dL, 3.6 mg/dL, 37 pg/mL, and 14.4 μg/L, respectively, and were stable in the normal range. Furthermore, pain also improved.

Immunohistochemical staining was performed on formalin-fixed and paraffin-embedded tissue from the resected NFomas, which demonstrated FGF23 weak

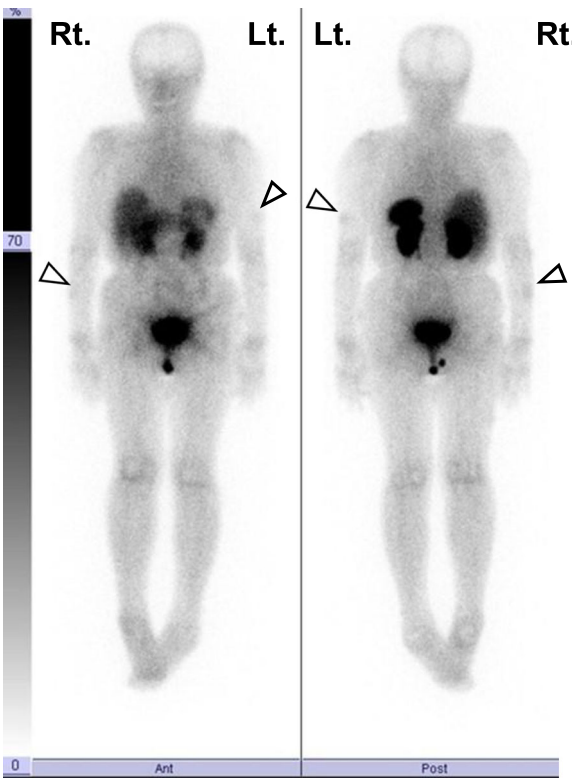

Fig. 2 Octreoscan images. The *arrow heads* indicate light uptake into neurofibromas located on the surface of her right forearm and left upper arm. *Lt.* left, *Rt.* right

positivity of the NFomas (Fig. 3). Pathological processing and evaluation was performed by GenoStaff Co., Ltd. (Tokyo, Japan).

Total ribonucleic acid (RNA) extraction from the formalin-fixed paraffin-embedded tissue samples was performed according to the manufacturer's instructions. Human pancreas total RNA (Zyagen, San Diego, California, USA) was prepared as a control [7]. Next, we performed real-time polymerase chain reaction (RT-PCR) testing for housekeeping genes and actin β gene (*ACTB*), and the fibroblast growth factor 23 gene (*FGF23*), according to the manufacturers' instructions. Amplification curve plotting using fluorescence intensity by ABI PRISM SDS 2.4 (Thermo Fisher Scientific Inc., USA) was performed (Fig. 4). All samples were amplified in triplicates. Once out of three times, the threshold cycle (C_T) value for *FGF23* was 35.95 in resected NFomas, but it was not detected in human pancreas (Table 2). Unfortunately, these results did not clearly confirm expression of *FGF23* in the excised NFomas. These tests were conducted by GeneticLab Co., Ltd. (Sapporo, Japan).

Discussion and conclusions

The patient described here is the first case of NF1 associated with hypophosphatemic osteomalacia, in which a high serum FGF23 level was confirmed. Our patient was a 65-year-old woman diagnosed as having NF1 at age 28. Her laboratory findings revealed hypophosphatemia due to renal phosphate wasting and a high serum level of FGF23. Her NFomas located on the surface of her right forearm and left upper arm, in which a slight abnormal accumulation of tracers was observed on Octreoscan, were surgically removed, but there was no improvement in hypophosphatemia or serum FGF23 after surgery. Immunohistochemical staining using anti-human FGF23 antibody revealed slightly positive results; however, only one out of three amplifications of the *FGF23* gene was observed by RT-PCR, and no clear *FGF23* gene expression in the resected NFomas could be confirmed. We administered eldecalcitol combination with dibasic calcium phosphate hydrate, which led to improvement in some of the abnormalities, including hypophosphatemia.

TIO, also known as oncogenic hypophosphatemic osteomalacia, is a rare acquired paraneoplastic disease. TIO was first described by McCance in 1947 [12]. It is usually induced by benign mesenchymal tumors secreting excessive FGF23 [13]; in fact, FGF23 has been cloned as a causative factor of TIO [7]. Approximately 500 cases of TIO were reported worldwide up to 2018 [14]. On the other hand, osteomalacia associated with NF1 was first recognized by Gould in 1918 [15]. It is extremely rare, with fewer than 50 cases being reported [6, 16–21].

In our case, the typical biochemical pattern included low serum phosphate, increased phosphate excretion in

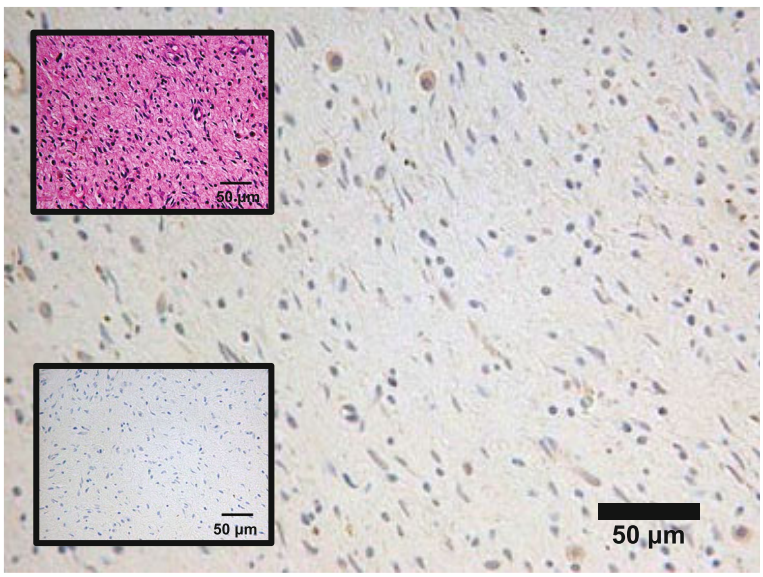

Fig. 3 Immunohistochemical staining of fibroblast growth factor 23 in the resected neurofibromas. Single immunolabeling (peroxidase and diaminobenzidine tetrahydrochloride) of the resected neurofibromas. The *upper inset* shows hematoxylin and eosin staining. Ossified metaplasia, poorly differentiated foci of cartilage tissue, and osteoclast-like giant cells contained in many mesenchymal tumors are not observed, and dense proliferation of small short spindle-shaped cells against the background of hyaline or myxoma-like stroma are observed. The *lower inset* shows a negative control using normal rabbit immunoglobulin. The stromal cells in the tissue stained weakly positive using polyclonal rabbit anti-human fibroblast growth factor 23 antibodies

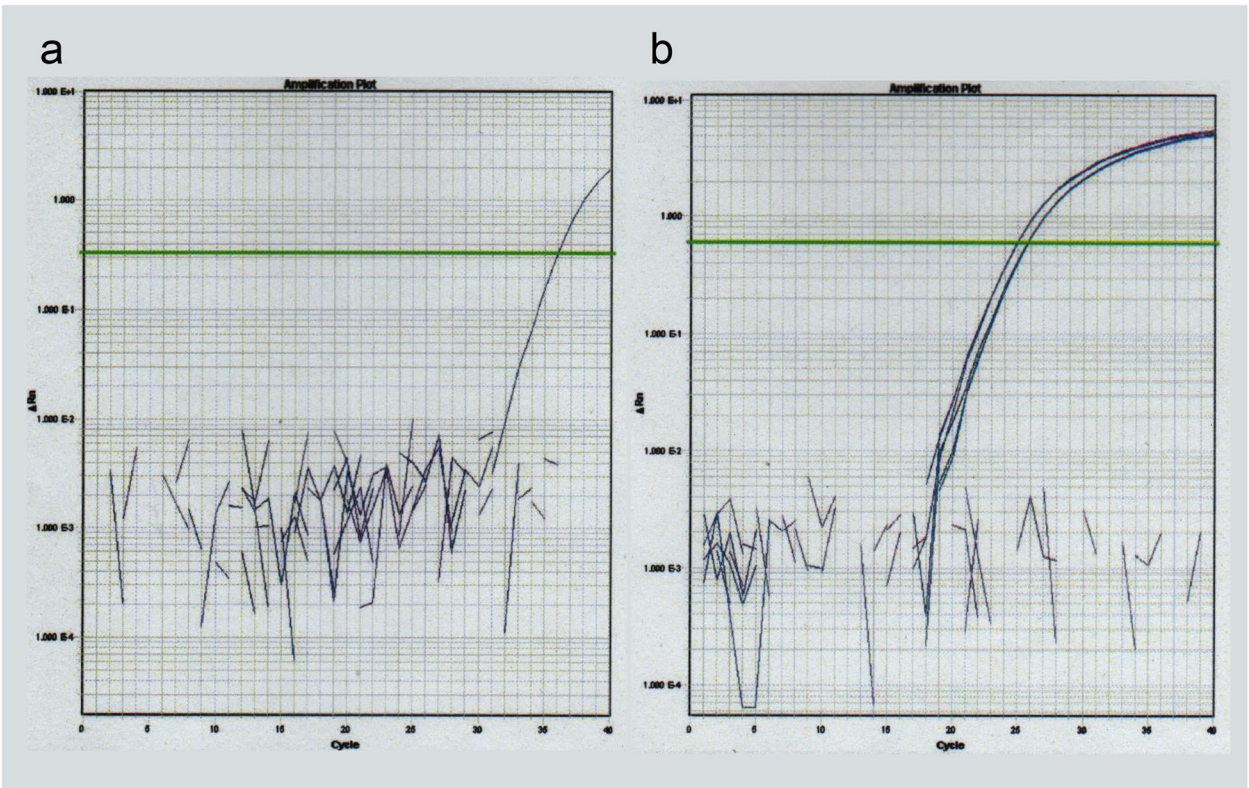

Fig. 4 Fibroblast growth factor 23 gene expression analysis by real-time polymerase chain reaction in the resected neurofibromas. Amplification curve of fluorescence intensity. Amplification curves were drawn for the fibroblast growth factor 23 (**a**) and actin β (**b**) genes

urine with TmP/GFR reduction, and elevated ALP, BAP, TRACP 5b, and ucOC, indicating increased bone metabolism, along with elevated FGF23 concentrations and normal creatinine levels in serum (Table 1). We also observed elevation of serum intact PTH levels (Table 1). The serum levels of PTH are reportedly variable in TIO, although the reasons for these discrepancies remain unclear. Elevated levels of circulating FGF23 have been shown to promote the development of secondary hyperparathyroidism in predialysis patients through the suppression of 1α-hydroxylation of $25(OH)D_3$ [22], suggesting that excessive FGF23 might stimulate the parathyroid either directly or indirectly. Our patient's $1\alpha25(OH)_2D_3$ levels were normal (Table 1). Since phosphate depletion stimulates renal 1α-hydroxylation of $25(OH)D_3$, resulting in elevation of serum $1\alpha25(OH)_2D_3$ concentrations, the normal level of $1\alpha25(OH)_2D_3$ in this case should actually be regarded as inappropriately low levels. Low values of $25(OH)D_3$ were also observed (Table 1). Low serum $25(OH)D_3$ concentrations, as seen in our patient, have been previously described in NF1 [17, 23].

Table 2 C_T value and mean C_T value of *FGF23* and *ACTB* by RT-PCR

Sample name	FGF23			ACTB		
	C_T	mean C_T	SD	C_T	mean C_T	SD
Resected NFoma	UD	–	–	25.7	25.76	0
	UD			25.8		
	36			25.8		
Human pancreas	UD	–	–	25	24.97	0
	UD			25		
	UD			25		

ACTB actin β gene, C_T threshold cycle, *FGF23* fibroblast growth factor 23 gene, NFoma neurofibroma, RT-PCR real-time polymerase chain reaction, SD standard deviation, UD undetermined

In our patient, a slight increase in radiotracer uptake on Octreoscan (Fig. 2) was observed in the relatively large NFomas on the surface of her right forearm and left upper arm (Fig. 1). TIO-associated tumors express a series of somatostatin receptors (SSTRs) [24, 25], and Octreoscans reportedly effectively detect occult mesenchymal tumors [26]. In recent years, it has been recommended that entire body functional imaging tests, including SSTR imaging, should be conducted first for the localization of TIOs [15]. Our experience in this case showed that NFomas are likely to produce and secrete FGF23. Octreotide 50 μg, however, did not inhibit FGF23 until 8 hours after its administration (data not shown). According to a previous report, the role of

somatostatin signaling in the causation of osteomalacia by phosphaturic mesenchymal tumors is unclear, and the efficacy of the somatostatin analogue in the treatment of patients with TIO is inconsistent [27].

A previous report on NF1-associated osteomalacia showed that hypophosphatemia improved after surgical resection of two large NFomas in a patient with neurofibromatosis [18]. When we provided this information to our patient, she wanted to remove her two large NFomas. Hence, we removed the two NFomas surgically, although it did not improve the hypophosphatemia. The mechanism behind hypophosphatemia in the setting of NF1 is not known. Only one case of NF1-associated hypophosphatemic osteomalacia, in which serum FGF23 was elevated, has been reported in the past, although immunohistochemical staining did not show FGF23 expression in the NFomas [21]. In our patient, immunohistochemical staining using anti-human FGF23 antibody revealed weak positive results (Fig. 3), but we could not prove *FGF23* expression in the resected NFomas by RT-PCR (Fig. 4 and Table 2). The reason why hypophosphatemia was not improved by excision of the NFomas is presumed to be continued production and secretion of FGF23 from FGF23-secreting tumor of unknown location. Reportedly, oral phosphate and vitamin D therapy is effective treatment for osteomalacia associated with NF1 [6, 18]. Hence, we administered eldecalcitol, although this, by itself, did not improve hypophosphatemia or other abnormal blood parameters, making it necessary to combine it with dibasic calcium phosphate hydrate. This also suggests that vitamin D deficiency is not the main cause of hypophosphatemia in NF1.

A limitation of our report is that we do not know why the increase in FGF23 was mild in our case. In a retrospective study of 144 cases of TIOs without NF1, however, cases with normal FGF23 levels (20.1 pg/mL) were also reported [28]. Our experience suggests that under hypophosphatemic conditions, normal to mildly high levels of FGF23 might need to be considered as obviously abnormal values. In addition, the possibility that a very small amount of FGF23 is synthesized and secreted from NFomas cannot be denied. A second limitation is that the possibility of increased production of FGF23 from osteocytes cannot be denied. Kamiya *et al.* reported that serum FGF23 levels showed a four-fold increase in NF1 conditional knockout mice (cKO) compared with age-matched controls, and immunohistochemistry showed significantly increased FGF23 protein in the cKO bones [29]. Further evaluations about this should be conducted in future. A third limitation is that lack of venous sampling has not completely ruled out the possibility of the presence of other tumors. A fourth limitation is that the possibility of genetic hypophosphatemic rickets could not be excluded in this case.

In conclusion, we reported a first rare case of NF1 associated with hypophosphatemic osteomalacia, in which a high serum FGF23 level was confirmed.

Abbreviations

C_T: Threshold cycle; L2–4: Second to fourth lumbar vertebrae; NF1: Neurofibromatosis type 1; NFomas: Neurofibromas; FGF: Fibroblast growth factor; FGF23: Fibroblast growth factor 23; *NF1*: Neurofibromatosis type 1 tumor suppressor gene; TIO: Tumor-induced osteomalacia; 25(OH)D_3: 25-hydroxyvitamin D_3; 1α25$(OH)_2D_3$: 1α25-dihydroxyvitamin D_3; IP: Inorganic phosphorus; TmP/GFR: Maximum transport of phosphorus in the renal proximal tubules; ALP: Alkaline phosphatase; PTH: Parathyroid hormone; BAP: Bone-specific alkaline phosphatase; TRACP 5b: Tartrate-resistant acid phosphatase 5b; ucOC: Undercarboxylated osteocalcin; BMD: Bone mineral density; YAM: Young adult mean; MDPB: Methylene diphosphonate bone; Octreoscan: ^{111}indium-pentetreotide scintigraphy; RT-PCR: Real-time polymerase chain reaction; *ACTB*: Actin β gene; *FGF23*: Fibroblast growth factor 23 gene; SSTRs: Somatostatin receptors; cKO: Conditional knockout mice

Acknowledgements

We wish to thank GenoStaff Co., Ltd., Tokyo, Japan, for the immunohistochemical staining, and GeneticLab Co., Ltd., Sapporo, Japan, for gene expression analysis by RT-PCR. We also thank the patient for her permission to publish this manuscript. Furthermore, we thank medical editing services on Forte, Inc.

Authors' contributions

TO, NK, and AT attended to the patient; TO and NK wrote the manuscript; TO, NK, AT, KO, and YN gave conceptual advice. NK supervised management of the case and contributed to writing and editing the manuscript. All authors have read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Both the removal of the neurofibromas and the immunohistochemical examinations on the excised tissue were approved by the clinical ethical review committee of Kagoshima Medical Center (Authorization number 17010, December 28, 2017). The patient gave written informed consent for the surgical procedure and subsequent evaluation of the tissue.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

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Received: 21 January 2020 Accepted: 25 March 2020
Published online: 09 May 2020

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Publisher's Note

Arch Clin Med Case Rep 2020; 4 (4): 699-706 *DOI: 10.26502/acmcr.96550253*

Case Report

Japanese Adult-Onset Type 1 Diabetic Sisters with Different Disease States: A Case Report

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Received: 14 June 2020; **Accepted:** 01 July 2020; **Published:** 15 July 2020

Abstract

We encountered type 1 diabetic sisters with different islet-associated antibodies and pancreatic β-cell injury rates. The younger sister had different disease susceptibility human leukocyte antigen (HLA) haplotypes (DRB1*0901-DQB1*0303/DRB1*0802-DQB1*0302) on both chromosomes, while the older sister showed a disease susceptibility HLA haplotype (DRB1*0901-DQB1*0303/-) on one chromosome. Furthermore, the younger sister was positive for anti-glutamic acid decarboxylase antibody (GADA), anti-insulinoma-associated protein-2 antibody (IA-2A), and zinc transporter 8 antibody (ZnT8A), and showed depleted endogenous insulin secretory ability at the time of diagnosis. On the other hand, the older sister was positive only for GADA and ZnT8A, and the ability to secrete endogenous insulin was relatively retained at onset. From our cases and existing reports, we verified that: 1) having a HLA haplotype for disease susceptibility on both chromosomes; 2) having HLA-DQ8 and HLA-A24, -DQA1*03 and -DR9; 3) having more islet autoantibodies including IA-2A and ZnT8A may be involved in accelerating the progression of type 1 diabetes by enhancing the damage to pancreatic β-cells.

Keywords: Type 1 diabetes mellitus; Human leukocyte antigen; Anti-glutamic acid decarboxylase antibody; Anti-insulinoma-associated antigen 2 antibody; Autoantibody to zinc transporter-8

1. Case Report

Type 1 diabetes is caused by a pancreatic β cell-specific mechanism of autoimmune destruction based on the actions of both genetic factors constructed by multiple candidate genes (disease susceptibility genes) and environmental factors [1]. This multifactorial disease usually leads to absolute insulin deficiency [2]. The disease susceptibility gene most strongly involved in type 1 diabetes has been shown to be human leukocyte antigen (HLA) [3]. HLA has class I molecules resulting from A, B and C genes, which mainly present as endogenous antigens to cytotoxic T cells and function as restraining factors in the final stage of immune response, and class Ⅱ molecules resulting from DR, DQ and DP genes, which mainly present foreign antigens to helper T cells and function as restraining factors in the initiation stage of immune response. In particular, class II DR and DQ genes are strongly associated with type 1 diabetes, and DR4 and DR9 are important in serological typing. Haplotypes DRB1* 0405-DQB1* 0401, DRB1* 0802-DQB1* 0302 and DRB1* 0901-DQB1* 0303 in DNA typing have been reported as disease susceptibility types in Japanese populations [4].

On the other hand, the prevalence of siblings among Japanese individuals with type 1 diabetes is reportedly 1–4%, clearly higher than the prevalence of type 1 diabetes in the general population (0.01–0.02%) [5]. This pathology has thus been shown to accumulate in families, but case reports related to this issue remain rare [6-8]. Here, we encountered Japanese type 1 diabetic sisters with different islet-associated antibodies and pancreatic β-cell injury rates. Focusing on the relationship between HLA and islet autoantibodies, we compared and verified the pathological conditions based on existing reports.

2. Case Report

The younger sister became aware of thirst, polydipsia, and polyuria at 24 years old, with an associated weight loss of 4 kg/month. She had a preceding history of drinking a large amount of soft drink. She visited a family doctor, where hyperglycemia was confirmed (hemoglobin (Hb)A1c, 14.3%). No ketoacidosis was observed. No contributory medical or family history was elicited, and there was no history of obesity. She lived with her mother, her sister, her sister's husband and their daughter. Height was 152.6 cm, weight was 54.2 kg, body mass index (BMI) was 23.3 kg/m^2, blood pressure was 109/61 mmHg and heart rate was 75 beats/min. No other physical abnormalities or complications were identified. Fasting blood C-peptide immunoreactivity (CPR) was 0.15 ng/mL, CPR index (CPI) was 0.2, and 24-h urinary (24-h UCPR) was 22 μg/day at the time of onset, revealing that endogenous insulin secretory capacity was almost depleted (Table 1). Islet autoantibody titers were 791.6 U/mL for anti-glutamic acid decarboxylase antibody (GADA), 6.2 U/mL for anti-insulinoma-associated protein-2 antibody (IA-2A), and 406 U/mL for zinc transporter 8 antibody (ZnT8A), and negative results were obtained for islet cell antibody (ICA) (Table 1). Regarding thyroid-related antibodies, anti-thyroglobulin antibody (TgA) showed a normal value of 19 U/mL and anti-thyroperoxidase antibody (TPOA) showed a slightly high value of 17 U/mL (Table 1). HLA displayed A24 and both disease-susceptible haplotypes DRB1* 0901-DQB1* 0303 and DRB1* 0802-DQB1* 0302 (Table 2) [4]. The patient was treated with 24 units/day of insulin aspart and 14 units/day of glargine U300.

At 29 years old (2 years after the onset of the younger sister), the older sister became aware of thirst and malaise, accompanied by weight loss of 5 kg/month. She visited a family doctor, who confirmed hyperglycemia (HbA1c, 9.6%). No ketoacidosis was observed. At the same time, vulvar and vaginal candidiasis was identified. The patient had a history of obesity (up to 81 kg at 24 years old) and had given birth by Caesarean section, although the baby was not abnormally large. She smoked 10 cigarettes/day. Height was 161.5 cm, weight was 64.9 kg, BMI was 24.9 kg/m^2, blood pressure was 110/65 mmHg and heart rate was 76 beats/min. Similar to her younger sister, no other physical abnormalities or complications were apparent. Fasting blood CPR was 1.06 ng/mL, CPI was 0.8, and 24-h UCPR was 37.5 μg/day at the time of onset, revealing that endogenous insulin secretory capacity remained present (Table 1). Islet autoantibody titers were 81.2 U/mL for GADA, < 0.6 U/mL for IA-2A, and 509 U/mL for ZnT8A, with negative results for ICA (Table 1). Both TgA and TPOA showed high values of 297 U/mL and 26 U/mL, respectively (Table 1). HLA showed A24 and disease-susceptible haplotypes DRB1* 0901-DQB1* 0303 [4] (Table 2). She was treated with insulin lispro at 8 units/day and glargine U100 at 9 units/day.

Insulin auto-antibody did not evaluate because it could not collect blood samples before using insulin.

	Younger sister	**Older sister**	**Reference value**
Age at onset (years)	**24**	**29**	
Sex	**Female**	**Female**	
GADA (U/mL)	791.6	81.2	< 5.0
IA-2A (U/mL)	6.2	< 0.6	< 0.6
ICA (JDF units)	negative	negative	negative
ZnT8A (U/mL)	406	509	< 15.0
TgA (U/mL)	19	297	< 28.0
TPOA (U/mL)	17	26	< 16.0
HbA1c at onset (%)	14.3	9.6	4.9-6.0
Fasting CPR at onset (ng/mL)	0.15	1.06	0.61-2.09
Fasting CPI at onset	0.2	0.8	-
24-h UCPR at onset (μg/day)	22	37.5	29.2-167.0

GADA, anti-glutamic acid decarboxylase antibody; IA-2A, anti-anti-insulinoma-associated protein-2 antibody; ICA, islet cell antibody; ZnT8A, zinc transporter 8 antibody; TgA, anti-thyroglobulin antibody; TPOA, anti-thyroperoxidase antibody; CPR, C-peptide immunoreactivity; CPI, CPR index; 24-h UCPR, 24-h urinary CPR. GADA, IA2A and ZnT8 were measured by enzyme-linked immunosorbent assay. ICA was measured by indirect method with immunofluorescent antibody. TgA and TPOA were measured by electrochemiluminscence immunoassay.

Table 1: Laboratory findings.

	Younger sister	**Older sister**
HLA-A	24:02/26:01	24:02/26:01
	A24/A26	A24/A26
HLA-B	35:01/39:01	39:01/40:06
	B35/B3901	B3901/B61
	Bw6/-	Bw6/-
HLA-C	03:03/07:02	07:02/08:01
	Cw9/Cw7	Cw7/Cw8
HLA-DRB1	08:02/09:01	09:01/-
	DR8/DR9	DR9/-
HLA-DRB3/4/5	4*01:03:02	4*01:03:02
	DR53/-	DR53/-
HLA-DQA1	03:01/03:02	03:02/-
	DQ8/DQ9	DQ9/-
HLA-DQB1	03:02/03:03	03:03/-
	DQ8/DQ9	DQ9/-
HLA-DPA1	02:02/-	01:03/02:02
HLA-DPB1	05:01/-	03:01/05:01
Haplotype	DRB1*0802-DQB1*0302 DRB1*0901-DQB1*0303	DRB1*0901-DQB1*0303

HLA, human leukocyte antigen

Table 2: HLA genotyping.

3. Discussion

The younger sister displayed different disease susceptibility HLA haplotypes (DRB1*0901-DQB1*0303/DRB1*0802-DQB1*0302) on both chromosomes, while the older sister had a disease susceptibility HLA haplotype (DRB1*0901-DQB1*0303/-) on one chromosome (Table 2). Furthermore, the younger sister was positive for GADA, IA-2A and ZnT8A, and endogenous insulin secretory capacity was depleted at the time of onset (Table 1). On the other hand, the older sister was positive only for GADA and ZnT8A, and the ability to secrete endogenous insulin at the onset remained relatively intact (Table 1).

3.1 HLA and endogenous insulin secretory capacity

Three subtypes of type 1 diabetes are known: acute onset; slowly progressive; and fulminant [9]. In addition, acute onset type 1 diabetes develops when the disease-susceptible HLA haplotype is present on both chromosomes, while slowly progressive type 1 diabetes can develop with the involvement of only one chromosome. That is, the HLA types of both subtypes are reported to be quantitatively different [10]. The younger sister, who had disease-susceptible HLA haplotypes on both chromosomes, had already been depleted of endogenous insulin secretory capacity by the time of onset (Tables 1, 2), suggesting a relatively rapid β-cell injury type. On the other hand, the

older sister, who had a disease-sensitive HLA haplotype on only one chromosome (Table 2), was considered to show a relatively slow type of β-cell injury, because the ability to secrete endogenous insulin was still present at onset (Table 1). However, Nakanishi et al. reported that HLA-A24, -DQA1*03, and -DR9 are involved in acute onset and early complete destruction of pancreatic β-cells [11], and both sisters showed these (Table 2), and the residual endogenous insulin secretory capacity of the older sister is considered likely to become depleted relatively early. On the other hand, HLA-A24 has also been reported to be associated with accelerated disease progression of type 1 diabetes, limited to relatives with HLA-DQ8 and positive results for anti-IA-2 antibody or ZnT8 antibody [12]. The lack of HLA-DQ8 in the older sister (Table 2) may be one factor contributing to the retention of endogenous insulin secretion compared to the younger sister.

3.2 Islet-associated autoantibodies and endogenous insulin secretory capacity

In the younger sister, islet autoantibodies were all positive except for ICA (Table 1). The frequency of positive results for the four types of islet autoantibodies has been shown to be significantly lower in adult-onset disease compared to the childhood-onset version [13]. Pancreatic beta-cell damage has also been reported to be more likely to progress in patients with multiple islet antibodies (GADA, IA-2A, and ZnT8A) [14]. This was considered to be one of the reasons why the younger sister showed greater pancreatic β-cytotoxicity than the older sister, who was positive for the two types of islet autoantibodies (Table 1). In addition, Yasui et al. have reported that GADA ≥28.0 U/mL (sensitivity 88.2%, specificity 91.7%), age at onset of diabetes <47 years (sensitivity 60.3%, specificity 78.0%), diabetes period <5 years until a GADA-positive finding (sensitivity 65.1%, specificity 67.1%), or fasting serum CPR <0.65 ng/ml (sensitivity 61.4%, specificity 97.6%) predict the need for insulin treatment in diabetic patients who were positive for GADA and had autoimmune thyroid disease [15]. The younger sister met all these conditions, while the older sister met the conditions other than those related to fasting serum CPR (Table 1), and both required insulin treatment. On the other hand, in addition to GADA titer, age of onset, disease duration and fasting serum CPR value, Tanaka et al. reported that a low BMI and positive ICA (IA-2A was detected as positive in analysis excluding ICA) is a risk factor for progression to an insulin-dependent state [16]. We speculated that the fact that only the younger sister showed IA-2A (Table 1) might have also influenced the difference in residual insulin secretory level between the younger and older sisters. Furthermore, in Japanese populations, ZnT8A has been shown to be present in 28% at the time of onset of type 1 diabetes [17], reportedly reflecting progression of the disease before and after diagnosis [18]. Since both sisters had ZnT8A (Table 1), the older sister appears likely to go through a progressive deterioration in the future. ZnT8A has also been reported as a marker leading to diabetic ketoacidosis at the onset of type 1 diabetes [19], but neither sister exhibited acidosis at onset.

A key limitation in this case report was that it was difficult to perform further detailed examinations and consideration, because HLA typing of family members other than the sisters had not been performed and no searches had been conducted for type 1 diabetes susceptibility genes other than HLA [20].

4. Conclusion

We experienced the Japanese cases of two sisters with type 1 diabetes. From our cases and existing reports, we reconfirmed that: 1) presence of HLA haplotypes for disease susceptibility on both chromosomes; 2) presence of HLA-DQ8 and HLA-A24, -DQA1*03 and -DR9; 3) higher titers of islet autoantibodies including IA-2A and ZnT8A may be involved in accelerating the progression of type 1 diabetes by enhancing the damage to pancreatic β-cells. In Japanese acute-onset type 1 diabetes that does not meet the above three conditions, protection of residual pancreatic β-cells by achieving more stringent glycemic control from the early stages of the onset may be able to maintain the honeymoon period longer.

Acknowledgments

We wish to thank HLA Laboratory, Kyoto, Japan, for the HLA genotyping, and SRL, Inc, Tokyo, Japan, for measurements of islet-related antibodies by Enzyme-linked immunosorbent assay, *Radioimmunoassay* or indirect methods with immunofluorescent antibody, and for measurements of TgA and TPOA by Electro chemiluminescence immunoassay. We also thank the patients for their permission to publish this manuscript. Furthermore, we acknowledge the medical editing services of Forte, Inc.

Compliance with Ethical Standards

Disclosure statement

There is nothing to disclose.

Human rights statement and informed consent

All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki of 1964 and later versions.

Consent for publication

Informed consent was obtained from the patients for publication of this case report.

Conflicts of interest

Yoshihiko Nishio has received honoraria for scientific lectures from Eli Lilly, Novo Nordisk Pharma and Sanofi, and a scholarship donation from Novo Nordisk Pharma. Koshi Kusumoto, Nobuyuki Koriyama, Nami Kojima and Maki Ikeda have nothing to disclose.

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Citation: Koshi Kusumoto, Nobuyuki Koriyama, Nami Kojima, Maki Ikeda, Yoshihiko Nishio. Japanese Adult-Onset Type 1 Diabetic Sisters with Different Disease States: A Case Report. Archives of Clinical and Medical Case Reports 4 (2020): 699-706.

Basal insulin ameliorates post-breakfast hyperglycemia via suppression of post-breakfast proinsulin/C-peptide ratio and fasting serum free fatty acid levels in patients with type 2 diabetes

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Diabetology International

ISSN 2190-1678
Volume 12
Number 2

Diabetol Int (2021) 12:161-170
DOI 10.1007/s13340-020-00457-3

Springer

Diabetology International (2021) 12:161–170
https://doi.org/10.1007/s13340-020-00457-3

ORIGINAL ARTICLE

Basal insulin ameliorates post-breakfast hyperglycemia via suppression of post-breakfast proinsulin/C-peptide ratio and fasting serum free fatty acid levels in patients with type 2 diabetes

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Received: 29 May 2020 / Accepted: 27 July 2020 / Published online: 3 August 2020

Abstract

Background In general, basal insulin targets fasting plasma glucose (FPG) levels, and prandial insulin targets postprandial glucose (PPG) levels. However, the effects of basal insulin on PPG levels are controversial. We investigated the effect of basal insulin on postprandial hyperglycemia using a test meal at breakfast as well as compared differences between degludec and glargine.

Methods A total of 20 participants with type 2 diabetes were randomly assigned to degludec ($n=10$) or glargine ($n=10$). We initiated basal–bolus insulin therapy and titrated only basal insulin until FPG was < 6.1 mmol/L. We evaluated changes in post-breakfast glucose levels and changes in clinical parameters such as serum C-peptide (CPR), proinsulin (PI), and free fatty acids (FFA) levels between the pre- and post-titration periods. Differences between degludec and glargine in the post-titration period were also evaluated.

Results Post-breakfast glucose levels significantly decreased by 46.1% in the post-titration period compared with the pre-titration period ($n=20$, $p<0.001$). These decreases correlated positively with decreases in the post-breakfast PI/CPR ratio ($r=0.692$, $p<0.001$) and in fasting FFA levels ($r=0.720$, $p<0.001$). There were no significant differences in post-breakfast glucose levels between degludec and glargine. However, the hypoglycemic rate with degludec was significantly lower than with glargine.

Conclusion Our results suggest that basal insulin with either degludec or glargine decreases the incidence of post-breakfast hyperglycemia accompanied by decreasing the post-breakfast PI/CPR ratio and fasting FFA levels in patients with type 2 diabetes.

Keywords Basal insulin · Postprandial hyperglycemia · Glucose spike · Proinsulin · Free fatty acid · Degludec

Introduction

Insulin analogs, such as degludec and glargine, are classified as long-acting insulins and are used as basal insulins to control fasting plasma glucose (FPG) levels. These analogs are often used for glycemic control in patients with type 2 diabetes, because they can be easily combined with oral anti-diabetic agents (OADs) to improve hemoglobin A1c (HbA1c) levels. In particular, when HbA1c levels are ≥ 8%, basal insulin is very important because it can effectively reduce HbA1c levels by decreasing FPG levels, which contribute more to HbA1c levels than postprandial plasma glucose (PPG) levels [1, 2]. Although the impact of PPG on HbA1c is comparatively less than that of FPG, PPG is a residual contributor of elevated HbA1c levels at lower ranges (close to 7%). Therefore, if an HbA1c level is still

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13340-020-00457-3) contains supplementary material, which is available to authorized users.

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above target despite adequate FPG levels, a basal–bolus regimen is recommended [3].

Subcutaneous long-acting insulin analogs are slowly absorbed and maintain constant insulin levels in serum and decrease FPG levels via suppression of hepatic glucose production [4, 5]. Subcutaneous rapid-acting insulin analogs are rapidly absorbed, resulting in transient hyperinsulinemia and decreasing PPG levels via an increase in peripheral glucose uptake and a reduction of hepatic glucose production [6]. Based on these mechanisms, basal insulin may have few effects on PPG levels. The effects of basal insulin on PPG levels, however, are controversial. Janka et al. reported that the decreases in PPG levels were the same as those in FPG levels after titration of basal insulin [7]. Conversely, Philis-Tsimikas et al. showed a greater effect on PPG levels than FPG levels after basal insulin treatment [8].

Several long-acting insulin analogs have been developed to reproduce the physiological action of basal insulin. The duration of action of each long-acting insulin differs. Degludec has a flat, stable profile and a duration of action longer than 42 h [9]. Glargine has a shorter duration of action (20.5 h) than degludec [10]. Profiles of mean 24-h glucose infusion rates in a euglycemic glucose clamp study were flatter and more stable with degludec versus glargine [11]. These differences between degludec and glargine may influence differences in the effect of basal insulin on PPG levels.

In this study, we investigated 1) the effects of basal insulin on postprandial hyperglycemia, and 2) differences of the effect on postprandial hyperglycemia between degludec and glargine in patients with type 2 diabetes. In particular, we focused on PPG levels after breakfast, because post-breakfast hyperglycemia has been shown to worsen the progression of type 2 diabetes [12].

Research design and methods

Participants

Patients with type 2 diabetes who had been admitted to Kagoshima Medical Center for the treatment of hyperglycemia were enrolled. Recruitment ended when 20 participants completed the study. The inclusion criteria were (1) patients with type 2 diabetes who were hospitalized for diabetes education, (2) age 20–80 years, (3) current treatment consisting of only of lifestyle modifications or OADs, and (4) FPG < 11.1 mmol/L. Exclusion criteria were patients who were admitted for preoperative glycemic control, specific comorbidities including severe hyperglycemia (FPG ≥ 11.1 mmol/L), advanced diabetic neuropathy, unstable retinopathy, cardiovascular event within the last 3 months, renal failure (estimated glomerular filtration rate < 30 mL/min/1.73 m^2), infections, cancer, or pregnancy. We also excluded patients who had received insulin or glucagon-like peptide-1 (GLP-1) analogs in these past 3 months.

The Ethics Committee at Kagoshima Medical Center approved this study (approval number, 27-6, 2015/5/7), and the protocol was registered in UMIN-CTR (UMIN000017637). All patients provided written informed consent.

Study design

This study was open-label, single-center, comparative, interventional, prospective study. Participants were newly treated with basal–bolus insulin therapy and were not taking OADs. We randomly assigned participants to degludec ($n = 10$) or glargine ($n = 10$).

Figure 1 shows the study design. The study consisted of the following 3 periods: (1) pre-titration period, (2) titration period, and (3) post-titration period. The pre-titration period was from the day of admission to the day before starting titration of basal insulin. On day 1 of admission, participants started degludec (Tresiba® FlexTouch, Novo Nordisk A/S, Bagsvaerd, Denmark) or glargine (Lantus SoloSTAR®, Sanofi S.A., Paris, France) at a dose of 0.1 units/kg/day as basal insulin once a day before dinner, and started lispro (Humalog® Injection, Eli Lilly K.K., Indianapolis, IN, USA) at a dose of 0.2 units/kg/day (divided into 3 doses to cover each meal) as prandial insulin 3 times a day before each meal (08:00 am, 12:00 pm, and 06:00 pm). These starting doses of basal and prandial insulin were determined based on previous reports; basal insulin doses were recommended to start at 0.1–0.2 units/kg/day [3], and total daily doses of bolus insulin were reported to be about 2 times of basal insulin doses in Japanese subjects with type 2 diabetes treated with basal–bolus insulin therapy [13]. On day 2 of admission, continuous glucose monitoring (CGM) was initiated in the morning and continued for 4 days using iPro2 (Medtronic PLC., Dublin, Ireland). While monitoring glycemic variability with CGM, post-breakfast glucose levels were evaluated as incremental areas under the curve of post-breakfast interstitial glucose values (iAUC-B) determined by CGM between 08:00 am and 12:00 pm according to the trapezoidal rule. Post-lunch and -dinner glucose levels for 4 h (12:00 pm to 04:00 pm, iAUC-lunch [L]; and 06:00 pm to 10:00 pm, iAUC-dinner [D], respectively) were also monitored. All iAUC values were obtained 3 times per day for 4 days, and they were averaged. CGM data were used if data were obtained more than 80% of the time, and missing glucose values were calculated based on values before and after the missing glucose values. On day 3 of CGM, blood samples were collected at 08:00 and 10:00 am, and urine samples were collected for 24 h (details are provided under "Laboratory measurements"). Among patients who had been taking OADs, and who stopped these drugs on day

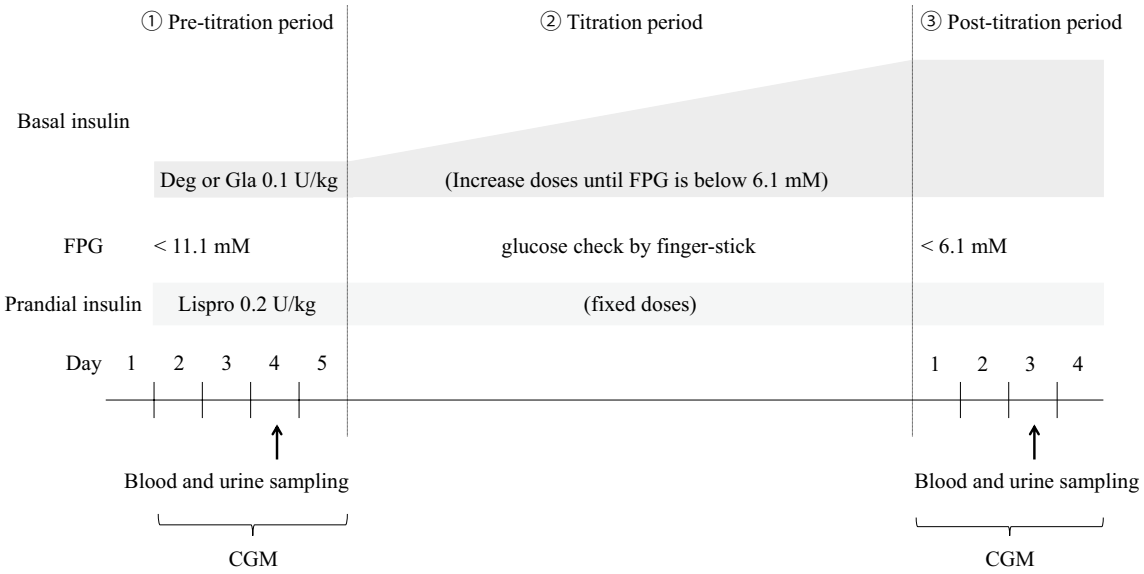

Fig. 1 Schema of study design. Basal insulin was titrated during the titration period until FPG was < 6.1 mM. We evaluated differences in postprandial hyperglycemia and clinical parameters between the pre- and post-titration periods. Prandial insulin was fixed throughout the study. *Deg* degludec, *Gla* glargine, *U* unit, *CGM* continuous glucose monitoring, *FPG* fasting plasma glucose

1 of admission, the initiation of CGM was delayed to day 3 of admission. Subsequent examinations were also delayed by 1 day.

The titration period was from the day of finishing CGM (day 5) to the day of achieving target FPG levels. After collecting CGM data, basal insulin was increased by 2–4 units every 2 days until FPG reached the target range of < 6.1 mmol/L. Prandial insulin (lispro) was maintained at initial doses throughout the study.

The post-titration period was from the day of achieving target FPG level to the day of finishing CGM. After FPG was < 6.1 mmol/L, basal insulin titration was stopped at the final dose. CGM was initiated again to evaluate PPG levels for 4 more days. Mean glucose values, standard deviation (SD) of glucoses levels, and hypoglycemic rate were evaluated using CGM data. Hypoglycemia was defined glucose levels < 3.9 mmol/L, and the hypoglycemic rate was calculated as the total number of hypoglycemic episodes divided by the total number of glycemic measurements with CGM. On day 3 of the post-titration period, blood and urine samples were collected again. After collecting CGM data, the study was completed.

Throughout all periods, capillary blood glucose levels were measured 6 times per day (before and 2 h after every meal) with test strips and a glucometer (Medisafe Fit, Termo Co., Tokyo, Japan). CGM was calibrated with capillary blood glucose levels before every meal, and its accuracy was evaluated by mean absolute relative difference (MARD) between CGM glucose levels and capillary blood glucose levels before and 2 h after every meal [14, 15]. At breakfast, all participants consumed our institute-specific test meal that consisted of 2 pieces of bread, a single-serve jam pack, yogurt, and a boiled egg. The total caloric content of our test meal was 466 kcal (carbohydrates 62%, fat 18%, protein 15%, and others 5%). At lunch and dinner, participants consumed our ordinary hospital meals. Total daily intake, including the test meal, was set based on the ideal body weight (BW) multiplied by 28.

Laboratory measurements

On day 3 of CGM during the pre- and post-titration periods, clinical parameters such as FPG, fasting serum C-peptide (fasting CPR), pro-insulin (fasting PI), fasting PI/CPR ratio, free fatty acid (FFA), high-sensitivity tumor necrosis factor α (hsTNFα), interleukin 6 (IL-6), high-sensitivity C-reactive protein (hsCRP), and high molecular weight adiponectin (HMWA) levels, which are thought to reflect β-cell function or insulin resistance, were measured as predictors of ⊿iAUC-B. Plasma glucose and serum CPR, PI levels, and PI/CPR ratio were also measured 2 h after breakfast, and are reported as 2 h-PPG, 2 h-CPR, 2 h-PI, and 2 h-PI/CPR ratio, respectively. Changes in CPR and PI between fasting and postprandial conditions are reported as incremental CPR and PI. On the same day, 24-h urine CPR (uCPR) was measured. These parameters were analyzed by SRL Inc. (Tokyo, Japan).

Changes in BW, FPG, fasting CPR, 2 h-CPR, incremental CPR, fasting PI, 2 h-CPR, incremental PI, fasting PI/CPR ratio, 2 h-PI/CPR ratio, FFA, hsTNFα, IL-6, hsCRP,

HMWA, and uCPR between pre- and post-titration periods are reported as ⊿BW, ⊿FPG, ⊿fasting CPR, ⊿2 h-CPR, ⊿incremental CPR, ⊿2 h-CPR, ⊿incremental PI, ⊿fasting PI/CPR ratio, ⊿2 h-PI/CPR ratio, ⊿FFA, ⊿hsTNFα, ⊿IL-6, ⊿hsCRP, ⊿HMWA, and ⊿uCPR, respectively.

Trial endpoints

The primary endpoint of this study was assessment of the effect of basal insulin on post-breakfast glucose levels. It was evaluated by changes in post-breakfast glucose levels between the pre- and post-titration period, which was reported as ⊿iAUC-B. We also assessed the relationship between clinical parameters and post-breakfast glucose levels as exploratory endpoints. It was evaluated based on correlations between changes in clinical parameters and ⊿iAUC-B, and assessed using multivariate linear regression analysis.

Differences of the effect on post-breakfast glucose levels between degludec and glargine were the secondary endpoint, which was evaluated by differences in ⊿iAUC-B. To clarify the clinical impacts between groups, differences between degludec and glargine in mean glucose values, SD of glucose levels, and hypoglycemic rates in the post-titration period were also assessed.

Statistical analysis

Data are expressed as means (SD) if normally distributed or as medians with 25th and 75th percentile (interquartile range [IQR]) if not normally distributed. The paired t test or Wilcoxon signed-rank test was used to determine differences in PPG levels (iAUC) and clinical parameters between the pre- and post-titration period, and Student's t test or Mann–Whitney U test was used to determine differences between degludec and glargine, and the difference in iAUC-B between non-hypoglycemia and hypoglycemia group. Microvascular complications and OADs at baseline were analyzed using Fisher's exact test. Univariate regression analysis using Pearson's correlation coefficient was performed to assess statistical associations between ⊿iAUC-B and differences in clinical parameters, such as ⊿BW, ⊿FPG, ⊿fasting CPR, ⊿2 h-CPR, ⊿incremental CPR, ⊿fasting PI, ⊿2 h-PI, ⊿incremental PI, ⊿fasting PI/CPR ratio, ⊿2 h-PI/CPR ratio, ⊿FFA, ⊿hsTNFα, ⊿IL-6, ⊿hsCRP, ⊿HMWA, and ⊿uCPR. Stepwise multiple regression analysis was also conducted to identify clinical factors independently correlated with ⊿iAUC-B. The level of statistical significance was set at $p < 0.05$. All statistical analyses were performed with the Statistical Software R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Participants' characteristics

Between May 2015 and March 2017, 26 patients with type 2 diabetes mellitus were recruited. Of these, 6 participants were excluded for following reasons: 3 due to failure in collecting CGM data, 2 due to excessive FPG (≥ 11.1 mmol/L) in the pre-titration period, and 1 due to withdrawal of consent.

Table 1 shows baseline characteristics of subjects. Eight participants (40%) were women. The mean age was 63.7 years (SD 6.3). The median BW and mean body mass index (BMI) was 61.8 kg (IQR 55.2–73.4) and 24.7 kg/m^2 (SD 4.0), respectively. The median duration of diabetes was 5.0 years (IQR 2.0–11.3), and mean HbA1c was 10.6% (SD 1.7). The mean hospital stay was 22.9 days (SD 3.0). Nine patients (45%) took OADs. There were no significant differences in any participant characteristics between the degludec and glargine groups.

The effect of basal insulin on post-breakfast glucose levels

Figure 2 shows incremental PPG levels and iAUC with CGM in the pre- and post-titration periods after meals in all patients ($n = 20$). In the post-titration period, mean iAUC-B significantly decreased from 213.2 mmol h/L (SD 73.7) to 114.9 mmol h/L (SD 60.4) ($p < 0.001$), whereas mean iAUC-L and iAUC-D did not change between the pre- and post-titration periods ($p = 0.1327$ and $p = 0.3408$, respectively). Mean iAUC-B was reduced by 46.1%.

For clinical parameters, CPR and PI levels significantly decreased in the post-titration period compared with the pre-titration period (Table 2); median fasting CPR, from 1.1 ng/mL (IQR 0.8–1.8) to 0.5 ng/mL (IQR 0.3–1.0) ($p = 0.008$); median 2 h-CPR, from 3.0 ng/mL (IQR 1.9–4.0) to 2.3 ng/mL (IQR 1.6–3.4) ($p = 0.047$); median fasting PI, from 12.7 pmol/L (IQR 6.9–19.6) to 4.6 pmol/L (IQR 3.1–10.4) ($p = 0.004$); median 2 h-PI, from 47.4 pmol/L (IQR 29.2–60.7) to 28.5 pmol/L (IQR 14.9–35.0) ($p < 0.001$); and median incremental PI, from 30.3 pmol/L (IQR 16.2–45.8) to 21.5 pmol/L (IQR 10.8–27.3) ($p < 0.001$). As a result, although median fasting PI/CPR did not significantly change ($p = 0.698$), mean 2 h-PI/CPR ratio significantly decreased from 15.2 (SD 3.0) to 11.2 (SD 3.2) ($p < 0.001$). Mean FFA levels also significantly decreased from 457.3 μmol/L (SD 174.0) to 249.2 μmol/L (SD 97.3) ($p < 0.001$, Table 2). Mean FFA levels were reduced by 45.5%.

Throughout the study, mean basal insulin doses significantly increased from 6.6 units (SD 1.3) to 18.8 units

Table 1 Baseline characteristics of the participants

Charastaristics	Total ($n=20$)	Degludec ($n=10$)	Glargine ($n=10$)	p
Age, mean (SD) years	63.7 (8.3)	62.9 (8.6)	64.5 (8.5)	0.680
Gender, *n* (%)				
Male	12 (60)	6 (60)	6 (60)	1.000
Female	8 (40)	4 (40)	4 (40)	1.000
BW, median (IQR) kg	61.8 (55.2–73.4)	62.6 (55.0–68.5)	61.7 (56.0–75.7)	0.739
BMI, mean (SD) kg/m^2	24.7 (4.0)	24.5 (4.7)	25.0 (3.4)	0.780
Duration of diabetes, median (IQR) years	5.0 (2.0–11.3)	7.5 (1.25–11.3)	4.5 (3.0–10.0)	0.685
HbA1c, mean (SD) %	10.6 (1.7)	10.7 (2.2)	10.6 (1.1)	0.950
Hospital stay, mean (SD) days	22.9 (3.0)	22.6 (3.5)	23.2 (2.6)	0.669
Microvascular complications				
Diabetic neuropathy, *n* (%)	9 (45)	4 (40)	5 (50)	1.000
Diabetic retinopathy, *n* (%)	4 (20)	2 (20)	2 (20)	1.000
Diabetic nephropathy, *n* (%)	6 (30)	3 (30)	3 (30)	1.000
Pre-admission antidiabetic medications, *n* (%)	9 (45)	4 (40)	5 (50)	1.000
Sulfonylurea	5 (25)	2 (20)	3 (30)	1.000
Metformin	9 (45)	4 (40)	5 (50)	1.000
Dipeptidyl peptidase-4 inhibitor	9 (45)	4 (40)	5 (50)	1.000
α-Glucosidase inhibitor	2 (10)	1 (10)	1 (10)	1.000

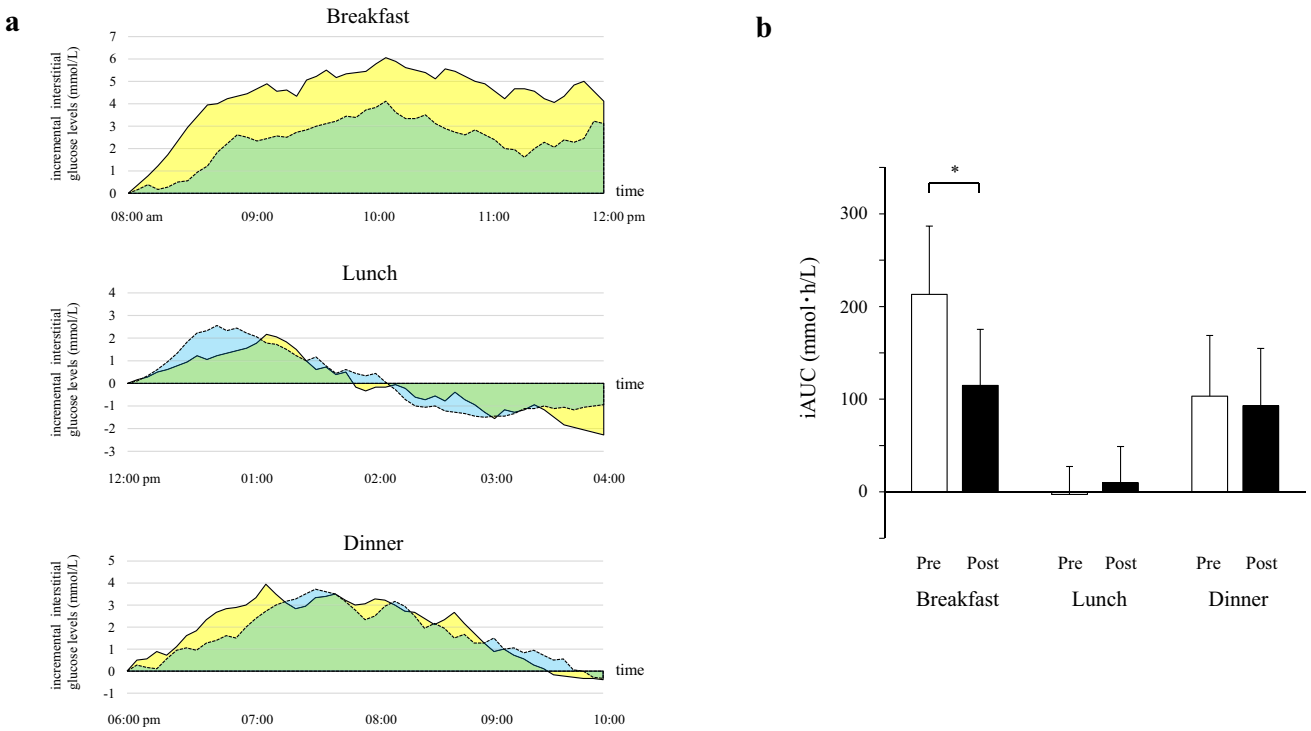

Fig. 2 Mean postprandial glucose levels in the pre- and post-titration periods after each meal in all patients ($n=20$). **a** Profiles of mean postprandial incremental interstitial glucose levels for 4 h by CGM after each meal in the pre- (solid line) and post-titration period (dashed line). Yellow and blue area represents the incremental areas under the curve of postprandial interstitial glucose values in the pre- and post-titration period, respectively. Green area is the overlap of yellow and blue area. **b** The incremental areas under the curve of postprandial interstitial glucose values for 4 h by CGM after each meal in the pre- (open bar) and post-titration period (closed bar). The error bars indicate standard deviation. *iAUC* incremental areas under the curve of postprandial interstitial glucose values for 4 h, *pre* pre-titration period, *post* post-titration period, *CGM* continuous glucose monitoring. *$p<0.001$; paired *t* test

Table 2 Changes in clinical parameters between the pre- and post-titration period ($n = 20$)

	Pre-titraion period	Post-titration period	p
Insulin doses, mean (SD) units	6.6 (1.3)	18.8 (6.4)	< 0.001
Insulin doses, mean (SD) units/kg	0.10 (0.01)	0.28 (0.07)	< 0.001
BW, median (IQR) kg	61.8 (55.2–75.4)	59.6 (55.9–73.3)	0.654
FPG, median (IQR) mmol/L	8.3 (8.1–9.1)	5.5 (5.3–5.9)	< 0.001
fasting CPR, median (IQR) ng/mL	1.1 (0.8–1.8)	0.5 (0.3–1.0)	0.008
2 h-CPR, median (IQR) ng/mL	3.0 (1.9–4.0)	2.3 (1.6–3.4)	0.047
incremental CPR, median (IQR) ng/mL	1.6 (1.0–2.6)	1.7 (1.0–2.7)	0.498
fasting PI, median (IQR) pmol/L	12.7 (6.9–19.6)	4.6 (3.1–10.4)	0.004
2 h-PI, median (IQR) pmol/L	47.4 (29.2–60.7)	28.5 (14.9–35.0)	< 0.001
incremental PI, median (IQR) pmol/L	30.3 (16.2–45.8)	21.5 (10.8–27.3)	< 0.001
fasting PI/CPR ratio, median (IQR)	10.4 (8.4–13.9)	10.2 (7.9–12.4)	0.698
2 h-PI/CPR ratio, mean (SD)	15.2 (3.0)	11.2 (3.2)	< 0.001
uCPR, median (IQR) μg/day	56.5 (33.8–91.5)	39.2 (21.5–74.7)	0.129
FFA, mean (SD) μmol/L	457.3 (174.0)	249.2 (97.3)	< 0.001
hsTNFα, mean (SD), pg/mL	1.6 (0.5)	1.4 (0.6)	0.056
IL-6, median (IQR), pg/mL	2.3 (1.7–2.6)	2.1 (2.0–2.6)	0.963
hsCRP, median (IQR) mg/dL	232.5 (116.8–504.5)	194.0 (133.5–479.0)	0.825
HMWA, median (IQR), μg/mL	3.8 (1.6–5.2)	3.0 (1.2–4.6)	0.474

HMWA high molecular weight adiponectin

(SD 18.8) ($p < 0.001$), and median FPG significantly decreased from 8.3 mmol/L (IQR 8.1–9.1) to 5.5 mmol/L (IQR 5.3–5.9), respectively ($p < 0.001$) (Table 2). The mean titration period was 9.1 days (SD 2.4). Median BW did not significantly change in spite of increasing basal insulin doses (from 61.8 to 59.6 kg, $p = 0.654$).

The total subjects of hypoglycemia were thirteen (degludec, 5; glargine, 8) in the post-titration period. Median hypoglycemic rate was 0.111% (IQR 0–0.722). The mean hypoglycemic levels were 3.8 mmol/L (SD 0.1) and the minimum was 3.3 mmol/L. Clinically significantly hypoglycemia (< 3.0 mmol/L) was not observed throughout the study. All hypoglycemia was observed only during the night (between 11:00 pm and 05:00 am). Subjects with hypoglycemia did not complain any symptoms associated with hypoglycemia, and did not receive any treatment such as reduction of basal insulin or ingestion of glucose. There was no difference in iAUC-B between non-hypoglycemia ($n = 7$) and hypoglycemia group ($n = 13$) in the post-titration period (mean, 132.1 vs. 105.7 mmol h/L; SD, 84.6 vs. 44.0, respectively, $p = 0.366$).

Total measurements of capillary blood glucose levels were 18 times per subjects in each period. The mean MARD between CGM glucose levels and these matched reference levels was 9.4% (SD 9.1%) and 10.5% (SD 9.7%) in the pre- and post-titration periods, respectively.

Correlation between changes in clinical parameters and changes in post-breakfast glucose levels

We examined the correlation between changes in each clinical parameter and changes in post-breakfast glucose levels (i.e., ⊿iAUC-B) in all patients ($n = 20$) and found that ⊿fasting PI/CPR ratio ($r = 0.449$, $p = 0.047$), ⊿2 h-PI/CPR ratio ($r = 0.692$, $p < 0.001$), and ⊿FFA ($r = 0.720$, $p < 0.001$) were significantly correlated with ⊿iAUC-B (Fig. 3). Other clinical parameters, including ⊿BW and ⊿FPG, were not significantly correlated with ⊿iAUC-B (Supplemental Table 1).

Stepwise multiple regression analysis of clinical parameters to assess contribution to post-breakfast glucose levels

To assess the contribution to changes in ⊿iAUC-B, we performed stepwise multiple regression analysis in all 20 patients using each clinical parameter. Results showed that ⊿2 h-PI/CPR ratio ($\beta = 0.501$, $p = 0.001$) and ⊿FFA ($\beta = 0.545$, $p < 0.001$) were significantly correlated with ⊿iAUC-B (Table 3). Multicollinearity among the independent variables was not notable, because the variance inflation factor was 1.139.

Differences of the effect on post-breakfast glucose levels between degludec and glargine

We compared degludec and glargine in the post-titration period. There were no significant differences between groups in ⊿iAUC-B in terms of glycemic control.

There were also no significant differences between groups in mean glucose values and SD of glucose levels. Only the hypoglycemic rate was significantly lower in the degludec group than in the glargine group (0.001% vs. 0.692%, $p=0.032$) in the post-titration period (Table 4).

The differences in the titration period and final insulin doses between degludec and glargine were not significant: titration period, 8.6 days (SD 2.6) vs. 9.5 days (SD 2.3) ($p=0.424$), respectively; and final insulin doses, 0.26 units/kg (SD 0.07) vs. 0.31 units/kg (SD 0.07) ($p=0.140$), respectively. There were no significant between-group differences in other clinical parameters including ⊿2 h-PI/CPR ratio and ⊿FFA (Supplemental Table 2).

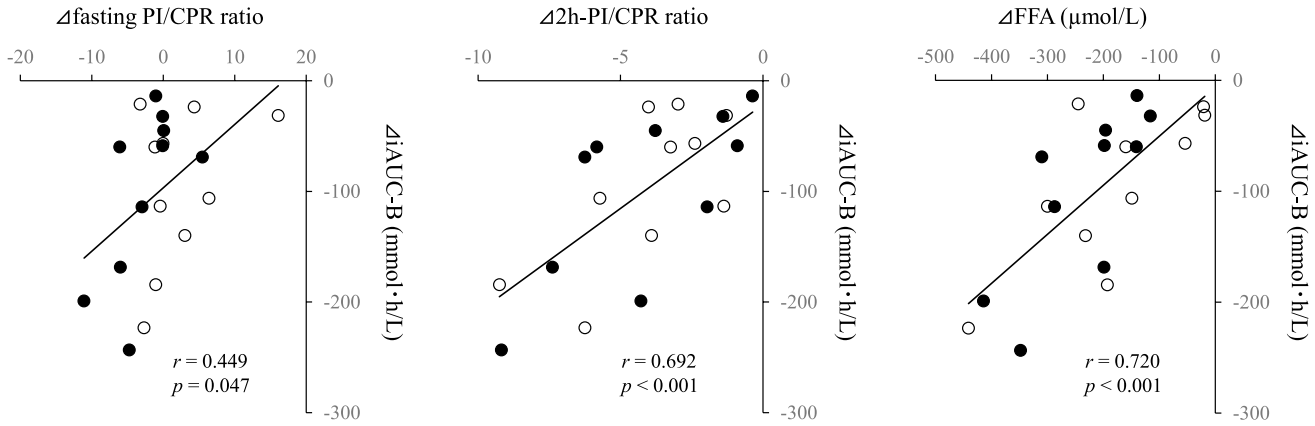

Fig. 3 Correlation between changes in clinical parameters and changes in post-breakfast glucose levels in all patients ($n=20$). White and black circles, degludec ($n=10$) and glargine ($n=10$) respectively. *iAUC-B*, incremental areas under the curve of post-breakfast interstitial glucose values for 4 h; ⊿, changes in values between pre- and post-titration period; *PI* proinsulin, *CPR* C-peptide, *FFA* free fatty acids

Table 3 Stepwise multiple regression analysis of the relationship between changes in clinical parameters and changes in post-breakfast glucose levels

Explanatory variable	B	SE	95%CI			β	*p*
⊿2 h-PI/CPR ratio	13.58	3.582	6.022	to	21.14	0.501	0.001
⊿FFA	0.335	0.081	0.164	to	0.506	0.545	< 0.001

SE standard error, *CI* confidence interval, *PI* proinsulin, *FFA* free fatty acid

Table 4 Comparisons between degludec and glargine

	Total ($n=20$)	Degludec ($n=10$)	Glargine ($n=10$)	*p*
⊿iAUC-B, mean (SD) mmol h/L	−98.2 (72.1)	−96.1 (70.1)	−100.4 (77.9)	0.897
mean glucose values, mean (SD) mmol/L	8.1 (1.4)	8.3 (1.5)	8.0 (1.4)	0.596
SD of glucose levels, mean (SD) mmol/L	2.3 (0.7)	2.2 (0.5)	2.4 (0.8)	0.457
Hypoglycemic rate, median (IQR) %	0.111 (0–0.722)	0.001 (0–0.114)	0.692 (0.064–1.628)	0.032

iAUC-B, incremental areas under the curve of post-breakfast interstitial glucose values for 4 h; ⊿, changes in values between pre- and post-titration period

p value was calculated by Mann–Whitney U test

Discussion

In the current study, we report that both degludec and glargine as basal insulins decreased PPG levels after breakfast in patients with type 2 diabetes. Linear regression analysis showed that decreases in 2 h-PI/CPR ratio and FFA levels were positively correlated with decreases in post-breakfast glucose levels. There were no significant differences in ⊿iAUC-B between degludec and glargine. The frequency of hypoglycemia during sleeping time was significantly lower with degludec than with glargine.

The pathogenesis of postprandial hyperglycemia in patients with type 2 diabetes is complicated by many contributing factors. According to a previous report, about one-third of orally administered glucose is taken up in the liver and about two-thirds in the skeletal muscle by postprandial insulin secretion. However, glucose uptake rates in the liver and skeletal muscle may be impaired up to 85% (liver 30%, skeletal muscle 55%), and postprandial glucose levels appear high in patients with type 2 diabetes, because insulin effects are attenuated by insulin resistance and β-cell dysfunction [16]. Thus, the effect of basal insulin on post-breakfast hyperglycemia in this study may be due to improved β-cell function or insulin sensitivity in the liver and skeletal muscle. In fact, stepwise multiple regression analysis showed that the improvement in 2 h-PI/CPR ratio and FFA levels correlated with the improvement of post-breakfast hyperglycemia. Therefore, we focused on the 2 h-PI/CPR ratio and FFA levels.

First, fasting PI levels reflect insulin resistance and account for 50% of fasting insulin levels in patients with type 2 diabetes and 10% in people without diabetes [17–19]. On the other hand, fasting and postprandial PI/immunoreactive insulin (IRI) ratios reflect β-cell function, especially the efficiency of the conversion of proinsulin to insulin [20]. When demand for insulin is augmented during excess nutrient load and hyperglycemia, proinsulin synthesis increases and mature insulin granules in β-cells decrease [21]. Conversely, β-cell rest improves β-cell function immediately and reduces the PI/IRI ratio [21, 22]. Ohta et al. reported that glargine added to OADs in patients with type 2 diabetes improved 2 h-PI/CPR ratio, suggesting that exogenous basal insulin improved β-cell function due to resting of β-cells (the PI/CPR ratio was similar to the PI/IRI ratio under the condition of administration of any insulin analog) [23]. Although the mechanisms for the beneficial effects of β-cell rest by exogenous insulin are not entirely clear, several explanations have been suggested: restocking of cellular insulin stores [24], recovery of glucokinase [25], and reduction in reactive oxygen species [26, 27]. In the present study, sufficient basal insulin improved fasting and 2 h-PI/CPR ratios, and diminished post-breakfast hyperglycemia, probably via improved function among resting β-cells.

Second, serum FFA levels increase moderately in type 2 diabetes due to the attenuating inhibitory effect of insulin on lipolysis [28–30]. High serum FFA levels can cause insulin resistance in the liver and skeletal muscle [31, 32]. It has been reported that rapid administration of FFA enhances hepatic glucose production [33] and attenuates glucose uptake in the liver and skeletal muscle [34, 35] via activation of protein kinase C (PKC) and I kappa B kinase (IKK) [36–38]. In addition, when serum FFA levels were reduced by approximately 50% from around 400 to 200 μmol/L under the glucose clamp method, hepatic glucose production decreased by 41%, and glucose uptake increased by 26.4% [39]. In the present study, serum FFA levels were decreased by 45.5% after basal insulin, and iAUC-B decreased by 46.1%. Simple regression/multiple regression analysis showed a significant correlation between the decrease in serum FFA levels and the decrease in post-breakfast glucose levels, suggesting that sufficient basal insulin can improve post-breakfast hyperglycemia by suppressing hepatic glucose production and increasing glucose uptake in the liver and skeletal muscle via reduction of serum FFA levels.

BW did not change significantly despite the increasing basal insulin doses, and tended to decrease due to caloric restriction in the hospital. There was no correlation between the change in BW and post-breakfast glucose levels. FPG was significantly reduced by basal insulin titration, but the decrease in FPG was not correlated with the decrease in post-breakfast glucose levels, indicating that FPG per se was not the primary factor in improving post-breakfast hyperglycemia in this study. Inflammatory cytokines (hsTNFα and IL-6), inflammatory markers (hsCRP), and HMWA, which are related to insulin resistance, tended to decrease with basal insulin titration, but the changes were not significant. Similarly, these changes were not correlated with decreases in post-breakfast glucose levels.

In the comparison of degludec and glargine, we did not find any significant differences in ⊿iAUC-B between agents. There were also no significant differences between groups in ⊿2 h-PI/CPR and ⊿FFA, which were estimated to be relevant factors in ⊿iAUC-B. These results suggest that basal insulin analogs suppress post-breakfast glucose levels depending on the amount of suppression of ⊿2 h-PI/CPR and ⊿FFA, regardless of the type of insulin analog used. Although other clinical parameters including BW, FPG, and glucose fluctuation (SD of glucose levels) did not differ between groups, hypoglycemia occurred significantly less frequently with degludec than with glargine. All hypoglycemia was observed at night. Previous studies have reported that nocturnal hypoglycemia was higher with glargine than with degludec [40], which is consistent with our results. If

the target FPG is set strictly (< 6.1 mM) as in this study, titration of degludec may be safer than that of glargine.

This study has several limitations. First, the sample size was small. Although only 20 patients were included, we were able to see a significant improvement in post-breakfast hyperglycemia by increasing basal insulin. It is possible that changes in some clinical parameters such as hsTNFα, IL-6, and HMWA, which showed nonsignificant decreases, could potentially be seen with a larger sample group. Second, insulin resistance was not evaluated. As such, we did not directly indicate whether basal insulin improved insulin resistance in the liver and skeletal muscle, although we evaluated the PI/CPR ratio as an indicator of β-cell function. To clarify the relationship between basal insulin effects on post-breakfast hyperglycemia and insulin resistance, we need to evaluate insulin resistance using the glucose clamp technique or more feasible tests such as insulin tolerance test and steady-state plasma glucose levels in pre- and post-titration periods. Third, serum glucagon and GLP-1 levels were not examined. It has been reported that postprandial hyperglycemia after fasting is due not only to the increases in serum FFA levels but also to decreases in insulin response caused by increasing serum glucagon and decreasing serum GLP-1 levels [41]. We also need to further examine changes in serum glucagon and GLP-1 levels after basal insulin titration. Finally, nocturnal hypoglycemia might affect post-breakfast glucose levels. We were not able to exclude that possibility, because we did not evaluate counterregulatory hormone responses to nocturnal hypoglycemia such as catecholamine and cortisol. However, there was no difference in iAUC-B between non-hypoglycemia and hypoglycemia group, suggesting that the impact of nocturnal hypoglycemia on post-breakfast glucose levels was limited in this study.

In conclusion, we demonstrated that basal insulin diminished post-breakfast hyperglycemia regardless of the type of insulin analog, accompanied by decreasing the post-breakfast PI/CPR ratio and suppressing fasting serum FFA levels in patients with type 2 diabetes. Because morning postprandial hyperglycemia is progressive in patients with type 2 diabetes [12], we believe that sufficient basal insulin supplementation with a basal-supported oral, basal–bolus regimen, or basal insulin plus GLP-1 analog therapy may be clinically useful for achieving target HbA1c levels in such patients. In addition, degludec was associated with significantly lower rates of nocturnal hypoglycemia.

Compliance with ethical standards

Conflict of interest Yoshihiko Nishio has received honoraria for scientific lectures from Eli Lilly Japan, Sanofi, and Novo Nordisk Pharma; and received grants/research support from Novo Nordisk Pharma. Kazuma Ogiso, Nobuyuki Koriyama, Takahiko Obo and Akinori Tokito have nothing to disclose.

Human rights statement All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (National Hospital Organization Kagoshima Medical Center, Ethics Committee, date of approval: 7 May 2015, approval no. 27-6) and with the Helsinki Declaration of 1964 and later versions.

Informed consent All participants provided written informed consent.

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Clinical Diabetes and Endocrinology

CASE REPORT Open Access

Central pontine myelinolysis during treatment of hyperglycemic hyperosmolar syndrome: a case report

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Abstract

Background: Central pontine myelinolysis (CPM) is a non-inflammatory demyelinating lesion of the pons. CPM and extrapontine demyelination (EPM) are together termed osmotic demyelination syndrome (ODS), a known and serious complication of acute correction of hyponatremia. Conversely, hyperglycemic hyperosmolarity syndrome (HHS) develops in patients with type 2 diabetes who still have some insulin secretory ability due to infection, non-compliance with treatment, drugs, and coexisting diseases, and is often accompanied by ketosis. HHS represents a life-threatening endocrine emergency (mortality rate, 10–50%) associated with marked hyperglycemia and severe dehydration. HHS may develop ODS, and some cases have been associated with hypernatremia.

Case presentation: The patient was an 87-year-old woman with hyperglycemia, dehydration, malnutrition, and potential thrombus formation during long-term bed rest. HHS was suspected to have developed due to progression of hyperglycemia and dehydration caused by pneumonia. Furthermore, ketoacidosis developed from ketosis and prerenal renal failure associated with circulating hypovolemia shock, which was also associated with disseminated intravascular coagulation. Treatment was started with continuous intravenous injection of fast-acting insulin and low-sodium replacement fluid. In addition, ceftriaxone sodium hydrate, heparin sodium, thrombomodulin α, human serum albumin, and dopamine hydrochloride were administered. Blood glucose, serum sodium, serum osmolality, and general condition (including vital, infection/inflammatory findings, and disseminated intravascular coagulation) improved promptly, but improvements in disturbance of consciousness were poor. Diffusion-weighted imaging of the brain 72 h after starting treatment showed no obvious abnormalities, but high-intensity signals in the midline of the pons became apparent 30 days later, leading to definitive diagnosis of CPM.

Conclusions: Fluctuation of osmotic pressure by treatment from hyperosmolarity due to hyperglycemia and hypernatremia in the presence of risk factors such as malnutrition, severe illness, and metabolic disorders may be a cause of CPM onset. When treating HHS with risk factors, the possibility of progression to ODS needs to be kept in mind.

Keywords: Central pontine myelinolysis, Osmotic demyelination syndrome, Hyperglycemic hyperosmolarity syndrome, Hypernatremia, Diffusion-weighted imaging

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Background

Central pontine myelinolysis (CPM) with extrapontine demyelination (EPM) is called osmotic demyelination syndrome (ODS), and is now recognized as a serious complication following acute correction of hyponatremia [1]. It is believed that When osmotic pressure is rapidly increased by correction of low sodium, the blood–brain barrier (BBB) is thought to be destroyed and cytotoxic factors in the blood cause demyelination and subsequent ODS [2, 3]. However, alongside hyponatremia, many other factors are considered to be involved in the onset of ODS [4–7]. CPM is a non-inflammatory demyelinating lesion of the pons, as first reported by Adams et al. in 3 cases of chronic alcoholism and 1 case of malnutrition [4], and EPM was reported later [8].

On the other hand, hyperglycemic hyperosmolarity syndrome (HHS) develops in type 2 diabetic patients who still have some degree of insulin secretory ability due to infections, non-compliance with treatment, drugs, or coexisting diseases (endocrine diseases, cancer, etc.), and is often accompanied by ketosis. In addition, HHS is a life-threatening endocrine emergency (mortality rate, 10–50%) associated with marked hyperglycemia and severe dehydration [9]. HHS may develop to ODS [10–22], and some cases have been reported in association with hypernatremia [10–12, 15, 16].

Here, we report a rare case of ODS developing during treatment of HHS with marked hypernatremia.

Case presentation

The patient was an 87-year-old woman with a history of venous stasis dermatitis in both lower legs. She had no history of either diagnosis of or treatment for diabetes, but hemoglobin (Hb)A1c had been recorded as 6.8% about 1 year before this presentation. She had been admitted to a psychiatric hospital for about 1 year, due to exacerbations of both depression and Alzheimer-type dementia that had developed 10 years earlier and 12 years earlier, respectively. About 2 months before presentation, her dietary intake decreased and infusion of glucose, electrolytes and water was started. She had been in a bedridden state with no speech and almost no appetite from about 1 month before presentation. At that point, hyperglycemia and hypernatremia were inferred to have already been present for a long time. Two days before presentation, sudden high fever (38 °C) and involuntary movements of the trunk and upper limbs appeared. One day later, she entered a coma. A blood glucose level (BG) of 1000 mg/dL and a serum sodium (Na) level of 179 mmol/L (glucose-corrected Na level: 194 mmol/L) were confirmed, and the patient was referred to our department for emergency hospitalization.

Glasgow coma scale score was 3 (eye opening, 1; best verbal response, 1; best motor response, 1), the pupils were 3 mm on both sides, and light reflex was rather dull, accompanied by involuntary movements of the whole body. Body temperature was 37.6 °C, blood pressure was 57/40 mmHg, heart rate was 114 beats/min, and peripheral oxygen saturation was maintained at 95% under mask administration of oxygen at 10 L/min. The tongue was very dry, and turgor of the skin was low. No abnormalities were observed in other physical findings except for the presence of moist rales at the end of inspiration in bilateral lower lung fields. Drugs being administered were limaprost alfadex at 5 mg/day, furosemide at 10 mg/day, and paroxetine at 5 mg/day.

Results of blood and biochemical examinations and blood gas analysis are shown in Table 1. Negative results were obtained for anti-glutamic acid decarboxylase antibodies (< 5.0 U/mL) (Table 1). Computed tomography of the chest showed infiltrative shadows in both lower lung fields (image not shown). This patient with hyperglycemia, dehydration, malnutrition, and potential thrombus formation during long-term bed rest was suspected to have developed into HHS and ketosis due to progression of hyperglycemia and dehydration caused by pneumonia. Furthermore, ketoacidosis had developed from ketosis and prerenal renal failure associated with circulating hypovolemia shock, which was also associated with disseminated intravascular coagulation (DIC).

Treatment was started with intravenous infusion of fast-acting insulin (Humalin R; Eli Lilly, Kobe, Japan) (starting at 4 units/h and gradually decreasing) and low-sodium replacement fluid [23]. In the first 24 h, 6000 mL of replacement fluid (95.8 g of glucose, 0.3% Na) was added, and 2000 mL of replacement fluid (20.8 g of glucose, 0.2% Na) was administered within the period of 24–48 h. At 48–72 h, 1000 mL of replacement solution (75 g of glucose, 0.1% Na) was administered, and combined use of tube feeding was started (Fig. 1). Correction of K was performed appropriately. Although BG was ≥ 1000 mg/dL at 8 h after starting treatment, Na improved to 149.5 mmol/L (glucose-corrected Na level: 164.4 mmol/L). After 24 h, although BG, Na and sOsm had decreased to 716 mg/dL, 154.0 mmol/L and 402.3 mOsm/kg H_2O, respectively, glucose-corrected Na level remained almost unchanged (164.2 mmol/L). At 48 h later, BG had improved to 110 mg/dL, Na to 154 mmol/L, and sOsm to 370.0 mOsm/kg H_2O. However, glucose-corrected Na level (166.0 mmol/L) was not showing improvement. At 72 h later, BG had improved to 283 mg/dL, Na to 150 mmol/L (glucose-corrected Na level: 152.5 mmol/L), and sOsm to 345.5 mOsm/kg H_2O (Table 2). In addition, ceftriaxone sodium hydrate at 1 g/day, heparin sodium at 8000 units/day, thrombomodulin α at 6400 units/day, total human serum albumin at 62.5 g, and dopamine hydrochloride at 3 μg/kg were administered. General condition, including vital signs, infection/inflammatory

Table 1 Laboratory findings on admission

Peripheral blood	WBC	11,800	/μL	[3300-8600]	Cr	3.16	mg/dL	[0.46-0.79]
	Neu	10,900	/μL	[1500-7500]	UA	12.8	mg/dL	[2.6-5.5]
	Lym	800	/μL	[1000-4000]	eGFR	11.3	mL/min/1.73 m^2	
	RBC	475	×10^4/μL		LDL	79	mg/dL	
	Hb	15.1	g/dL	[11.6-14.8]	HDL	22	mg/dL	[48-103]
	PLT	10.9	×10^4/μL	[15.8-34.8]	TG	301	mg/dL	[30-117]
Coagulation	PT-INR	1.44		[0.91-1.08]	nonHDL	141	mg/dL	
	APTT	22	s	[24.0-33.0]	CRP	2.6	mg/dL	[0.00-0.14]
	D-D	24.83	μg/mL	[< 1.0]	BG	1056	mg/dL	
	FDP	20.83	μg/mL	[< 5.0]	HbA_{1c}	10.8	%	[4.9-6.0]
Biochemistry	AST	16	IU/L		3HB	2029.0	μmol/L	[< 85]
	ALT	17	IU/L		TK	2371	μmol/L	[< 130]
	LDH	313	IU/L	[124-222]	F-CPR	1.9	ng/mL	
	ALP	262	IU/L	[106-322]	F-CPI	1.1		
	γ-GTP	15	IU/L		GADA	< 5.0		
	T.Bil	0.61	mg/dL		sOsm	459.0	mOsm/kg H_2O	[276-292]
	AMY	70	U/L		Blood gas analysis	pH	7.27	μg/L	[7.36-7.44]
	CK	141			(O_2 mask 10 L/min)	PCO_2	28	mmHg	[36-44]
	Alb	2.73	g/dL	[4.1-5.1]		HCO_3^-	12.9	mmol/L	[22-26]
	Na	176	mmol/L	[138-145]		BE	-12.4	mmol/L	[-2.0-2.0]
	K	5.1	mmol/L	[3.6-4.8]		Lac	12.2	mmol/L	[1.0-1.5]
	Cl	134	mmol/L	[101-108]					
	cCa	9.5	mg/dL						

For abnormal values only, reference ranges are shown in brackets

WBC white blood cells, *Neu* neutrophils, *Lym* lymphocytes, *RBC* red blood cells, *Hb* hemoglobin, *PLT* platelets, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *γ-GTP* γ-glutamyltransferase, *T.Bil* total bilirubin, *AMY* amylase, *CK* creatine kinase, *TP* total protein, *Alb* albumin, *Na* sodium, *K* potassium, *Cl* chlorine, *Ca* calcium, *cCa* corrected Ca, *IP* inorganic phosphorus, *Mg* magnesium, *BUN* blood urea nitrogen, *Cr* creatinine, *UA* uric acid, *eGFR* estimated glomerular filtration rate, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol, *TG* triglycerides, *CRP* C-reactive protein, *BG* blood glucose, *HbA1c* glycated hemoglobin, *AA* acetic acid, *3HB* 3-hydroxybutyrate, *TK* total ketone bodies, *F-CPR* fasting C-peptide, *CPI* CPR index, *GADA* anti-glutamic acid decarboxylase antibody, *sOsm* serum osmolality, *BE* base excess, *Lac* lactate

findings, and DIC improved promptly (Fig. 1). After 72 h, the patient opened her eyes. However, because the state of no response to the stimulus and involuntary movements continued for 7 days, ODS was suspected and magnetic resonance imaging (MRI) of the brain was performed. No clear abnormalities were evident on diffusion-weighted imaging (DWI) (Fig. 2a), and no definitive diagnosis was reached. The patient was subsequently able to move in response to instructions, but we could not exclude the possibility of pseudobulbar paralysis associated with ODS, as she could barely speak and showed no improvement of dysphagia. A high-intensity signal in the pons was identified on DWI of the brain at 30 days after starting treatment (Fig. 2b), leading to definitive diagnosis of CPM. After the life-threatening state was averted and general condition improved, she was transferred to a long-term care facility. As of about 1 year after onset, we obtained information that the patient had recovered to the point that she could speak spontaneously and responded to conversation in a manner reflective of a good condition.

Discussion and Conclusions

Although ODS has been reported to rarely develop in HHS [10–22], fewer reports have described development of ODS in HHS with hypernatremia [10–12, 15, 16], and causes of ODS development have yet to be clarified in terms of marked hyperosmolarity or changes in osmotic pressure associated with treatment. Within 7 days of onset, findings of ODS are not detectable on MRI [24, 25]. On the other hand, Ruzek et al. reported DWI as extremely useful for early diagnosis of CPM, based on the possibility of diagnosing CPM by MRI 24 h after onset [26]. MRI findings, including DWI, are also known to be observed 24 h after onset [25, 27]. In this case, no clear abnormality was observed on DWI at 72 h after symptom onset. Relatively rapid improvement (fluctuation) of osmotic pressure by treatment for hyperosmolarity due to hyperglycemia and hypernatremia was thought to be the cause of CPM onset in this case. A similar case in which CPM and EPM developed due to rapid improvement of hypernatremia was reported by Go et al. [28].

The issue that we would have changed in our treatment of this case was the performance of dehydration correction using a hypotonic solution. We speculated that rapid changes in osmotic pressure might have been avoidable using physiological saline or at least half-saline. On the other hand, slowly reducing blood glucose may be a meaningful strategy from the perspective of preventing the onset of ODS. Regarding

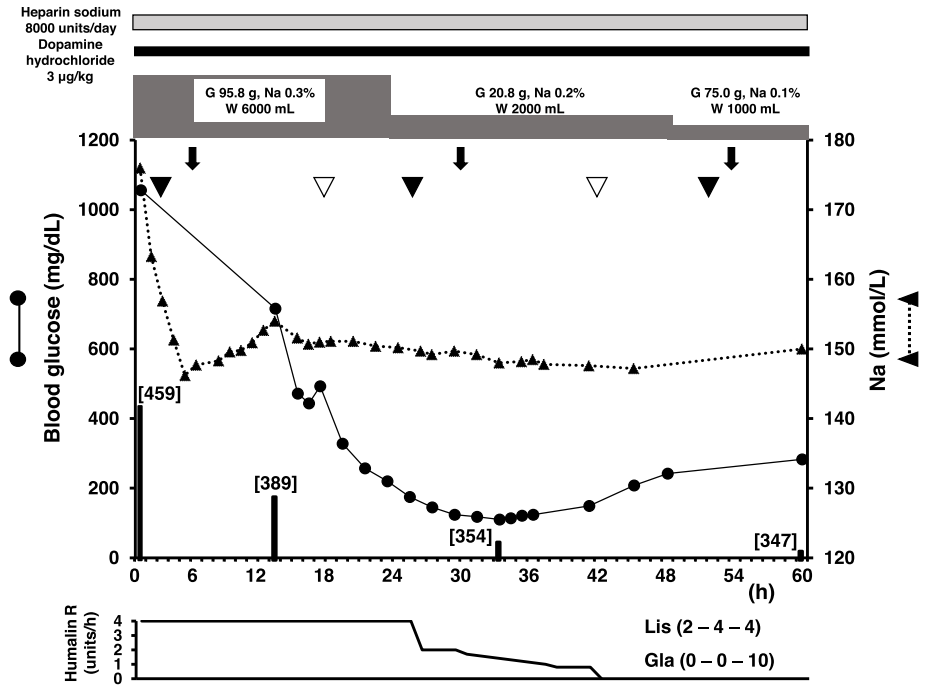

Fig. 1 Clinical course. The clinical course up to 60 h after admission. Closed circles and solid lines show changes in blood glucose levels, and closed triangles and dotted lines show changes in serum sodium. Down arrow indicates infusion of 6400 units of thrombomodulin α. Closed and open arrowheads indicate infusions of 1 g of ceftriaxone sodium hydrate and 12.5 g of human serum albumin, respectively. Closed bar and numbers in brackets indicate serum osmolality. The line graph at the bottom shows insulin usage. Numbers in parentheses indicate, from left to right, the number of insulin units used just before breakfast, just before lunch, and just before dinner. G, glucose content; Na, sodium concentration; W, amount of water; Lis, insulin lispro; Gla, biosimilar insulin glargine

the pathogenesis of ODS, rapid changes in osmotic pressure presumably induce apoptosis of astrocytes [2] and disrupt the blood–brain barrier. As a result, cytotoxic factors in blood become able to enter the brain, injuring oligodendrocytes and leading to demyelination [3]. Furthermore, microglia reportedly activate early in the onset of ODS and accumulate in the demyelinating region, and may express inflammatory cytokines and participate in the progression of demyelination, leading to "myelin melting" [29]. With these mechanisms, dexamethasone reportedly acts to prevent breakdown of the blood–brain barrier, while minocycline may prevent the onset and development of ODS by suppressing the expression of inflammatory cytokines from microglia and migration and accumulation of microglia to demyelinated parts; that is, by suppressing microglial activation [30]. Dexamethasone and minocycline may thus have potential as clinical therapeutic agents for ODS in the future. However, the use of dexamethasone in patients with severe hyperglycemia requires careful consideration and may not represent a suitable first-line option for the treatment of DOC. Further, alcohol poisoning, liver diseases including liver transplantation, malnutrition, malignant tumors, severe diseases or sepsis during pregnancy or postpartum, adrenal insufficiency,

Table 2 Changes in glucose, serum sodium, glucose-corrected serum sodium and serum osmotic pressure due to acute treatment

Time from start of treatment (h)	Glucose (mg/dL)	Sodium (mmol/L)	Glucose-corrected sodium (mmol/L)	Osmotic pressure (mOsm/kg H_20)
0	1000	179.0	194.0	488.2
8	1000	149.5	164.4	429.0
24	716	154.0	164.2	402.3
48	110	154.0	166.0	370.0
72	283	150.0	152.5	345.5

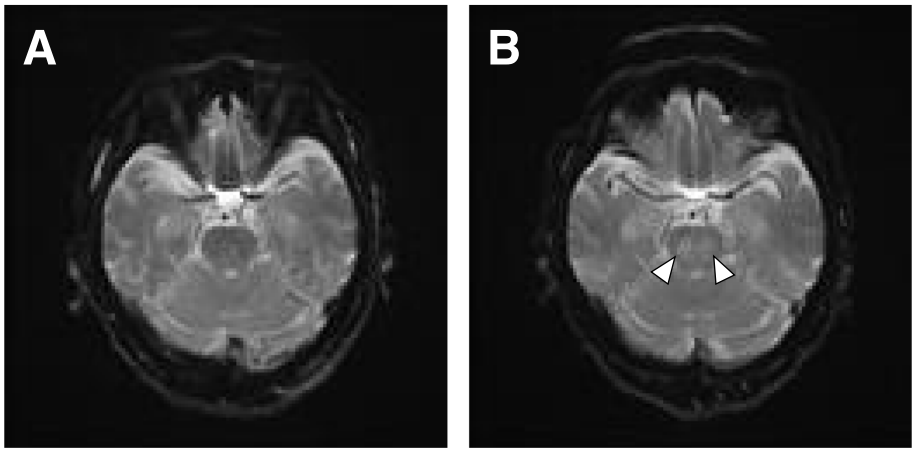

Fig. 2 Diffusion-weighted imaging of the brain. **a** Image 72 h after admission. **b** Image 30 days after admission. Arrowheads indicate high-intensity regions in the pons

and metabolic disorders have been mentioned as risk factors for the development of ODS [7]. Our patient also showed malnutrition, severe illness, and metabolic disorders as risk factors.

A key limitation of this report was that the condition of the patient before admission to our hospital could not be accurately gauged due to a lack of data from the referring facility. In addition, the interval to follow-up MRI was about 1 month, providing a weak basis for estimating the time of ODS onset.

In conclusion, we have reported a rare case involving an 87-year-old woman with CPM during treatment of HHS with marked hypernatremia. Fluctuations in osmotic pressure with treatment for hyperosmolarity due to hyperglycemia and hypernatremia in the presence of risk factors such as malnutrition, severe illness, and metabolic disorders were considered as the causes of CPM onset. When treating HHS with risk factors, the possibility of progression to ODS should always be kept in mind.

Abbreviations

CPM: Central pontine myelinolysis; EPM: Extrapontine demyelination; ODS: Osmotic demyelination syndrome; HHS: Hyperglycemic hyperosmolarity syndrome; BG: Blood glucose level; Na: Sodium; K: Potassium; sOsm: Serum osmolality; DIC: Disseminated intravascular coagulation; MRI: Magnetic resonance imaging; DWI: Diffusion-weighted imaging

Acknowledgements

We wish to thank the patient's family for their permission to publish this manuscript. Furthermore, we would like to thank Forte Science Communications (Tokyo, Japan) for providing medical editorial services.

Authors' contributions

K.K., N.Koji., and M.I. attended the patient; K.K. and N.Kori wrote the manuscript; N.Koji., N.Kori., M.I., and Y.N. provided conceptual advice. N.Kori supervised management of the case and contributed to writing and editing the manuscript. All authors have read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written, informed consent was obtained from the patient's family for publication of this case report and all accompanying images.

Competing interests

Yoshihiko Nishio has received honoraria for scientific lectures from Eli Lilly, Novo Nordisk Pharma, and Sanofi, and a scholarship donation from Novo Nordisk Pharma. Koshi Kusumoto, Nobuyuki Koriyama, Nami Kojima and Maki Ikeda have nothing to disclose.

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Received: 11 June 2020 Accepted: 26 October 2020
Published online: 16 November 2020

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Publisher's Note

ORIGINAL ARTICLE

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Impact of antithrombotic therapy on the outcomes with focus on bleeding and thromboembolic events in patients undergoing pancreticoduodenectomy

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Key words

antithrombotic therapy, heparin bridging, pancreaticoduodenectomy, post-pancreatectomy haemorrhage, thromboembolic complications.

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Accepted for publication 14 April 2020.

doi: 10.1111/ans.15932

Abstract

Background: We investigated perioperative outcomes of pancreaticoduodenectomy (PD) in patients receiving antithrombotic therapy (ATT) with a focus on the incidence of perioperative bleeding and thromboembolic complications.

Methods: A total of 77 patients who underwent PD at our institution between 2013 and 2019 were retrospectively reviewed. Clinical findings and surgical outcomes including bleeding and thromboembolic complications were compared in patients with or without ATT. Interruption of ATT and perioperative heparin bridging were based on our hospital protocol.

Results: Among ATT (30) and non-ATT (47) groups, ATT group had a significantly higher age and history of cardiocerebrovascular diseases. No significant difference was observed in intraoperative and post-pancreatectomy haemorrhage (PPH) between the groups. ATT group was associated with a significantly higher rate of post-operative complications, Clavien–Dindo classification ≥II and thromboembolic events. Operative mortality in ATT and non-ATT groups was 2 (6.7%) and 1 (2.1%), respectively. There was no significant association between ATT and excessive intraoperative blood loss (≥1000 mL), PPH (≥grade B) and thromboembolic complications (Clavien–Dindo classification ≥II).

Conclusion: In patients with ATT, PD is a feasible procedure with no major impact on intraoperative bleeding or PPH.

Introduction

With continuously growing ageing population, the number of patients with pre-existing cardiovascular and/or cerebrovascular diseases who require gastroenterological surgery is also increasing, and these patients usually receive antithrombotic therapy (ATT). Owing to an increased risk of perioperative bleeding and thromboembolic complications, optimal perioperative management during gastroenterological surgery is complex. While interruption of ATT appears to increase the risk of thromboembolic events, continuation of ATT or perioperative heparin bridging could link to a higher risk of perioperative bleeding complications. This leads surgeons to confront a challenging dilemma in determining the optimal management plan for ATT-burdened patients undergoing gastroenterological surgery.

Pancreaticoduodenectomy (PD) is the procedure of choice for resection of pancreatic head, distal bile duct and periampullary tumours, and the number of aged population undergoing PD in Japan is increasing.[1] Despite recent advances in surgical techniques and perioperative management, PD is associated with substantial post-operative morbidity and mortality.[2,3] Post-pancreatectomy haemorrhage (PPH) carries an added risk of surgical mortality.[4,5] Despite an increasing number of patients undergoing PD, the impact of ATT on perioperative outcomes remains unclear.

This study investigated the surgical outcomes in patients with ATT undergoing PD, with a focus on perioperative bleeding and thromboembolic complications.

Methods

Patients and data collection

We retrospectively reviewed the medical records, background, perioperative and outcome variables of 77 patients who underwent PD for benign and malignant periampullary tumours at our institution between August 2013 and October 2019. The patients' general

well-being and activities of daily life were assessed according to the American Society of Anesthesiologists Physical Status score.[6]

Operative procedures

Standard subtotal stomach-preserving PD (SSPPD) followed by invaginated pancreatogastrostomy (PG), hepaticojejunostomy and antecolic gastrojejunostomy were performed. SSPPD was preferred to prevent delayed gastric emptying (DGE) and to preserve the pooling ability of the stomach, followed by invaginated PG to prevent post-operative pancreatic fistula (POPF). To minimize surgical blood loss and shorten the operation time, Thunderbeat (Olympus Medical Systems Corp., Tokyo, Japan) was used. Conventional PD with pancreaticojejunostomy and laparoscopic SSPPD were also included.

Perioperative antithrombotic management

Interruption of ATT with or without perioperative heparin bridging was based on our hospital protocol. Antiplatelet (mainly aspirin) therapy was interrupted 1 week before surgery and resumed early after surgery in low thromboembolic risk patients. In patients with high risk of thromboembolic events, antiplatelet therapy (APT) was interrupted 1 week before surgery and heparin bridging was adopted 4 days before surgery. Patients on anticoagulants (especially warfarin) were managed by interruption of anticoagulants 4 days before surgery, bridging with heparin and early post-operative reinstitution. Intravenous heparin was started at 10 000 U per day, stopped 6 h before surgery and restarted 24–48 h after surgery, after confirming the absence of bleeding complications. Heparin infusion was adjusted daily based on the percent change in activated partial thromboplastin time (i.e. about 150%). If patients were on direct oral anticoagulant, it was stopped for a day before surgery. In patients receiving both APT and anticoagulation therapy, perioperative management of ATT was based on our hospital protocol. For prevention of venous thromboembolism, use of elastic stockings, intermittent pneumatic compression and enforced early mobilization were routinely incorporated, while low molecular weight heparin was not administered.

Definitions

Post-operative complications were based on Clavien–Dindo classification (CDC),[7] CDC II or higher was considered significant. Major morbidity was defined as complications with CDC equal to or higher than III. POPF was defined and graded according to the International Study Group of Postoperative Pancreatic Fistula.[8] DGE was defined according to the International Study Group of Pancreatic Surgery.[9] The severity of PPH was classified based on the recommendation of the International Study Group of Pancreatic Surgery.[4] PPH was graded based on time of onset, location and severity. Post-operative thromboembolic complications were defined according to the adverse events corresponding to CDC ≥II. Operative mortality was defined as the death within 30 days of surgery.

Outcomes of interest

Baseline characteristics, perioperative factors and outcome variables were compared between patients with ATT (ATT group) and without ATT (non-ATT group). The primary outcomes included excessive intraoperative estimated blood loss (1000 mL or more), PPH (grades B and C) and post-operative thromboembolic complications.

Statistical analysis

The categorized data in each group were compared by chi-squared or Fisher's exact test. Kruskal–Wallis test was used to compare continuous variables (expressed as a median with range) and to interpret non-parametric variables. Univariate and multivariate regression analyses were used to assess the risk factors. Variables with $P < 0.05$ were included in subsequent multivariable analysis. A value of $P < 0.05$ was considered significant. Statistical analyses were conducted with SPSS software (version 26; SPSS Inc., Chicago, IL, USA).

Ethical approval

This study was approved by the Institutional Review Board of National Hospital Organization Kagoshima Medical Center, Japan (approval number 2019-48). All procedures involving human participants were conducted in accordance with the ethical standards of the institutional research committee and with the 1975 Declaration of Helsinki.

Results

Patient demographics and operative variables (ATT versus non-ATT)

Thirty-nine percent (30/77) of patients undergoing PD received ATT, including 20 patients with perioperative heparin bridging. Baseline characteristics of the patients are summarized in Table 1. ATT group had a significantly higher age than non-ATT (77 versus 72 years, $P = 0.019$). History of percutaneous coronary intervention (PCI, $P < 0.001$), coronary artery bypass grafting (CABG, $P = 0.010$) and cerebral infarction ($P < 0.001$) were more common in the ATT group. This study included bile duct cancer in 24 (31%), pancreatic cancer in 18 (23%), ampullary cancer in 14 (18%) and intraductal papillary mucinous neoplasms in 11 (14%) patients; the distribution of diseases was similar between the groups. SSPPD (86%) and PG (88%) were adopted as preferred procedures; no difference in the type of PD was observed between the groups. The incidence of an additional visceral resection including colectomy, splenectomy and hepatectomy was lower in the ATT group (3.3% versus 21.3%, $P = 0.028$). There were no differences in the operation time, blood loss, rates of excessive blood loss (≥1000 mL) and blood transfusion up to 24 h after surgery between the groups.

Table 1 Baseline characteristics (ATT versus non-ATT)

Variables	Total (*n* = 77)	ATT (*n* = 30)	Non-ATT(*n* = 47)	*P*-value
Patient demographics				
Sex, male/female (*n*)	53/24	21/9	32/15	0.860
Age (years, median (range))	75 (43–90)	77 (62–89)	72 (43–90)	0.019
BMI (kg/m^2, median (range))	22.0 (16.0–29.0)	22.5 (16.0–27.7)	21.7 (16.4–29.0)	0.515
ASA-PS score 1/2/3 (*n*)	4/52/21	0/19/11	4/33/10	0.118
DM, *n* (%)	26 (34)	13 (43)	13 (28)	0.121
Previous upper abdominal surgery, *n* (%)	19 (25)	7 (23)	12 (26)	0.827
H/O PCI, *n* (%)	12 (16)	12 (40)	0 (0)	<0.001
H/O CABG, *n* (%)	4 (5.2)	4 (13)	0 (0)	0.010
H/O cerebral infarction, *n* (%)	10 (13)	10 (33)	0 (0)	<0.001
ATT				N/A
Antiplatelet/anticoagulant/both (*n*)	21/3/6	21/3/6	—	
Periop. heparin bridging, *n* (%)	20 (30)	20 (67)	—	
Operative characteristics				
Diseases, *n* (%)				0.849
Bile duct cancer	24 (31)	9 (30)	15 (32)	
Pancreatic cancer	18 (23)	9 (30)	9 (19)	
Ampullary cancer	14 (18)	5 (17)	9 (19)	
IPMN	11 (14)	4 (13)	7 (15)	
Others	10 (13)	3 (10)	7 (15)	
Operation, *n* (%)				0.363
SSPPD	66 (86)	27 (90)	39 (83)	
Conventional PD	8 (10)	3 (10)	5 (11)	
Laparoscopic SSPPD	3 (3.9)	0 (0)	3 (6.4)	
Additional visceral resection, *n* (%)	11 (13.3)	1 (3.3)	10 (21.3)	0.028
PV reconstruction, *n* (%)	9 (12)	4 (13)	5 (11)	0.720
Pancreatic reconstruction, *n* (%)				0.713
PG	68 (88)	27 (90)	41 (87)	
PJ	9 (12)	3 (10)	6 (13)	
Operation time (min, median (range))	342 (213–699)	362 (220–439)	341 (213–699)	0.372
EBL (mL, median (range))	913 (250–3870)	995 (430–3340)	770 (250–3870)	0.454
Excessive EBL (≥1000 mL, *n* (%))	32 (42)	15 (50)	17 (36)	0.230
Blood transfusion, *n* (%)	30 (39)	13 (43)	16 (34)	0.412

ASA-PS, American Society of Anesthesiologists Physical Status; ATT, antithrombotic therapy; BMI, body mass index; CABG, coronary artery bypass grafting; DM, diabetes mellitus; EBL, estimated blood loss; H/O, history of; IPMN, intraductal papillary mucinous neoplasm; PCI, percutaneous coronary intervention; PD, pancreaticoduodenectomy; Periop., perioperative; PG, pancreatogastrostomy; PJ, pancreaticojejunostomy; PV, portal vein; SSPPD, subtotal stomach-preserving PD.

Post-operative outcomes (ATT versus non-ATT)

Table 2 shows post-operative morbidity and mortality in each group. Post-operative complications (CDC ≥II) and operative mortality developed in 51% and 3.9% of all patients, respectively. ATT group was associated with significantly higher rate of post-operative complications (67% versus 40%, $P = 0.025$) and post-operative thromboembolic events (13% versus 0%, $P = 0.020$). No difference was observed between the groups in terms of major morbidity (CDC ≥III), PPH (grades B and C), intensive care unit stay, length of post-operative hospital stay or mortality. The incidence of POPF (grades B and C) and DGE (grades B and C) was similar between the groups. Operative mortality in the ATT and non-ATT groups was 2 (6.7%) and 1 (2.1%), respectively. In the ATT group, one patient died of cardiac arrest following sudden massive haematemesis 17 days after surgery and the other died from aspiration of vomitus 8 days after surgery. In the non-ATT

Table 2 Post-operative outcomes (ATT versus non-ATT)

Variables	Total (*n* = 77)	ATT (*n* = 30)	Non-ATT (*n* = 47)	*P*-value
Post-operative complications (CDC ≥II), *n* (%)	39 (51)	20 (67)	19 (40)	0.025
Major morbidity (CDC ≥III), *n* (%)	26 (34)	13 (43)	13 (28)	0.156
POPF (grades B and C), *n* (%)	6 (7.8)	2 (6.7)	4 (8.5)	1
DGE (grades B and C), *n* (%)	6 (7.8)	2 (6.7)	4 (8.5)	1
PPH (grades B and C), *n* (%)	8 (10.4)	5 (16.7)	3 (6.4)	0.250
Post-operative thromboembolic complications (CDC ≥II), *n* (%)	4 (5.2)	4 (13.3)	0 (0)	0.020
ICU stay (days, median (range))	1 (1–55)	2 (1–18)	1 (1–55)	0.076
LOS (days, median (range))	33 (8–344)	33 (8–344)	33 (21–288)	0.938
Operative mortality, *n* (%)	3 (3.9)	2 (6.7)	1 (2.1)	0.557

ATT, antithrombotic therapy; CDC, Clavien–Dindo classification; DGE, delayed gastric emptying; ICU, intensive care unit; LOS, length of post-operative hospital stay; POPF, post-operative pancreatic fistula; PPH, post-pancreatectomy haemorrhage.

group, one patient died of multiorgan failure following hepaticojejunostomy failure and intra-abdominal bleeding 22 days after surgery.

Post-operative bleeding and thromboembolic complications

We encountered PPH in eight patients (10.4%) (Table 3) that occurred from 2 to 35 days after surgery, and included grade B in six (four intraluminal and two extraluminal) and grade C in two patients (two intraluminal). One case of grade C PPH recovered with urgent relaparotomy, whereas the other died. Four patients developed thromboembolic complications (5.2%): two with arterial thromboembolism and two with portal vein thromboembolism (data not shown). Thromboembolic complications occurred within 8–48 days of surgery. One patient with acute myocardial infarction recovered with emergency PCI, while three patients recovered with conservative therapy. All were on APT; two of them were on dual antiplatelet therapy and one with anticoagulation therapy, and one underwent perioperative heparin bridging. None of the patients developed venous thromboembolism such as deep vein thrombosis or pulmonary embolism.

Univariate and multivariate analyses of the primary outcomes

Univariate and multivariate analyses for increased rate of surgical blood loss and PPH are demonstrated in Tables 4 and 5, respectively. Univariate analysis showed that male sex, diabetes mellitus, history of PCI and multiple APT were associated with higher operative blood loss. In the subsequent multivariate analysis, diabetes mellitus ($P = 0.001$, odds ratio (OR) 6.930) and history of PCI ($P = 0.037$, OR 5.115) were independently associated with higher operative blood loss (Table 4). Likewise, previous upper abdominal surgery ($P = 0.019$, OR 18.14), history of CABG ($P = 0.033$, OR 22.87) and portal vein reconstruction ($P = 0.008$, OR 35.38) were significantly associated with PPH (grades B and C) in another multivariate analysis (Table 5). We observed that age equal or higher than 80 years ($P = 0.035$, OR 22.57) and history of PCI ($P = 0.011$, OR 42.01) were independent predictor of post-operative thromboembolic complications in multivariate analysis (data not shown).

Discussion

In this study, a substantial number of elderly patients undergoing PD at our centre was receiving ATT, predominantly indicated for prevention of secondary cardiocerebrovascular events. ATT-burdened patients, who underwent PD, were at higher risks of post-operative complications and thromboembolic events. ATT with or without preoperative heparin bridging was not associated with haemorrhagic complications that include operative blood loss and PPH. ATT did not affect the operative mortality. The results from this study suggest that PD is a feasible procedure, without an increase in the rate of operative blood loss, PPH or mortality, even in ATT-burdened patients; however, post-operative complications (CDC ≥II) and thromboembolic events are of concern.

Gastroenterological surgery was found to be associated with higher perioperative bleeding complications when performed on ATT-burdened patients.[10,11] On the contrary, some evidence deny the adverse impact of ATT on perioperative bleeding complications during gastroenterological surgery.[12–14] In context of pancreatic surgery, Mita *et al.* concluded that strict thromboprophylaxis including antiplatelet continuation and heparin bridging was significantly associated with PPH,[11] while Fujikawa *et al.* reported that PD could be safely performed under Kokura protocol without increased perioperative bleeding complications in patients receiving ATT.[14] In our study, PD in patients receiving ATT was not associated with higher surgical blood loss and PPH. In our institution, the rates of ATT-burdened patients requiring major hepatobiliary and pancreatic surgery have been recently increasing to almost 30–40%. This demands a simple and strong haemostasis device and technique, especially in this critical population. Thunderbeat did not only make the dissection rapid, but also offered additional benefits of reliable vessel sealing without jeopardizing the safety and oncological clearance.[15] Invaginated PG with 4-0 Prolene® (Ethicon Inc., USA)

Table 3 Details of PPH

Case	Clinical signs	Occurrence date†	Location	Grade	Treatment	Antithrombotic therapy	Heparin bridging	Outcomes
1	Haematemesis	17	Intraluminal	C	Conservative	Aspirin, apixaban	Yes	Died (POD 17)
2	Blood in the abdominal drain output	6	Extraluminal	B	Conservative	Aspirin, cilostazol, ethyl icosapentate, warfarin	Yes	Recovered
3	Haematemesis	23	Intraluminal	B	Conservative	Aspirin	Yes	Recovered
4	Melena	7	Intraluminal	B	Conservative	Cilostazol	No	Recovered
5	Epigastralgia with anaemia	35	Intraluminal	B	Conservative	Aspirin, clopidogrel	Yes	Recovered
6	Haematemesis	5	Intraluminal	C	Reoperation	None	No	Recovered
7	Blood in the abdominal drain output	2	Extraluminal	B	Conservative	None	No	Recovered
8	Haematemesis	6	Intraluminal	B	Conservative	None	No	Recovered

†POD when the PPH occurred. POD, post-operative day; PPH, post-pancreatectomy haemorrhage.

Table 4 Univariate and multivariate analyses for increased surgical blood loss (≥1000 mL)

Variables	Univariate *P*-value	Multivariate *P*-value	Odds ratio	95% CI
Age ≥80 years	0.850			
Male sex	0.024	0.057	3.571	0.963–13.25
ASA-PS 3	0.421			
DM	0.000	0.001	6.930	2.231–21.52
Previous upper abdominal surgery	0.850			
H/O PCI	0.014	0.037	5.115	1.101–23.77
H/O CABG	0.182			
H/O cerebral infarction	0.503			
Single APT	0.892			
Multiple APT	0.012	0.200	4.767	0.437–51.94
ACT	0.786			
APT plus ACT	0.189			
Heparin bridging	0.122			
Additional visceral resection	0.302			
PV reconstruction	0.100			

ACT, anticoagulation therapy; APT, antiplatelet therapy; ASA-PS, American Society of Anesthesiologists Physical Status; CABG, coronary artery bypass grafting; CI, confidence interval; DM, diabetes mellitus; H/O, history of; PCI, percutaneous coronary intervention; PV portal vein.

Table 5 Univariate and multivariate analyses for post-pancreatectomy haemorrhage (grades B and C)

Variables	Univariate *P*-value	Multivariate *P*-value	Odds ratio	95% CI
Age ≥80 years	0.982			
Male sex	0.254			
ASA-PS 3	0.029	0.156	6.281	0.496–79.58
DM	0.020	0.147	4.310	0.599–31.01
Previous upper abdominal surgery	0.017	0.019	18.14	1.607–204.7
H/O PCI	0.445			
H/O CABG	0.026	0.033	22.87	1.284–407.3
H/O cerebral infarction	0.965			
Single APT	0.327			
Multiple APT	0.233			
ACT	0.233			
APT plus ACT	0.080			
Heparin bridging	0.116			
Additional visceral resection	0.064			
PV reconstruction	0.030	0.008	35.38	2.493–502.1

ACT, anticoagulation therapy; APT, antiplatelet therapy; ASA-PS, American Society of Anesthesiologists Physical Status; CABG, coronary artery bypass grafting; CI, confidence interval; DM, diabetes mellitus; H/O, history of; PCI, percutaneous coronary intervention; PV, portal vein.

performed in our institution was a simple, rapid and reliable technique, which likely reduced POPF to <10% in the current study.

Despite a declining incidence of PPH in recent years, it still holds a poor prognosis. A recent study conducted by Izumo *et al.* reported 3–16% incidence; however, mortality among patients with PPH was as high as 11–36%.[16] We observed incidence and mortality rates of 10.4% (8/77) and 12.5% (1/8) in patients with PPH, which correspond to the previous studies. The high incidence of PPH was associated with previous upper abdominal surgery, history of CABG and portal vein reconstruction; however, no difference was observed between the groups. Thus, occurrence of PPH appears to be associated with the adopted technique and patient population rather than the use of ATT.

Haigh *et al.* analysed 2610 patients undergoing PD and found that the rates of major adverse cardiovascular events (MACE) and cardiac arrest, stroke or pulmonary embolism after PD in the elderly population (age >70 years) were 2.1%, 1.1% or 1.0%, respectively.[17] The present study demonstrated that the incidence of MACE (cardiac arrest) and cerebrovascular stroke (amaurosis fugax) was limited to 1.3% (1/77) that corresponds to the previous report. We did not encounter pulmonary embolism or deep vein thrombosis; however, we had two cases of portal vein thrombosis. ATT-burdened elderly patients were more likely to develop perioperative thromboembolic complications including MACE, stroke and portal vein thrombosis after PD.

This is a retrospective cohort study from a single institution, which possess an inherent potential for bias. A well-designed multi-institutional randomized controlled trial would better comprehend our findings.

Conclusion

ATT have no major impact on intraoperative or post-operative haemorrhagic complications in patients undergoing PD; however, the overall complications were more but without any difference in mortality. Although, thromboembolic events appeared to be higher in the ATT group, PD can safely be performed in patients on ATT, with judicious perioperative management of anticoagulant therapy.

Conflicts of interest

None declared.

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Surgical Case Reports

CASE REPORT Open Access

Central hepatectomy for hepatocellular carcinoma in a patient with anti-Gerbich antibody

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Abstract

Background: Anti-Gerbich (Ge) alloantibody against high-frequency erythrocyte antigen is extremely rare. Owing to incomplete evidence regarding the degree and severity of adverse events induced by hemolytic transfusion reactions, the transfusion management often remains cumbersome in these patients. We report an anti-Ge alloantibody positive patient with hepatocellular carcinoma (HCC) who underwent central hepatectomy (CH) without the need for an allogeneic blood transfusion.

Case presentation: A 76-year-old Japanese woman was diagnosed with HCC measuring 9.5 × 8.0 cm in segments 4, 5, and 8 of the liver. This patient with anti-Ge alloantibody had a history of two pregnancies without transfusion. CH was planned, and based on the suggestion from the multidisciplinary team meeting, preoperative autologous donation (PAD) and acute normovolemic hemodilution (ANH) were performed. CH was successfully performed by using CUSA and Thunderbeat® with Pringle maneuver and infra-hepatic inferior vena cava clamping without perioperative need for an allogeneic blood transfusion. She has been alive without recurrence after a follow-up period of 45 months.

Conclusion: To our knowledge, this is the first case report of hepatectomy in a patient with anti-Ge alloantibody. A multidisciplinary team approach, PAD and ANH, and bloodless liver surgical techniques appear to be useful for major hepatectomy in patients with extremely rare blood type.

Keywords: Anti-Gerbich Antibody, Central hepatectomy, Preoperative autologous donation, Acute normovolemic hemodilution, Hepatocellular carcinoma

Background

Gerbich (Ge) is known to be a high-prevalence erythrocyte antigen that is present in more than 99% of the population [1]. Transfusion management in patients with positive anti-Ge alloantibody is complex in a surgical setting often requiring blood transfusion. A diverse clinical significance of anti-Ge alloantibody has been described; however, the degree and severity of adverse events induced by hemolytic transfusion reactions (HTRs) after incompatible transfusion are not precisely clear in the published literature [2].

Central hepatectomy (CH) is one of the technically challenging hepatectomies that is classified as a major liver resection based on Couinaud's classification, and is also described as a high complexity liver resection [3]. Given the anatomical proximity of lesions to major hepatic veins, presence of two transection planes and larger exposed raw surface area, CH appears to be associated with increased risk of intra-operative blood loss and blood transfusion ratio [4, 5].

We describe an anti-Ge alloantibody positive patient with hepatocellular carcinoma (HCC) who had a

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successful central hepatectomy without the need of an allogeneic blood transfusion.

Case presentation

A 76-year-old Japanese woman was referred to our department for evaluation of a mass in the middle section of the liver. She had no subjective symptoms and a mass was incidentally identified by an ultrasonography on her routine medical check-up. Her medical history included moderate to severe aortic stenosis, atrial fibrillation under warfarin, and mild chronic kidney disease. On presentation, her hemoglobin (Hb) level was 11.5 mg/dL, hematocrit (Ht) was 36%, and platelet count was 199,000/μl. Her total bilirubin was 0.6 mg/dl, aspartate aminotransferase (AST) was 59 U/l. alanine aminotransferase (ALT) was 19 U/l, albumin was 4.08 g/dl, and prothrombin time (PT) was 51% (INR 1.54) with warfarin use. A computed tomography (CT) scan and a magnetic resonance image (MRI) demonstrated a large tumor of 9.5 cm in diameter in the segment 4 (S4), 5 (S5), and 8 (S8) of the liver (Fig. 1). The serum alpha-fetoprotein (AFP) level was 54 ng/ml and protein induced by vitamin K absence or antagonist II (PIVKA-II) level was 210,000 mAU/ml. Hepatitis C virus antibody was positive and hepatitis B virus antigen was negative. She denied history of alcohol intake. Her Child-Pugh grade was corresponding to A with a score of point six and indocyanine green retention rate at 15 minutes was 15.8%. With the diagnosis of hepatitis C virus (HCV)-induced hepatocellular carcinoma, CH without caudate lobectomy was planned. The remnant liver volume (RLV) was estimated to be 633 mL on a three-dimensional volume analyzer (SYNAPSE VINCENT; FUJIFILM Medical Co., Tokyo, Japan). The standard liver volume (SLV) was estimated to be 942 mL by the Urata formula [6]. The RLV/SLV ratio was estimated to be 67%.

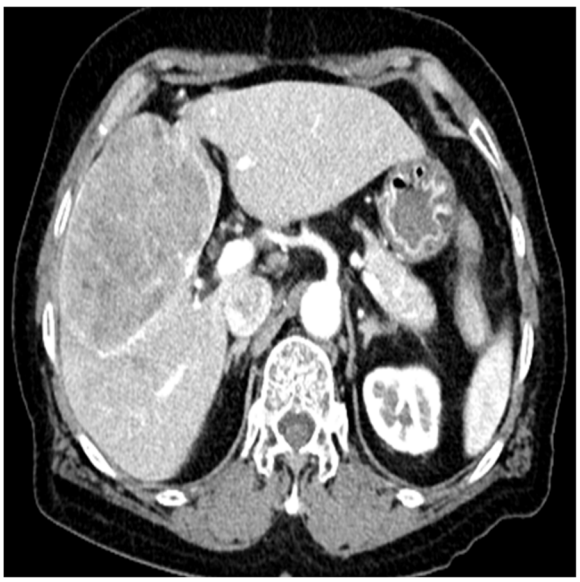

Fig. 1 Computed tomography (CT) demonstrating a large tumor (9.5 cm in diameter) in the medial and anterior segments of the liver

She had a history of two pregnancies with no history of blood transfusion. She was group B and RhD-positive as classified by ABO and Rh respectively. A preoperative antibody test using a polyethylene glycol/Coombs showed 3+ reactivity with all 11 panel cells (Table 1). However, additional identification test using an enzyme card revealed no reaction. The autocontrol and direct antiglobulin test were negative. Suspecting the existence of an antibody to a high-prevalence antigen, further tests

Table 1 Result of antibody screening

		Rh-hr								KELL						DUFFY		KIDD		Xg	LEWIS		MNS				P	Lutheran		Results
Cell #	Rh-hr	D	C	E	c	e	f	C^W	V	K	k	Kp^a	Kp^b	Js^a	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	Xg^a	Le^a	Le^b	S	s	M	N	P_1	Lu^a	Lu^b	PEG/Coombs
1	R1wR1	+	+	0	0	+	0	+	0	0	+	0	+	0	+	+	0	+	+	+	0	+	0	+	+	+	+	0	+	3+
2	R1R1	+	+	0	0	+	0	0	0	+	+	0	+	nt	+	0	+	+	0	0	+	0	+	+	+	+	+	0	+	3+
3	R2R2	+	0	+	+	0	0	0	0	+	+	0	+	nt	+	+	+	0	+	+	0	0	0	+	+	0	+	0	+	3+
4	R_0r	+	0	0	+	+	+	0	+	0	+	0	+	0	+	0	0	+	0	0	0	0	+	+	+	+	+	0	+	3+
5	r′r	0	+	0	+	+	+	0	0	0	+	0	+	0	+	+	+	+	+	0	+	0	+	+	+	0	+	0	+	3+
6	r″r	0	0	+	+	+	+	0	0	0	+	0	+	0	+	0	+	0	+	+	0	+	+	+	+	+	+	0	+	3+
7	rr	0	0	0	+	+	+	0	0	+	+	+	+	0	+	0	+	+	+	+	0	+	+	+	+	+	+	0	+	3+
8	rr	0	0	0	+	+	+	0	0	0	+	0	+	nt	+	0	+	+	0	+	+	0	0	+	0	+	+	0	+	3+
9	rr	0	0	0	+	+	+	0	0	0	+	0	+	nt	+	+	+	0	+	+	0	+	+	0	+	0	0	0	+	3+
10	rr	0	0	0	+	+	+	0	0	0	+	0	+	0	+	+	0	+	+	0	0	+	0	+	0	+	0	0	+	3+
11	R1R1	+	+	0	0	+	0	0	0	0	+	0	+	nt	+	0	+	0	+	+	0	+	+	0	+	0	+	+	+	3+
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nt not tested, *PEG* polyethylene glycol

on erythrocyte antigens and antibodies were requested from the reference laboratory (the Kyusyu Blood Center of the Japanese Red Cross Society in Fukuoka, Japan) where the anti-Ge antibody with titer of 32 was detected. Negative results for Ge antigen were also shown using sera including anti-Ge. Results from additional blood type antigen test other than those for the Ge antigens were as follows: C+c+E+e+, M+N+, S−s+, Le(a−b−), P_2, Fy(a+b−), Jk(a−b+), Di(a−b+), Xg(a+), Jr(a+). There was neither frozen blood stored nor Ge negative donor registered in Japan. There were no other Ge negative members in her family.

The management of the patient was intensively discussed with a multidisciplinary team of experts from the departments of hematology, clinical laboratory, oncology, hepatology, radiology, and anesthesiology. Since it was hard to predict the degree and severity of adverse events related to HTRs by incompatible transfusion, preoperative autologous donation (PAD) and acute normovolemic hemodilution (ANH) were planned to avoid perioperative allogenic blood transfusion as far as possible. After explaining the risks and benefits of the surgical intervention with the possibility of incompatible transfusion to the patient, she agreed to proceed for the surgery. A total of 800 ml autologous blood was preserved preoperatively under erythropoietin therapy, epoetin beta 6000 IU intravenous administration three times a week, supplemented by the daily administration of iron. Warfarin was interrupted 4 days before surgery, subsequently intravenous unfractionated heparin was started at 10,000 units per day, and stopped 6 h before surgery.

Several measures were incorporated after the induction of general anesthesia. These included insertion of Swan-Gantz catheter for evaluation of cardiac function for moderate to severe aortic stenosis; insertion of a flexible double lumen catheter for continuous hemodiafiltration (CHDF) in preparation to deal acute HTRs preceded by an unanticipated transfusion; a collection of 700 ml autologous blood as ANH; and a "stand-by" set up of intraoperative cell salvage. Surgery was performed through an inverted T-shaped incision. The tumor was located in the S4, S5, and S8 of the liver (Fig. 2a). First, a cholecystectomy with an insertion of a 6 Fr. tube via a cystic duct for post-hepatectomy bile leakage test was performed, and was followed by the dissection of the hepatic hilum. The middle hepatic artery and the anterior branch of the right hepatic artery originated from the superior mesenteric artery were ligated and divided. Infra-hepatic inferior vena cava (IVC) above the confluence of the left renal vein was encircled by a cotton tape with a tourniquet (Fig. 2b). Mobilization of the right lobe of the liver was performed with the division of the right coronary, triangle, and the hepato-renal ligaments, while the short hepatic veins were not divided. Liver transection was performed with Thunderbeat® (TB) (Olympus Medical Systems Corp., Tokyo, Japan) and a cavitron ultrasonic surgical aspirator (CUSA) along with the

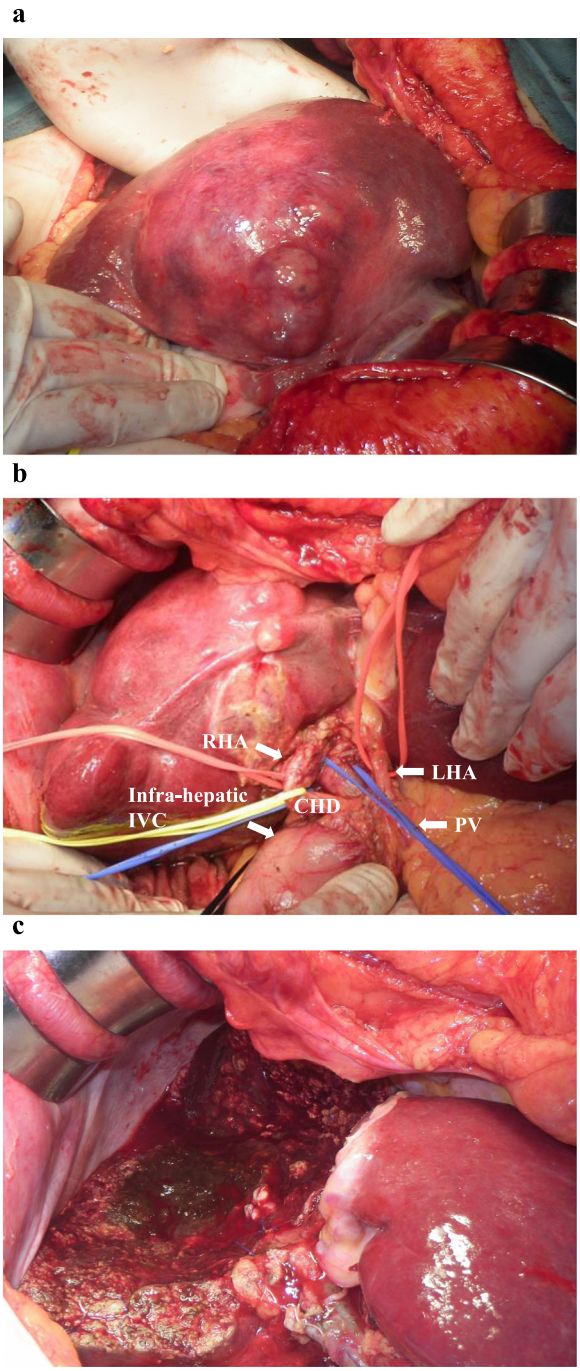

Fig. 2 Intra-operative finding. **a** An elastic hard expanding tumor in the segments 4, 5, and ventral site of the segment 8. **b** Hepatic hilum dissection and encircling of the infra-hepatic IVC with a tape. RHA: right hepatic artery; LHA: left hepatic artery; CHD: common hepatic duct; PV: portal vein; IVC: inferior vena cava. **c** Completion of the central hepatectomy without the caudate lobectomy of the liver

Pringle maneuver in cycles of clamp/unclamp time of 15/5 min. After intravenous administration of 100 mg of hydrocortisone, parenchymal transection was initiated just right to the falciform ligament, during which inflow structures of S4 arising off of the hilar plate were ligated and divided. During the transection of parenchyma on this plane, down to the para-caval portion of the caudate lobe, we encountered a longitudinal split injury on the dorsal side of the middle hepatic vein at the confluence of one of the drainage veins from S4B. The liver was transected just left to the right hepatic vein by using TB alone under simultaneous Pringle maneuver and infrahepatic IVC clamping, while preserving hemostasis with digital compression of the injured portion. The middle hepatic vein was clamped about 2 cm distal from its root, divided, and double ligated at the proximal site. Glissonian pedicles of S5 and S8 was double ligated and divided, respectively, and a CH without caudate lobectomy was performed (Fig. 2c). However, a small portion of S8 and S4B was spared. Frozen sections of the surgical margins revealed negative margins. Hemostasis of the transection line was achieved with suture ligation and soft coagulation. Bile leakage test was performed by using indigocarmine dye. Tachosil® was applied to the raw surface and a closed suction drain was placed. The estimated blood loss was 1380 ml without requiring intraoperative cell salvage and an allogenic blood transfusion. The operative time was 260 min. The weight of resected liver specimen was 342 g. The peri- and intraoperative course of Hb and Ht values with description of PAD and ANH under erythropoietin therapy was demonstrated in Fig. 3. Pathologically, the tumor was found to be a moderately differentiated HCC measuring 9.5 × 8.0 cm with negative surgical margins (Fig. 4).

On postoperative day (POD) 1, the Hb level was 8.7 mg/dl and the Ht was 27%. The total bilirubin was 0.7 mg/dl, AST was 621 U/l, ALT was 451 U/l, and PT was 67% (INR 1.27). Anticoagulation therapy was resumed on POD 2 after confirming the absence of bleeding complications. The postoperative course was uneventful except for congestive heart failure classified as grade II by Clavien-Dindo classification [7]. On POD 18, the patient was discharged from the hospital with her Hb level, 9.8 mg/dl; Ht, 32%; total bilirubin, 0.6 mg/dl; AST, 29 U/l; ALT, 40 U/l and PT, 50% (INR: 1.56). She is alive with no sign of recurrence after 45 months after surgery.

Discussion

In this report, we demonstrated how CH for HCC could be successfully performed in a patient with positive anti-Ge alloantibody without the need for allogeneic blood transfusion. A multidisciplinary team approach tailored with utmost technical adjustments appears to be crucial in this challenging and high-risk surgery.

Preoperative management included PAD [8] facilitated by erythropoietic therapy with recombinant human

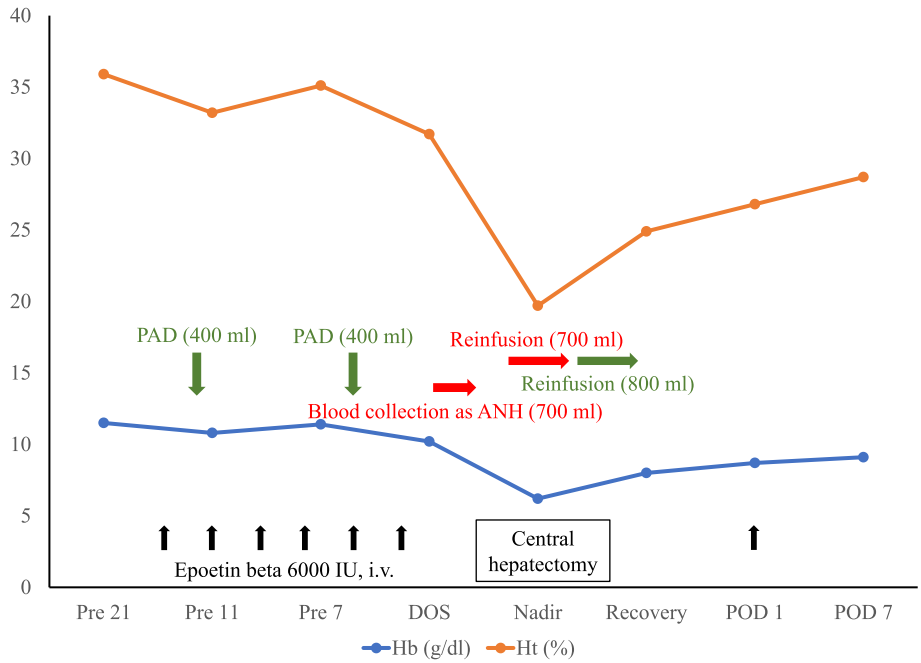

Fig. 3 Peri- and intra-operative course of Hb and Ht values with description of PAD and ANH under erythropoietin therapy. Hb: hemoglobin; Ht: hematocrit; PAD: preoperative autologous donation; ANH: acute normovolemic hemodilution; Pre: preoperative day; DOS: day of surgery; Nadir: intraoperative hemoglobin nadir; Recovery: in recovery room

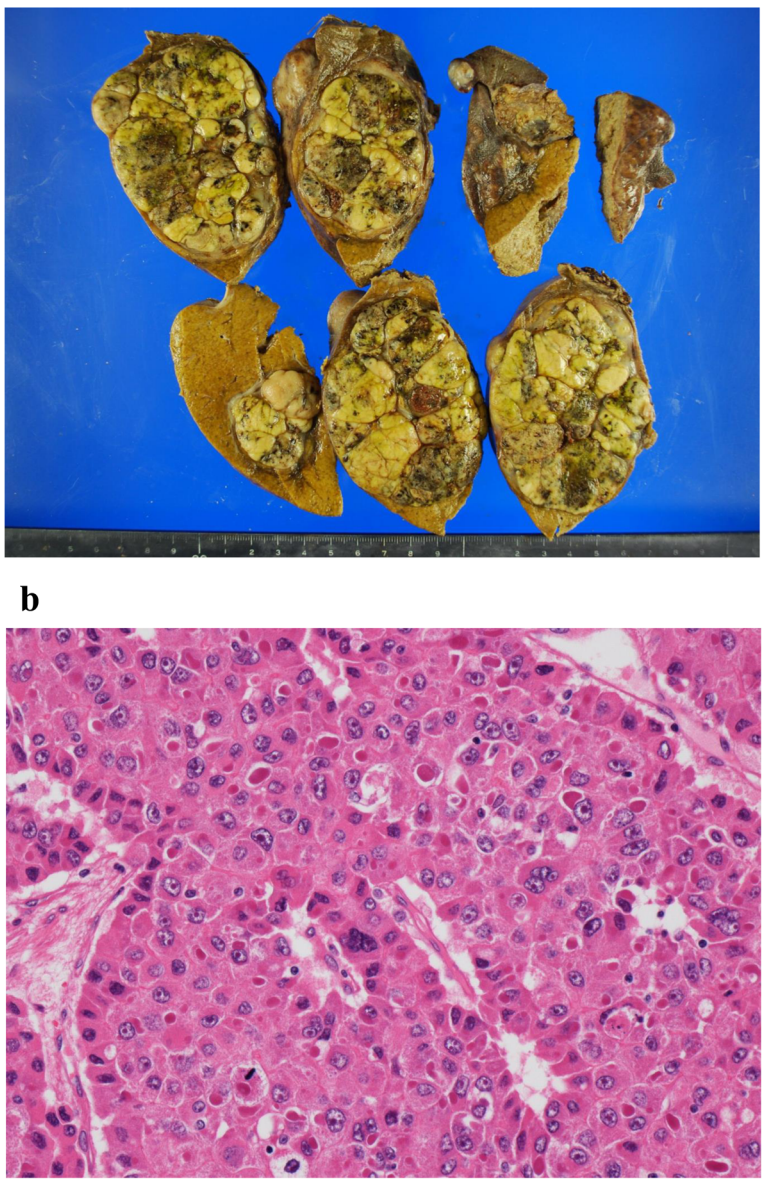

Fig. 4 Pathological finding of the specimen. a The tumor macroscopically showed a confluent multinodular type. **b** The tumor was moderately differentiated hepatocellular carcinoma (Hematoxylin and eosin staining)

erythropoietin supplemented by daily administration of iron [9, 10]. The patient underwent 2 times of PAD as often as once a week with 400 ml withdrawal of whole blood until 72 h before surgery [11]. In addition, extensive discussions regarding the natural course of the disease [12], the treatment options [13], the standard surgical strategies, the expected intraoperative blood loss [5], and the prediction and preparation for adverse events in case of incompatible blood transfusion [2] are pivotal. We had three separate meetings and repeatedly discussed all the details with the patient and the team before we agreed to proceed for the surgery.

The intraoperative transfusion management included measures to avoid and at the same time, prepare, for incompatible transfusion; autologous blood collection as ANH immediately prior to operation [14]; setting for blood salvage with a cell saver [15]; insertion of a flexible double lumen catheter for CHDF [16]. ANH is known to be one of the best strategies to prevent perioperative red blood cells (RBCs) transfusion; however, the amount of

blood withdrawal, leading hemodilutional coagulopathy and fluid overload remain major concern [14]. The withdrawal volume of whole blood as ANH was determined by the anesthesiological team according to estimation of initial blood volume (65 ml/kg) and initial and target hemoglobin. Thus, 700 ml of blood to be collected was determined by the formula [17]: $V = \mathrm{EBV} \times (\mathrm{H_i}-\mathrm{H_f})/\mathrm{H_{av}}$, where V was the volume of blood to be withdrawn (700 ml in this case), EBV was the estimated blood volume of the patient (2860 ml in this case), H_i was the initial hematocrit before the procedure (32% in this case), H_f was the target final hematocrit after hemodilution (25% in this case), and H_{av} was the average of the H_i and H_f (28.5% in this case). In fact, her Hb level during liver resection immediately after hepatic vein injury dropped up to 6.2 g/dl. Autologous blood reinfusion was also performed under preference by anesthesiologists based on the Hb level, hemodynamics, and the progression status of the operation. We escaped using blood salvage system as many onco-surgeons are reluctant to use the blood for the theoretical risk of tumor dissemination [18]. However, surgeon should decide to use or spare the cell salvage depending on the patients' condition, as no concrete evidence on the sequelae of the salvaged blood in cancer patients exists. Acute and delayed HTRs by incompatible transfusion in patients with anti-Ge alloantibody have not been well-documented. While there were a few reports documented on successful transfusion of Ge-positive RBCs to patients with an anti-Ge alloantibody [19, 20], Baughn and colleagues reported a case of acute HTRs induced by multiple transfusion [2]. Taking into consideration the possibility of life-threating complications by acute HTRs such as vital shock, renal failure and disseminated intravascular coagulation, we inserted a flexible double lumen catheter and prepared for CHDF along with steroid and immunoglobulin.

The surgical strategy included precise surgical techniques with careful dissection; meticulous hemostasis; anesthesiologist-guided low central venous pressure during liver transection; bloodless liver transection with Pringle maneuver and infra-hepatic IVC clamping; and use of TB with CUSA. The liver transection time from the beginning of the parenchyma resection to the removal of the specimen of liver in the patient was 45 min. With this experience, we have been advocating this procedure (TB liver transection under simultaneous Pringle maneuver and infra-hepatic IVC clamping) for especially high complexity major liver resection [21, 22].

Postoperative management included the continuation of erythropoietic therapy supplemented with the daily administration of iron and reinstitution of anticoagulation therapy. A decline in postoperative serum Hb and Ht levels without active evidence of bleeding until POD 3 after liver resection was reported [23]. Careful observation and continuation of erythropoietic therapy are recommended, even if the patient does not have any obvious symptoms of anemia [9]. Early reinstitution of anticoagulation therapy was also essential in this elderly patient. On POD 2, heparin was restarted after confirming the absence of bleeding complications and was switched to warfarin to prevent thromboembolic complications such as major adverse cardiovascular events, cerebrovascular stroke, pulmonary embolism, or portal vein thrombus [24].

Conclusions

To our knowledge, this is the first case report of hepatectomy in a patient with anti-Ge alloantibody. A multidisciplinary tailored approach remains crucial in establishing a concrete treatment and management modality. PAD and ANH with perioperative erythropoietic therapy combined with bloodless liver resection should be advocated during major hepatectomy in patients with extremely rare blood type.

Abbreviations

Ge: Gerbich; HTRs: Hemolytic transfusion reactions; CH: Central hepatectomy; HCC: Hepatocellular carcinoma; Hb: Hemoglobin; Ht: Hematocrit; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PT: Prothrombin time; INR: International normalized ratio; CT: Computed tomography; MRI: Magnetic resonance image; S: Segment; AFP: Alpha-fetoprotein; PIVKA-II: Protein induced by vitamin K absence or antagonist II; HCV: Hepatitis C virus; RLV: Remnant liver volume; SLV: Standard liver volume; PAD: Preoperative autologous donation; ANH: Acute normovolemic hemodilution; CHDF: Continuous hemodiafiltration;; IVC: Inferior vena cava; TB: Thunderbeat®; CUSA: Cavitron ultrasonic surgical aspirator; POD: Postoperative day

Acknowledgements

None

Authors' contributions

All authors participated in the operation or management of the patient in this case report. TK, HY, BA, and MK performed the operation. TK, MI, and BA drafted and revised the manuscript. The authors read and approved the final manuscript.

Funding

No funding was obtained from the private or public sector for this research.

Availability of data and materials

Not applicable

Ethics approval and consent to participate

Not applicable

Consent for publication

The patient provided consent for publication.

Competing interests

The authors declare that they have no competing interests.

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Received: 1 April 2020 Accepted: 5 June 2020
Published online: 12 June 2020

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Publisher's Note

Annals of Medicine and Surgery 62 (2021) 207–210

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Case Report

Pancreaticoduodenectomy after transcatheter aortic valve implantation in an elderly patient with severe aortic stenosis and pancreas cancer: A case report

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ARTICLE INFO

Keywords:
Pancreatic head cancer
Pancreaticoduodenectomy
Aortic stenosis
Transcatheter aortic valve implantation

ABSTRACT

Introduction and importance: Not only pancreatic cancer but also aortic stenosis (AS) is increasing with the aging population. There is no optimal strategy for elderly patients with both pancreatic cancer and AS. We report a case of pancreatic head cancer with severe AS undergoing pancreaticoduodenectomy (PD) after transcatheter aortic valve implantation (TAVI).

Case presentation: An 88-year-old woman was referred to our hospital because of severe AS with symptoms of heart failure. Preoperative examination revealed resectable pancreatic head cancer, so TAVI was performed before PD to reduce the perioperative risk. The patient underwent PD 34 days after TAVI, with no significant postoperative complications, and was transferred to the other hospital for rehabilitation on postoperative day 45. No recurrence was observed at more than 7 months without adjuvant therapy.

Clinical discussion: Aortic valve replacement (AVR) is recommended before non-cardiac surgery in patients with symptomatic severe AS. Surgical aortic valve replacement (SAVR) is the standard treatment. However, owing to the highly invasive procedure and increased perioperative risk, SAVR is usually avoided in elderly patients with malignancy and severe AS. We demonstrated that TAVI followed by PD could be safely performed in high-risk elderly patients presenting with both severe AS and pancreatic head cancer. To our knowledge, this is the first case report of PD after TAVI in a patient with severe AS.

Conclusion: We demonstrated that TAVI followed by PD could be safely performed in high-risk elderly patients presenting with severe AS and co-existing malignancy.

1. Introduction

The number of patients with pancreatic cancer is increasing with the aging population [1]. Surgical treatment is recommended in resectable pancreatic cancers [2]. Pancreaticoduodenectomy (PD) is the standard procedure for pancreatic head cancer, but it is one of the most demanding procedures and the European Society of Cardiology guidelines suggests it as a high-risk procedure with a 30-day risk of cardiovascular deaths and myocardial infarction [3]. This warrant preoperative evaluation of complications in patients with co-existing cardiovascular diseases to ensure safe perioperative management after PD.

Aortic stenosis (AS) is another disease that is increasing with the aging population [4]. The standard treatment for severe AS is surgical aortic valve replacement (SAVR). However, due to the higher perioperative risk in the elderly and cancer patients, they have been considered unsuitable for SAVR [5]. Recently, for such cases, minimally invasive transcatheter aortic valve implantation (TAVI) is increasingly being performed [6].

In elderly patients with cancer and AS, the optimal treatment is not

Abbreviations: PD, Pancreaticoduodenectomy; AS, Aortic stenosis; SAVR, Surgical aortic valve replacement; TAVI, Transcatheter aortic valve implantation; CT, computed tomography; DAPT, dual antiplatelet therapy; CPB, Cardiopulmonary bypass.

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https://doi.org/10.1016/j.amsu.2021.01.050
Received 29 November 2020; Received in revised form 14 January 2021; Accepted 15 January 2021
Available online 21 January 2021

well established and complex choices have to be made. Preceding TAVI may be a useful therapeutic strategy for earlier and safer surgical intervention for malignancy. In this article, we report a case of pancreatic head cancer with severe AS undergoing PD after TAVI that highlights the importance of efficient therapeutic strategy and secure management in elderly patient with gastroenterological malignancy and severe AS. This work was done in compliance with SCARE checklist [7].

2. Case presentation

An 88-year-old woman was referred to our hospital because of severe AS with symptoms of heart failure (New York Heart Association class II). The patient's medical history included appendectomy in her twenties, cataract surgery 10 years ago, chronic kidney disease, hypertension, hyperlipidemia, hyperuricemia, and osteoporosis. She was a non-smoker and non-alcoholic and was taking imidapril (5 mg), amlodipine (5 mg), rosuvastatin (2.5 mg), carvedilol (0.625 mg), and eldecalcitol (0.75 μg) per day orally at home. Family history was negative. Echocardiography showed very severe AS with an aortic valve area of 0.61 cm^2, a mean aortic pressure gradient of 78 mmHg, a maximum jet velocity of 5.6 m/s, and an ejection fraction of 76%. SAVR or TAVI was indicated, but pancreatic head cancer was diagnosed on preoperative computed tomography (CT) (Fig. 1). The cancer graded T3, N0, M0, clinical Stage IIA based on the 7th edition of the General Rules for the Study of Pancreatic Cancer, resectable on CT, required surgical intervention. However, due to severe AS, the perioperative risk of PD was high. The European Society of Cardiology guidelines recommend that SAVR or TAVI should be prioritized in symptomatic severe AS patients with non-cardiac surgery [8], and we decided to prioritize the treatment of severe AS in this case as well. Although the predicted risk of mortality of SAVR was moderate at 5.6% according to the Society of Thoracic Surgeons web-based calculator (http://riskcalc.sts.org/stswebriskcalc/calculate), TAVI instead of SAVR was performed by a senior cardiologist and a cardiovascular surgeon because of the advanced age, the risk of dissemination of cancer cells by immunosuppression due to extracorporeal circulation during SAVR and to avoid the possibilities that would delay PD because of the highly-invasive nature of SAVR.

The patient underwent TAVI through the right femoral artery in May 2020 (Fig. 2). A 23 mm SAPIEN 3 valve (Edwards Lifesciences Corp., Tokyo, Japan) was placed under rapid pacing (180 bpm). There were no perioperative complications. Echocardiography showed an improvement in an aortic valve area of 1.63 cm2, a mean aortic pressure gradient of 10 mmHg, and a maximum jet velocity of 2.5 m/s.

After TAVI, the patient was treated with dual antiplatelet therapy (DAPT) including aspirin and clopidogrel. Aspirin and clopidogrel were discontinued for 7 days and 14 days respectively, prior to the surgery and were replaced with unfractionated heparin for 7 days with target activated partial thromboplastin time of 1.5–2 times the control value. Subtotal stomach-preserving PD followed by invaginated pancreaticogastrostomy, hepaticojejunostomy and ante colic gastrojejunostomy was performed by a senior general surgeon 34 days after TAVI. The operation time was 279 minutes and the estimated blood loss was 900 ml. Aspirin was resumed on postoperative day 3 and clopidogrel was resumed on postoperative day 7. There were no complications, including post-pancreatectomy hemorrhage, postoperative pancreatic fistula, delayed gastric emptying, or valve thrombosis after surgery. The pathological diagnosis was T3, N0, M0, tubular adenocarcinoma, pathological Stage IIA (Fig. 3). The patient was transferred to another hospital 45 days after surgery for rehabilitation for disuse muscle weakness. No recurrence and symptoms of heart failure were observed at more than 7 months without adjuvant therapy.

33. Discussion

The incidence of AS is increasing with the aging population [4]. Similarly, the number of patients with malignant tumors is also increasing. Although the exact prevalence of malignancy in patients with AS has not been reported, the most recent meta-analysis found that 368 (7.1%) of the 5162 patients who underwent TAVI in three studies had co-existing malignancy [9–12]. In AS patients with concomitant malignancy, the treating surgeons may have difficulty establishing therapeutic priorities. The European Society of Cardiology guidelines recommend preoperative AVR in cases of symptomatic severe AS, as in this case, or even asymptomatic severe AS undergoing non-cardiac surgery with high risk of perioperative cardiovascular complications [13].

Although SAVR had been established as the standard treatment for severe AS, however, due to its highly invasive nature and increased perioperative risk, SAVR is often avoided in patients with co-existing malignancy [5]. This led to frequent treatment dilemma if surgery for malignant tumors should be considered in these patients. In recent years, with the introduction of TAVI, which is less invasive than SAVR, the perspective of management has been shifting in these high-risk patients [6]. There are two major benefits of TAVI in cancer patients: by avoiding cardiopulmonary bypass (CPB), bleeding from the tumor along with tumor dissemination associated with immunosuppression can be prevented [14–17], and second, TAVI does not require sternotomy and CPB offering benefits of a minimally invasive procedure that allows for faster postoperative recovery and a shorter transition time for the treatment of malignant tumor. Complications after TAVI were reported to be no different between patients with and without cancer, demonstrating the safety of TAVI in cancer patients [9]. However, the mortality rate at 1 year after TAVI is significantly higher in cancer patients with Stage III-IV than in patients without cancer [10], and the indication should be carefully considered. In this case, although the perioperative risk of SAVR was moderate at 5.6% according to the Society of Thoracic Surgeons web-based calculator (http://riskcalc.sts.org/stswebriskcalc/calculate), considering the age and frailty (Clinical Frailty score 4/9)

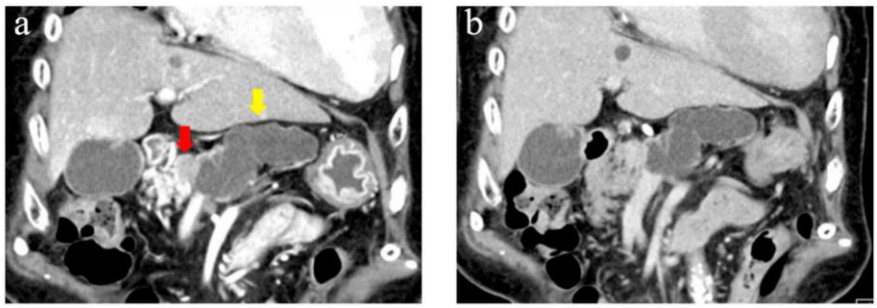

Fig. 1. Preoperative computed tomography findings. **a** Hypovascular mass (red arrow) compared to the pancreatic parenchyma in the early phase and main pancreatic duct dilatation (yellow arrow). **b** Mass shadow with a contrast-enhancing effect in the late phase. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

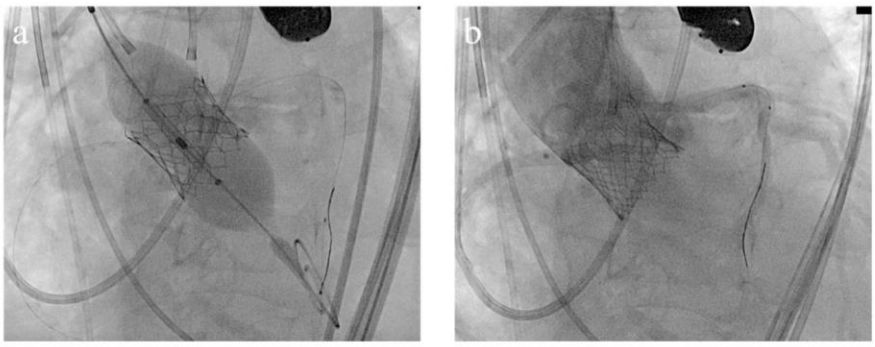

Fig. 2. Fluoroscopy during transcatheter aortic valve implantation. **a** Implantation of a self-expanding 23-mm SAPIEN 3 valve. **b** Aortography after valve deployment.

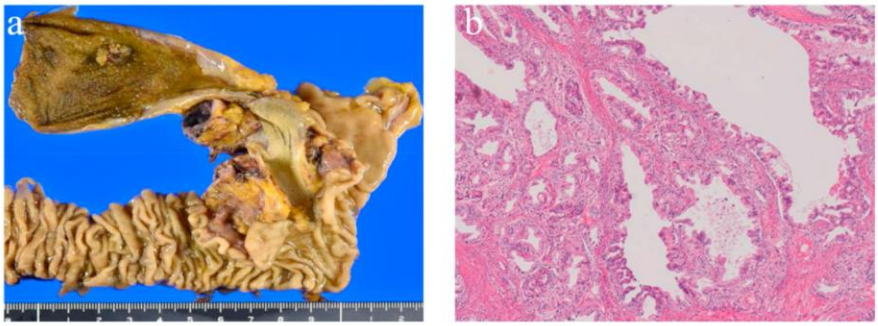

Fig. 3. Pathological findings of the specimen. **a** Resected specimen showed a 30 × 15 mm white nodular lesion in the head of the pancreas. **b** Histological specimens showed an invasive adenocarcinoma.

of the patient and pancreatic head cancer that required surgical intervention (cStage IIA, resectable), we preceded with TAVI.

Since the patient had no pancreatic head cancer-related symptoms, she was treated with DAPT after TAVI and allowing a month gap before PD. There is no clear consensus suggesting the time between TAVI and non-cardiac surgery. Also, DAPT including aspirin and clopidogrel is recommended for 3–6 months as antithrombotic therapy after TAVI to prevent valve thrombosis [18]. In this case, there was about a month gap to PD with no risk of bleeding from the tumor, so DAPT was performed as recommended, and heparin replacement was also performed during the withdrawal period. However, a recent report showed no difference in the development of emboli after TAVI and a lower risk of bleeding with aspirin alone compared to DAPT [19]. Clopidogrel has a long withdrawal period of 14 days, antithrombotic therapy with aspirin alone may be useful in cases that require early surgical intervention after TAVI in cases where there is a risk of tumor progression or bleeding from the tumor, such as gastric or colon cancer.

PD is a complex surgical procedure with a high risk of cardiovascular complications, but by correcting severe AS before PD, the perioperative period could be managed safely without complications such as bleeding events, embolism and valve thrombosis, even with DAPT. To the best of our knowledge, this is the first case report of PD after TAVI in a patient with severe AS.

4. Conclusion

Preceding TAVI in elderly patients with malignancy and severe AS may be a useful therapeutic strategy for earlier and safer surgical intervention for malignancy. However, the number of cases of non-cardiac surgery after TAVI is still few, and there is no clear consensus on perioperative antithrombotic therapy or time to non-cardiac surgery. Further high quality and larger cohort studies are required to get a better insight in identifying a solid therapeutic strategy in operable cancer patients with severe AS.

Provenance and peer review

Not commissioned, externally peer reviewed.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. Patient perspective: “I am glad that many doctors will learn from my case and I do not mind my name or my condition being addressed on the case study."

Ethical approval

N/a.

Funding

No source of funding was received.

Author contribution

Ryo Imada drafted the manuscript and provided the original pictures. Teruo Komokata revised the manuscript critically. All authors read and approved the final manuscript.

Research registration (for case reports detailing a new surgical technique or new equipment/technology)

N/a.

Guarantor

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Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.amsu.2021.01.050.

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Journal of Dermatological Science 99 (2020) 152–157

Contents lists available at ScienceDirect

Journal of Dermatological Science

journal homepage: www.jdsjournal.com

Original Article

Prediction of the invasive level of basal cell carcinomas in the facial area: Analysis of 718 Japanese cases

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ARTICLE INFO

Article history:
Received 21 March 2020
Received in revised form 17 June 2020
Accepted 2 July 2020

Keywords:
Basal cell carcinoma
Invasion level
Tumor thickness
Vertical edge

ABSTRACT

Background: Basal cell carcinoma (BCC) is the most common skin cancer. While Mohs micrographic surgery is commonly accepted for BCC treatment, surgical excision with free margins is widely considered the best treatment modality for BCCs in Japan. However, little is known about the predictors of the invasion levels of BCCs.
Objective: To investigate the optimization of deep surgical margins by identifying factors significantly influencing the invasion levels of facial BCCs.
Methods: The tumor invasion level was defined as the deepest part of a tumor. Tumor thickness was measured from the top of the granular layer to the deepest extension of the tumor or from the ulcer base overlying the deepest point of invasion in ulcerated lesions. Factors independently associated with tumor thickness and invasion level were identified by multivariate analysis. Six variables were tested: age, sex, anatomical region (nose, orbit, others), histologic pattern (aggressive, non-aggressive), presence of pigmentation, and diameter.
Results: We included 718 cases of facial BCCs involving 705 Japanese patients. The most frequent anatomical region and histologic pattern were the nose and nodular pattern, respectively. Only tumor diameter showed a correlation with tumor thickness ($\beta = 0.377$, $P < 0.001$). Tumor diameter (AOR = 71.189, 95 % CI: 11.420–430.931, $P = 0.01$) and the following anatomical regions showed correlations with the invasion level: nose/others: AOR=2.769, 95 % CI: 1.235–6.493, $P = 0.01$; orbit/others: AOR=6.369, 95 % CI: 2.728–15.429, $P < 0.001$; orbit/nose: AOR=2.300, 95 % CI: 1.056–4.984, $P = 0.04$.
Conclusions: This study serves as a guide for optimizing deep surgical margins and planning surgery for facial BCCs considering independently associated factors.

1. Introduction

Basal cell carcinoma (BCC) is the most common skin cancer, and its incidence rate is increasing [1]. BCC characteristically arises in body parts that are exposed to the sun and is most common on the head and neck (80 %), followed by the trunk (15 %), and the arms and legs [2]. Since BCC has low metastatic potential, treatment focuses on local control.

Treatment options for BCCs include standard surgical excision, Mohs micrographic surgery (MMS), curettage with or without electrodesiccation, cryosurgery, photodynamic therapy, radiation therapy, and medical therapy with topical agents or intralesional injections [3,4]. MMS is commonly accepted for the treatment of BCC with non-pigmented lesions and/or poorly defined clinical borders. However, Asian patients tend to develop BCCs with pigmented and/or well-defined clinical borders [5–7]. Moreover, MMS requires specialized equipment and a trained technician. Therefore, surgical excision with free margins is widely considered the best treatment modality for BCC in Japan.

Although an optimized lateral surgical margin has been identified [8], little is known about the appropriate deep surgical margin for BCCs in the facial area. In the current National

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https://doi.org/10.1016/j.jdermsci.2020.07.001
0923-1811/

Comprehensive Cancer Network (NCCN) Guidelines for BCC, the recommended surgical treatment strategies are standard excision with optimized side margins or the use of MMS [8]; no references to appropriate deep margins are mentioned. Since the facial area has a variety of tissue constructions among the anatomical regions, consideration of aesthetic and functional aspects are needed for the surgical treatment of BCC.

This study has the largest sample size for an Asian population. Here, we investigated the optimization of adequate deep surgical margins by identifying factors that significantly influence the invasion levels of BCCs arising in facial areas.

2. Materials and methods

2.1. Patients

We retrospectively collected data from 705 patients with 718 cases of primary BCC treated by surgical excision at either Kagoshima Medical Center from 2014 to 2017, Saitama Medical University International Medical Center from April 2008 to July 2018, or University of Tsukuba from April 2004 to January 2018. Caucasian patients were excluded. All surgery was conducted by board-certified dermato-oncologists, and dermatologists with guidance of a supervisor who possesses dermatosurgery skills in each institution. The study was started after approval was issued by those three institutions, according to the institutions' respective Institutional Review Board guidelines. The requirement for written informed consent for retrospective deidentified patient data was waived, and the study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki (2013 revision).

Data of patients' characteristics, including anatomical regions (nose, orbit, lip, auricle, or others, including the cheek, chin, forehead, and temporal region), histologic characteristics, tumor diameter, tumor thickness, invasion levels (dermis, subcutis, muscle, or cartilage/bone), and modalities of surgery were extracted from medical records. The tumor diameter, tumor thickness, and invasion levels were determined independently or cooperatively by 14 dermatologists (8 board-certified dermato-oncologists and 6 dermatologists under training) at each institution.

2.2. Histologic evaluation for tumor invasion levels and tumor thickness

Resected tumors were examined with routine hematoxylin and eosin (H&E) staining. Histologic patterns were classified as either nodular, superficial, micronodular, infiltrative, morpheic, or mixed as previously reported [9]. The micronodular, infiltrative, morpheic, and mixed types were classified as aggressive patterns based on the NCCN guidelines [8]. Tumor invasion levels were defined as the deepest part of the tumor. In the dermis, the invasion levels were distinguished according to Clark's scales for melanoma: invasion to the papillary dermis as *upper dermis*; invasion throughout the papillary dermis and impinging on the reticular dermis as *mid dermis*; and invasion to the reticular dermis as *deep dermis* [10]. Tumor thickness was determined according to Breslow's thickness for melanoma by measuring from the top of the granular layer to the deepest extension of the tumor; in ulcerated lesions, measurement was from the ulcer base overlying the deepest point of invasion [10]. The excised specimens were measured along multiple axes and the maximum length was adopted as the tumor thickness.

2.3. Statistical analysis

The Fisher-Freeman-Halton test was performed for the analysis of categorical variables. Spearman's rank correlation test was used to assess the correlation between tumor thickness and diameter. Six variables were included in the study: age, sex, anatomical region (nose, orbit, others), histologic pattern (aggressive, non-aggressive), presence of pigmentation, and diameter. Multiple regression analysis was performed to identify the factors independently correlating with tumor thickness. Multiple logistic regression analysis was used to identify factors that correlated with invasion levels up to the subcutis or to the muscle and below. All statistical analyses were performed with JMP version 14.2.0 (SAS institute, NC, USA) and EZR (Saitama Medical Center, Jichi Medical University; www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html) [11]. All P-values were two sided, and P-values of 0.05 or less were considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 705 patients with 718 cases of facial BCC were treated at 3 institutions: 276 patients at Kagoshima Medical Center, 183 patients at Saitama Medical University International Medical Center, and 259 patients at University of Tsukuba (Table 1). The study included 391 men (54.5 %) and 327 women (45.5 %) with a mean age of 74.8 years (range: 23–101 years). BCC regions were distributed as follows: 35.8 % nose, 15.3 % orbit, 8.2 % lip, and 5.2 % auricle. Clinically, most BCCs showed pigmentation (90.7 %). The histologic patterns were 70.3 % nodular (n = 505), 7.9 % infiltrative (n = 57), 5.9 % micronodular (n = 42), 2.0 % superficial (n = 14), 1.4 % morpheic (n = 10), and 12.5 % mixed (n = 90). Tumor diameters and

Table 1
Patients characteristics.

Characteristics	n (%)
No. of cases	718
Sex	
Male	391 (54.5)
Female	327 (45.5)
Age (years)	
Range	23–101
Mean	74.8
Anatomical region	
Nose	257 (35.8)
Orbit	110 (15.3)
Lip	59 (8.2)
Auricle	37 (5.2)
*Other	255 (35.5)
Presence of pigmentation	
Non-pigmented	67 (9.3)
Pigmented	651(90.7)
Histologic pattern	
Nodular	505 (70.3)
Superficial	14 (2.0)
Micronodular	42 (5.9)
Infiltrative	57 (7.9)
Morpheic	10 (1.4)
Mixed	90 (12.5)
Tumor diameter (mm)	
Range	0.5–45
Mean	9.19
Tumor thickness (mm)	
Range	0.1–23.7
Mean	2.86
Invasion level	
Upper dermis	26 (3.6)
Mid dermis	152 (21.2)
Deep dermis	403 (56.1)
Subcutis	92 (12.8)
Muscle	40 (5.6)
Cartilage/bone	5 (0.7)

* Other, including the cheek, chin, forehead, and temporal region.

thickness were in the range of 0.5–45 mm (mean: 9.19 mm) and 0.1–23.7 mm (mean: 2.86 mm), respectively. The invasion levels were 3.6 % upper dermis (n = 26), 21.2 % mid dermis (n = 152), 56.1 % deep dermis (n = 403), 12.8 % subcutis (n = 92), 5.6 % muscle (n = 40), and 0.7 % cartilage/bone (n = 5).

3.2. Tumor invasion level

Using the Fisher-Freeman-Halton test, tumor invasion levels showed significant correlation (P < 0.001) with histologic patterns, with morpheic-type BCCs showing invasion levels deeper than that of other types (Table 2). Tumor invasion levels were also significantly correlated with anatomical region (Fisher-Freeman-Halton test, P = 0.03); in 15 of 110 cases (13.6 %), tumors localized in the orbital region invaded significantly into the muscle and below, while more than 90 % of tumors in the other regions were limited to within the dermis (Table 3). Tumor invasions to the cartilage/bone (0.7 %, 5 of 718 cases) or the tarsus in the orbit (0.9 %, 1 of 110 cases) were extremely low (Tables 2 and 3). The tumor invasion levels did not correlate with the nasal sub-regions (i.e., the dorsum, sidewall, ala, tip, and soft triangle as defined according to the subunit principle [12]) by the Fisher-Freeman-Halton test (P = 0.27, data not shown). Multiple logistic regression analysis revealed that anatomical region and tumor diameter showed significant correlations with invasion to the subcutis or to the muscle and below: nose/others: AOR=2.769, 95 % CI: 1.235–6.493, P = 0.01; orbit/others: AOR=6.369, 95 % CI: 2.728–15.429, P < 0.001; orbit/nose: AOR=2.300, 95 % CI: 1.056–4.984, P = 0.04; diameter: AOR=71.189, 95 % CI: 11.420–430.931, P = 0.01 (Table 4).

3.3. Tumor thickness

Tumor thickness was significantly correlated with tumor diameter (Spearman's rank correlation coefficient; ρ = 0.465, P < 0.001) (Fig. 1a). The nodular and aggressive histologic patterns (micronodular, infiltrative, morpheic, and mixed) also showed significant correlation between tumor thickness and tumor diameter (Spearman's rank correlation coefficient; ρ = 0.481, P < 0.001, and ρ=0.423, P < 0.001, respectively) (Fig. 1b, c). However, the superficial type showed no correlation between tumor thickness and tumor diameter (Spearman's rank correlation coefficient; ρ = 0.414, P = 0.14) (Fig. 1d). In multiple regression analysis, only tumor diameter showed a significant correlation with tumor thickness (β = 0.377, P < 0.001) (Table 5).

3.4. Positive vertical edge

Microscopically assessed incomplete excision at the vertical edge was achieved in 14 of 718 cases (1.9 %). The proportion of a positive vertical edge was significantly correlated with the histologic pattern but not with the anatomical region (Fisher-Freeman-Halton test, P = 0.004 and P = 0.41, respectively) (Tables A1, A2). In particular, aggressive types showed a higher positive rate than the nodular type; there was no positivity in the superficial type. Tumor diameter was significantly correlated with a positive vertical edge (Fisher-Freeman-Halton test, P = 0.015), and tumors with ≥10 mm diameter showed a significantly higher positive rate (Fisher-Freeman-Halton test, P = 0.002) (Table A3). Since the multiple logistic regression analysis revealed that the tumor diameter and anatomical region were independent

Table 2
Correlation between histologic pattern and tumor invasion levels.

Histologic pattern	Upper dermis (%)	Mid dermis (%)	Deep dermis (%)	Subcutis (%)	Muscle (%)	Cartilage/Bone (%)	P
Nodular	12 (2.4)	133 (26.3)	282 (55.8)	51 (10.1)	26 (5.1)	1 (0.2)	< 0.001
Superficial	14 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Micronodular	0 (0)	7 (16.7)	24 (57.1)	9 (21.4)	1 (2.4)	1 (2.4)	
Infiltrative	0 (0)	9 (15.8)	34 (59.6)	9 (15.8)	5 (8.8)	0 (0)	
Morpheic	0 (0)	1 (10.0)	2 (20.0)	1 (10.0)	4 (40.0)	2 (20.0)	
Mixed	0 (0)	2 (2.2)	61 (67.8)	22 (24.4)	4 (4.4)	1 (1.1)	

Table 3
Correlation between anatomical region and tumor invasion levels.

Anatomical region	Upper dermis (%)	Mid dermis (%)	Deep dermis (%)	Subcutis (%)	Muscle (%)	Cartilage/Bone (%)	P
Nose	6 (2.3)	53 (20.6)	146 (56.8)	35 (13.6)	14 (5.4)	3 (1.2)	0.03
Orbit	6 (5.5)	22 (20.0)	61 (55.5)	6 (5.5)	14 (12.7)	1 (0.9) (tarsus)	
Lip	1 (1.7)	16 (27.1)	31 (52.5)	7 (11.9)	4 (6.8)	0 (0)	
Auricle	3 (8.1)	5 (13.5)	19 (51.4)	9 (24.3)	1 (2.7)	0 (0)	
Other	10 (3.9)	56 (22.0)	146 (57.3)	35 (13.7)	7 (2.7)	1 (1.4)	

Table 4
Multiple logistic regression analysis for identifying independent correlative factor with invasion level up to the subcutis or the muscle and below.

Factor	AOR (95 % CI)	P
Age (/1)	1.000 (0.973–1.030)	> 0.99
Sex (M/F)	1.125 (0.591–2.132)	0.72
Anatomical region (Nose/Others)	2.769 (1.235–6.493)	0.01
(Orbit/Others)	6.369 (2.728–15.429)	< 0.001
(Orbit/Nose)	2.300 (1.056–4.984)	0.04
Histologic pattern (Aggressive[1]/Non-aggressive[2])	1.606 (0.805–3.130)	0.18
Pigmentation (Non-pigmented/Pigmented)	0.510 (0.128–1.610)	0.27
Diameter (mm) (entire range)	71.189 (11.420–430.931)	0.01

AOR, adjusted odds ratio; CI, confidential interval.
[1] Micronodular, infiltrative, morpheic, or mixed.
[2] Superficial and nodular features in any parts of the tumor.

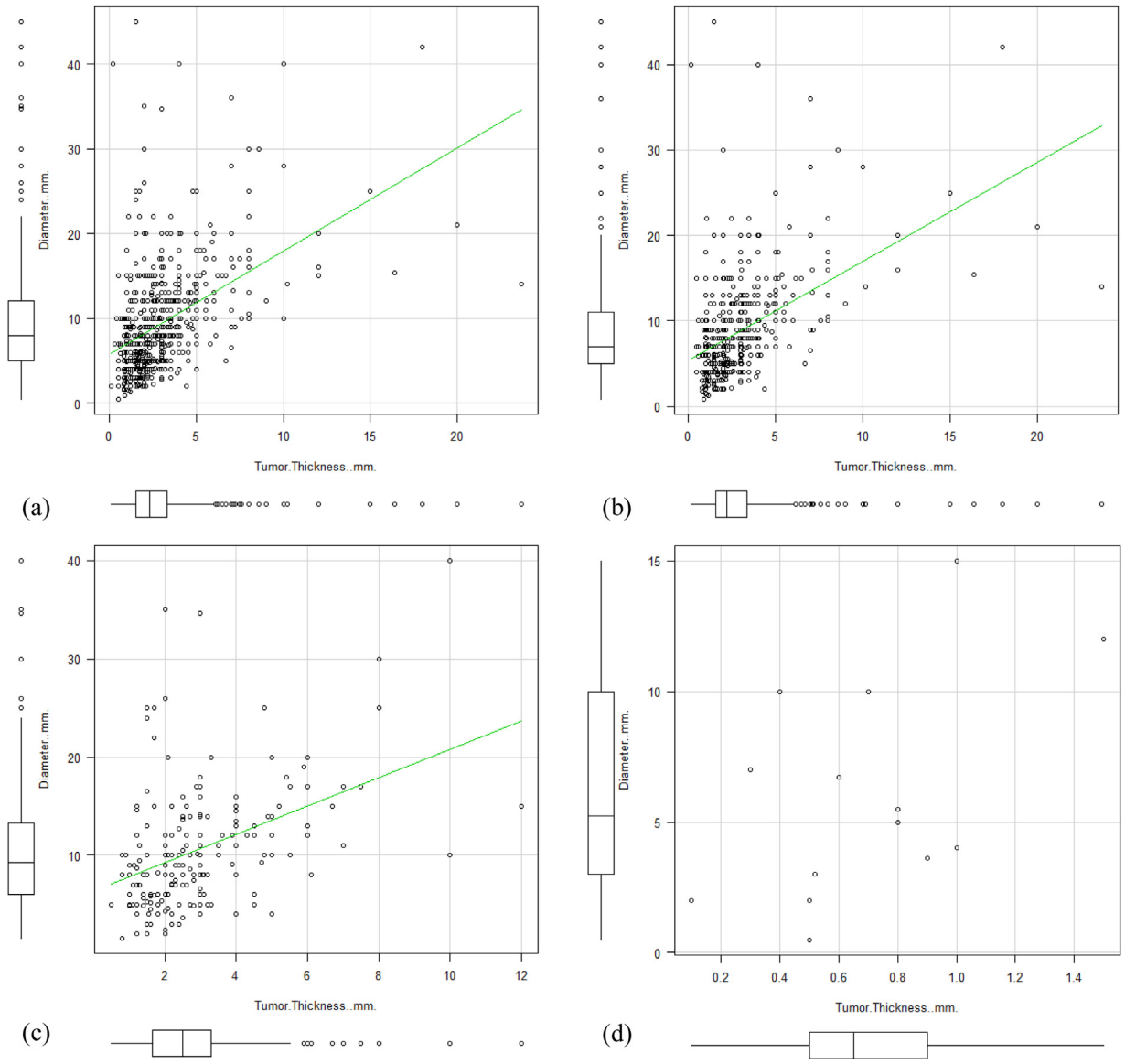

Fig. 1. Correlation between tumor thickness and diameter.
Tumor thickness was significantly correlated with tumor diameter (a) combined data for all types (Spearman's rank correlation coefficient; ρ = 0.465, P < 0.001); (b) the nodular type and (c) aggressive growth patterns (micronodular, infiltrative, morpheic, and mixed type) showed positive correlations with tumor thickness and tumor diameter (Spearman's rank correlation coefficient; ρ = 0.481, *P* < 0.001, and ρ=0.423, P < 0.001, respectively); (d) the superficial type showed no correlation between tumor thickness and tumor diameter (Spearman's rank correlation coefficient; ρ=0.414, P=0.14).

Table 5
Multiple regression analysis for identifying independent correlative factor with tumor thickness.

Variables	Regression coefficient	Standard Error	Standardized regression coefficient	t	*P*
Constant	0.380	0.642	0.000	0.59	0.55
Age	0.008	0.008	0.033	0.91	0.36
Sex	−0.051	0.102	−0.018	−0.50	0.62
Anatomical region	−0.169	0.144	0.042	−1.17	0.24
(nose, orbit, others)	0.169	0.117	0.040	1.11	0.27
Histologic pattern ([1]Aggressive, [2]Non-aggressive)	−0.189	0.117	−0.006	−0.16	0.87
Presence of pigmentation	0.108	0.198	0.216	0.55	0.59
Diameter (mm)	0.182	0.018	0.377	10.28	< 0.001

[1] Micronodular, infiltrative, morpheic, or mixed.
[2] Superficial and nodular features in any parts of the tumor.

influencing factors for the tumor invasion to the subcutis, or to the muscle and below, we further analyzed the correlation between the anatomical region and tumor invasion levels divided into <10 mm or ≥10 mm diameter, and found significant correlation (Fisher-Freeman-Halton test, P < 0.001) (Table A4). The proportion of a positive vertical edge was also significantly correlated with the anatomical region, likewise divided to <10 mm or ≥10 mm diameter (Fisher-Freeman-Halton test, P < 0.001) (Table A5). No

patients developed postoperative local recurrence during the follow-up periods (data not shown).

4. Discussion

In this study, we tried to identify the factors associated with BCC invasion levels using the largest reported Asian cohort. Our data revealed that tumor invasion levels up to the subcutis, or to the muscle and below, were significantly correlated with tumor diameter and anatomical region (nose, orbit, others). Furthermore, multiple regression analysis showed that tumor diameter was the only factor correlated with tumor thickness; the histologic patterns were not significantly correlated.

With a sample size of 235 Japanese BCCs, Takenouchi et al. showed that tumor diameter and histologic pattern were independently correlated with deeper invasion [13]. Other reports indicated that BCCs with infiltrative, morpheic, or micronodular histologic patterns were correlated with locally aggressive behavior, deep invasion into the subcutaneous tissue, and frequent recurrence as compared with nodular BCCs [9].

Although our study showed that histologic patterns were significantly correlated with tumor invasion levels in univariate analysis (Fisher-Freeman-Halton test, Table 2), and that 60 % of morpheic BCCs invaded the muscle and below, no statistical significance was found for histologic patterns, classified as aggressive (micronodular, infiltrative, morpheic, or mixed) or non-aggressive, as independently correlated factors in multiple logistic regression analyses. However, our study revealed that both the aggressive and non-aggressive nodular types showed a significant correlation between tumor thickness and tumor diameter. Under these considerations, the histologic pattern (aggressive or non-aggressive) might not be an independent factor for the tumor invasion level and tumor thickness. We suggest that the tumor thickness correlates with the level of invasion of the tumor. In addition, our data demonstrate a significant correlation between tumor thickness and diameter in both aggressive and non-aggressive nodular types, which can present similar invasion patterns regardless of the histopathological risk classification.

In our study, the anatomical region was regarded as an independent predictive factor of invasion levels up to the subcutis or to the muscle and below. A previous study showed that BCCs on the eyelid, nose, and lip had deep margin involvements due to the complexity of the structures [14]. Our study confirmed that anatomical differences should be considered in invasion levels of BCCs, since the variety in tissue construction among anatomical regions, particularly in the orbital region, leads to invasion of the muscle and below. Moreover, while the tumor thickness shows less objectivity in estimating the degree of invasion of BCC and varies in clinical findings (e.g., presence of ulceration, elevated lesions), the invasion level is the critical parameter guiding the adequate surgical layer, particularly as a correlative factor for determining the invasion level up to the subcutis or the muscle and below.

Our study also indicated that the histologic pattern and tumor diameter were significantly correlated with a positive vertical edge, especially for tumors $\geq$10 mm in diameter, which showed a higher positive rate. Moreover, aggressive types showed a higher positive rate than nodular types; no positivity was observed in superficial types. Our data supports previous reports that showed that recurrence and positive vertical edge are more common in aggressive types [9,15]. In terms of vertical surgical edges, Japanese Guidelines recommend that tumors of aggressive types and those with wide tumor diameters need to be excised with a deeper lesion including the subcutis [16].

Consistent with previous reports, our data strongly suggest that the determination of the vertical surgical edge should be carefully considered in patients with facial BCCs with tumor diameter $\geq$10 mm, with an exception for superficial types. Our data was extracted from the surgery performed in each institution by board-certified dermato-oncologists, and dermatologists with the guidance of a supervisor who possesses dermatosurgery skills. Therefore, while the positive rate for the vertical surgical edge depends on the physicians' skill, our data regarding the vertical surgical edge could be a reliable surgical guide for general dermatologists; however, it is essential to maintain a high level of surgical skill.

Based on our results, an adequate excision level up to the subcutis or including the muscle could be proposed in accordance with the anatomical region and tumor diameter, which were the independent influencing factors for the tumor invasion. While tumors <10 mm in diameter localized in regions other than the orbital and the nasal regions rarely invaded the muscle and below (1.1 %, 1 forehead and 1 lip of 182 cases, Table A4) and showed that a negative vertical surgical edge (Table A5) resection up to the subcutis would be sufficient in these tumors. The tumors localized in the orbital region significantly invaded the muscle and below as shown in Table 3, and were mostly resected at the muscle or below (85.5 %, 94/110 cases, data not shown) resulting in a relatively lower rate for the positive vertical edge regardless of the tumor diameter (Table A2). Moreover, the tumors $\geq$10 mm in diameter that were in the nasal region invaded the muscle and below (Table A4) and showed a higher vertical surgical edge (Table A5). These results indicate that resections that include the muscle might be required for tumors localized in the orbital region regardless of the diameter; the tumors $\geq$10 mm in diameter localized in the nasal regions should consider the anatomical structural complexity in the surgical decision.

Although no statistical significance was found in histologic patterns (aggressive or non-aggressive) as an independent factor for tumor invasion levels, precise determination of the vertical surgical level is needed for morpheic-type BCCs, which invaded deeper than other types (Table 2) and showed a significantly higher positive rate of surgical edge (Table A1). Since the tumor invasions to the cartilage/bone or the tarsus were extremely low (Tables 2 and 3), 'two-step' surgery, composed of tumor resection and delayed reconstruction after the histological confirmation of the negative surgical edge, without removal of cartilage/bone or the tarsus, should be recommended for the facial BCCs where deeper invasion is indicated by a larger diameter or the morpheic-type.

While our study identified factors correlated with the depth of tumor invasion, the experience of surgeons remains important for planning and performing BCC surgery. Previous reports have shown that knowledge of the clinical and biological characteristics of skin cancers derived from training and daily experience plays a crucial role in the ability to define margins and reduces the risk of incomplete excisions [14,17]. Furthermore, presurgical ultrasound sonography, confocal microscopy (RCM), optical coherence tomography (OCT), and combined RCM−OCT are recommended for non-invasive detection of subclinical lesions of facial BCC [18–21] and should be used as reliable instruments for planning surgery.

Our study has some limitations. First, the data were collected and analyzed by a limited number of dermatologists from only three Japanese institutions. Second, unlike with MMS, the entire areas of the deep margins were not evaluated histologically. Third, recurrence rates were not fully investigated because of a short follow-up period.

Despite these limitations, our study included the largest sample size for an Asian population (718 BCCs) and showed that tumor diameter and anatomical region were independent influencing factors for the depth of invasion of facial BCCs. These two predictive factors, combined with knowledge of the characteristic

types of BCCs, provide a more reliable guide for determining adequate surgical deep margins than conventional risk classifications of Japanese BCC patients.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jdermsci.2020.07.001.

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Photosensitive Dermatitis Induced by Nivolumab/Ipilimumab Combination Therapy in a Patient with Malignant Melanoma

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Accepted Oct 28, 2020; Epub ahead of print Nov 2, 2020

Photosensitive dermatitis is clinically recognized as sunlight-induced dermatitis. It develops through 2 mechanisms: phototoxicity and photoallergy. Of these, photoallergic dermatitis is a type IV hypersensitive photoreaction against an external or internal antigen, which is mediated largely by ultraviolet A (UVA) (1, 2). Although various antigens, including antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are reported to induce photosensitivity (1), there is no report that indicates the possibility of immune checkpoint inhibitor-associated photosensitivity. We report here a case of photosensitive dermatitis possibly induced by nivolumab/ipilimumab combination therapy (NIV/IPI) in a patient with malignant melanoma.

CASE REPORT

A 64-year-old, previously healthy, male developed nail apparatus melanoma of the right thumb (**Fig. 1**a). He underwent wide local excision and sentinel lymph node biopsy. Histological examination showed no evidence of metastasis and he was followed up carefully. After 7 months, positron-emission tomography/computed tomography revealed multiple metastases in the brain. Soon after gamma knife treatment (24 Gy/1 Fr) for brain metastases, NIV/IPI therapy was initiated.

One week after the first NIV/IPI therapy, red, palpable papules appeared on the patient's trunk, and he was treated with topical difluprednate ointment. Immediately after the second NIV/IPI therapy, the erythema augmented and was predominantly localized in the sun-exposed area (Fig. 1b). Photo-tests showed a markedly decreased minimal erythema dose (MED) of 3 J/cm^2 UVA. No obvious decreases in the MED of UVB or visible light

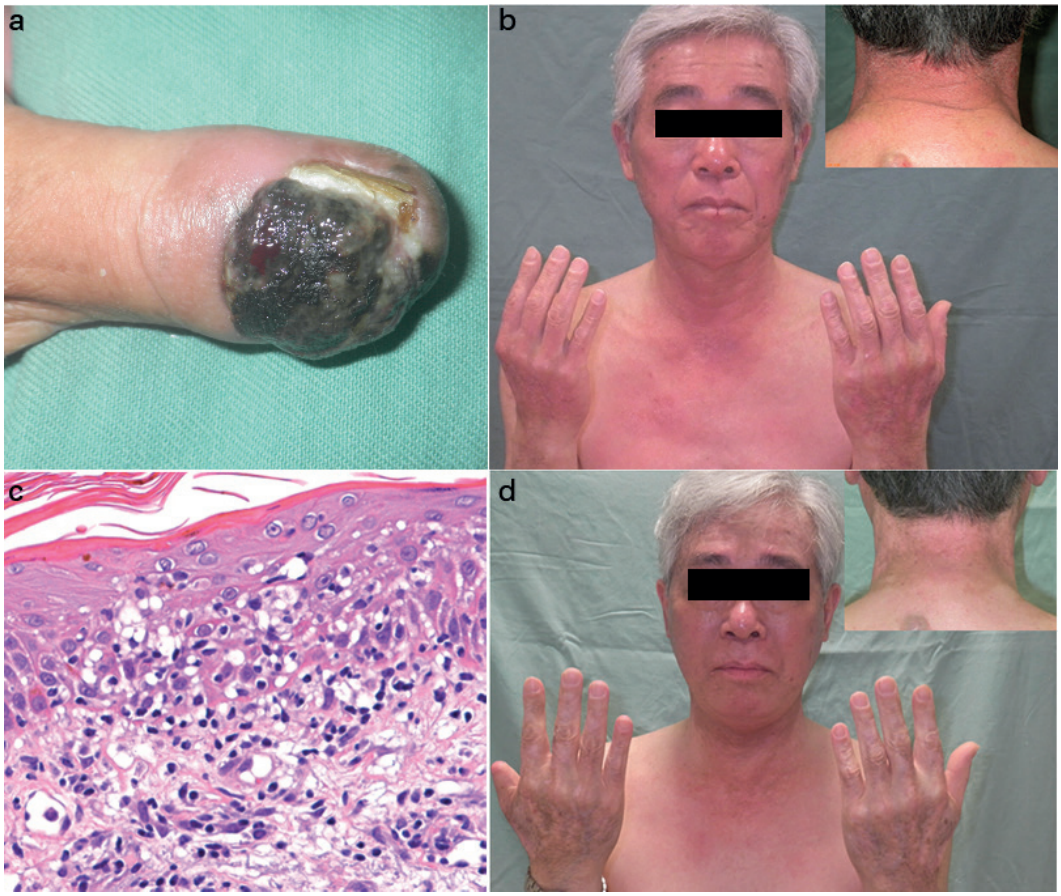

Fig. 1. Clinical and histological images of the patient. (a) Primary lesion. (b) Worsened erythema and erosive lesion on the back of the neck. (c) Histological findings of erythema on the right forearm. Mild acanthosis, focal parakeratosis, and a few necrotic keratinocytes visible within the spongiotic epidermis. Within the superficial dermis, there is a perivascular, predominantly lymphocytic infiltrate. (d) One month after treatment with oral prednisolone, the erythema was ameliorated. Permoission is given by the patient to publish these photos.

doi: 10.2340/00015555-3681
Acta Derm Venereol 2020; 100: adv00335

were observed. The histological appearance was consistent with that of photosensitive dermatitis (Fig. 1c). Because the patient did not take any other medications or have any apparent episodes of complications with viral or bacterial infection before and during NIV/IPI therapy, this case was diagnosed as photosensitive dermatitis possibly induced by NIV/IPI therapy. Because erythema became erosive and spread from the distal to the proximal area, NIV/IPI therapy was discontinued and oral prednisolone treatment for photosensitive dermatitis was initiated (60 mg/day, gradually tapered to 20 mg/day over 4 months). After amelioration of the skin eruption (Fig. 1d), photo-tests were performed again, which confirmed the persistence of UVA sensitivity with a MED of 3 J/cm^2. Although NIV/IPI therapy was discontinued and the patient has not taken any other anti-cancer agents over 7 months' follow up, his melanoma has been well controlled.

DISCUSSION

In this case, the patient developed severe skin erythema during NIV/IPI therapy. From the clinical distribution of the erythema, his medication history, hypersensitivity to UVA and histopathological features (3), a diagnosis of photosensitive dermatitis was considered. Since the patient received no oral medication during NIV/IPI therapy, the possibility of hypersensitivity against external antigens with oral administration was excluded. Therefore, the patient was hypothesized to have developed photosensitivity induced by an autoimmune response to an endogenous antigen. His symptoms may be associated with NIV/IPI treatment because he had not exhibited any photosensitive symptoms before NIV/IPI therapy, although he often went outdoors for his hobby of insect collecting.

Previous reports suggest another immunomodulator has potential to induce photosensitive dermatitis (1, 4). Mogamulizumab, a monoclonal antibody targeting CCR4, was shown to induce photosensitive dermatitis (4), possibly due to serving as an immunomodulator, but not as a photoantigen. Therefore, photoallergic dermatitis may have occurred, not due to an external antigen but due to an internal antigen. This might indicate that an immunomodulator including NIV/IPI could induce immune-related photosensitive dermatitis.

In conclusion, we report here the first case of photosensitive dermatitis during NIV/IPI therapy possibly occurring as an immune-related adverse event. In contrast to previously reported photoallergic dermatitis, which is generally resolved after withdrawal of the culprit drugs (5), the finding of a decrease in the MED of UVA in photo-tests, 2 times, 4 months after the last administration of NIV/IPI, suggests that this immune-related side-effect could last longer than that of common photosensitive dermatitis.

The authors have no conflicts of interest to declare.

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Rare case of sarcomatoid carcinoma of the prostate with metastatic skin tumor manifestation

Dear Editor,

Sarcomatoid carcinoma is a rare type of prostate cancer representing less than 1% of all prostate neoplasms.[1] In particular, skin metastasis is extremely rare and there are no papers that describe metastatic skin lesions including histological characteristics in detail.[2,3] Here, we report a case of sarcomatoid carcinoma of the prostate diagnosed from the manifestation of a metastatic skin tumor.

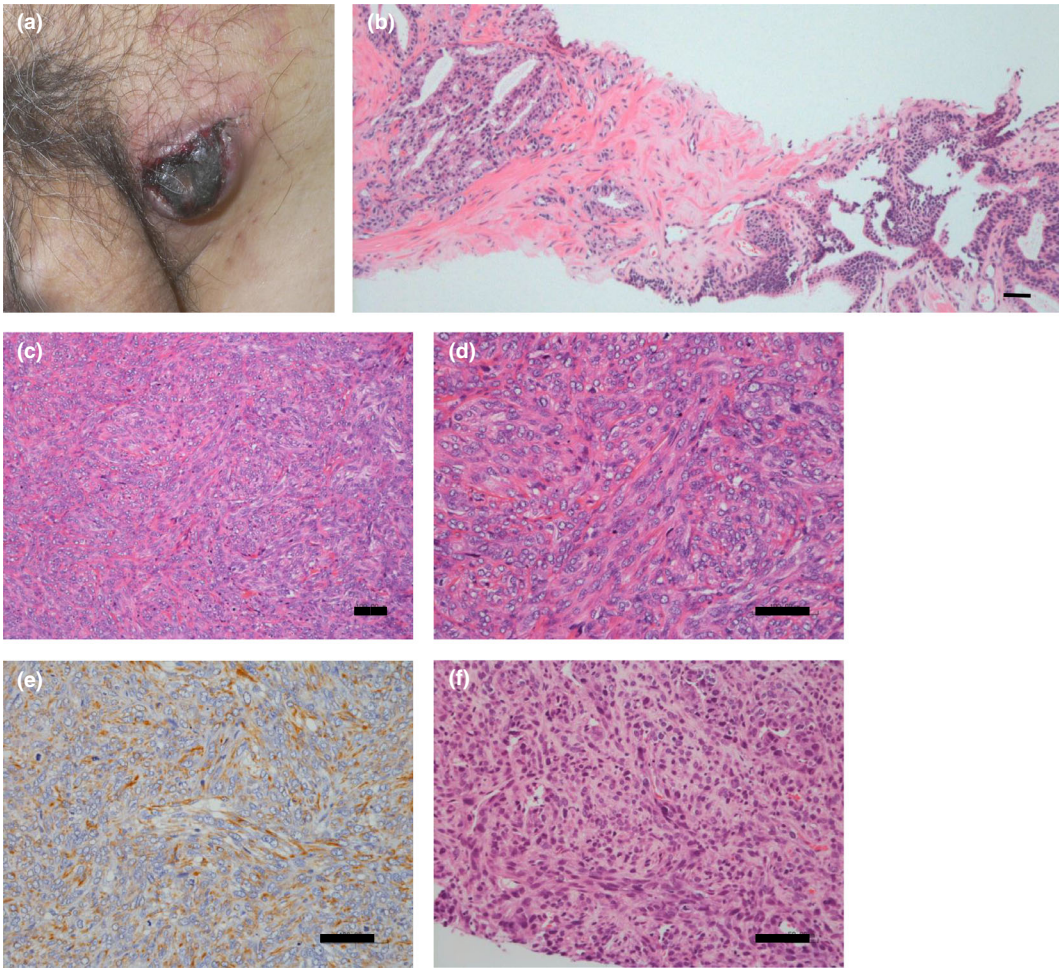

Figure 1. Clinical presentation and pathological pictures. (a) Tumor of 33 mm × 30 mm with central necrosis in the left groin region. (b) Initial histological findings of the prostate (hematoxylin–eosin [HE]; bar, 100 μm). There were some atypical cells around tubules of Gleason grade 4 + 3 (score = 7). (c) Histological findings of the skin tumor (HE; bar, 100 μm). (d) High-magnification view of (c) (HE; bar, 100 μm). (e) Immunohistochemical staining for vimentin (bar, 100 μm). (f) Histological findings of the prostate of the second biopsy (HE; bar, 100 μm).

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A 77-year-old man with past history of prostate cancer was referred to our department due to the presentation of a 33 mm × 30 mm skin tumor in his left groin. The tumor had grown in a month and bled easily (Fig. 1a). The patient had experienced no pain, fever or abdominal distension from the tumor.

Three years before his first visit to our hospital, the patient had suffered from frequent urination, urinary retention and dysuria. Serum prostate-specific antigen (PSA) level had then been 68 ng/mL (normal, 0–4). A subsequent prostate biopsy specimen was consistent with prostate cancer (Fig. 1b). Because of bone metastasis, he had been administrated systemic bicalutamide-based chemotherapy and sequential leuprorelin acetate treatment until his first visit to our hospital.

Biopsy of the skin tumor was performed and the specimen showed a tumor nest located in the dermis to subcutis. The tumor was composed of both ductal epithelioid and stromal cells with nuclear atypia and mitoses (Fig. 1c,d). The atypical stromal cells were positive for vimentin (Fig. 1e) and Ki-67 (labeling index, 60%), but negative for CD34 and cytokeratin AE1/AE3. From these histological findings, we suspected the lesion as sarcoma of unknown origin.

Magnetic resonance imaging revealed an irregularly enlarged prostate. ^{18}F-Fluorodeoxyglucose-positron emission tomography/computed tomography showed glucose uptake in the skin tumor, enlarged prostate and multiple lung nodules. A biopsy from the prostate showed similar histological findings as the skin tumor (Fig. 1f). We diagnosed the skin tumor as a sarcomatoid carcinoma of the prostate. Because the patient had multiple organ metastases of the tumor, chemotherapy with doxorubicin hydrochloride was administrated and the result was progressive disease. The patient died 8 months after being diagnosed with sarcomatoid carcinoma of the prostate.

Sarcomatoid carcinoma of the prostate is a rare and highly aggressive malignant tumor.[1] The majority of initial symptoms are urinary retention and hematuria, and the serum PSA value is usually normal.[1,2] Sarcomatoid carcinoma of the prostate is defined by the admixture of malignant epithelial and stromal components.[4] In addition, stroma of the tumor is positive for vimentin and Ki-67, and negative for CD34 and AE1/AE3.[3] Taking into account the history of prostate cancer and the similarity of its immunohistochemical patterns, we considered our case to be sarcomatoid carcinoma of the prostate because of the histological concordance of the skin lesion and prostate lesion.

Our case is a rare example of sarcomatoid carcinoma of the prostate that was diagnosed from both the prostate lesion and the metastatic skin lesion. It adds evidence that sarcomatoid carcinoma of the prostate has metastatic potential in the skin and that the prognosis is extremely poor.

CONFLICT OF INTEREST: None declared.

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doi: 10.1111/1346-8138.15426

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Surgical invasion resulted in increased programmed death ligand 1 expression in a case of multicentric Merkel cell carcinoma with six primary lesions

Dear Editor,

Successful results of immune checkpoint therapy, including programmed death ligand 1 (PD-L1) blockade for Merkel cell carcinoma (MCC), have been reported.[1] Before initiating this epochal treatment, high expression of PD-L1 in MCC is suggested to correlate with better clinical outcomes in contradiction to other solid carcinomas.[2–4] PD-L1 expression is heterogeneous, however, even within the same case.[5] We report a case of multicentric MCC with six simultaneously developed primary lesions in which the findings support the notion that surgical invasion may be one cause of PD-L1 heterogeneity.

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編集後記

この臨床研究部業績年報は、2020（令和 2）年 4 月から 2021（令和 3）年 3 月までの当院の研究活動報告をまとめたもので、第 21 号となります。

今年度の研究業績集から、掲載内容をこれまでのものに比べて大幅に改訂することにしました。毎年機構本部に提出している研究業績ポイント表に掲載する項目を中心にしました。各診療科が現在オンゴーイングで研究に取り組んでいて、まだ結果が出ていない研究報告については、病院年報や他の掲載誌に任せることにして、この研究業績集には、その年度に成果が出た研究業績が分かるような形にしました。国内および外国での研究発表および論文発表は、これからも掲載を続けることにし、当院職員が筆頭で執筆して外国の一流誌に掲載された英語論文にスポットライトをあてる目的で、筆頭執筆英文論文は全文載せることにしました。このことにより、後で振り返っても、その年度の当院を代表する英語論文がすぐわかるようになると思います。

最後になりましたが、この臨床研究部業績集の編集に際しご協力戴きました関係者の皆様に厚く御礼申し上げます。

臨床研究部長　城ヶ崎　倫久