Vol. 71 No. 1-3 December 2019

CODEN: KDIZAA
ISSN 0368-5063

鹿児島大学医学雑誌
MEDICAL JOURNAL OF KAGOSHIMA UNIVERSITY

鹿 大 医 誌
Med J
Kagoshima Univ

鹿 児 島 大 学 医 学 会
MEDICAL SOCIETY OF KAGOSHIMA UNIVERSITY

Medical Journal of Kagoshima University Vol.71, No1-3 2019

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鹿児島大学医学雑誌 第 71 巻　1-3 号　2019 年発行

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鹿児島大学医学会
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※鹿児島大学医学雑誌のホームページ：
http://www.kufm.kagoshima-u.ac.jp/~medjkago/index.html

発　行 2019 年 12 月

Editorial Office
c/o Department of Epidemiology and Preventive Medicine
Kagoshima University
Graduate School of Medical and Dental Sciences
8-35-1, Sakuragaoka,
Kagoshima 890-8544 Japan

編集と発行
鹿児島大学医学会　鹿児島大学医学雑誌編集委員会
〒 890 － 8544
鹿児島市桜ケ丘８丁目３５－１
鹿児島大学大学院 医歯学総合研究科
疫学・予防医学分野内

鹿児島大学医学雑誌　2019年 3 月
Med. J. Kagoshima Univ., March, 2019

胆石症術後に腸閉塞をきたした回腸子宮内膜症の１例

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A CASE OF ENDOMETRIOSIS OF THE ILEUM PRESENTING WITH INTESTINAL OBSTRUCTION AFTER CHOLECYSTECTOMY

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(Received 2018 Oct. 1 ; Revised Dec. 3; Accepted Jan. 7)

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Abstract

The patient was a 34-year-old woman, who was treated with hormone therapy for endometriosis. She visited local doctor because of upper abdominal pain. She was detected cholelithiasis and consulted our hospital. She was treated with low-dose pill（LUNABELL®）which has a risk of thrombosis. After 4-weeks drug withdrawal, we operated laparoscopic cholecystectomy. Histopathological examination showed chronic cholecystitis. The 24th post-operative day, she had ileus due to a terminal ileum stenosis. An ileocecal resection was performed. Intestinal endometriosis was confirmed on pathological examination. There is a possibility that first symptoms caused by the intestinal endometriosis or progressed by the interruption of hormone therapy. We should keep in mind intestinal endometriosis especially in endometriosis patients as the underlying disease with digestive symptoms.
Key words: ileum, endometriosis, ileus

和文抄録

症例は34歳の女性．子宮内膜症のため婦人科でホルモン療法中であった．心窩部痛を主訴に近医を受診し胆石症を指摘され当院紹介となった．血栓症リスクの為に周術期の投与が禁忌である低用量ピル（ルナベル®）を内服中で，4 週間の休薬後に腹腔鏡下胆嚢摘出術を行った．胆嚢内にコレステロール結石を認め，病理組織学的検査では慢性胆嚢炎の診断であった．術後24日目に腸閉塞をきたし再入院となり，消化管造影で回腸の狭窄を認め解除術を行った．終末回腸の狭窄と同部位への周囲臓器の癒着を認め回盲部切除を施行した．病理組織学的検査では回腸壁全層に子宮内膜組織を認め，異所性子宮内膜症による回腸狭窄の診断であった．

初診時に回腸子宮内膜症の初期症状を呈していた可能性や，胆石症手術に伴うホルモン療法の中断により症状が増悪したことが考えられ，子宮内膜症を有する患者の消化器症状においては特に本疾患を念頭におく必要があると考えられた．

キーワード：回腸，子宮内膜症，腸閉塞

はじめに

回腸子宮内膜症は子宮内膜が回腸に増殖することで生じる稀な疾患であり，多くは腸閉塞で発症し，術前診断が困難とされる．今回われわれは胆石症術後に腸閉塞をきたし，回盲部切除により診断に至った回腸子宮内膜症の 1 例を経験したので報告する。

症例

症例：34歳，女性.
主訴：心窩部痛，嘔気.
既往歴：子宮内膜症.
現病歴：2017年 1 月，2 か月前から出現した心窩部痛と嘔気を主訴に近医受診．腹部超音波検査で胆石症を指摘され，当科を紹介された．月経周期と関連のない間欠的な腹痛と嘔気症状があり，下血や血便，便秘は認めなかった．子宮内膜症に対して，血栓症の副作用から周術期の投与が禁忌とされる低用量ピル（ルナベル®）を内服中であり，4 週間の休薬後に腹腔鏡下胆嚢摘出術を行った．胆嚢内にコレステロール結石を認め，病理組織学的検査では慢性胆嚢炎の診断であった．術後に嘔気症状が残存したが，腹部レントゲン検査では消化管の通過障害は明らかでなく，保存的治療で軽快し術後17日目に退院となった．術後24日目に腹痛症状で再診され腸閉塞を認め入院となった．再入院時子宮内膜症に対する治療は再開していなかった.

入院時現症：身長158.0cm，48.7kg，体温36.7℃，血圧123/82mmHg，脈拍84回/分・整.
腹部はやや膨隆し，蠕動痛を認めた.
入院時検査所見：WBC 8000/μL，Hb 10.3g/dl，CRP 6.2mg/dl，Na 130mEq/l，Cl 93mEq/lと貧血に加え炎症反応の上昇，低Na・Cl血症を認めた.
腹部単純X線検査：鏡面形成を伴う小腸ガス像を認めた（Fig. 1 ）.
腹部CT検査：透視検査後のCTで終末回腸の狭窄所見と口側小腸の拡張を認めた（Fig. 2 ）.
以上の所見と子宮内膜症の既往から異所性子宮内膜症による腸閉塞を疑い婦人科受診を依頼したところ，同様の診断となり2017年 3 月イレウス解除術を行った.

手術所見：臍部に開腹法で12mmカメラポートを留置し腹腔鏡下に腹腔内を観察したところ，骨盤底に癒着した大網により終末回腸が狭窄し，同部位より口側小腸の拡張を認めた（Fig. 3 ）．腹腔鏡下に大網の癒着を剥離したが，腸管の狭窄は改善されず開腹手術に移行した．狭窄部位にS状結腸や腹膜，小腸間膜が強固に癒着しており回盲部切除を行った.
切除標本所見：終末回腸の粘膜面に潰瘍化を伴う腫瘤形成と内腔狭窄を認めた（Fig. 4 ）.
病理組織学的所見：腸管壁全層にわたって島状に散在する子宮内膜組織と反応性二次性変化を認め，回腸子宮内膜症と診断した（Fig. 5 ）.
術後経過：術後経過は良好で，術後第14日目に退院した．退院後婦人科受診により，周術期の投与が可能な子宮内膜症治療薬ジエノゲスト（ディナゲスト®）の内服を開始し，術後 1 年再発なく経過中である.

考察

子宮内膜症とは子宮内膜組織の異所性増殖により，多様な臨床症状を呈する疾患で，子宮筋層内に発生する内性子宮内膜症（子宮腺筋症）と，それ以外の外性子宮内膜症に大別される．腸管子宮内膜症は後者に分類され，子宮内膜が腸管壁に浸潤・増殖することで発症し，子宮内膜症の 6 〜 12%を占める[1]．発生機序は諸説あるが，月経時に正常子宮内膜組織が逆行性に卵管を通り腹腔内に流出し，骨盤内臓臓器に移植・増殖するというSampsonの経卵管移植説が有力とされる[2]．子宮近傍の腸管に好発し，腸管子宮内膜症の84％はS状結腸や直腸に発生し，小腸は 7 ％と稀である[3]．症状は腹痛，血便，便秘などの消化器症状であり，小腸子宮内膜症の70％は

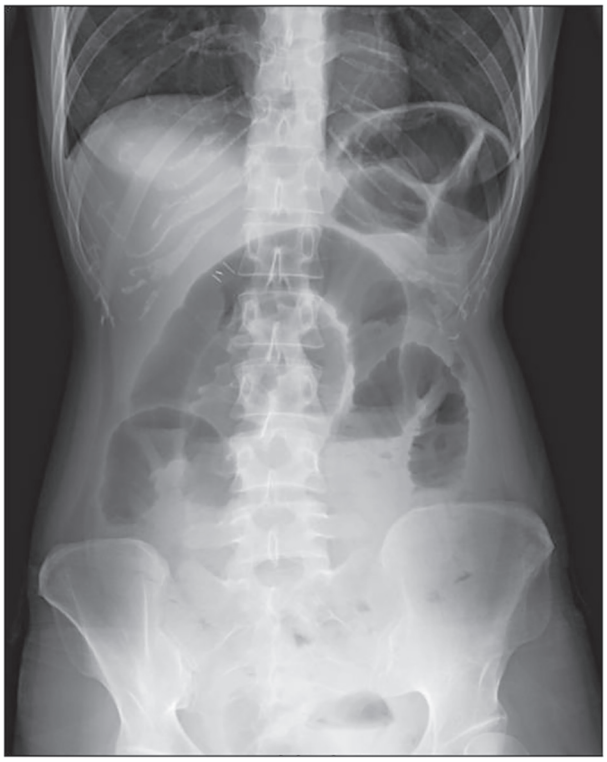

Fig. 1　拡張した小腸ガス像とniveau像を認めた.

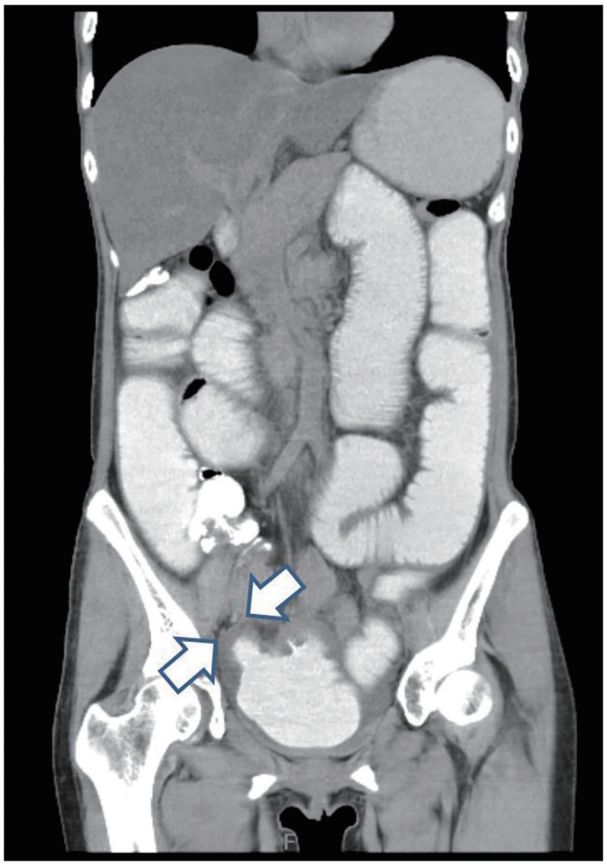

Fig. 2　終末回腸に狭窄所見を認めた（矢印）.

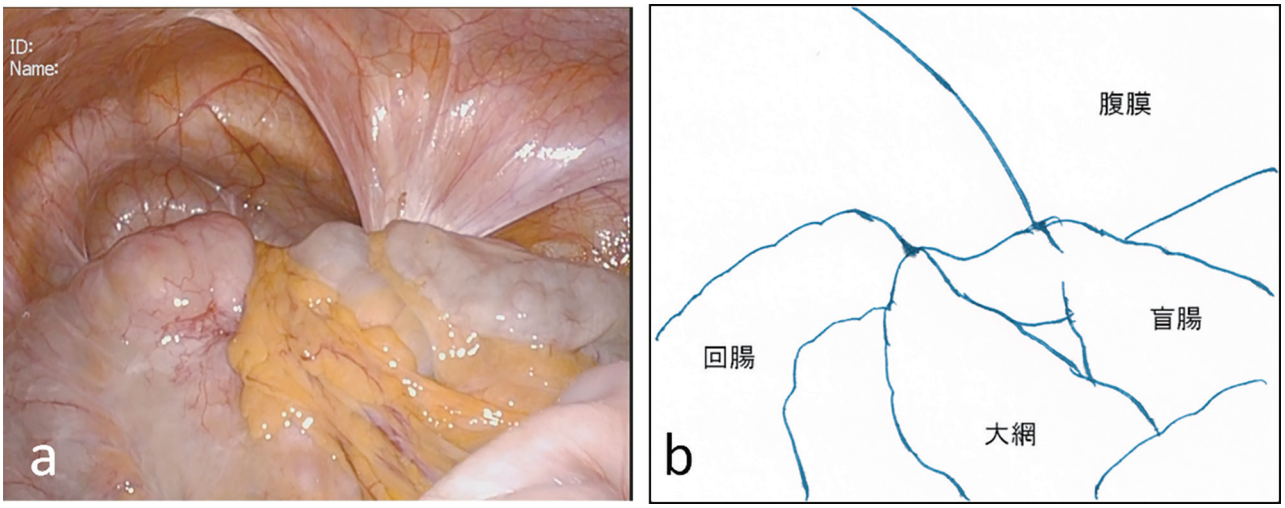

Fig. 3　手術所見：a) 終末回腸を越えて大網が骨盤底に癒着していた. b) シェーマ.

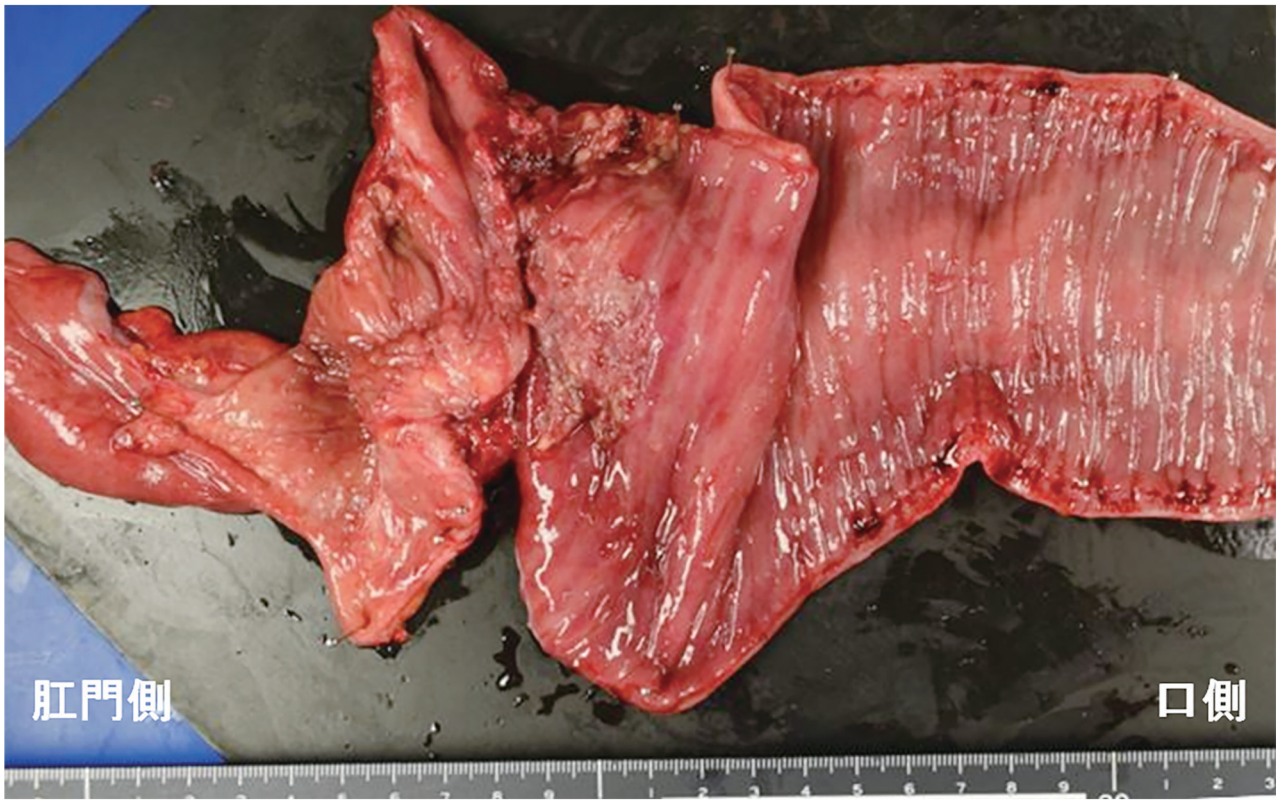

Fig 4　切除標本:回腸の粘膜面に潰瘍化を伴う腫瘤形成と内腔狭窄を認めた.

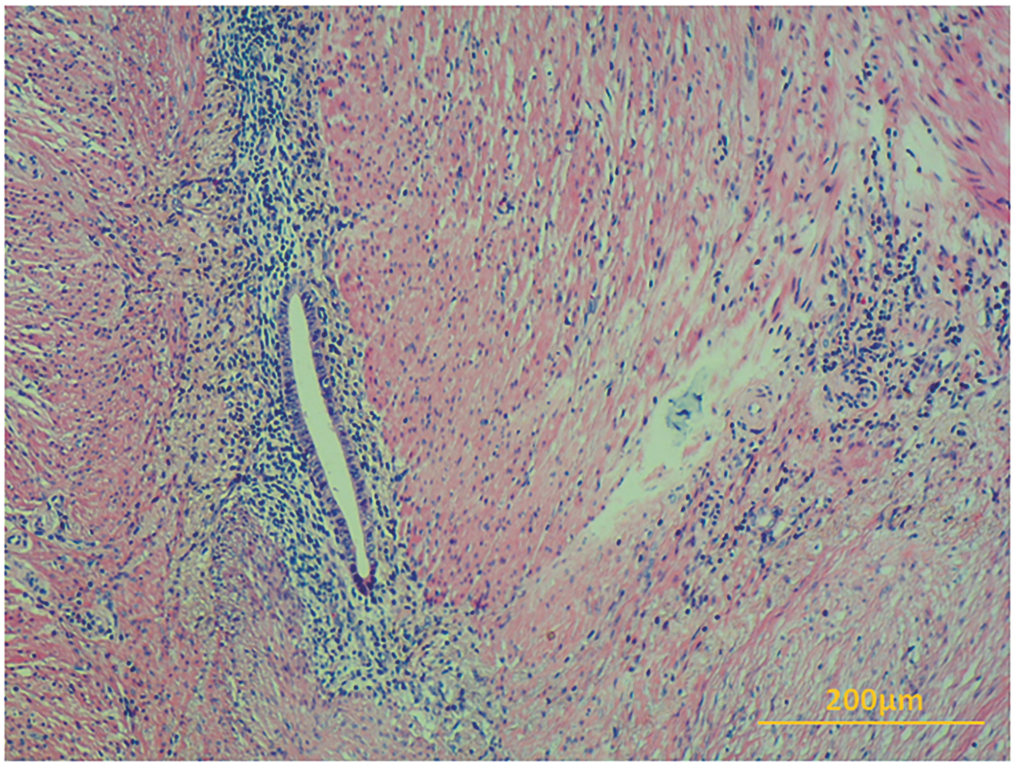

Fig. 5　病理組織学的所見：腸管壁全層にわたって島状に散在する子宮内膜組織と反応性二次性変化を認めた(H.E染色，200倍).

腸閉塞で発症し[4]，特異的な症状がなく術前診断が困難とされる．月経周期と同期して増悪と軽快を繰り返すことがあり，問診が有用とされる一方で[5]，腸管壁の線維化が進み狭窄が強くなると月経周期と症状が同調しなくなり[6]，問診での鑑別が困難な症例も多い[7]．臨床経過では，これまでの報告から，数カ月をかけて亜急性に進行する特徴があるとされる[8]．自験例では初診時に月経周期と関連のない間欠的な消化器症状があり，症状出現から約 4 カ月後に腸閉塞を発症した．胆石症と鑑別を有するが，初診時の消化器症状は回腸子宮内膜症に起因する症状であった可能性も考えられた．

回腸子宮内膜症の診断に関しては，粘膜下病変が主体であり内視鏡検査や注腸検査での術前診断は困難とされる[9]．特異的な検査法がないことから多くの症例は外科的切除後の病理組織学的検査で診断されている[10]．自験例も子宮内膜症の治療歴と小腸の狭窄所見から，腸管子宮内膜症を疑ったが術前に確定診断には至らなかった．

治療は手術治療とLH-RH agonistなどによるホルモン療法が選択肢とされ，高度の腸管狭窄を呈する症例ではホルモン療法に抵抗性で，診断と治療をかねて手術療法が選択される[7) 11)]．低侵襲かつ整容性に優れた腹腔鏡下手術の報告が増加しており[12]，本症例も腹腔鏡下での治療を試みたが高度な癒着のため開腹操作へ移行した．

自験例では初診時の消化器症状を胆石症ととらえ胆嚢摘出術を行ったが，前述のように回腸子宮内膜症の初期症状であった可能性も考えられた．ホルモン療法中の発症で，すでに腸管狭窄をきたし手術治療が避けられない状況であったと考えるが，本症の関与を積極的に疑うことで早期に治療を行えた可能性があった．一方で胆石症手術に際して行ったホルモン療法の中断が回腸子宮内膜症の発症に影響を与えた可能性もあり，周術期にも投与可能な他剤ホルモン剤への変更を考慮すべきであったと考える．自験例は退院後の婦人科受診により，周術期の投与が可能な子宮内膜治療薬ジエノゲスト（ディナゲスト®）の内服をすみやかに開始し術後 1 年再発なく経過中である．

結語

胆石症術後に腸閉塞を発症した回腸子宮内膜症の 1 例を経験した．子宮内膜症を有する患者の消化器症状の原因として，本疾患も念頭におく必要があると考えられた．また子宮内膜症治療の中断が本疾患の増悪をきたす可能性を考慮し，周術期も投与可能な治療薬への変更や，術後早期の治療再開が必要と考えられた．

参考文献

1） Stepniewska A, Pomini P, Bruni F, Mereu L, Ruffo G, Ceccaroni M, et al. Laparoscopic treatment of bowel endometriosis in infertile women. Hum Reprod. 2009；24：1619-1625

2） Sampson JA. Perforating hemorrhagic(chocolate)cysts of the ovary ; their importance and especially their relation to pelvic adenomas of the endometrorial type. Arch Surg. 1921；3：245-323

3） 小平進：腸管子宮内膜症の病態．胃と腸 1998；40：1323-1328

4） 袖山治嗣,門馬正志，花崎和弘，若林正夫，大塚満洲雄，安里進：腸閉塞をきたした回腸子宮内膜症の 1 例．日臨外会誌　1996；51：241-244

5） 篠原寿彦，水谷央，下野聡，長谷川拓男，高橋宣胖，西井寛ほか：腸閉塞にて発症した回腸子宮内膜症の 1 例．日消外会誌　2001；34：277-281

6） 原仁司，立川伸雄，佐藤宏喜：腹腔鏡手術を施行した腸管子宮内膜症による回腸狭窄の 1 例．日外科系連会誌　2016；41：255-261

7） 高橋啓，林昌俊，栃井航也，小久保健太郎，丹羽真佐夫：腸閉塞をきたした回腸子宮内膜症の 1 例．日腹部救急医会誌　2016；36：103-106

8） 古谷正敬，浅井哲，芥川英之，辻紘子，有馬宏和，浅田弘法ほか：腸閉塞をきたした回腸子宮内膜症の 2 例．日エンドメトリオーシス会誌．　2009；30：78-81

9） 三松謙司，宇賀神若人，小出浩史，竹川義則，福澤正洋：腸閉塞にて発症した回腸子宮内膜症の 2 例．日臨外会誌　2002；63：1541-1545

10） 愛新啓志，坂下吉弘，小倉良夫，近藤成，繁本憲文，上田祐華：回盲部腸重積を形成した回腸子宮内膜症の 1 例．日臨外会誌　2009；42：78-83

11） 石引佳郎，根上直樹，北畠俊顕，藤澤稔，浦尾正彦，児島邦明ほか：腸閉塞をきたした回腸子宮内膜症の 1 例．日臨外会誌　2007；68：99-102

12） 永吉絹子，植木隆，真鍋達也，遠藤翔，永井俊太郎，梁井公輔ほか：腸管子宮内膜症に対する腹腔鏡手術の経験．日消外会誌　2016：49：762-771

鹿児島大学医学雑誌　2019年 6 月
Med. J. Kagoshima Univ., June, 2019

上腸間膜静脈血栓症にヘパリン起因性血小板減少症を併発した 1 例

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Superior Mesenteric Venous Thrombosis Complicated by Heparin-induced Thrombocytopenia: A Case Report

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(Received 2018 Sep. 26 ; Revised 2019 Jan. 22; Accepted Apr. 5)

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Abstract

A 47-year-old man was referred to our hospital with the chief complaint of abdominal pain. Contrast-enhanced Computed Tomography (CT) revealed thrombus in the superior mesenteric vein. Based on a diagnosis of superior mesenteric venous thrombosis (SMVT), conservative treatment was started with heparin and urokinase. However, CT performed on the following day revealed an area with poor blood flow in the small intestine; therefore, emergency surgery was performed. After resection of approximately 3 m of necrotized small intestine, anastomosis was performed. Immediately after surgery, nafamostat was administered. From postoperative day 3, heparin was continuously administered. On postoperative day 5, pulmonary thrombosis appeared on CT findings; therefore, the heparin dose was increased. Nevertheless, on postoperative day 7, the patient's platelet count decreased to 54,000 /μl. Therefore, heparin-induced thrombocytopenia (HIT) was suspected, and heparin administration was discontinued, while continuous administration of argatroban was started. Discontinuation of heparin resulted in normalization of platelet count; contrast-enhanced CT indicated that the size of pulmonary thrombosis had decreased. The patient subsequently progressed well and was discharged to his home on postoperative day 28. In SMVT, the formation of a thrombus in the superior mesenteric vein causes impaired blood flow in the intestinal tract, due to congestion. Heparin is primarily used for conservative treatment in the acute phase. HIT is an adverse effect of heparin administration that can sometimes cause severe thromboembolism. Here, we describe a rare case of HIT that occurred during pulmonary thromboembolism treatment following surgery for SMVT.

Key words: Superior mesenteric venous thrombosis (SMVT), Heparin-induced thrombocytopenia (HIT), Pulmonary thromboembolism (PE)

緒言

上腸間膜静脈血栓症 (superior mesenteric venous thrombosis：以下SMVT) は，上腸間膜静脈内に血栓を形成することにより，うっ血による腸管の血行障害をきたす疾患で，急性期の保存的加療中に主にヘパリンが用いられる[1)]．ヘパリンの副作用として，ヘパリン起因性血小板減少症 (heparin-induced thrombocytopenia：以下HIT) があり，時に重篤な血栓塞栓症を引き起こすことがある．今回われわれはSMVTの術後に肺血栓塞栓症とそのヘパリンによる治療中にHITを続発した症例を経験したので報告する．

症例

患者：47歳，男性．

主訴：腹痛，嘔吐．

既往歴：糖尿病．

家族歴：近親者に血栓症の既往なし．

現病歴：2017年 9 月　深夜に急激な腹痛と嘔吐を認め，近医を受診し，当院へ紹介された．来院時，腹痛は改善していた．

来院時現症：身長 172.0 cm，体重 80.0 kg，BMI 27.0，血圧 154/93 mmHg，脈拍 82 回/分，体温 36.6 ℃，SpO_2 99 %(room air)．意識清明，腹部はやや膨満し，左側腹部に圧痛を認めたが，反跳痛や筋性防御など腹膜刺激症状は認めなかった．

来院時血液検査所見：WBC 15,740 /mm^3，Hb 15.5 g/dL，Plt 19.2×104 /mm^3，CRP 4.6 mg/dL，D-dimer 13.2 μg/μl，プロテインS活性 47.0 %，プロテインS抗原量 86.0 %，プロテインC活性 95.0 %，抗カルジオリピン抗体 0.7 U/ml未満

腹部造影CT検査所見：上腸間膜静脈末梢から門脈左枝にかけて連続する血栓を認めた．腸管の造影効果は保たれていたが，約20 cmにわたり小腸の浮腫性の壁肥厚を認めた（図 1 ）．肺動脈に血栓は認められなかった．

当院入院後経過：CT所見よりSMVTと診断した．小腸の血流は保たれていると判断し，ヘパリン持続投与(10,000単位/日)，ウロキナーゼ投与（24万単位/日）を開始した．しかし，翌日に腹痛が再燃し，造影CT再検査で小腸の造影不良域が出現したため，緊急手術の方針とした（図 2 ）．

手術所見：審査腹腔鏡で一部の空腸が暗赤色に変化し，壊死が疑われた．上腹部正中切開で開腹し，変色した空腸を約 3 m切除，自動縫合器を用いて機能的端々吻合で再建を行った．

術後経過：活性化凝固時間Activated clotting time（ACT値）を150~200秒に保つようにナファモスタットを投与し，また術翌日からウロキナーゼを再開した．術後 3 日目にナファモスタットからヘパリン持続投与（10,000単位/日）に切り替えた（図 3 ）．しかし，術後 5 日目 SpO_2 80 %と低下，D-dimerの上昇を認めたため，緊急CT検査を行ったところ，右下肺動脈に血栓を認めた（図 4 ）．ヘパリンを増量し抗凝固療法を強化したが，術後 7 日目に血小板の減少（5.4×104 /mm^3）を認めた．DIC徴候や症状悪化がないにも関わらず血小板減少を認めたため，すぐにHITを疑い，ヘパリンを中止して，アルガトロバンを開始した．ヘパリン中止後に一度D-dimerの再上昇を認めたものの，症状の増悪はなく，血小板数は徐々に改善し，術後12日目には酸素投与は不要となった．抗血小板第 4 因子・ヘパリン複合体抗体（以下：HIT抗体）11.5 U/mlと高値を示し，臨床症状と合わせてHITと確定診断した．術後21日目，造影CT再検査で肺動脈血栓の縮小を確認し，抗凝固療法の維持療法としてアルガトロバンからエンドキサバン内服へ切り替えた．その後D-dimerの再上昇がないことを確認し，術後28日に自宅退院した．術後12 ヵ月の現在，再発なく外来で経過観察している．

考察

SMVTは比較的まれな疾患で，上腸間膜動脈血栓症と比較して緩徐に進行することが多い．SMVTの原因は特発性と続発性に大別され，約75~80 %が続発性であり，その原因として凝固線溶系の異常，肝硬変，門脈圧亢進症，炎症，手術，外傷，悪性腫瘍，薬剤性，多血症などがあげられる[1-2)]．本症例は入院時プロテインS活性の低下を認めたが，退院前の再検で正常範囲に改善しており，そのほか，凝固線溶系の異常所見なく，血栓の原因となる基礎疾患や遺伝性を疑う家族歴なども認めなかったため，特発性と診断した．

SMVTの治療方針は腸管壊死を疑う所見があれば外科的治療が選択され，腸管壊死の所見がなければ，抗凝固療法・血栓溶解療法などの保存的治療が選択される．医学中央雑誌（会議録除く，検索期間1983 ～ 2017年）でわれわれの調べ得た限りでは，上腸間膜静脈血栓症の報告例は194例であった．詳細な記載がなかった28例を除き，われわれが経験した 1 例を加え167例を集計した結果，167例中99例に保存的治療が選択されており，99例中75例（76 %）は保存的治療のみで寛解していた（図 5 ）．原因別でみると，急性虫垂炎や憩室炎などの炎症性の場合は原疾患に対する治療と保存的治療のみで寛解する例が多く，プロテインS欠乏症などのなんらかの凝固異常による場合は腸管壊死の頻度が高く，緊急手術を行う報告例が多い傾向にあった（表 1 ）．また保存的加療99例中 9 例では，経過中に腸管壊死のため緊急手術が行われており，本症例のように保存的加療中に症状の増悪を認

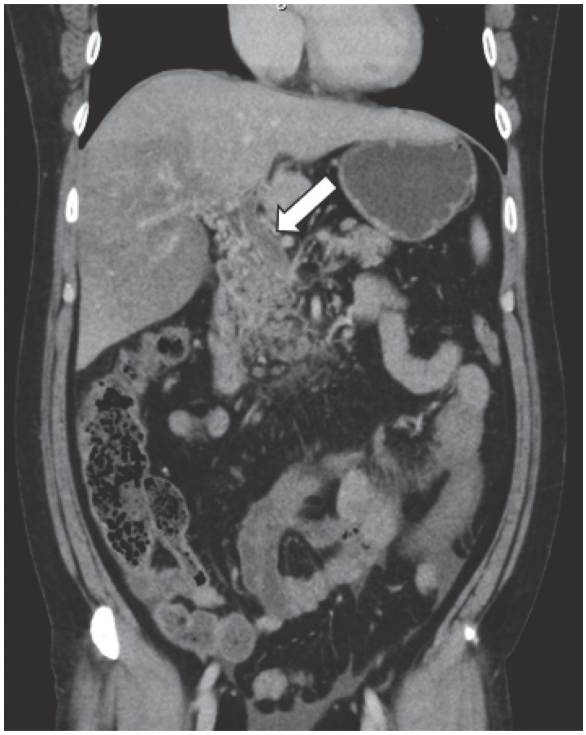

図 1 : Abdominal enhanced Computed Tomography (CT) findings on the day of onset
Thrombus was noted from the portal vein to the superior mesenteric vein (arrow).

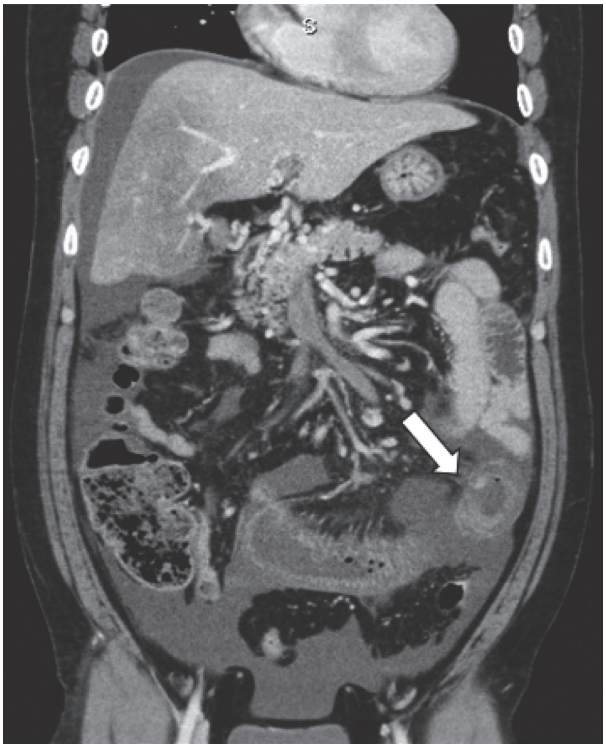

図 2 : Abdominal enhanced CT findings on day 2 after onset
Ascites had worsened and reduced contrast effects were noted in some parts of the intestinal tract.

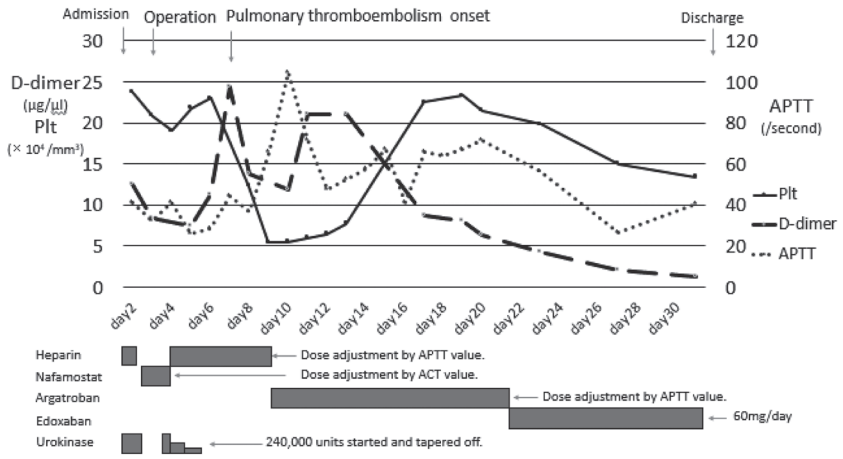

図 3：Clinical course
This figure showed changes over time in platelet counts, D-dimer levels, APTT.

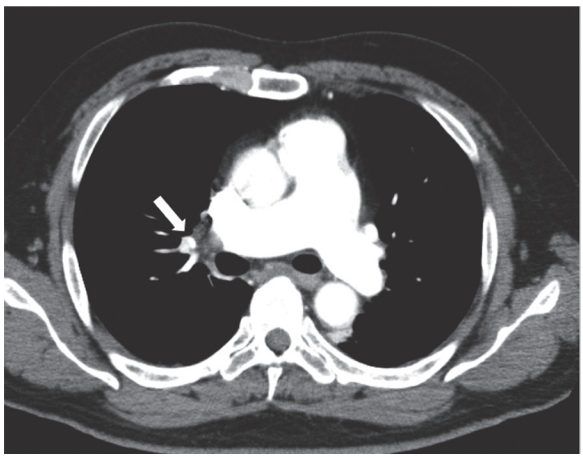

図 4：Chest enhanced CT findings on postoperative day 4
Thrombus was noted in the lower right section of the pulmonary artery.

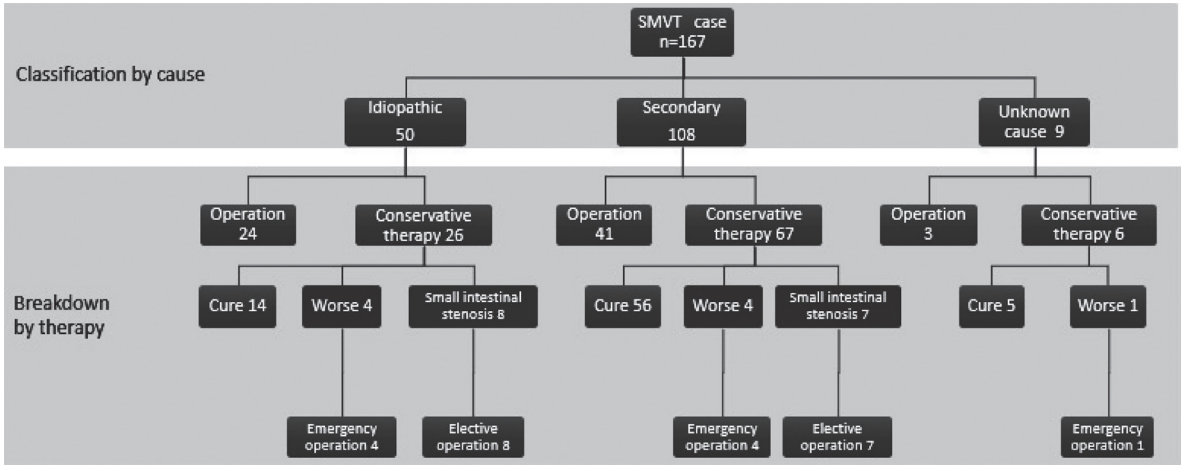

図 5：Summary of cases of superior mesenteric venous thrombosis in Japan
This algorithm showed the outcome of the therapy for SMVT in 168 cases reported in Japan.

表1：Details of cases of secondary superior mesenteric venous thrombosis in Japan.

Secondary SMVT	cases	operation*	conservative therapy†
● Coagulation disorder			
Protein S deficiency	11	7	4
Protein C deficiency	11	6	5
Protein S・Protein C deficiency	5	4	1
Antitronbin III disorder	7	4	3
Plasminogen deficiency	2	2	0
Antiphospholipid syndrome	3	2	1
● Inflammation			
Appenditis	18	2	16
Diverticulitis	6	0	6
Sepsis	4	0	4
Crohn disease・Ulcerative Colitis	2	1	1
Liver abscess	3	0	3
● Potal hypertension/Liver cirrhosis	14	6	8
● Post-operation	6	1	5
● Trauma	1	1	0
● Malignant tumor/neoplasm	5	2	3
● Polycytemia	3	1	2
● Hormone drugs used	4	1	3
● Others ‡	3	1	2
total	108	41	67

Supplementary explanation of Table 1:
*Cases who underwent emergency surgery without conservative treatment for SMVT, excluding patients who underwent emergency surgery while receiving conservative treatment and patients who underwent elective surgery for small intestine stenosis, and similar complications after undergoing conservative treatment.
† Cases diagnosed with SMVT who underwent treatment with anticoagulant therapy (+thrombolytic therapy), including patients who switched to emergency surgery while undergoing conservative treatment.
‡ Other cases diagnosed with SMVT included 1 following lower gastrointestinal endoscopy, 1 with nephrotic syndrome, and 1 with small intestinal anisakiasis.

める場合は，造影CT検査による精査を行い，躊躇することなく外科的治療を選択する必要がある．

興味深いことに本症例はSMVT術後に肺血栓塞栓症とHITを併発した．循環器領域や透析導入期，整形外科領域に比べ，腹部外科領域のHITの報告例は少なく，SMVTにおけるHITの合併例も本邦では本症例を含め3例のみであり決して多くはない．HITはⅠ型とⅡ型に分類され，Ⅰ型はヘパリンそのものの血小板凝集促進作用で起こる非免疫性血小板減少症で臨床上大きな問題とならない．Ⅱ型はヘパリンと血小板第4因子の複合体に対するHIT抗体が生じ，免疫複合体を形成して血小板凝集が起こることで発生する病態であり，ヘパリン投与患者の0.5-5.0 %と報告されている[3]．ヘパリン投与後5-14日目に血小板減少が引き起こされるとともにトロンビンの過剰産生によって血栓塞栓症を発症する可能性がある[4]．発症患者の20-50 %が血栓塞栓症を伴い，血栓症を合併すると死亡率は8-20 %と高い[5]．診断は4T`s ScoreやHIT Expert Probability Scoreなどによる臨床検査所見の

表 2：4T's score

Category	2 points	1 point	0 points
1. Thrombocytopenia	Platelet count fall > 50% and platelet nadir ≥ 20×10^9 L^{-1}	Platelet count fall 30%-50% or platelet nadir 10-19 × 10^9 L^{-1}	Platelet count fall < 30% or platelet nadir < 10×10^9 L^{-1}
2. Timing of platelet count fall	Clear onset between days 5 and 10 or platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5-10 fall, but not clear (e.g. missing platelet counts) or onset after day 10 or fall ≤ 1 day (prior heparin exposure 30-100 days ago)	Platelet count fall < 4 days without recent heparin exposure
3. Thrombosis or other sequelae	New thrombosis (confirmed) or skin necrosis at heparin injection sites or acute systemic reaction after intravenous heparin bolus	Progressive or recurrent thrombosis or nonnecrotizing (erythematous) skin lesions or suspected thrombosis (not proven)	None
4. Other causes for thrombocytopenia	None apparent	Possible	Definite

Total score of ≥ 6 points, high probability of HIT; 4-5 points, intermediate probability of HIT; ≤ 3 points, low probability of HIT. CPB, cardiopulmonary bypass.

(Lee GM et al. Hematology 2013; 2013: 668-674)

スコアリングシステムと血清学的診断を組み合わせることで行われる[6-8]（表 2，3）．治療はヘパリンの中止とアルガトロバンの持続投与が用いられ，維持療法としては主にワルファリンが用いられる．本症例はいずれの評価法も高リスク群に該当し，血清学的にも陽性であったことからHIT（Ⅱ型）と診断した．維持療法は食事指導などを守れずワルファリンでのコントロールは困難と判断しエンドキサバンで行った．SMVTにHITを合併した既報の 2 例は，いずれもⅡ型のHITであり，HITを疑った時点でヘパリンを中止し，アルガトロバンを開始し血小板の改善を待ってワルファリンへ切り替えられた[9-10]．1 例はアルガトロバン開始後も肺動脈血栓塞栓症の増悪を認めたが，その後改善が得られ軽快退院した．

SMVTにHITを合併した症例においてこれまで死亡例の報告はないが，山本らの報告のようにSMVT単独でもそのほかの血栓塞栓症を併発することがあり，HITによるトロンビンの過剰産生が加わると，血栓塞栓症の合併・増悪の危険性が増すことが推察されるため，早期にHITを疑い，治療介入することが重要と考えられる[9]．本症例は幸い臨床症状と血小板減少の乖離がありすぐにHITと診断し，早期に治療を開始することができたため，肺血栓の増悪や新たな血栓塞栓を発症することなく事なきを得ることができた．SMVTの治療中に血小板数減少や血栓塞栓の増悪を認めた際にはHITの合併も考え，早期の診断・治療介入が重要と考えられた．

結語

ヘパリン投与中の血小板減少時にはHITを鑑別に挙げ，D-dimer上昇時には血栓塞栓症の合併がないか注意し経過をみることが重要である．

利益相反：なし

文献

1) Kumar S, Sarr MG, Kamath PS.: Mesenteric venous thrombosis. N Engl J Med. 2001; 345: 1683-1688
2) Rhee RY, Gloviczki P, Mendonca CT, Petterson TM, Serry RD, Sarr MG, et al. Mesenteric venous thrombosis: still a lethal disease in the 1990s. J Vasc Surg 1994; 20: 688-697
3) Chong BH, Berndt MC.: Heparin-induced thrombocytopenia. Blut 1989; 58: 53–57
4) 宮田茂樹，山本晴子.: 血小板系Heparin-induced thrombocytopenia (HIT)　診断と治療，最近の進歩. Annu Rev血液2008; 199-210
5) Arepally GM, Ortel TL.: Clinical practice. Heparin-induced thrombocytopenia. N Engl J Med. 2006; 355: 809-817

表 3：HIT Expert Probability Score

Clinical feature	Score
1. Magnitude of fall in platelet count (measured from peak platele count to nadirplatele count since heparin exposure)	
a.< 30%	-1
b. 30%-50%	1
c.> 50%	3
2. Timing of fall in platelet count	
For patients in whom typical onset HIT is suspected	
a. Fall begins < 4 days after heparin exposure	0
b. Fall begins 4 days after heparin exposure	2
c. Fall begins 5-10 days after heparin exposure	3
d. Fall begins 11-14 days after heparin exposure	2
e. Fall begins > 14 days after heparin exposure	-1
For patients with previous heparin exposure in the last 100 days in whom rapid onset HIT is suspected:	
f. Fall begins < 48 h after heparin re-exposure	2
g. Fall begins > 48 h after heparin re-exposure	-1
3. Nadir platelet count	
a. $\leq 20 \times 10^9\ L^{-1}$	-2
b. $> 20 \times 10^9\ L^{-1}$	2
4. Thrombosis (select no more than one)	
For patients in whom typical onset HIT is suspected	
a. New VTE or ATE > 4 days after heparin exposure	3
b. Progression of pre-existing VTE or ATE while receiving heparin	2
For patients in whom rapid onset HIT is suspected	
c. New VTE or ATE after heparin exposure	3
d. Progression of pre-existing VTE or ATE while receiving heparin	2
5. Skin necrosis	
a. Skin necrosis at subcutaneous heparin injection sites	3
6. Acute systemic reaction	
a. Acute systemic reaction after intravenous heparin bolus	2
7. Bleeding	
a. Presence of bleeding, petechiae or extensive bruising	-1
8. Other causes of thrombocytopenia (select all that apply)	
a. Presence of a chronic thrombocytopenic disorder	-1
b. Newly initiation non-heparin medication known to cause thrombocytopenia	-2
c. Severe infection	-2
d. Severe DIC (defined as fibrinogen < 100 mg dL^{-1} and D-dimer > 5.0 $\mu g/mL^{-1}$)	-2
e. Indwelling intra-arterial device (e.g. IABP, VAD, ECMO)	-2
f. Cardiopulmonary bypass within previous 96 h	-1
g. No other apparent cause	3

VTE, venous thromboembolism; ATE, arterial thromboembolism; DIC, disseminated intravascular coagulation; IABP, intra-aortic balloon pump; VAD, ventricular assist device; ECMO, extracorporeal membrane oxygenation.

(Cuker A et al. J Thromb Haemost. 2010; 8: 2642-2650)

6) Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A.: Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost. 2006; 4: 759-765.
7) Cuker A, Arepally G, Crowther MA, Rice L, Datko F, Hook K, et al.: The HIT Expert Probability (HEP) Score: a novel pre-test probability model for heparin-induced thrombocytopenia based on broad expert opinion. J Thromb Haemost. 2010; 8: 2642-2650.
8) Lee GM, Arepally GM.: Heparin-induced thrombocytopenia. Hematology 2013; 2013: 668-674.
9) 山本澄治, 久保雅俊, 宇高徹総.: 上腸間膜静脈血栓症治療中にヘパリン起因性血小板減少症を発症した 1 例. 日本腹部救急医学会雑誌 2016; 36: 761-765
10) 古川健太, 森口聡, 野中亮児, 野呂浩史, 吉川浩之, 中場寛行, 他. : ヘパリン起因性血小板減少症を発症した上腸間膜静脈血栓症の 1 例. 日本臨床外科学会雑誌 2011; 72: 796-800

鹿児島大学医学雑誌　2019年 8 月
Med. J. Kagoshima Univ., August, 2019

急性虫垂炎に対する待機，非待機手術の検討

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Primary or Interval Operation for Patients with Acute Appendicitis

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（Received 2019, Apr. 28; Revised 2019, June 8; Accepted July 12）

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Abstract

Purpose: To assess the clinical usefulness, problems, and indication of interval appendectomy（IA）in comparison with those of primary appendectomy（PA）.

Methods: A total of 50 acute appendicitis patients who underwent appendectomy from July 2012 to November 2015 in Ohshima Prefectural Hospital were enrolled. Thirty-six patients, who underwent appendectomy as primary treatment without medication, were included in the PA group and 14 patients who underwent interval appendectomy were included in the IA group. The clinicopathological factors between the two groups were compared and the preoperative risk factors for postoperative complications in the PA group were analyzed.

Results: Nine（25%）patients had a postoperative complication in the PA group versus no complication in the IA group（P<0.05）. In the PA group, the patients with postoperative complication had significantly higher pulse rate（PR）, body temperature（BT）, and C-reactive protein（CRP）level than those without postoperative complications（P<0.01）. More than two clinical parameters among PR, BT, and CRP level significantly correlated well with postoperative complications（P<0.01）.

Conclusion: Some patients in the PA group had a risk of postoperative complications. Preoperative clinical parameters（PR, BT, and CRP level）enable us to predict postoperative complications after appendectomy. IA may be suitable for such patients.

Key words: acute appendicitis, interval appendectomy, postoperative complication, systemic inflammatory response syndrome（SIRS）

はじめに

重症急性虫垂炎に対して、非待機的虫垂切除術（primary appendectomy, 以下PA）が一般的とされているが[1) 2)]、術後に創部感染や腹腔内膿瘍、イレウス等の合併症が発生し[3)]、必ずしも良好な経過を取らない。近年、虫垂周囲膿瘍や腫瘤を形成した虫垂炎に対して保存的治療を行った後に手術を行う待機的虫垂切除術（interval appendectomy，以下IA）の有用性が報告されているが[4) 5) 6)]、IAの適応基準は明らかになっていない。

今回われわれは、IAの有用性および問題点、PAにおける術後合併症発生の予測因子をretrospectiveに検討し、急性虫垂炎に対するIAの適応について考察した。

対象および方法

2012年 7 月から2015年11月までの 3 年 4 ヶ月の間に急性虫垂炎と診断され、虫垂切除を行った50例を対象とした（表 1 ）。前期（2012年 7 月～ 2014年 6 月）の36例にはPAが、後期（2014年 7 月～ 2015年11月）の14例にはIAが施行されており、これらの 2 群間で臨床病理学的因子について比較検討した。また、PA群において術後合併症の有無により 2 群に分けそれぞれの特徴を明らかにし、PA群の術後合併症予測因子について検討した。

通常の術後経過から逸脱した症状を術後合併症と定義した。IA群の保存的治療は入院のうえで抗菌薬の経静脈投与が行われ、腹腔内膿瘍を形成した症例については主治医の判断で経皮的膿瘍ドレナージが施行された。IA群における入院期間は保存的治療と手術の際に要した入院日数とし、保存的治療終了後から手術までの期間はこれまでの報告をもとに糞石のない症例は 3 ヶ月、糞石を有する症例は 2 ヶ月とした[4) 6) 7)]。

2 群間の単変量解析にはFisherの直接確率検定、Mann-WhitneyのU検定を行い、PA群における多変量解析にはロジスティック回帰分析を行った。$P<0.05$をもって有意差ありとした。統計はフリー統計ソフトEZR version 1.32を用いた[8)]。

結果

患者背景では、IA群とPA群の間で年齢、性別、発症から入院までの期間、初診時の脈拍（以下PR）、体温（以下 BT）、白血球数、CRP値、CT所見に差は認められなかった（表 1 ）。

入院期間はPA群が8.5日、IA群が18日とIA群が有意に長かった（$P<0.01$）。また、手術時間はIA群が72.5分、PA群が88.5分と有意にIA群で短かった（$P<0.05$）。ドレーン留置はIA群 0 例、PA群28例（77.8%）、術後合併症はIA群 0 例、PA群 9 例（25%）に認められ、有意にPA群に高率に認められた（$P<0.01$）。病理診断では壊疽性虫垂炎の割合がPA群で有意に高率であった（$P<0.01$）（表 2 ）。

IA群のうち 2 例（14.3%）は治療中に腹腔内膿瘍形成を認め、1 例は経皮的ドレナージを要した（図 1 ）。一方、PA群のうち、術後合併症例の全入院期間の中央値は15日（ 9 ～ 54日）であり、全IA症例の入院期間との間で有意差は認めなかった（$P = 0.449$）。PA群の術後合併症は 9 例にみられ、その内訳はイレウス 3 例、腸炎、心 不 全、Disseminated Intravascular Coagulation（DIC）/ Acute Respiratory Distress Syndrome（ARDS）、Surgical site infection（SSI）、肝機能障害、腹腔内膿瘍が各 1 例ずつであった（表 3 ）。PA群を術後合併症の有無により 2 群に分けて臨床病理学的因子の関連性を検討した。術後合併症例の初診時のPR、BT、CRP値の中央値はそれぞれ105回/分（57-122回/分）、38.1℃（37.6-39.6℃）、CRP値 11.5mg/dl（4.9-14.1mg/dl）であり、非合併例の82回/分（61-111回/分）、37.1℃（35.6-39.8℃）、CRP値 1.5mg/dl（0-33.9mg/dl）と比較して有意に高値であった（それぞれ$P<0.01$）。さらにCT所見では虫垂径、虫垂周囲脂肪織濃度上昇、糞石や腹水の有無に両群間で有意差はなく、虫垂周囲の膿瘍形成のみが術後合併症群において有意に高率であった（$P<0.01$）（表 4 ）。

PR、BT、CRP、虫垂周囲の膿瘍形成の 4 因子について多変量解析を行ったところ、術後合併症の独立した危険因子にいずれも選定されなかった（表 4 ）。ROC曲線を用いて各因子のカットオフ値を設定し（脈拍：カットオフ値≧96回/分、AUC 0.767、体温：カットオフ値≧37.9℃、AUC 0.858、CRP：カットオフ値≧9.2mg/dl AUC 0.844）、カットオフ値を満たす因子の数で術後合併症について検討を行った（図 2 ）。合併症を認めなかった群の中央値は 0 因子（0-2）、合併症を認めた群の中央値は 2 因子（1-3）であり、合併症を認めた群で有意に複数の因子を有していた（$P<0.01$）（図 3 ）。 1 因子以下と 2 因子以上の 2 群に分けて検討したところ、2 因子以上を満たす群で有意に術後合併症が多かった（$P<0.01$）。また、3 因子全てを満たす症例は全例合併症を認めていた（表 5 ）。

考察

本研究の結果からPA群は入院期間が短いものの、一部で腹腔内膿瘍やイレウス等の術後合併症が発生しており、PA群の中にはIAの適応となる症例が含まれている可能性が示唆された。一般的に虫垂周囲の膿瘍形成や腫瘤形成性虫垂炎では炎症が周囲臓器に進展しており、非待機的に手術を行うと、回盲部切除などの過大な手術となり、術後合併症発生のリスクが高くなることが知られている[9)]。このような症例では保存的治療が比較的奏効

表 1：PA 群と IA 群の患者背景の比較

		PA 群（n=36）	IA 群（n=14）	*P* 値
性別 *	男	19	10	n.s.
	女	17	4	
年齢 *（歳）	＜ 65	27	12	n.s.
	≧ 65	9	2	
発症から入院までの期間 **（日）		1（0-7）	1（0-17）	n.s.
脈拍 **（/ 分）		87（57-122）	93（69-116）	n.s.
体温 **（℃）		37.5（35.6-39.8）	37.6（37.0-39.6）	n.s.
WBC**（/ μ l）		14235（5570-23620）	11845（5920-21580）	n.s.
CRP**（mg/dl）		4.55（0.1-33.9）	3.9（0.1-24.3）	n.s.
CT 所見				
虫垂径 **（mm）		13（7-32）	13.5（8-18）	n.s.
虫垂周囲脂肪織濃度上昇 *	あり	30	12	n.s.
	なし	6	2	
糞石 *	あり	20	5	n.s.
	なし	16	9	
腹水 *	あり	19	3	n.s.
	なし	17	11	
虫垂周囲低吸収域 *	あり	2	0	n.s.
	なし	34	14	

* Fisher の直接確率検定
**Mann-Whitney の U 検定
n.s.: no significant differences

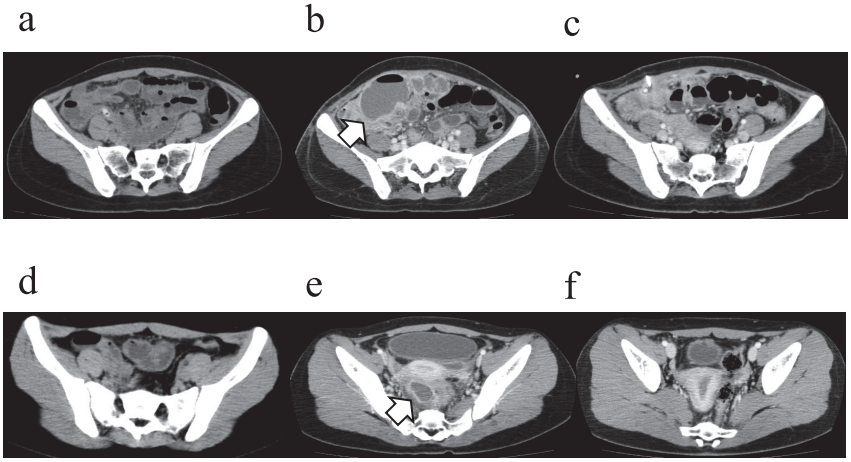

図 1　保存的治療期間中の膿瘍形成症例のCT画像
（a, b, c）症例 1：46歳女性。腹腔内膿瘍の経皮的ドレナージ後にIAが施行された。a：入院 1 日目、b：入院 2 日目、c：経皮的ドレナージ後。
（d, e, f）症例 2：13歳女性。保存的治療後にIAが施行された。d：入院 1 日目、e：入院 9 日目、f：保存的治療後。
白矢印：腹腔内膿瘍

表 2：PA 群と IA 群の臨床病理学的因子の比較

臨床病理学的因子		PA 群（n=36）	IA 群（n=14）	*P* 値
入院期間 **（日）	全入院期間	8.5（5-54）	18.0（8-47）	＜ 0.01
	手術時入院期間	8.5（5-54）	8.0（5-12）	n.s.
手術方法 *	腹腔鏡	32	12	n.s.
	開腹	4	2	
手術時間 **（分）		88.5（41-197）	72.5（29-121）	＜ 0.05
出血量 **（g）		0（0-340）	0（0-50）	n.s.
ドレーン留置 *	あり	28	0	＜ 0.01
	なし	8	14	
術後合併症 *	あり	9	0	＜ 0.05
	なし	27	14	
病理診断 *	壊疽性	22	0	＜ 0.01
	その他	14	14	

* Fisher の直接確率検定
**Mann-whitney の U 検定
n.s.: no significant differences

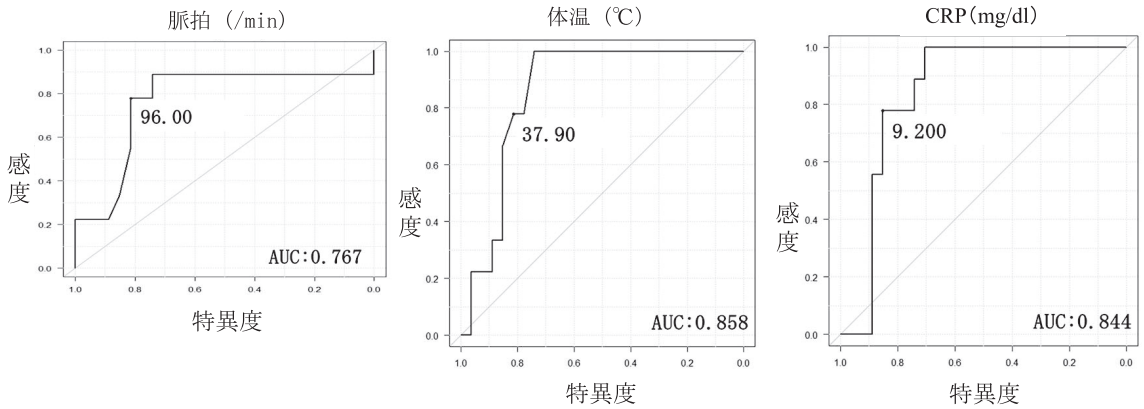

図 2　PA群におけるROC曲線（脈拍、体温、CRP）

表 3　PA 群の術後合併症症例

症例	性別	年齢（歳）	手術方法	合併症	病理診断	入院期間（日）
1	女	96	開腹	腸炎	壊疽性	41
2	女	85	腹腔鏡	心不全	壊疽性	11
3	男	78	腹腔鏡	イレウス	壊疽性	14
4	男	65	腹腔鏡	イレウス	蜂窩織炎性	17
5	男	47	開腹	DIC, ARDS	壊疽性	54
6	女	31	腹腔鏡	SSI	蜂窩織炎性	11
7	女	31	腹腔鏡	肝機能障害	壊疽性	9
8	男	17	腹腔鏡	イレウス	壊疽性	20
9	男	7	腹腔鏡	腹腔内膿瘍	壊疽性	15

表 4　PA 群における臨床病理学的因子と術後合併症の関係（単変量、多変量解析）

臨床病理学的因子		術後合併症		単変量解析	多変量解析
		あり（n=9）	なし（n=27）	*P* 値	*P* 値
発症から入院までの期間 **（日）		1（0-7）	0（0-3）	n.s.	
脈拍 **（/ 分）		105（57-122）	82（61-111）	＜ 0.05	n.s.
体温 **（℃）		38.1（37.6-39.6）	37.1（35.6-39.8）	＜ 0.01	n.s.
WBC**（/μ l）		14190（5570-18950）	14280（6590-23620）	n.s.	
CRP**（mg/dl）		11.5（4.9-14.1）	1.5（0.0-33.9）	＜ 0.01	n.s.
CT 所見					
虫垂径 **（mm）		13.0（12.0-32.0）	11.8（7.0-18.0）	n.s.	
虫垂周囲脂肪織濃度上昇 *	あり	8	22	n.s.	
	なし	1	5		
糞石 *	あり	6	14	n.s.	
	なし	3	13		
腹水 *	あり	4	15	n.s.	
	なし	5	12		
虫垂周囲低吸収域 *	あり	2	0	＜ 0.05	n.s.
	なし	7	27		
病理診断 *	壊疽性	7	15	n.s.	
	その他	2	12		

* Fisher の直接確率検定
**Mann-Whitney の U 検定
n.s.: no significant differences

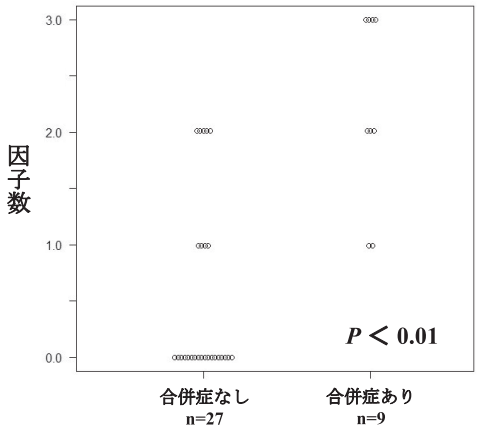

図 3 PA群における術後合併症と危険因子数との関係（脈拍≧96 /分、体温≧37.9℃、CRP≧9.2 mg/dL）

しやすいことが報告されており[10) 11)]、IAのよい適応と考えられている。今回の検討においてもPA群の膿瘍形成を認めた2例はいずれも術後合併症を発生していたが、IA群の2例は術後合併症を認めなかった。

一方、PA群の入院期間と比較してIA群では有意に長期であったが、PA群の術後合併症が発生した症例と比較したところ入院期間の中央値はそれぞれ15（9 - 54）日と18（8 - 47）日であり、有意な差は認められなかった（$P = 0.449$）。

PA群において術後合併症が発生した症例のPR、BT、CRP値は非合併症発生例と比較して有意に高値であり、多変量解析で独立した危険因子は抽出されなかったが、これらの因子が複数高値の場合には術後合併症の発生が有意に多かった。また、IA群14例のうち4例（28.6%）がこれらの危険因子を複数有していた。そのうちの2例は保存的治療期間中に膿瘍形成を伴った症例であったが、いずれも術後合併症の発生はなく、安全に手術が可能であった。

全身性炎症反応症候群（Systemic inflammatory response syndrome: SIRS）は1992年に米国胸部疾患医学会とクリティカルケア医学会の合同委員会により発表された敗血症に関連する臨床概念であり、その診断基準は①体温>38℃または<36℃、②脈拍>90回/分、③呼吸数>20回/分、PaCO2<32Torr、④白血球数>12000/mm³または<4000/mm³あるいは未熟顆粒球>10%の4項目のうち、2項目以上を満たすものとされている[12)]。術前のSIRS状態と虫垂炎の臨床転帰との関連性をPubMedで検索したところ3編の報告がみられた。2編は術前のSIRS scoreが穿孔性虫垂炎の予測因子となるという報告であり[13) 14)]、他の1編は17歳未満の小児での検討であるが，入院時にSIRS状態であった患者で術後合併症、入院期間が有意に長期であったという報告であった[15)]。本検討では呼吸数、$PaCO_2$の評価が行われていなかったが、合併症が発生した症例の9例中8例がSIRSの診断基準を満たしていた。以上のことから術前のSIRS状態が穿孔性虫垂炎を反映し、術後合併症発生と関連している可能性が示唆された。

結語

急性虫垂炎は日常診療遭遇する頻度の最も高い腹部救急疾患の一つではあるが、本邦においていまだその治療方針は定まっていない。急性期虫垂切除術の術後合併症発生の予測にはバイタルサイン、CRPを用いた全身の炎症の評価が有用であり、これらの因子が複数高値である症例については安全性の観点から十分なインフォームドコンセントのもとIAが選択され得ると考えられた。

文献

1. Vons C, Barry C, Maitre S, Pautrat K, Leconte M, Costaglioli B, et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial. Lancet. 2011; 377: 1573-1579.
2. Wilms IM, de Hoog DE, de Visser DC, Janzing HM. Appendectomy versus antibiotic treatment for acute appendicitis. Cochrane Database Syst Rev. 2011; 11: CD008359.
3. Wu JM, Lin HF, Chen KH, Tseng LM, Tsai MS, Huang SH. Impact of previous abdominal surgery on laparoscopic appendectomy for acute appendicitis. Surg Endosc. 2007; 21: 570-573.
4. 前田 大, 藤崎 真人, 高橋 孝行, 平畑 忍, 亀井 秀策, 戸倉 英之ほか. 成人 虫垂膿瘍に対するinterval appendectomy. 日臨外会誌 2003; 64: 2089-2094.
5. 道躰 幸二朗, 斉田 芳久, 榎本 俊行, 高林 一浩, 大辻 絢子, 中村 陽一ほか. 膿瘍を合併した急性虫垂炎に対するLaparoscopic interval appendectomyの有用性. Prog Dig Endosc 2011; 78: 126-127.
6. 片桐 秀樹, 宮野 省三, 町田 理夫, 北畠 俊顕, 藤澤 稔, 児島 邦明ほか. 腫瘤形成性虫垂炎に対するlaparoscopic interval appendectomyの検討. 日腹部救急医会誌 2012; 32: 781-784.
7. 家入 里志, 柳 佑典, 松浦 俊治, 宗崎 良太, 永田 公二, 林田 真ほか. Interval appendectomyの適応と至適手術時期についての検討. 日腹部救急医会誌 2012; 32: 771-774.
8. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013; 48: 452-458.
9. 原 和人, 横山 隆. 腫瘤を触知する虫垂炎の検討 とくに腸合併切除例について. 日臨外会誌 1987; 48: 534-542.
10. Yamini D, Vargas H, Bongard F, Klein S, Stamos MJ. Perforated appendicitis: is it truly a surgical urgency? Am Surg. 1998; 64: 970-975.
11. Gillick J, Velayudham M, Puri P. Conservative management of appendix mass in children. Br J Surg. 2001; 88: 1539-1542.
12. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA , et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/

Society of Critical Care Medicine. Chest. 1992; 101: 1644-1655.
13. Beltran MA, Mendez PE, Barrera RE, Contreras MA, Wilson CS, Cortes VJ, et al. Is hyperbilirubinaemia in appendicitis a better predictor of perforation than C-reactive protein? - a prospective study. Indian J Surg. 2009; 71: 265-72.
14. Hong YR, Chung CW, Kim JW, Kwon CI, Ahn DH, Kwon SW, et al. Hyperbilirubinemia is a significant indicator for the severity of acute appendicitis. J Korean Soc Coloproctol. 2012; 28: 247-252.
15. Raines A, Garwe T, Wicks R, Palmer M, Wood F, Adeseye A, et al. Pediatric appendicitis: the prevalence of systemic inflammatory response syndrome upon presentation and its association with clinical outcomes. J Pediatr Surg. 2013; 48: 2442-2445.

Med. J. Kagoshima Univ., September, 2019

Influences of Estrogen-dependent Diseases, Premature Oophorectomy and Anti-cancer Chemotherapy on Skin Age in Japanese Women

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(Received 2019 Feb. 26; 2nd Revised June. 17; Accepted July. 11)

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Abstract

Aim: The purpose of the present study was to investigate the influences of estrogen-dependent diseases, premature oophorectomy and anti-cancer chemotherapy on skin age in Japanese women.

Materials and methods: A total of 68 Japanese women were recruited between July 2016 and May 2018 at the Department of Obstetrics and Gynecology, Kagoshima University Hospital. This study included three subjects. Subject 1: A total of 57 premenopausal women were divided into two groups: those with estrogen-dependent diseases (n=19) and estrogen-independent diseases (n=38). Subject 2: A total of 26 premenopausal women were divided into two groups: those with premature oophorectomy (n=15) and ovarian preservation (n=11) during gynecological surgery. Subject 3: A total of 11 postmenopausal women who had received oophorectomy during their cancer operations were divided into two groups: those with postoperative anti-cancer chemotherapy (n=6) and those without chemotherapy (control, n=5). Facial skin parameters including skin age, relative skin age (i.e., skin age minus chronological age) and skin health conditions were assessed using a bioelectrical impedance analysis device.

Results: 1) Relative skin age was significantly younger in women with estrogen-dependent diseases than in those with estrogen-independent diseases (-1.0 ± 1.4 vs. 2.5 ± 0.6 years, respectively, $p<0.01$). 2) Longitudinal changes in relative skin age at 6 months postoperatively in the oophorectomy group had progressed significantly compared with the ovarian preservation group (3.5 ± 1.4 vs. -0.2 ± 0.8 years, respectively, $p<0.05$). 3) Longitudinal changes in relative skin age at 12 months after chemotherapy in postmenopausal women who received 6 courses of postoperative anti-cancer chemotherapy had progressed significantly compared with control (10.5 ± 3.3 vs. -3.8 ± 3.4 years, respectively, $p<0.05$). The ratio of young skin conditions was also significantly decreased after chemotherapy (from 5/6 to 1/6, respectively, $p<0.05$).

Conclusions: Women with estrogen-dependent diseases maintain a younger facial skin age than those with estrogen-independent diseases. However, skin aging is accelerated by premature oophorectomy and markedly accelerated by anti-cancer chemotherapy.

Key Words: words: anti-cancer chemotherapy, estrogen-dependent diseases, premature oophorectomy, skin age, skin health conditions

Introduction

Estrogens are the most important sex hormones that promote the development and maintenance of female characteristics. The menopause causes hypoestrogenism, accelerating age-related deterioration, which results in thinner skin, an increased number of wrinkles, increased skin dryness and decreased skin elasticity[1, 2]. From gynecological aspects, factors affecting the skin age include simple aging, natural or iatrogenic menopause (i.e., premature oophorectomy), radiotherapy and anti-cancer chemotherapy. As for estrogen-dependent gynecological diseases[3-5], developments of uterine leiomyoma and endometrial cancer are estrogen-dependent, differing from uterine cervical cancer. In particular, most risk factors for endometrial cancer are associated with prolonged and unopposed exposure of the endometrium to estrogen. The development of endometrial cancer reflects the cumulative effects of uncontrolled estrogen exposure[6]. Estrogen is one of the important determinants of women's skin conditions[1, 7-9]. Thus, it is likely that women with estrogen-dependent diseases have a younger skin age. Anti-cancer chemotherapy also affects patients' skin, mucous membranes, hair and nails[10]. Recent developments of anti-cancer chemotherapy have extended patients' survival. Thus, in cancer survivors as well, maintenance of the skin condition after anti-cancer chemotherapy is becoming more important. In the gynecological field, however, the relationship of estrogen-dependent diseases with skin aging and the effects of premature oophorectomy and anti-cancer chemotherapy on skin aging have been insufficiently investigated. One of the possible reasons for this may be the difficulty of objective assessment of skin aging by gynecologists. In addition, special attention has not been paid to the skin condition around the periods of premature oophorectomy and anti-cancer chemotherapy. Recent technological advances in bioelectrical impedance analysis have enabled us to objectively assess the skin age[11].

In the present study, we investigated the influences of estrogen-dependent diseases, premature oophorectomy and anti-cancer chemotherapy on the skin age in Japanese women with various gynecological diseases using bioelectrical impedance analysis.

Materials and methods

Japanese women with gynecological diseases were recruited between July 2016 and May 2018 at the Department of Obstetrics and Gynecology, Faculty of Medicine, Kagoshima University Hospital. Fully informed written consent was obtained from 68 patients before entry into the study. This study was conducted in accordance with IRB approval (No.28-84) at Kagoshima University Hospital, and was also conducted in accordance with Helsinki Declaration (as revised in Tokyo 2004).

Subjects

Subject 1: A total of 57 premenopausal women were divided into two groups: those with estrogen-dependent diseases (n=19) and estrogen-independent diseases (n=38). Estrogen-dependent diseases included endometrial cancer (n=12), atypical endometrial hyperplasia (n=1) and uterine leiomyoma (n=6). Estrogen-independent diseases included uterine cervical cancer (n=20), cervical intraepithelial neoplasia (n=5) and non-estrogen-producing ovarian tumor (n=13).

Subject 2: A total of 26 premenopausal women were divided into two groups: those with premature oophorectomy (n=15) and ovarian preservation (n=11) during gynecological surgery. The oophorectomy group included women with endometrial cancer (n=9), cervical cancer (n=4), ovarian cancer (n=1) and another gynecological disease (n=1). The ovarian preservation group included those with cervical cancer (n=7) and other gynecological diseases (n=4).

Subject 3: A total of 11 postmenopausal women who had received cancer operations were divided into two groups: those with postoperative anti-cancer chemotherapy (n=6) and those without chemotherapy (control, n=5). The principal cancer operations included hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy and/or omentectomy. Chemotherapy regimens included paclitaxel and carboplatin (TC) (n=5) and docetaxel and carboplatin (DC) (n=1).

Baseline characteristics included the chronological age (years), height (cm), body weight (kg), body mass index (BMI), parity, smoking status and amenorrhea status. Facial skin parameters including skin age, relative skin age (i.e., skin age minus chronological age) and skin health conditions were assessed using a bioelectrical impedance analysis device. BMI was calculated as the weight (kg) divided by height squared (m^2).

Some patients overlapped with Subject 1 and 2. Exclusion criteria included patients with skin disease, heart pace-maker, pregnancy, radiation exposure, excessive ultraviolet radiation exposure (e.g., female athletes), heavy makeup and a heavy drinking or smoking habit.

Measurement of skin age

Bioelectrical impedance of the skin shows an age-related increase[12]. This is due to the fact that hyaluronic acid, collagen and hydration contents in the skin show age-related declines and are negatively correlated with bioelectrical impedance[12]. In this study, the skin age was measured with a bioelectrical impedance analysis device, Well-Beauty® (AC100V, 50/60HZ) (Wellup, CO., Ltd., Yokohama, Japan). During measurements of skin age, wearing makeup did not matter. In subject 1, skin ages were measured after admission of patients and before gynecological treatments. In subject 2, skin ages were measured at three time points. The first measurements were performed after admission of patients and before gynecological treatments, the second measurements were performed at 6 months after the operation and the third measurements were performed at 12 months after the operation. In subject 3, skin ages were also measured at three time points: before cancer operations and 6 and 12 months after 6 courses of postoperative anti-cancer chemotherapy. We input their sex and age using the touch panel monitor of the device. After fixing electrodes to the patient's bilateral palms and cheek skin, impedance to the weak flow of an electric current between the layers of the epidermis and dermis was measured for 40 seconds. This impedance was plotted on an age-related decline curve of 1/impedance obtained from pooled standard data, and then the measurement result (i.e., skin age) was displayed on the touch panel. Facial skin health conditions were ranked from A to E according to the relative skin age (skin age minus chronological age) and results were displayed on the touch panel. The ranking comprised five categories: A (much younger skin), B (younger skin), C (normal range skin), D (older skin) and E (much older skin), compared with the chronological age, as shown in Table 1. In this study, skin health rank A or B was defined as a "young skin condition", whereas skin health rank D or E was defined as an "old skin condition", and C was a "normal skin condition".

Table 1. Facial skin health conditions (rank)

Rank		Relative skin age* (years)
A	Much younger skin	〜 -11
B	Younger skin	-10 〜 -5
C	Normal range skin	-4 〜 +4
D	Older skin	+5
E	Much older skin	+6 〜

* Relative skin age = skin age –chronological age (years)

Statistical analysis

All data show the mean ± standard error of the mean. Inter- and intra-group comparisons were made of the relative skin age, changes in the relative skin age and skin health conditions using paired or unpaired Student's t-test or the Chi-square test, as appropriate. $p<0.05$ was considered significant.

Results

The relationship of estrogen-dependent diseases with relative skin age in premenopausal women (Subject 1)

Table 2 shows comparisons of backgrounds of 57 premenopausal women with estrogen-dependent and estrogen-independent diseases. The chronological age was significantly older in women with estrogen-dependent diseases. The difference in skin age was not significant between the two groups. However, the relative skin age was significantly younger in women with estrogen-dependent diseases, compared with those with estrogen-independent diseases (-1.0 ± 1.4 vs. 2.5 ± 0.6 years, respectively, $p<0.01$) (Figure 1). Table 3 shows the differences in the facial skin health conditions of the 57 premenopausal women between the two groups. The ratio of young skin conditions (the number of A + B/the total number) was significantly higher in women with estrogen-dependent diseases than in those with estrogen-independent diseases (5/19 vs. 2/38, respectively, $p<0.05$). However, the ratio of old skin conditions (the number of D + E/the total number) was not different between the two groups.

The influence of premature oophorectomy on skin aging in premenopausal women (Subject 2)

We measured the skin age of oophorectomy and ovarian

Table 2. Background of 57 premenopausal women with estrogen-dependent and estrogen-independent diseases

	Estrogen-dependent disease (n=19)	Estrogen-independent disease (n=38)	p-value
Age (years)	44.1±1.6	38.1±1.1	p＜0.05
Skin age (years)	43.1±1.7	40.6±1.2	0.12
Height (cm)	157.6±1.3	156.9±0.9	0.67
Weight (kg)	60.7±2.47	55.8±1.32	0.06
BMI* (kg/m^2)	24.5±1.01	22.7±0.53	0.08
Parity	0.79±0.22	1.13±0.17	0.25
Amenorrhea (%)	0%	0%	NS†
Smokers (%)	15.8% (n=3)	36.8% (n=14)	0.10

Data are mean ±SEM
*BMI =body mass index
†NS = not significant

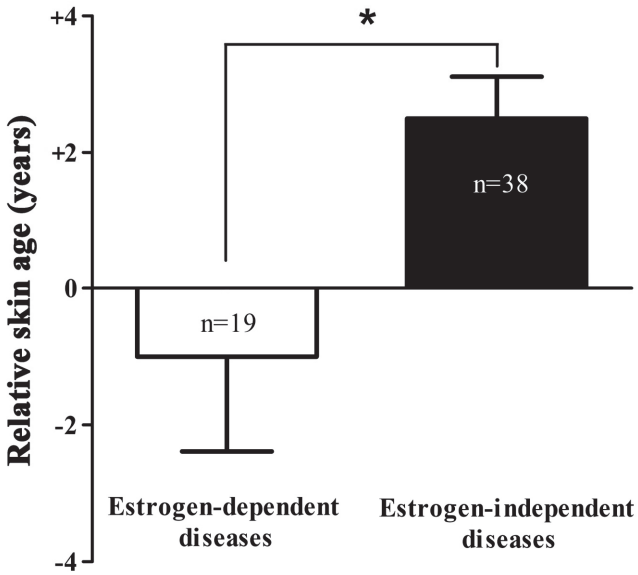

Figure 1. Relative skin age of 57 premenopausal women with estrogen-dependent and estrogen-independent diseases. *p<0.05

Table 3. Facial skin health conditions of 57 premenopausal women with estrogen-dependent and estrogen-independent diseases

Facial skin health conditions (rank)		Estrogen-dependent diseases (n=19)	Estrogen-independent diseases (n=38)	
Young skin	A+B	5	2	p＜0.05
	A	3	1	(5/19 vs. 2/38)
	B	2	1	
Normal skin	C	12	28	NS*
Old skin	D+E	2	8	p=0.32
	D	2	4	(2/19 vs. 8/38)
	E	0	4	

*NS = not significant

preservation groups before and 6 and 12 months after the operation. Tables 4 and 5 show the backgrounds of the two groups of premenopausal women (skin age measurements 6 and 12 months after the operation, respectively). At 6 months postoperatively, the chronological age and skin age in the oophorectomy group were both significantly older than in the ovarian preservation group. At 12 months postoperatively, the chronological age and skin age in the oophorectomy group were also older than in the ovarian preservation group, although the difference in the skin age was not significant. Longitudinal changes in relative skin age at 6 months postoperatively in the oophorectomy group had progressed significantly compared with that in the ovarian preservation group (3.5 ± 1.4 vs. -0.2 ± 0.8 years, respectively, $p<0.05$) (Figure 2). Longitudinal changes in relative skin age at 12 months postoperatively in the oophorectomy group tended to progress compared with that in ovarian preservation group (3.5 ± 1.8 vs. 0.1 ± 0.3 years, respectively, $p=0.08$) (Figure 3). On inter-group comparison in the oophorectomy group, longitudinal changes in relative skin age had progressed significantly at 12 months postoperatively (Figure 4, $p<0.05$). In the ovarian preservation group, the relative skin age showed no longitudinal change at 12 months postoperatively.

Table 4. Background of oophorectomy and ovarian preservation groups in 26 premenopausal women (skin age measurements at 6 months postoperatively)

	Oophorectomy (n=15)	Ovarian preservation (n=11)	p-value
Age (years)	47.2±1.3	37.1±1.4	$p<0.05$
Skin age (years)	46.6±1.7	39.7±1.5	$p<0.05$
Height (cm)	158.2±1.1	156.8±1.6	0.45
Weight (kg)	59.1±2.45	53.0±1.77	0.07
BMI* (kg/m^2)	23.7±1.02	21.6±0.70	0.14
Parity	1.00±0.31	0.91±0.25	0.83
Amenorrhea (%)	0%	0%	NS†
Smokers (%)	20.0% (n=3)	36.4% (n=4)	0.37

Data are mean ±SEM
*BMI =body mass index
†NS = not significant

Table 5. Background of oophorectomy and ovarian preservation groups in 17 premenopausal women (skin age measurements at 12 months postoperatively)

	Oophorectomy (n=10)	Ovarian preservation (n=7)	p-value
Age (years)	45.7±1.8	38.6±1.8	$p<0.05$
Skin age (years)	45.2±1.9	41.7±1.7	0.11
Height (cm)	157.4±1.4	158.3±2.2	0.72
Weight (kg)	62.6±4.06	53.1±2.56	0.09
BMI* (kg/m^2)	25.2±1.53	21.2±1.01	0.07
Parity	1.30±0.40	1.14±0.34	0.78
Amenorrhea (%)	0%	0%	NS†
Smokers (%)	20.0% (n=2)	42.9% (n=3)	0.34

Data are mean ±SEM
*BMI =body mass index
†NS = not significant

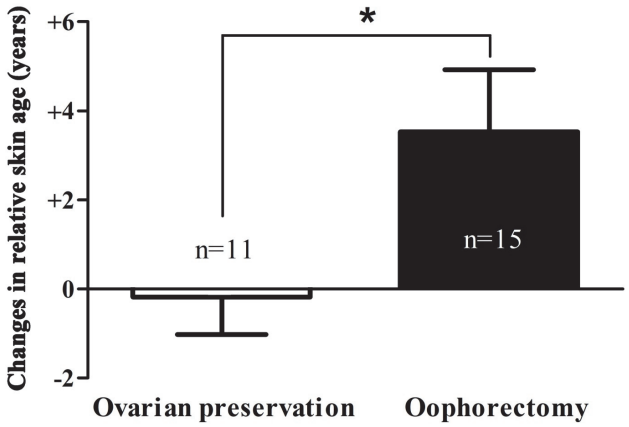

Figure 2. Changes in relative skin age of ovarian preservation and premature oophorectomy groups in 26 premenopausal women (6 months after operation). *p<0.05

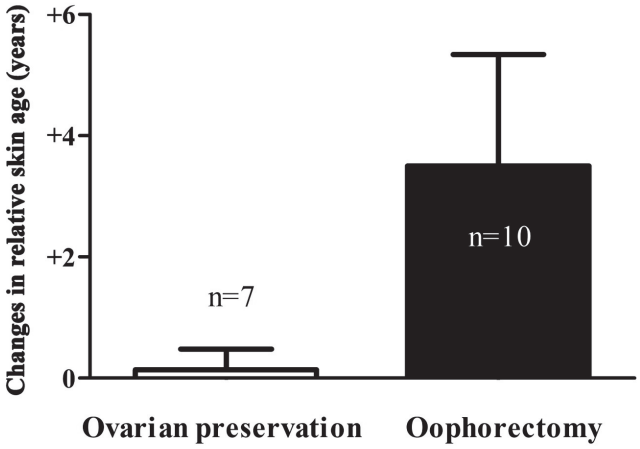

Figure 3. Changes in relative skin age of ovarian preservation and premature oophorectomy groups in 17 premenopausal women (12 months after operation). p=0.08

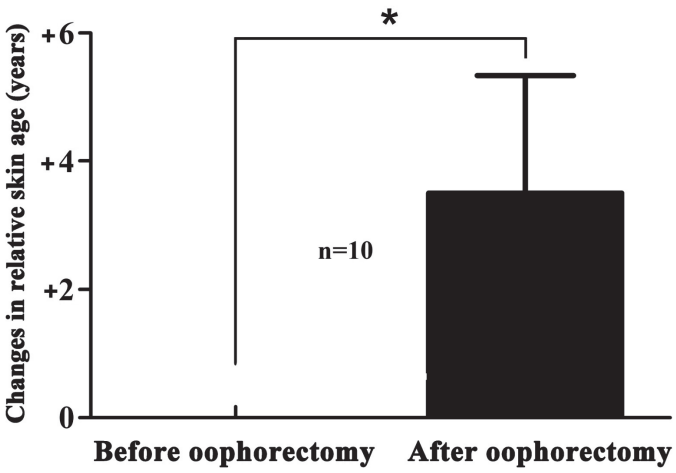

Figure 4. Longitudinal changes in relative skin age of premature oophorectomy group before and 12 months after oophorectomy (n=10). *p<0.05

The influence of anti-cancer chemotherapy on skin aging in postmenopausal women (Subject 3)

Table 6 shows the background of operation followed by chemotherapy and operation alone (control) groups (total of 11 postmenopausal women). Differences in the chronological age and skin age between the two groups were not significant. Longitudinal changes in relative skin age of the two groups were observed 6 and 12 months after chemotherapy. Six months after chemotherapy, longitudinal changes in relative skin age had progressed significantly in chemotherapy group compared with control group (8.7 ± 3.6 vs. -3.4 ± 3.0 years, respectively, $p<0.05$) (Figure 5). Twelve months after chemotherapy, similar results were obtained (10.5 ± 3.3 vs. -3.8 ± 3.4 years, respectively, $p<0.05$) (Figure 6). Table 7 presents the changes in the skin health condition before and 12 months after anti-cancer chemotherapy. The ratio of young skin conditions was also significantly decreased after chemotherapy (from 5/6 to 1/6, respectively, $p<0.05$). Longitudinal changes in relative skin age were observed before and after chemotherapy at 6-month intervals (Figure 7). Relative skin ages significantly progressed 6 and 12 months after chemotherapy, respectively.

Table 6. Background of chemotherapy and control groups in 11 postmenopausal women

	Chemotherapy (n=6)	Control (n=5)	p-value
Age (years)	63.3±1.3	58.6±2.6	0.12
Skin age (years)	53.5±2.8	57.8±3.0	0.16
Height (cm)	158.5±2.4	156.4±1.8	0.52
Weight (kg)	52.8±4.09	60.4±2.78	0.18
BMI* (kg/m^2)	21.0±1.46	24.8±1.40	0.10
Parity	1.67±0.56	1.40±0.40	0.72
Smokers (%)	0% (n=0)	20.0% (n=1)	0.34

Data are mean ±SEM
*BMI =body mass index

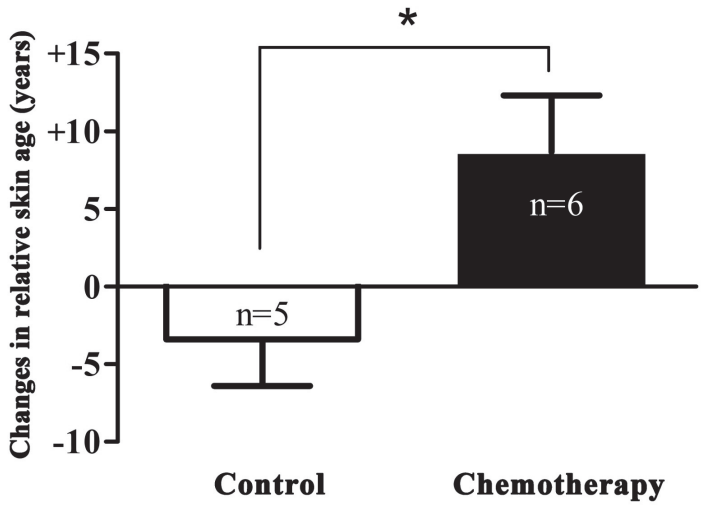

Figure 5. Changes in relative skin age of chemotherapy and control groups in 11 postmenopausal women (6 months after chemotherapy). *$p<0.05$

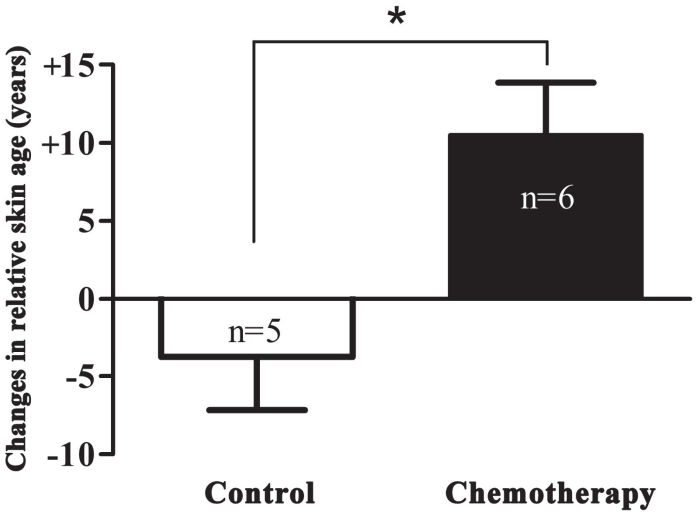

Figure 6. Changes in relative skin age of chemotherapy and control groups in 11 postmenopausal women (12 months after chemotherapy). *p<0.05

Table 7. Changes in skin health conditions before and 12 months after anti-cancer chemotherapy in 6 postmenopausal women

Facial skin health conditions (rank)		Before chemotherapy	After chemotherapy	
Young skin	A+B	5	1	p＜0.05 (5/6 vs. 1/6)
	A	5	1	
	B	0	0	
Normal skin	C	1	5	p＜0.05 (1/6 vs. 5/6)
Old skin	D+E	0	0	NS*
	D	0	0	
	E	0	0	

*NS = not significant

Figure 8 presents longitudinal changes in relative skin age in a 38-year-old patient with cervical cancer, who received 6 courses of anti-cancer TC chemotherapy after radical trachelectomy with ovarian preservation. Skin ages were measured before and 6 and 12 months after chemotherapy. The relative skin age markedly progressed from -10 years at the baseline to +3 years at 6 months after chemotherapy. During the 6-month period, the skin age became 13 years older. However, skin aging reached a plateau between 6 and 12 months after chemotherapy. Skin health conditions showed rank B at the baseline, and rank C at both 6- and 12-month intervals, being consistent with longitudinal changes in the relative skin age (Figures 5, 6 and 7). During chemotherapy and the follow-up period, she maintained her regular menstrual cycle.

Discussion

The skin is one of the important non-reproductive target organs of estrogen, which is known to play an essential role in regulating skin maintenance and turnover[13, 14]. Postmenopausal skin shows increased dryness[15, 16], decreased elasticity[17] and increased wrinkling[18]. Postmenopausal hormone replacement therapy (HRT) improves skin conditions[7, 19, 20] through

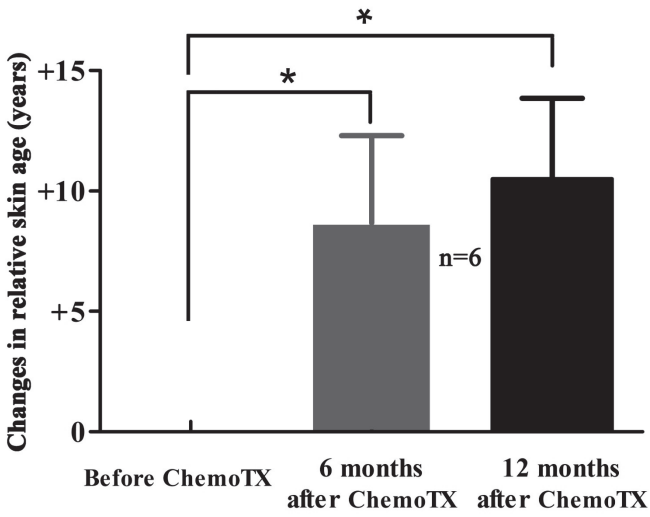

Figure 7. Longitudinal changes in relative skin age before and after chemotherapy in 6 postmenopausal women (at 6-month intervals). ChemoTX: chemotherapy. *p<0.05

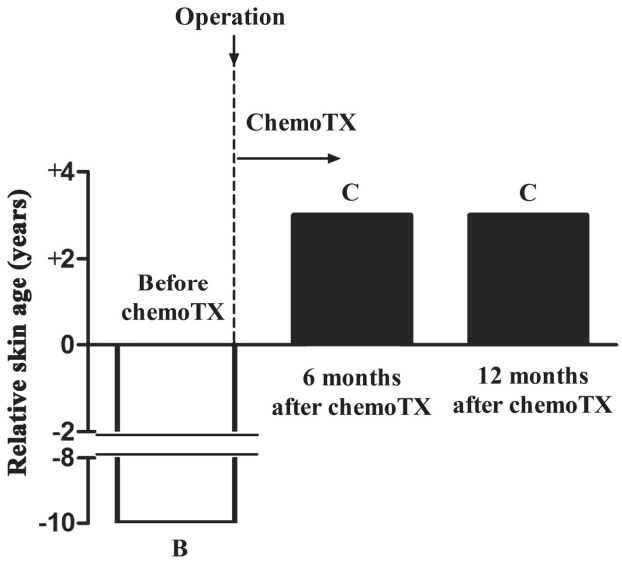

Figure 8. Relative skin age at 6-month intervals in a patient with cervical cancer who received 6 courses of postoperative anti-cancer chemotherapy after radical trachelectomy with ovarian preservation. ChemoTX: chemotherapy. B, C: Skin health condition ranks B and C.

increasing the skin collagen content, thickness, moisture and elasticity[21, 22]. A previous study showed that the decreases in the skin thickness and collagen content seen in elderly women may be more closely associated with estrogen deficiency than the chronological age[1]. In this study, we found that women with estrogen-dependent diseases had a younger skin age compared with their chronological age, and had a younger relative skin age compared with women with estrogen-independent diseases. To our best knowledge, there has been no other similar study. It is well-known that bone is also a target organ of estrogen, and that bone mineral density (BMD) is increased by HRT[23, 24]. Women with endometrial cancer have a higher BMD[25-29]. However, women with uterine cervical cancer as an estrogen-independent disease do not show a higher BMD[30]. Previous studies showed that a decrease in the skin collagen content parallels the reduction in BMD seen in postmenopausal women[1, 31]. In ovariectomized rats, marked structural alterations in skin and bone collagen

parallel hypoestrogenism[32]. Considering these findings, it is likely that cumulative estrogen exposure contributes to a younger skin age, higher BMD and the development of endometrial cancer and uterine leiomyoma.

In Japan, prophylactic salpingo-oophorectomy has been frequently performed for perimenopausal women undergoing hysterectomy even for benign conditions to prevent the later occurrence of ovarian cancer. However, women receiving premature oophorectomy have more severe and prolonged menopausal symptoms, and their risks of mood disturbance, heart disease, excessive bone resorption, sexual dysfunction and cognitive disorder are increased[33-38]. Although there have been many studies on the adverse effects of prophylactic oophorectomy on various organs to date[33-36], studies on the impact of prophylactic oophorectomy on skin conditions are limited. In the present study, longitudinal changes in the relative skin age of women who received premature oophorectomy progressed compared with the baseline level and controls with ovarian preservation at 6 months postoperatively. However, the relative skin age remained unchanged in women with ovarian preservation. Our study supports a report that prophylactic oophorectomy during hysterectomy is a significant and independent risk factor for accelerated skin aging in premenopausal women[39], reducing the quality of life (QOL). In addition, skin aging developed in an early period after oophorectomy, consistent with a previous report[39]. Many women feel a relatively early onset of skin aging several months after the beginning of menopausal symptoms[22, 40]. Thus, skin aging during menopausal transition may be an early symptom[40]. If skin aging is caused by premature oophorectomy alone, HRT soon after oophorectomy may delay the aging[7, 18], improving the QOL. However, long-term HRT may be necessary for the reversal of skin aging caused by oophorectomy, as well as the effect of postmenopausal HRT on the skin condition[7].

Standard operative procedures for ovarian cancer are hysterectomy and bilateral salpingo-oophorectomy with surgical staging (peritoneal washing cytology, omentectomy, retroperitoneal lymphadenectomy)[41]. It is well-known that the side effects of anti-cancer agents are nausea, vomiting, appetite loss, leucopenia and alopecia. Long-term side effects include the acceleration of neurocognitive decline, musculoskeletal complications such as early-onset osteoporosis, premature skin aging and ocular changes[42, 43]. Chemotherapy also affects the skin, mucous membranes, hair and nails, causing undesirable reactions including alopecia, stomatitis, hyperpigmentation, hypersensitivity reactions, and photosensitivity[10]. There is a report that skin aging is the most frequently reported unpleasant side effect[44]. In the present study, longitudinal changes in relative skin age markedly progressed in postmenopausal women with postoperative anti-cancer chemotherapy. In addition, facial skin aging in a cervical cancer patient who received radical trachelectomy with ovarian preservation markedly progressed after adjuvant anti-cancer chemotherapy. In this patient, chemotherapy-induced ovarian insufficiency (i.e., estrogen deficiency) was not observed. Based on the effects of premature oophorectomy and anti-cancer chemotherapy on the skin age, it is likely that the adverse effect of anti-cancer chemotherapy on the skin condition is greater than that of oophorectomy, leading to a greater reduction in the QOL.

We could not elucidate the underlying mechanism of skin aging induced by anti-cancer chemotherapy. In addition, it remained unresolved as to which of three anti-cancer agents has the greatest impact on skin aging. Our finding of a greater impact of chemotherapy compared with oophorectomy on skin aging suggests that mechanisms of skin aging are different between chemotherapy and premature oophorectomy. We should consider that every anti-cancer chemotherapeutic agent has potential mechanisms, including the accumulation of free-radical damage, accumulation of DNA damage, telomere shortening accompanying a decline in telomerase activity and damage to the neuroendocrine/immune function[43]. The mechanisms of cyclophosphamide-induced nail pigmentation have been reported to include a genetic predisposition, toxic effect of the drug on the nail bed and matrix, photosensitization, and focal stimulation of melanocytes in the matrix[45].

It remains unclear whether skin aging due to anti-cancer chemotherapy is reversible with medical intervention. In this respect, a long period was required for recovery from chemotherapy-induced alopecia. The pigmentation of nails, as a part of the skin, usually reverses several months after withdrawal of the drugs[46]. In ovarian cancer patients, oophorectomy and anti-cancer chemotherapy are usually performed, both of which affect skin conditions. Thus, the prevention and/or treatment against facial skin worsening may require a long period even though HRT is administered. Further extensive studies are needed.

In summary, women with estrogen-dependent diseases maintain a younger facial skin age than those with estrogen-independent diseases. However, skin aging is markedly accelerated by anti-cancer chemotherapy or premature oophorectomy, and the QOL is reduced. Considering the

possible occurrence of accelerated skin aging, we must pay special attention to prophylactic oophorectomy accompanying hysterectomy for benign conditions and anti-cancer chemotherapy.

Disclosure

The authors have no conflicts of interest to disclose.

Acknowledgments

This work was supported in part by a grant-in-aid for scientific research from the Japan Society for the Promotion of Science (No. 17K11284).

References

1) Brincat M, Moniz CJ, Studd JW, Darby A, Magos A, Emburey G, et al. Long-term effects of the menopause and sex hormones on skin thickness. Br J Obstet Gynaecol 1985; 92: 256-259.
2) Brincat MP. Hormone replacement therapy and the skin. Maturitas 2000; 35: 107-117.
3) Smith M, McCartney AJ. Occult, high-risk endometrial cancer. Gynecol Oncol 1985; 22: 154-161.
4) Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol 1983; 15: 10-17.
5) Huang BS, Yang MH, Wang PH, Li HY, Chou TY, Chen YJ. Oestrogen-induced angiogenesis and implantation contribute to the development of parasitic myomas after laparoscopic morcellation. Reprod Biol Endocrinol 2016; 14: 64.
6) Zhang Y, Kiel DP, Kreger BE, Cupples LA, Ellison RC, Dorgan JF, et al. Bone mass and the risk of breast cancer among postmenopausal women. N Engl J Med 1997; 336: 611-617.
7) Wolff EF, Narayan D, Taylor HS. Long-term effects of hormone therapy on skin rigidity and wrinkles. Fertil Steril 2005; 84: 285-288.
8) Verdier-Sevrain S. Effect of estrogens on skin aging and the potential role of selective estrogen receptor modulators. Climacteric 2007; 10: 289-297.
9) Wilkinson HN, Hardman MJ. The role of estrogen in cutaneous ageing and repair. Maturitas 2017; 103: 60-64.
10) Hood AF. Cutaneous side effects of cancer chemotherapy. Med Clin North Am 1986; 70: 187-209.
11) Nicander I, Nyren M, Emtestam L, Ollmar S. Baseline electrical impedance measurements at various skin sites - related to age and sex. Skin Res Technol 1997; 3: 252-258.
12) Fujita T, Ohue M, Fujii Y, Miyauchi A, Takagi Y. Comparison of the analgesic effects of bisphosphonates: etidronate, alendronate and risedronate by electroalgometry utilizing the fall of skin impedance. J Bone Miner Metab 2009; 27: 234-239.
13) Phillips TJ, Demircay Z, Sahu M. Hormonal effects on skin aging. Clin Geriatr Med 2001; 17: 661-672.
14) Emmerson E, Campbell L, Ashcroft GS, Hardman MJ. The phytoestrogen genistein promotes wound healing by multiple independent mechanisms. Mol Cell Endocrinol 2010; 321: 184-193.
15) Sator PG, Schmidt JB, Rabe T, Zouboulis CC. Skin aging and sex hormones in women -- clinical perspectives for intervention by hormone replacement therapy. Exp Dermatol 2004; 13 Suppl 4: 36-40.
16) Chiu AE, Chan JL, Kern DG, Kohler S, Rehmus WE, Kimball AB. Double-blinded, placebo-controlled trial of green tea extracts in the clinical and histologic appearance of photoaging skin. Dermatol Surg 2005; 31: 855-860.
17) Henry F, Pierard-Franchimont C, Cauwenbergh G, Pierard GE. Age-related changes in facial skin contours and rheology. J Am Geriatr Soc 1997; 45: 220-222.
18) Dunn LB, Damesyn M, Moore AA, Reuben DB, Greendale GA. Does estrogen prevent skin aging? Results from the First National Health and Nutrition Examination Survey (NHANES I). Arch Dermatol 1997; 133: 339-342.
19) Masuda Y, Hirao T, Mizunuma H. Improvement of skin surface texture by topical estradiol treatment in climacteric women. J Dermatolog Treat 2013; 24: 312-317.
20) Brincat MP, Baron YM, Galea R. Estrogens and the skin. Climacteric 2005; 8: 110-123.
21) Verdier-Sevrain S, Bonte F, Gilchrest B. Biology of estrogens in skin: implications for skin aging. Exp Dermatol 2006; 15: 83-94.
22) Archer DF. Postmenopausal skin and estrogen. Gynecol Endocrinol 2012; 28 Suppl 2: 2-6.
23) Silverman S, Christiansen C. Individualizing osteoporosis therapy. Osteoporos Int 2012; 23: 797-809.
24) Cleemann L, Hjerrild BE, Lauridsen AL, Heickendorff L, Christiansen JS, Mosekilde L, et al. Long-term hormone replacement therapy preserves bone mineral density in Turner syndrome. Eur J Endocrinol 2009; 161: 251-257.
25) Douchi T, Yamamoto S, Nakamura S, Oki T, Maruta

K, Nagata Y. Bone mineral density in postmenopausal women with endometrial cancer. Maturitas 1999; 31: 165-170.

26) Kim BK, Choi YH, Song YM, Park JH, Noh HM, Nguyen TL, et al. Bone mineral density and the risk of breast cancer: a case-control study of Korean women. Ann Epidemiol 2014; 24: 222-227.
27) Grenier D, Cooke AL, Lix L, Metge C, Lu H, Leslie WD. Bone mineral density and risk of postmenopausal breast cancer. Breast Cancer Res Treat 2011; 126: 679-686.
28) Mollerstrom G, Lagrelius A, Carlstrom K, Sjoberg HE. Denser trabecular bone in women with endometrial carcinoma. Int J Gynecol Cancer 1994; 4: 161-168.
29) Hirasawa A, Makita K, Akahane T, Yamagami W, Makabe T, Yokota M, et al. Osteoporosis is less frequent in endometrial cancer survivors with hypertriglyceridemia. Jpn J Clin Oncol 2015; 45: 127-131.
30) Lee Y, Kim A, Kim HY, Eo WK, Lee ES, Chun S. Bone Density in Patients with Cervical Cancer or Endometrial Cancer in comparison with Healthy Control; According to the stages. J Cancer 2015; 6: 686-693.
31) Castelo-Branco C, Pons F, Gratacos E, Fortuny A, Vanrell JA, Gonzalez-Merlo J. Relationship between skin collagen and bone changes during aging. Maturitas 1994; 18: 199-206.
32) Kafantari H, Kounadi E, Fatouros M, Milonakis M, Tzaphlidou M. Structural alterations in rat skin and bone collagen fibrils induced by ovariectomy. Bone 2000; 26: 349-353.
33) Rodriguez M,Shoupe D. Surgical Menopause. Endocrinol Metab Clin North Am 2015; 44: 531-542.
34) Shuster LT, Gostout BS, Grossardt BR, Rocca WA. Prophylactic oophorectomy in premenopausal women and long-term health. Menopause Int 2008; 14: 111-116.
35) Stavraka C, Maclaran K, Gabra H, Agarwal R, Ghaem-Maghami S, Taylor A, et al. A study to evaluate the cause of bone demineralization in gynecological cancer survivors. Oncologist 2013; 18: 423-429.
36) Yoshida T, Takahashi K, Yamatani H, Takata K, Kurachi H. Impact of surgical menopause on lipid and bone metabolism. Climacteric 2011; 14: 445-452.
37) Ozdemir S, Celik C, Gorkemli H, Kiyici A, Kaya B. Compared effects of surgical and natural menopause on climacteric symptoms, osteoporosis, and metabolic syndrome. Int J Gynaecol Obstet 2009; 106: 57-61.
38) Parker WH, Broder MS, Chang E, Feskanich D, Farquhar C, Liu Z, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. Obstet Gynecol 2009; 113: 1027-1037.
39) Toz E, Ozcan A, Balsak D, Avc ME, Eraslan AG, Balc DD. Potential adverse effects of prophylactic bilateral salpingo-oophorectomy on skin aging in premenopausal women undergoing hysterectomy for benign conditions. Menopause 2016; 23: 138-142.
40) Leitch C, Doherty V, Gebbie A. Women's perceptions of the effects of menopause and hormone replacement therapy on skin. Menopause Int 2011; 17: 11-13.
41) Fruscio R, Ceppi L, Corso S, Galli F, Dell'Anna T, Dell'Orto F, et al. Long-term results of fertility-sparing treatment compared with standard radical surgery for early-stage epithelial ovarian cancer. Br J Cancer 2016; 115: 641-648.
42) Douchi T, Kosha S, Kan R, Nakamura S, Oki T, Nagata Y. Predictors of bone mineral loss in patients with ovarian cancer treated with anticancer agents. Obstet Gynecol 1997; 90: 12-15.
43) Maccormick RE. Possible acceleration of aging by adjuvant chemotherapy: a cause of early onset frailty? Med Hypotheses 2006; 67: 212-215.
44) Hackbarth M, Haas N, Fotopoulou C, Lichtenegger W, Sehouli J. Chemotherapy-induced dermatological toxicity: frequencies and impact on quality of life in women's cancers. Results of a prospective study. Support Care Cancer 2008; 16: 267-273.
45) Daniel CR, 3rd, Scher RK. Nail changes caused by systemic drugs or ingestants. Dermatol Clin 1985; 3: 491-500.
46) Manigand G, Faux N, Dumas D, Taillandier J, Fixy P, Richerd F. [Nail pigmentation during therapy with cyclophosphamide and doxorubicin]. Sem Hop 1983; 59: 1840-1841.

Influences of Estrogen-dependent Diseases, Premature Oophorectomy and Anti-cancer Chemotherapy on Skin Age in Japanese Women

エストロゲン依存性疾患、外科的去勢および抗がん剤の肌年齢に及ぼす影響（日本人女性での検討）

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目的：皮膚にはエストロゲン（E）レセプターが存在し、E が複数の細胞に作用しヒアルロン酸などの生成を促進し、潤いや張りを与える。肌の老化（菲薄化、乾燥、皺の増加、弾力性の低下）には加齢、放射線療法、抗癌剤投与などが関与するが、閉経や外科的去勢でも起こる。しかし、低 E 状態による肌の老化はあまり研究されていない。我々は Bioelectrical Impedance Analysis（BIA）で肌年齢、肌の健康状態の客観的評価が可能であることに着目し、E 依存性疾患、外科的去勢および抗がん剤の肌年齢に及ぼす影響について検討した。

方法：2016 年 7 月から 2018 年 5 月までに当科を受診した患者 68 例を対象にした。Informed consent の後、肌年齢、肌加齢度（肌年齢 - 暦年齢）を Wellup 社製の肌年齢測定器（Well-Beauty、BIA 法）で測定した。①有経女性で E 依存性疾患患者（主に子宮筋腫や子宮体癌、n=19）と E 非依存性疾患患者（主に子宮頸癌、n=38）の肌年齢や肌加齢度を比較した。②有経女性で外科的去勢（n=15）による肌年齢、肌加齢度の推移を卵巣温存群（n=11）と比較した。③閉経女性で婦人科悪性腫瘍の標準手術（含:卵巣摘出術）と化学療法を受けた患者（n=6）と標準手術のみを受けた患者（対照、n=5）で肌年齢、肌加齢度の推移を比較した。有意差検定は Student t-test、χ^2 検定で適宜行った。

結果：1 ）E 依存性疾患患者では E 非依存性疾患患者に比較して肌が有意に若かった (肌加齢度:-1.0±1.4 歳 vs.+2.5±0.6 歳、$p<0.01$)。 2 ）去勢後 6 か月で肌年齢は有意に悪化したが、卵巣温存群では変化しなかった（肌加齢度の推移：+3.5±1.4 歳 vs.-0.2±0.8 歳、$p<0.05$)。 3 ）化学療法群の化学療法終了 12 か月後の肌年齢は、対照に比較して有意に悪化した（肌加齢度の推移：+10.5±3.3 歳 vs.- 3.8±3.4 歳、$p<0.05$)。化学療法により、肌年齢が 5 歳以上若い女性の割合も有意に減少した（5/6 から 1/6、$p<0.05$)。

結論：E 依存性疾患患者では肌年齢が若く、外科的去勢による低 E 状態は肌年齢にも悪い影響を及ぼす。一方、卵巣温存群では肌年齢は悪化しなかったため、有経期女性の予防的卵巣摘出術には慎重であるべきである。また、化学療法はより高度に肌年齢を悪化させることが判明したため、治療中のケアは重要である。

Author Index

第71巻　人名検索

Acknowledgement

All editorial board members deeply appreciate following reviewers. They sincerely estimated manuscripts and gave proper advices to the authors. Their gratuitous works support editing this journal.