J Surg 1961;49:80-89
5) 橋本恵介，林 勝吉，福本信介，他：大腸内視鏡および内視鏡的逆行性回腸末端造影法により診断しえた悪性リンパ腫の1例．Gastroenterol Endosc 2000;42:998-1005
6) 福原資郎，森真一郎：病期診断の実際．悪性リンパ腫治療マニュアル，改訂第2版，平野正美，他編，南江堂，東京，2003:51-54
7) 藤野雅之：悪性リンパ腫の治療方針．臨牀消化器内科 1998;13:377-383
8) 竹本洋人，関 寿人，久保田佳嗣，他：回腸原発悪性リンパ腫による成人腸重積症の1例．日消誌 1989;86:1154-1158
9) Vadala G, Salice M, L'Anfusa G, et al: Complications of ileal lymphoma. Minerva Chir 1995;50:963-966
10) 堀 公行：成人腸重積症．外科 1976;38:692-698
11) 窪田智行，山口晃弘，磯谷正敏，他：成人腸重積の検討．日腹部救急医会誌 1997;17:911-916
12) Naqvi MS, Burrow L, Kark AE: Lymphoma of gastrointestinal tract: prognostic guides based on 162 cases. Ann Surg 1969;170:221-231

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【総　説】

がんの補完代替医療

Complementary and Alternative Medicine in Cancer Treatment

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【要　旨】
世界的なインターネットの普及や予防医学，自己健康管理への関心，患者の治療選択における自己決定意識の高まりなどから，近年，補完代替医療（CAM; Complementary and Alternative Medicine）の利用者が急速に増加している．わが国のがん患者においてCAMのうち最も利用頻度の高いものは健康食品で，情報もこれに偏っているが，臨床試験で有効性を確認されたものはほとんどない．先進諸国では西洋医学的手法に則ったCAMの有効性を検証するための臨床試験を遂行しようとする機運が広がっている．米国補完代替医療センターでは，現在，多くの臨床試験が行なわれており，我が国でも厚生労働省がん研究助成金によるがんのCAMに関する研究班が設けられ，金沢大学医学部に我が国初のCAMの専門講座が開設され，この分野の本格的な研究がスタートしている．

【キーワード】
補完医療，代替医療，がん治療，臨床試験

1. はじめに

この総説を書き始めるにあたって著者の立場を明らかにしておきたい．著者は補完代替医療（Complementary and Alternative Medicine: CAM）として用いられる療法の専門家でも施術者でもなく，しばしばこれら療法を利用する患者の主治医として西洋医学の治療に当たっているものである．転移を生じているような進行した段階の患者の化学療法（抗がん剤治療）に従事している腫瘍内科医である．そこではエビデンスに基づくインフォームドコンセントを行ったうえで患者の自己選択権を尊重し，可能な限り科学的な治療を提供し客観的な評価を行うよう努めている．インフォームドコンセントの過程では標準的な治療法から始まり代替治療として有用性のエビデンスが劣るものをも紹介している．この代替治療の中には有効性が標準治療に劣るものも含まれているが，いまだ標準治療との優劣が明らかにされていない新規の有望な治療法も含まれている．しかし，代替治療といえども現在の科学的評価法によって有効性と安全性が一定の基準で実証されているものしか提示すべきでないことはもちろんである．このように近代西洋医学における代替治療とは標準治療の代わりに提供することができるだけの科学的検証を受けた治療法を指している．一方，CAMとは西洋医学的手法によって有効性や安全性が確認されていない医療と考えられている．代替という用語が同一であるため混乱や誤解を生じやすく，違和感をぬぐえないが，世界的にも名称については同様の状況にある．いずれにしろCAMは西洋医学的手法によって評価されていない医学ということになるが，それでは西洋医学的手法とは何か？それは臨床試験である．臨床試験の倫理的規範はヘルシンキ宣言に求められ，科学的検証法は近年ICH-GCP（International Conference on Harmonization—Good Clinical Practice）へと結実している．つまりCAMにおいては臨床試験がほとんど行われていないということである．CAMには古くからの経験に基づく療法があったり，自然界の生物を用いたりするものが多く，臨床試験には馴染まないとする意見も多い．確かに瞑想や民族哲学的な療法などに関しては臨床試験で評価することは困難を伴うが，医学的に臨床試験でしか評価しようのないサプリメントなども存在している．著者はCAMに対して否定的な立場を取るものではなく，臨床試験を通じてCAMの有用性を客観的に明らかにすべきであるとの立場を取るものである．この総説ではがんに関連した

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CAM について記載することにする.

CAM は近年急速に利用者が増加している. これには世界的なインターネットの普及や予防医学, 自己健康管理への関心の高まりなどが理由と考えられる. 近年, 我が国のインフォームドコンセントの形式は医師依存型—主導型から情報公開—患者自主選択・自立型の形態へと大きく変化し, 患者の治療選択の意識が大きくなっている. そのひとつに CAM があるが, 中にはこれが主体の医療に置き換わり問題となる例も知られている. このような背景から西洋医学的手法に則った有効性を検証するための臨床試験を遂行しようとする機運が先進諸国に広がっている. 米国国立補完代替医療センター (NCCAM: National Center for Complementary and Alternative Medicine) では現在 17 のがんに関連した CAM の臨床試験が行なわれている[1]. 我が国でも 2001 年度から日本内科学会認定専門医部会で健康食品に関するデータベースの作成が開始され, 厚生労働省がん研究助成金によるがんの代替療法に関する研究班が設けられ, 2002 年には金沢大学医学部に我が国初の CAM の専門講座が開設され, この分野の本格的な研究がスタートしている.

2. CAM の定義

大学医学部で教育されている現代西洋医学以外の医療とされているが, 近年, CAM の授業を取り入れる大学も増えてきている. 西洋医学は現代の主流の医学であり mainstream medicine とも呼ばれている. この西洋医学を通常医学 (conventional medicine) として代替医療を非通常医学 (unconventional medicine) と呼称したり, 漢方, 鍼, 灸を中心とした東洋医学や世界中の伝統的, 民族的な医療を伝統医学 (traditional medicine), その他に主流の医学の変わりになる医学あるいはこれにとって代わる医学として代替医学 (alternative medicine), あるいは補うものとして補完医学 (complementary medicine) とも呼ばれる. 日本補完代替医療学会では「現代西洋医学領域において, 科学的未検証および臨床未応用の医学・医療体系の総称」としている. 近年, 多額の研究費をつぎ込み精力的に CAM 研究を推し進めている米国では補完代替医療 (CAM: complementary and alternative medicine) と呼んでいる. 米国国立補完代替医療センター (NCCAM: National Center for Complementary and Alternative Medicine) では「通常の医療に加えて, あるいは代えて (替えて) 使用される治癒への思考体系, 方法, 治療 (Healing philosophies, approaches, and therapies used in addition to, or instead of conventional treatment)」と定義されていたが[2], 最近, 日本補完代替医療学会の CAM の定義と類似した内容に変更されている. そして CAM と考えられている分野は表 1 のように分類されている.

表 1 CAM の種類

分類と名称	内 容
代替医学系 Alternative medical systems	伝統医学系統, 民族療法 (東洋伝統医学, アーユルベーダ, ユナニ, シャーマニズム等)
精神・身体交流 Mind-body interventions	瞑想, 催眠, 舞踏, 音楽, 芸術療法, 祈り等
生物学に基づく療法 (代替バイオ療法) Biologically based therapies	ハーブ, 特殊食品, 生理活性分子 (マグネシウム, メラトニン, ビタミン等), サメ軟骨等を利用した治療
指圧など外部からの力で治療する方法 Manipulative and body-based methods	マッサージ, 整体, 整骨療法等
エネルギー療法 Energy therapies	気功, 霊気, タッチング療法, 電磁療法

このように CAM の範疇と考えられる医学体系は多数存在し, 哲学的医学体系を構成するものからサメの軟骨やメガビタミンなどの内服治療薬あるいは健康食品まで様々である. この中には漢方薬の一部, 鍼, 整体, 認知行動療法, 患者教育など世界中の多くの国々で主流医学に組み込まれているものも多い. また現在西洋医学で使用される治療薬には民間療法として使用されてきた植物などから抽出, 製造されたものも多数存在する. 従って, CAM を論ずるときには, その何を具体的に問題にしているのかを明確にする必要がある.

3. CAM の現状

3.1 世界の状況[3]

CAM は多くの発展途上国においては高い利用頻度を示し, 主流医学としての位置を占めている. 西欧の先進国においても CAM の利用頻度は近年急速に増加傾向にある. これまでに報告されている各国の CAM の利用頻度を図 1 に示した. エチオピアからウガンダまでは, 初期の医療として CAM が利用される頻度を示し, カナダからベルギーまでは利用経験者の比率を示している. つまり, 前者は通常医療として, 後者は主に補完医療として CAM が使用される頻度である.

このように先進国においても国民の 3 分の 1~2 の人々が CAM を利用したことがあると報告されている[3]. 米国での一般家庭を対象とした CAM 調査では, 1990 年 34

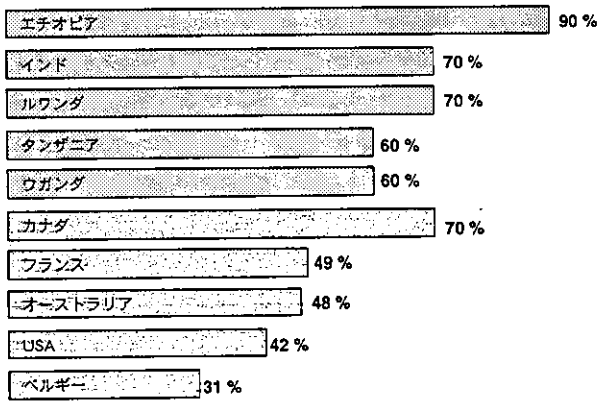


図1 世界の代替医療の利用状況
WHO Policy Perspectives on Medicines. Traditional Medicine 2002

%，1997 年 42%の利用率で，診療所に受診する回数よりも CAM 提供者のところを訪れる回数のほうが多くなっていると報告されている[4]．がん患者における CAM 利用率は 26 の論文において 7%から 64%と大きな違いがあるが，これは各論文間の調査方法，調査対象，CAM の定義などの違いに起因していると考えられる[5]．利用頻度ではハーブ，健康食品などが上位を占めている．

CAM の費用に関する統計資料は世界的にも少ない．マレーシアでは年間 5 億ドルが代替療法に費やされ，通常医療は 3 億ドル．米国では 1997 年の代替医療への国民支出は 277–344 億ドル（約 3 兆～4 兆円）であり，同年の通常医療費の総自己負担費に相当すると見積もられている．英国では 23 億ドル，カナダでは 24 億ドルと推定されている．世界中の CAM で使用されるハーブ療法の支出は 600 億ドルと推定され，米国では 1996 年から 1998 年の 2 年間でハーブの売上は倍増している．

3.2 日本の現状

我が国では医療者のがんの CAM に対する認識は希薄で，これまでに系統だった研究はほとんどなされてこなかった．しかも，インターネットやその他のメディアを通して，健康食品あるいは民間療法に関する情報は大量に流布しているが，医学的，科学的見地からして信頼性の置ける正確で有用な情報は決して多くない．このような現状の中で多くのがん患者が医学的根拠に乏しい CAM を利用し，医療従事者は参照すべき情報不足から，この問題に対処せず，医療現場では患者と家族は氾濫する情報に振り回されるという好ましくない状況を招いている[6]．これまで日本においては CAM の実態は不明であった．そこで著者らは厚生労働省がん研究助成金による援助を受け，「我が国におけるがんの代替療法に関する研究」班を組織し，2001 年から 2002 年にかけて全国 56 施設の協力を得て大規模患者アンケート調査を実施した．3099 人のがん患者から有効回答が得られ，CAM 利用率は 44.6%であった．CAM の内訳は健康食品 89.1%，漢方 7.1%，気功 3.8%，灸 3.7%，鍼 3.6%であった．CAM を利用する理由としては進行抑制・改善を期待 67.1%，治癒を期待 44.5%，症状軽減を期待 27.1%．がん患者一人当たりの CAM に要する費用は月平均 5.7 万円であった．CAM のほとんどは健康食品であることが明らかとなったが，使用されている健康食品はアガリクス，プロポリス，AHCC などである．これら健康食品のがんに対する効果を検証するための臨床試験は未だ十分とはいえない．しかし現実には動物を用いた基礎的研究や体験本を通してがんに対する効果が強調され多くのがん患者で使用されている．この研究班では本アンケート調査の他，がんに対する健康食品のデータベースの作成，がんの代替療法の評価と臨床試験の可能性などについて研究を行っている．

4. CAM 研究

米国では 1992 年国立衛生研究所（NIH: National Institute of Health）内に代替医療事務局（Office of Alternative Medicine）が創設され本格的な CAM 研究が開始された．その目標は 1）代替薬物治療評価を進める，2）CAM の効果の調査と評価，3）市民との情報を交換するための情報収集センターの設置，4）CAM の研究支援などであった．この研究施設は 1998 年に NCCAM に昇格され 2003 年には，11,400 万ドル（約 135 億円）の年間予算が計上され，臨床試験を含めた多くの研究活動を行なっている．米国国立がん研究所（NCI）内にはがん領域における CAM 研究を目的とするがんの CAM に関する事務局（OCCAM: Office for Cancer CAM）が設けられ NCCAM と連携しながら研究を進めている．

ここで少し米国における CAM の評価方法を紹介する．これは NCI のホームページの Cancer Fact: Complementary and alternative medicine in cancer treatment: Questions and Answers に掲載されているもので基本的には次の 3 項目からなっている．1）通常医療で用いられる評価法を CAM にも当てはめて評価する．つまり臨床試験を行なって客観的な評価を行なう．2）CAM に特徴的な評価過程として 1991 年から代替医療の早期データの評価法 Best Case Series（BCS）Program を開始している．3）NCI が資金提供して臨床試験を行なう．表 2 に現在 NCI が行なっている CAM を用いたがん治療の臨床試験の一部をまとめた．その中には鍼治療やマッサージ

表2 NCIが行なっているCAMのがん臨床試験（一部のまとめ）

試験治療（CAM治療）	対象がん種	試験の相	症例数	評価項目	対照（標準）治療
標準治療＋サメ軟骨（Benefin）	進行乳癌，進行大腸癌	III	600	生存期間，安全性，QOL	標準治療
白金抗がん剤＋放射線サメ軟骨抽出物（Neovastat）	非小細胞肺癌（IIIA/IIIB期）	III 二重盲検	756	生存期間，無増悪生存期間奏効率，安全性	白金抗がん剤＋放射線＋プラセボ
強化膵蛋白分解酵素療法（Kelley/Gonzalez regimen）	切除不能膵癌 Stage II, III, IV	III 患者選択	72–90	生存期間，QOL	ゲムシタビン
セレニウム＋プラセボ ビタミンE＋プラセボ セレニウム＋ビタミンE	前立腺癌予防	III 二重盲検	32,400	前立腺がん発癌率，その他のがんの発癌率など	プラセボ
ヤドリギレクチン（Mistletoe lectin, Recombinant viscumin）皮下注射＋ゲムシタビン	膵癌，大腸癌，非小細胞肺癌，乳癌	I	40–50	至適投与量の決定，毒性評価，薬物動態検討，免疫パラメーターの検討	なし
朝鮮人参 イチョウ 朝鮮人参＋イチョウ	健常者（がん予防）	II 無作為化 二重盲検	60	薬物／ハーブ相互作用の検討 4つの薬物を使用した代謝能の測定も含まれる	プラセボ
本当の鍼治療 見せかけの鍼治療	2種類の化学療法に抵抗性を示した進行大腸癌	I 無作為化 単一施設	170	終末期の苦痛改善	通常の緩和ケア
カルニチン（L-carnitine）	末期がん	II 無作為化 二重盲検	130	終末期の疲労の改善 カルニチン欠乏を対象	プラセボ
とりなしの祈り（Distant healing; DH）	脳腫瘍（グリオブラストーマ）	II 無作為化	150	生存期間，機能改善	DHなし
マッサージ（REST: reducing end-of life symptoms with touch）	末期がん患者	II	440	疼痛緩和，QOL改善	−
マッサージ	乳癌治療に伴う上肢のリンパ浮腫	− 無作為化	88	リンパ浮腫改善	マッサージ＋圧迫包帯
スウェーデン・マッサージ	乳癌，卵巣癌，前立腺癌，大腸癌	II 無作為化	60	疲労改善	通常ケア

や写真を用いた遠隔地からの“とりなしの祈り”（他人のために祈るあるいは治癒を願う）など，臨床試験が困難に思える治療法も含まれている．そのような治療法をも現代医学の検証法に当てはめて科学的に解明しようとする姿勢には驚かされる．しかし，NCIがスポンサーとなって臨床試験を開始するには，ある程度のエビデンスが必要とされており，その最初の段階がBCS Programである．

新たなCAMは多くの場合，既に実践されはじめてから，つまり市井に出回ってから初めて医療者や患者に知られるところとなる．したがってNCIのOCCAMのBCS担当者（薬剤開発の知識を有する医師や看護婦）はCAM実践者から5〜10例の有効例を報告させ，内容の批判的な吟味が行なわれる．この報告には，あらかじめ記載されるべき内容が規定された症例報告書（case report form）が必要とされているが，提出された報告書には次のような様々な問題点が指摘されている．

1. 診断が正確に為されていない，あるいは記載されていない
2. アジュバント設定でありながら病巣が残存しているか否か，明らかにされていない
3. 主観的な評価項目（気分が良くなった，元気を取り戻したなど）を使用している
4. 例外的な長期生存を取り上げている
5. 直前あるいは同時期に通常医療が施行されている
6. 製品の製造過程や成分の均質性などが不明確
7. 後ろ向きの報告のため必要とされるデータが欠損している

8. 患者は死にそうなのにひとつの腫瘍塊が縮小したと報告

このような内容は体験本でしばしば経験するところである．いずれにしろこのような検討を行なった後，がんに対する効果が示唆される CAM については Cancer Advisory Panel for CAM（CAPCAM）に上げられ，さらに詳細な検討が行われる．この CAPCAM は 1999 年に NCI と NIH の NCCAM とが協力して結成されたもので，腫瘍医，腫瘍専門看護師，代替医療専門家，FDA の統計家，疫学専門研究者，患者代表などの計 15 名のメンバーで構成されている．ここでの検討において BCS process の次のステップが以下のいずれかに決定される．1）小規模の前向き試験（数十例の prospective trial あるいは 100 例以下の無作為化比較試験），2）NCI から CAM 実践者への実地調査，3）作用機序などの基礎的研究．これらを行なった後，有望なものに関しては NCI 主導の大規模第Ⅲ相試験が行なわれる．以上の試験結果も含め，これまでに発表された論文は CAM 専用のエビデンス評価基準で評価される．4 段階の試験デザイン（無作為化比較試験～有効症例報告）による証拠の強さ（Strength of study design）と同じく 4 段階の評価項目（全生存率～奏効率）による証拠の強さ（Strength of endpoints measured）の両者を組み合わせて判定する方法である．しかし，これは専門的な医療関係者でもわかり難い複雑な評価方法であり，もっと簡便な方法を考案する必要があると思われる．

グローバルなレベルでは世界保健機構（WHO: World Health Organization）が 1970 年代から CAM に関する取り組みを開始し，1990 年代以降ガイドラインやレビューを相次いで公表している．Guideline for the assessment of herbal medicine（1991）[7]，Research guideline for evaluating the safety and efficacy of herbal medicines（1993）[8]，Guidelines for clinical research on acupuncture（1995）[9]，Regulatory situation of herbal medicine: a worldwide review（1998）[10]，Guideline on basic training and safety in acupuncture（1999）[10]，WHO traditional medicine strategy 2002–2005[3] これらの解説は省略するが CAM に関する世界的関心は急速に増し，その科学的評価や正確な情報を求める機運は高まっている．

我が国では 1998 年に日本で初めて CAM に関する学術会議が開催され，日本補完代替医療学会として現代西洋医学の立場から CAM の科学的な検証を事業の主たる目的として活動がスタートしている．また 2002 年 3 月に日本で初めて金沢大学医学部に CAM 研究を専門とする補完代替医学講座が開設された．この分野における我が国の取り組みは端緒についたばかりといわざるを得ない．ここまでのまとめとして CAM に関する日米比較を表 3 に示した．

表 3　CAM の日米比較

	米　国	日　本
利用頻度	42%	66–76%[12,13]，（がん患者で 45%）
費用（年間）	270 億ドル（約 3 兆円）以上	通常医療の自己負担費の 50%[13]，（がん患者で約 530 億円以上）
医学教育	75/117 大学	16/80 大学[14]*
推進者	60% は医師	不祥（がん領域では企業が主体）
研究機関	NCCAM（NIH）	金沢大学医学部に専門講座（基礎・臨床系）
	OCCAM（NCI）	山梨大学医学部に専門講座（基礎系）
研究予算	1993 年 200 万ドル**	2003 年，文部科学省科学研究費の細目として「代替医療」が初登場
	2003 年 11400 万ドル** （約 135 億円）	

*東洋医学の講義・講座が主体，**NCCAMの年間予算

5. 臨床医の CAM に対する認識

CAM に関するさまざまな疑問を持ち，それを利用する患者にどのように対処すべきか悩んでいる臨床医は多い．あるいは有効性の科学的証明に乏しいことから CAM を無視し関心を示さず放置していることも多い．確かに遺伝子研究は飛躍的に進み，がんの生物学的特性が明らかにされ，分子標的薬も次々に臨床に登場している現代，ますます医学は専門化，分業化し複雑さを増している．このような中で CAM に対して科学的評価を行なうだけの価値は無く，人的，経済的医療資源と時間は有効に使われなければならないとする意見には説得力がある．このような実態は多くの西欧医学を主流医学としている国々の共通の問題となっている[15,16]．しかし米国の腫瘍関連学会でも，近年，様々なジョイントシンポジウムが催され，臨床腫瘍医の CAM に対する関心も少しずつ広がりを見せ始めている[16–18]．その理由としては，CAM 提供者によるインターネット，新聞広告，体験本などを利用した巧妙な宣伝とインターネット販売をはじめとする通販機構の進歩により CAM 利用者が増加していること，それに伴い患者や家族から CAM の有効性や有害事

象についての質問が多くなったこと，利用者が増すにつれ有害反応に対する危惧が増していること，同時に患者からの有効性検証の要望が増していることなどが考えられる．次第に我が国でも臨床腫瘍医にとって避けて通れない問題となりつつある．最近，日本の医師の CAM に対する認識を調査した論文が，いくつかの英文誌に掲載されている[19,20]．全国 751 名の臨床腫瘍医のアンケート調査結果では，腫瘍医の 82%は CAM で使用される健康食品類にはがんに対する有効性は無いと考え，その理由として信頼できるエビデンスが無いことをあげている．また 84%の腫瘍医が抗がん剤との相互作用を危惧していると答えている．

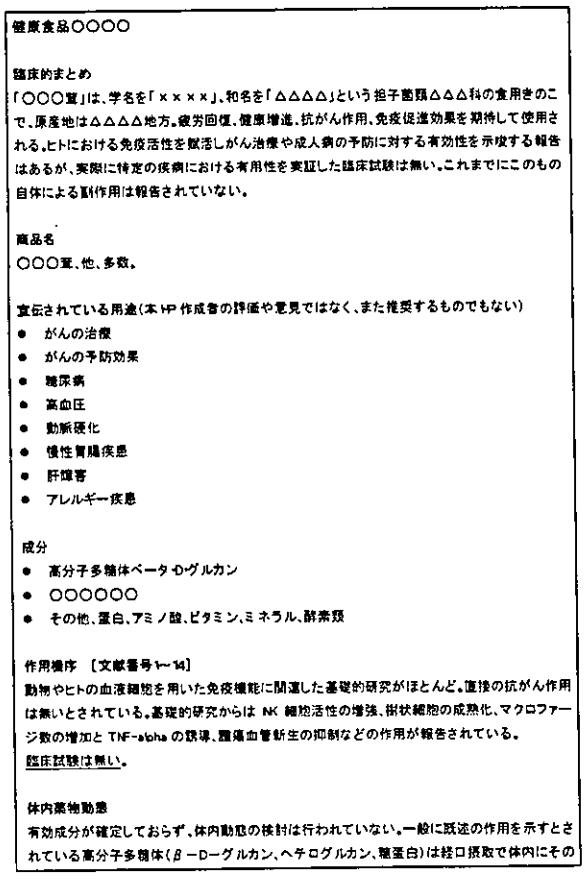
6. 健康食品の問題

がんで使用される CAM のうち健康食品の利用は最も多い．しかし，これまでに健康食品ががん患者に対していかなる効果であれ，明らかな効果をもたらしたという明快な科学的証拠はほとんど無い．現在，健康食品を定義する法律はなく，一般的に健康維持の目的で用いられ，通常の食品とは異なる形態の粒状，カプセル状などの食品と考えられている．薬理的作用により疾病の予防や改善が期待される食品（高血圧や糖尿病などに良いとされるものなど）で，法的に規定されているものには特定保健用食品がある．平成 15 年 10 月 7 日現在，396 品目が厚生労働省より認可されている．これはあくまで通常の食品のかたちをしたもので，錠剤やカプセル状の形態をしていないものとされている．健康食品と呼ばれるものの中には錠剤，カプセル，粉末状のものを業者が健康食品と勝手に名づけて市販しているものが多い．現在，このような健康食品に対しては財団法人日本健康・栄養食品協会が含有成分などの製品規格，製造と加工の基準，適切な表示と広告（食品衛生法，薬事法，栄養改善法などに適合しているか）などを審査し JHFA マークを付与している．しかし，実際にはこのマークの無い健康食品が非常に多く存在している．

サメ軟骨の抗腫瘍効果，血管新生抑制効果が報告され[21]，現在，米国では NCI をスポンサーとして NCCTG（North Central Cancer Treatment Group）を中心に，切除不能乳がんと大腸がん患者を対象としたプラセボを使用した二重盲検無作為化比較第 III 相試験が行なわれている（表 2）．エンドポイントは生存，毒性，QOL である．国の医療事情や研究体制の違いもあるが，我が国においてもがん患者に使用される頻度の高い健康食品については，きちんとした臨床試験を行う必要がある．そのステップとして健康食品は既に世間に広く使用されているものであるから，まず確実な有効例（Best case series）の収集，次に小規模な比較試験，そして最終的には充分な検出力を有する大規模比較試験が行なわれなければならない．これと同時に副作用症例の積極的な報告が為される必要がある．

健康食品の一部には健康被害を生じているものも報告されているが[22,23]，多くのものでは健康に害を及ぼすことは無いかあるいはまれとされている．しかし，薬物と併用される場合には相互作用の可能性もあり注意しておく必要がある．グレープフルーツの成分が CYP 3A3/4 を抑制し，スタチン系の薬剤や抗ヒスタミン剤内服患者に筋肉痛や不整脈を生じることは良く知られている．現在までに抗がん剤との明らかな相互作用を有する健康食品は報告されていないが，サリチル化ハーブ類などでは理論的にはメソトレキセートや類似薬の尿への排泄を阻害する可能性がある．また前立腺がんに効果があるとされるハーブの合剤にエストロゲン作用を有する成分が含まれていたという報告もある[24]．

わが国の CAM に関する情報は，健康食品に関するものに偏っており，その圧倒的多数が「驚異の治癒力」とか「末期がんからの生還」，「○○学会で絶賛」「フェーズ III で実証」といった文言をちりばめた単行本やインターネット上のホームページによる．しかし，このようなあたかも多くの医師が認めているかのような語調の見出しでも，当該学会の実際の学会抄録には発表された形跡がなかったり，臨床試験に関する専門用語を使っただけで実体のないものが多い．かろうじて論文の体裁をとっているものでも，その多くが試験管レベルの基礎研究か一例報告であり，その効果を検証するための前向きな臨床試験あるいはメタアナリシスの結果は皆無に近いのが現状である．医薬品にしか許可されていない効能の表示は違法であり薬事法，食品衛生法，景品表示法，栄養改善法などにより規制されている．しかし，がんの予防や治療に有効性を謳う健康食品は多数存在している．医療者にとってハーブ（薬草・生薬）やキノコ類，その他の自然界の生物から得られる成分を含む健康食品に関する適切な情報の提供は緊急の課題である．最近，Memorial Sloan-Kettering Cancer Center（NY）内に設置されている Integrative Medicine Service が作成・運営しているウェブサイト（http://www.mskcc.org/mskcc/html/11570.cfm）に 135 種類のハーブや植物性薬品について，治療に用いる際の条件や有害作用，薬物相互作用などの情報を掲載している．このサイトではサプリメントに関して文献に基づき科学的検証を行った上で，その臨床的効果について客観的に記載した情報を発信している．厚生労働省の研究班においても医学的，客観的な立場から，現在我が国



健康食品○○○○

臨床的まとめ
「○○○茸」は、学名を「××××」、和名を「△△△△」という担子菌類△△△科の食用きのこで、原産地は△△△△地方。疲労回復、健康増進、抗がん作用、免疫促進効果を期待して使用される。ヒトにおける免疫活性を賦活しがん治療や成人病の予防に対する有効性を示唆する報告はあるが、実際に特定の疾病における有用性を実証した臨床試験は無い。これまでにこのもの自体による副作用は報告されていない。

商品名
○○○茸、他、多数。

宣伝されている用途(本HP作成者の評価や意見ではなく、また推奨するものでもない)
- がんの治療
- がんの予防効果
- 糖尿病
- 高血圧
- 動脈硬化
- 慢性胃腸疾患
- 肝障害
- アレルギー疾患

成分
- 高分子多糖体ベータ-D-グルカン
- ○○○○○○
- その他、蛋白、アミノ酸、ビタミン、ミネラル、酵素類

作用機序 [文献番号1~14]
動物やヒトの血液細胞を用いた免疫機能に関連した基礎的研究がほとんど。直接の抗がん作用は無いとされている。基礎的研究からは NK 細胞活性の増強、樹状細胞の成熟化、マクロファージ数の増加と TNF-alpha の誘導、腫瘍血管新生の抑制などの作用が報告されている。
臨床試験は無い。

体内蓄物動態
有効成分が確定しておらず、体内動態の検討は行われていない。一般に既述の作用を示すとされている高分子多糖体(β-D-グルカン、ヘテログルカン、糖蛋白)は経口摂取で体内にその

図2 がん患者に利用されている健康食品のまとめの一例

でがん患者に利用されている健康食品に関するサマリーを作成し，公表する予定である．その一例を図2に示した．

7. 今後の課題

世界規模で西洋医学的手法を用いた CAM に対する研究が進められている．我が国では早急に evidence に基づく CAM のデータベースの作成，学会や公的機関による臨床試験体制の確立が望まれる．その他，CAM 奏効例の収集，検証システムの開発，副作用例の集積と使用者や医療機関への周知方法，健康食品の利用方法や安全性に関するガイドラインの作成なども必要とされている．

最後に CAM に関して将来的なあり方という観点からすると，医学はひとつであり主流／非主流あるいは通常／代替などと相対すべきものではないはずである．同一の患者に二つの医学あるいは医療が存在することはありえない．これはある意味で患者にとって不幸であり，それを許容することは医学の怠慢とも考えられる．よく計画された臨床試験から得られる充分な証拠に基づいた医療こそ真の医療であり，多くの不確かなことが補完代替の名のもとに漫然と継続されることなく，順次，有効／無効，有害／無害が明らかにされていくべきであろう．

参 考 文 献

1) National Institutes of Health, National Center for Complementary and Alternative Medicine, Clinical Trials [See: http://nccam.nih.gov/clinicaltrials/cancer.htm]
2) National Cancer Institute, Office of Cancer Complementary and Alternative Medicine [See: http://nccam.nci.nih.gov/health/whatiscam/#1]
3) World Health Organization, WHO Policy and Strategy on Traditional Medicine [See: http://www.who.int/medicines/organization/trm/orgtrmmain.shtml]
4) Eisenberg DM, Kessler RC, Foster C, et al. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. N Engl J Med 1993; 328(4): 246–252.
5) Ernst E, Cassileth BR. The prevalence of complementary/alternative medicine in cancer: A systematic review. Cancer 1998; 83: 777–782.
6) Eguchi K, Hyodo I, Saeki H. Current status of cancer patients' perception of alternative medicine in Japan. A preliminary cross-sectional survey. Support Care Cancer 2000; 8(1): 28–32.
7) Guideline for the assessment of herbal medicines. Geneva: WHO, 1991.
8) Research guideline for evaluating the safety and efficacy of herbal medicines. Manila: WHO Regional Office for the Western Pacific, 1993.
9) Guidelines for clinical research on acupuncture. Manila: WHO Regional Office for the Western Pacific, 1995.
10) Regulatory situation of herbal medicine: a worldwide review. WHO/TRM/98.1. Geneva: WHO 1998.
11) Guideline on basic training and safety in acupuncture. WHO/EDM/99.1. Geneva: WHO 1999.
12) Kamohara S. Alternative Medicine. Tokyo. Tyuou Kouron Shinsha. 2002: 30–35.
13) Yamashita H. Tsukayama H. and Sugishita C. Popularity of complementary and alternative medicine in Japan: a telephone survey. Complement Ther Med 2002; 10: 84–93.
14) Tsuruoka K, Tsuruoka Y, Kajii E. Complementary medicine education in Japanese medical schools: a survey. Complement Ther Med. 2001; 9(1): 28–33.
15) Angell M, Kassirer JP. Alternative medicine—the risks of untested and unregulated remedies. N Engl J Med 1998; 339(12): 839–841.
16) Markman M. Interactions between academic oncology and alternative/complementary/ integrative medicine: complex but necessary. J Clin Oncol 2001; 19(18 Suppl): 52S–53S.
17) Antman K, Benson MC, Chabot J, et al. Complementary and alternative medicine: the role of the cancer center. J Clin Oncol

2001; 19(18 Suppl): 55S–60S.
18) Cassileth BR. Enhancing doctor-patient communication. J Clin Oncol 2001; 19(18 Suppl): 61S–63S.
19) Imanishi J, Watanabe S, Satoh M, et al: Japanese doctors' attitudes to complementary medicine. Lancet 1999; 354: 1735–1736.
20) Hyodo I, Eguchi K, Nishina T, et al. Perception and attitude of clinical oncologists on complementary and alternative medicine. Cancer 2003; 97(11): 2861–2868.
21) Falardeau P, Champagne P, Poyet P, et al. Neovastat, a naturally occurring multifunctional antiangiogenic drug, in phase III clinical trials. Semin Oncol 2001; 28(6): 620–625.
22) Slifman NR, Obermeyer WR, Aloi BK, et al. Contamination of botanical dietary supplements by Digitalis lanata. N Engl J Med 1998; 339(12): 806–811.
23) Beigel Y, Ostfeld I, Schoenfeld N. Clinical problem-solving. A leading question. N Engl J Med 1998; 339(12): 827–830.
24) DiPaola RS, Zhang H, Lambert GH, et al. Clinical and biologic activity of an estrogenic herbal combination (PC-SPES) in prostate cancer. N Engl J Med 1998; 339(12): 785–791.

ABSTRACT

Complementary and Alternative Medicine in Cancer Treatment

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Interest in complementary and alternative medicine (CAM) has grown rapidly, fueled by Internet marketing, dissatisfaction with mainstream medicine, and the desire of patients to be actively involved in their own health care. CAM products in cancer medicine (herbs and other natural products, such as shark cartilage, mushrooms, and so on) are widely available in Japan as well as in western countries. With little reliable information and few clinical trials to assess the efficacy of such products, there is a great need for public and professional education regarding this subject.

Key words: complementary medicine, alternative medicine, cancer treatment, clinical trial

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Association between hydration volume and symptoms in terminally ill cancer patients with abdominal malignancies

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Background: To explore the association between hydration volume and symptoms during the last 3 weeks of life in terminally ill cancer patients.

Patients and methods: This was a multicenter, prospective, observational study of 226 consecutive terminally ill patients with abdominal malignancies. Primary responsible physicians and nurses evaluated the severity of membranous dehydration (dehydration score calculated from three physical findings), peripheral edema (edema score calculated from seven physical findings), ascites and pleural effusion (rated as physically undetectable to symptomatic), bronchial secretion, hyperactive delirium (Memorial Delirium Assessment Scale), communication capacity (Communication Capacity Scale), agitation (Agitation Distress Scale), myoclonus and bedsores.

Results: Patients were classified into two groups: the hydration group ($n=59$) who received 1 l or more of artificial hydration per day, 1 and 3 weeks before death, and the non-hydration group ($n=167$). The percentage of patients with deterioration in dehydration score in the final 3 weeks was significantly higher in the non-hydration group than the hydration group (35% versus 14%; $P=0.002$), while the percentages of patients whose symptom scores for edema, ascites and pleural effusion increased were significantly higher in the hydration group than the non-hydration group (44% versus 29%, $P=0.039$; 29% versus 8.4%, $P<0.001$; 15% versus 5.4%, $P=0.016$; respectively). After controlling for multiple covariates and treatment settings, the association between hydration group and dehydration/ascites score was statistically significant. Subgroup analysis of patients with peritoneal metastases identified statistically significant interaction between hydration group and dehydration/pleural effusion score. There were no significant differences in the degree of bronchial secretion, hyperactive delirium, communication capacity, agitation, myoclonus or bedsores.

Conclusions: Artificial hydration therapy could alleviate membranous dehydration signs, but could worsen peripheral edema, ascites and pleural effusions. It is suggested that the potential benefits of artificial hydration therapy should be balanced with the risk of worsening fluid retention symptoms. Further clinical studies are strongly needed to identify the effects of artificial hydration therapy on overall patient well-being, and an individualized treatment and close monitoring of dehydration and fluid retention symptoms is strongly recommended.

Key words: dehydration, neoplasm, palliative care, rehydration, water depletion

Introduction

The dehydration–rehydration problem has been one of the most important issues in palliative or end-of-life care literature over the two last decades [1]. Current discrepancies in the practice of artificial hydration therapy for terminally ill cancer patients have the potential to cause serious clinical problems: patients could suffer from unnecessary dehydration-related

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symptoms or experience iatrogenic over-hydration symptoms [2–5]. These discrepancies are largely due to the lack of evidence about the effects of artificial hydration therapy on patient well-being [3].

Traditionally, artificial hydration therapy has been thought not to benefit the terminally ill [6–11]; however, some recent studies have demonstrated that appropriate hydration can contribute to patient comfort [12–16]. The majority of studies on this topic are limited by methodological issues [17], and do not provide enough of a basis for the evidence-based practice of artificial hydration therapy in terminally ill patients. The aim of the present study was to explore systematically the associations between hydration volume and dehydration and fluid retention symptoms in the last 3 weeks of life in terminally ill patients with abdominal malignancies.

Patients and methods

Patients

The study subjects were consecutive terminally ill cancer patients treated in 14 oncology units, 19 palliative care units and four home-based palliative care programs in Japan. The participating institutions recruited potential participants following the same inclusion criteria: age >20 years; life expectancy estimated by a physician to be ≤3 months; and incurable malignancy of abdominal origin (excluding hepatic malignancies). Exclusion criteria were: liver cirrhosis of any etiology, renal failure, nephrotic syndrome, protein-losing enteropathy, intra-abdominal shunt for ascites, hypercalcemia, adrenalopathy, thyroid diseases, and other complications of the circulatory, respiratory, hepatic, or renal system unrelated to underlying malignancies; surgical, radiological or oncological treatments with the primary intent of tumor reduction in the 3 weeks prior to study inclusion; existing communication difficulty such as aphasia or aphonia; and the use of artificial enteral nutrition. Patients were enrolled from August 2002 to February 2003, and followed until March 2003.

Study design

This was a multicenter, prospective, observational study. From the time of study inclusion, primary responsible physicians prospectively recorded patients' dehydration and fluid retention symptoms on a structured data-collecting sheet every week as a part of daily practice. In addition, symptoms observed very close to death were assessed after patients died, because it was impossible to predict when the patients would die, and because assessments on a daily basis would present a high burden for patients and physicians. Thus, within 72 h after patient death, patients' dehydration and fluid retention symptoms 24 h before death, communication capacity during the 3 days before death and degree of agitation in the week before death were recorded. To minimize the recall bias, the evaluations were based on the full agreement of the primary physicians and primary nurses.

The patients received the usual treatments from their institutions. The indications for hydration therapy, administration methods and modification of treatment regimen over time were dependent on each physician's clinical decisions. We did not standardize hydration treatments, because patients' and families' wishes and each physician's philosophy strongly influenced actual hydration practice [3], and adopting a single hydration protocol was regarded as inappropriate outside experimental study designs. Instead, we described the details of hydration treatments actually performed for interpretation of the results.

This study was approved by the Institutional Review Board of each hospital, and conducted in accordance with the Declaration of Helsinki.

End points and measurements

The primary end points of this study were dehydration and fluid retention symptoms in the last 3 weeks of life. Although patient-reported symptoms and satisfaction are important outcomes in palliative care [18], we chose symptoms that could be objectively evaluated as the end points for this study. The rationale for this decision was that adopting self-report measures could result in higher rates of patient exclusion and unacceptable selection bias, because patient reports are often impossible in the very late stages of cancer due to cognitive impairment, and because symptom evaluations based on patient self-reports are not routinely used in many participating institutions [19, 20].

Physical symptoms

Physicians were requested to perform physical examinations in the morning at least 1 h after patients had eaten. The degree of dehydration was assessed on the basis of three physical findings: moisture on the mucous membranes of the mouth (0, moist; 1, somewhat dry; 2, dry), axillary moisture (0, moist; 1, dry) and sunkenness of eyes (0, normal; 1, slightly sunken; 2, sunken). These signs were selected due to their significant correlations with biological dehydration, as previously confirmed in elderly patients [21–23]. Empirical studies have found that the sensitivity/specificity of each sign in identifying dehydration is 85%/58%, 50%/82% and 62%/82%, respectively [21–23]. *Ad hoc* dehydration score (range 0–5) was calculated as the total of these three scores. A higher score thus indicated a higher level of dehydration.

The severity of peripheral edema was determined through the examination of seven regions: the hands, forearms, upper arms, feet, lower legs, thighs and trunk. Peripheral edema severity was scored based on the degree of increased skin thickness in the middle of each region (0, none; 1, mild, thickness of <5 mm; 2, moderate, 5–10 mm; 3, severe, >10 mm). If peripheral edema was asymmetric, the more severe side was rated unless the asymmetry was caused by a unilateral vascular obstruction; in these cases, the non-obstructed side was rated. The peripheral edema score (range 0–21) was calculated as the total of the severity scores for the seven regions. A higher score indicated more severe edema.

Pleural effusion and ascites were each rated on a scale of 0 to 2 (0, physically non-detectable; 1, physically detectable but asymptomatic; 2, symptomatic or tense ascites). Myoclonus and bedsores were considered present when they were observed at any time in the final 3 weeks of life.

Bronchial secretion was defined as sounds audible at the bedside produced by movement of secretions in the hypopharynx or the bronchial tree in association with respiration [8]. The severity of bronchial secretion was evaluated using a previously proposed scale: 'inaudible' (score 0), 'audible only very close to the patient' (score 1), 'clearly audible at the end of the bed in a quiet room' (score 2) and 'clearly audible at about 6 m or at the door of the room' (score 3) [24]. Bronchial secretions were considered present when patients had a severity score of 1 or more, received any anti-muscarinic medications to reduce bronchial secretion or received oral/bronchial suctioning at least once during the final 3 weeks of life. Severe bronchial secretion was defined as severity score of 2 or 3 at any time during the final 3 weeks.

Psychiatric symptoms

We used selected items of the Communication Capacity Scale, the Agitation Distress Scale and the Memorial Delirium Assessment Scale to evaluate psychiatric symptoms [25, 26]. The Communication Capacity Scale is a validated five-item observer-rating scale used to quantify communication

capacity in terminally ill patients [25]. The Agitation Distress Scale is a six-item observer-rating scale used to quantify the levels of agitation in delirious terminal patients [25]. Although using all items of a scale is psychometrically ideal, we used select items in order to reduce physician burden and increase patient enrollment [27].

The patients' communication capacity was assessed using the highest scores measured in the last 3 days of life on three items: the 'reduced level of consciousness' item of the Memorial Delirium Assessment Scale, and the 'answers to closed-ended questions' and 'voluntary communication' items from the Communication Capacity Scale. Communication score (range 0–9) was calculated as the total of these three items, such that a higher score indicated a greater capacity for communication (Cronbach's α coefficient = 0.94). The correlations between total score on this abbreviated scale and the total score on the Communication Capacity Scale was high in the original validation data (Spearman's $\rho = 0.94$; $P < 0.001$) [25].

The degree of agitation was defined as the most severe symptoms experienced during the last week of life, and quantified using four items from the Agitation Distress Scale: the frequency of motor anxiety, extent of motor anxiety, contents of motor anxiety and psychological instability. The agitation score (range 0–12) was calculated as the total of these four items; a higher score indicated higher levels of agitation (Cronbach's α coefficient = 0.87). The correlations between total score on this abbreviated scale and the total score on the Agitation Distress Scale was high in the original validation data (Spearman's $\rho = 0.95$; $P < 0.001$) [25].

Hyperactive delirium was assessed using the 'psychomotor activity' item of the Memorial Delirium Assessment Scale, which grades increased psychomotor activity on a scale of 0 (normal) to 3 (severe) [26]. Hyperactive delirium was defined as a score of 2 or 3 on this scale.

Covariates of main outcomes

We recorded the presence or absence of the following potential covariates: stomatitis, oxygen requirement, and use of opioids, diuretics and anticholinergic medication (dehydration score); vascular obstruction, and use of non-steroidal anti-inflammatory drugs (NSAIDs), steroids and diuretics (edema score); peritoneal and liver metastasis (ascites); lung and pleural metastasis, and pneumonia (pleural effusion); and intestinal obstruction and oral intake of fluids (for all symptoms) [6, 8, 15, 28].

Statistical analyses

We analyzed data for patients who died at least 3 weeks after their initial evaluation. The rationale for this decision was that we had no appropriate instruments to indicate reliable base-line points for analyses, and hydration therapy was likely to influence patient symptoms after a considerable time lag (i.e. hydration volume the patients had received 1–3 weeks before death could affect patients symptoms 48 h before death). To examine a bias, we compared patient backgrounds between the excluded and included patients.

We divided patients into two groups: those who received artificial hydration of 1 l/day or more both 1 week and 3 weeks before death (hydration group: total $n = 59$; 31 from oncology and 28 from palliative/home-care settings) and those who did not (non-hydration group: total $n = 167$ [18], from oncology and 149 from palliative/home-care settings). This classification was determined on the basis of actual data distributions, and the results using the other classifications achieved the similar conclusions.

To explore the potential association between hydration groups and patient symptoms, we compared the number of patients whose symptom scores increased in the final 3 weeks (dehydration and edema scores by three or more points; ascites and pleural effusion scores by one or more point) between the hydration and non-hydration groups. The results using the other cut-off points achieved the same conclusions. We also compared the prevalence of bronchial secretion, hyperactive delirium, myoclonus and bedsores, the degree of communication capacity, and the degree of agitation between the two groups.

To explore the effects of covariate factors and treatment settings, we examined the potential interactions between hydration groups and changes in dehydration score, edema score, and ascites and pleural effusion severity scores by the repeated measurement analysis with the covariates entered into the models (robust variance with the Proc mixed procedure). No covariates except for peritoneal metastasis and treatment settings statistically influenced the outcomes. In addition, subgroup analyses for patients who drank <500 ml/day of fluids throughout the last 3 weeks of life ($n = 108$), patients with intestinal obstruction ($n = 114$) and patients who received no intestinal drainage ($n = 192$) achieved the same results. We therefore reported the results for the entire sample with adjusted P values to allow for difference in peritoneal metastasis and treatment settings, as well as subgroup analysis of patients with peritoneal metastases ($n = 145$).

Finally, to provide additional information for interpreting data, we compared the changes in blood urea nitrogen/creatinine levels between hydration and non-hydration groups using repeated measurement analysis. We also calculated the prevalence of fluid retention symptoms 24 h before death among dehydrated patients, defined as presence of dry axillary (diagnosis on the basis of sunken eyes achieved similar results).

Univariate analyses were conducted using the χ^2-test (Fisher's exact method) and the Mann–Whitney U-test, where appropriate. All analyses were performed using the statistical package SAS.

Results

Patient background

All 498 patients who met the inclusion criteria were consecutively recruited for this study, but a total of 272 patients were excluded for the following reasons: death within 3 weeks of initial assessment ($n = 200$), survival beyond the observation period ($n = 35$), medical complications ($n = 17$), prior communication difficulty ($n = 15$) and discharge ($n = 5$). Thus, a total of 226 patients (49 from oncology units and 177 from palliative/home-care settings) were finally analyzed. There were no statistically significant differences in patient age and primary tumor sites between the patients excluded from the study due to death within 3 weeks and those analyzed, but the former was more likely to be male (Table 1).

Patient backgrounds are summarized in Table 2. There were significant differences in primary tumor sites, prevalence of lung and peritoneal metastases, vascular obstruction, intestinal obstruction, the use of NSAIDs and steroids, and oral intake 3 weeks and 1 week before death between the hydration and non-hydration groups. Chemotherapy was performed in seven patients.

Table 3 summarizes hydration practice in the study subjects. The mean hydration volume in the hydration group ranged from 838 to 1405 ml/day during the last 3 weeks, and the median hydration volume in the non-hydration group was 200 ml/day at all three observation points.

At baseline, ascites was present but asymptomatic in 27% ($n = 62$) and symptomatic in 20% ($n = 44$) of all patients.

Table 1. Characteristics of excluded and included patients

	Excluded patients[a] ($n=200$)	Included patients ($n=226$)	P
Age, years (mean ± SD)	67 ± 12	68 ± 12	0.63
Gender			
Male	114	106	0.037
Female	86	120	
Primary site			
Stomach	76	74	0.25
Colon	35	47	
Pancreas	36	35	
Rectum	15	31	
Bile duct	15	12	
Ovary	5	10	
Others	18	17	

[a]Patients who died within 3 weeks of initial assessment.
SD, standard deviation.

Pleural effusion was present but asymptomatic in 12% ($n=27$) and symptomatic in 6.6% ($n=15$) of all patients.

Dehydration

The percentage of patients whose dehydration score increased by three or more points in the final 3 weeks of life was significantly higher in the non-hydration group than in the hydration group [35% ($n=59$) versus 14% ($n=8$); $P=0.0020$]. After controlling for covariates and treatment settings, there was a statistically significant interaction between hydration group and changes in the dehydration score (1.6 ± 1.4 3 weeks before death to 2.7 ± 1.6 24 h before death in the hydration group versus 1.3 ± 1.3 to 3.2 ± 1.5 in the non-hydration group; $P=0.0043$) (Figure 1).

Edema

The number of patients whose edema scores increased by three or more points was significantly higher in the hydration group than in the non-hydration group [44% ($n=26$) versus 29% ($n=49$); $P=0.039$]. After controlling for covariates and treatment settings, the interaction between hydration group and changes in the edema score did not reach statistical significance (2.2 ± 3.3 3 weeks before death to 6.1 ± 6.4 24 h before death in the hydration group versus 3.5 ± 4.5 to 5.2 ± 5.2 in the non-hydration group; $P=0.15$) (Figure 1).

Ascites

The percentage of patients whose symptom score increased by one or more point during the final 3 weeks was significantly higher in the hydration group than in the non-hydration group [29% ($n=17$) versus 8.4% ($n=14$); $P<0.001$]. After controlling for covariates and treatment settings, there was a statistically significant interaction between hydration group and changes in the ascites score (0.73 ± 0.78 3 weeks before death to 0.92 ± 0.88 24 h before death in the hydration group versus 0.64 ± 0.79 to 0.58 ± 0.74 in the non-hydration group; $P=0.035$) (Figure 1).

Table 2. Patient characteristics

Characteristic	Hydration group ($n=59$) [% (n)]	Non-hydration group ($n=167$) [% (n)]	P
Age, years (mean ± SD)	67 ± 13	68 ± 11	0.36
Gender			
Male	58 (34)	43 (72)	0.055
Female	42 (25)	57 (95)	
Primary site			
Stomach	49 (29)	27 (45)	0.008
Colon	20 (12)	21 (35)	
Pancreas	19 (11)	14 (24)	
Rectum	5.1 (3)	17 (28)	
Bile duct	3.4 (2)	6.0 (10)	
Ovary	0	6.0 (10)	
Others	3.4 (2)	9.0 (15)	
Metastatic sites			
Lung	12 (7)	30 (50)	0.006
Pleura	15 (9)	15 (25)	0.96
Liver	46 (27)	44 (73)	0.79
Peritoneum	78 (46)	59 (99)	0.010
Performance status at enrolment			
≥2	29 (17)	19 (31)	0.59
3	37 (22)	42 (70)	
4	34 (20)	40 (66)	
Medical complications			
Stomatitis	12 (7)	23 (39)	0.060
Vascular obstruction of both extremities	1.7 (1)	12 (20)	0.018
Intestinal obstruction	64 (38)	46 (76)	0.013
Pneumonia	15 (9)	16 (27)	0.87
Medical treatments			
Oxygen	69 (41)	55 (92)	0.053
NSAIDs	53 (31)	71 (119)	0.009
Opioids	81 (48)	84 (141)	0.58
Steroids	54 (32)	75 (126)	0.002
Diuretics	34 (20)	32 (53)	0.76
Anti-cholinergic medications	20 (12)	25 (42)	0.46
Oral intake fluids ≥500 ml/day			
3 weeks before death	80 (47)	42 (70)	<0.001
1 week before death	83 (49)	57 (96)	<0.001
24 h before death	86 (51)	84 (140)	0.63

SD, standard deviation; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 3. Hydration practice in the final 3 weeks

	3 weeks before death [% (*n*)]	1 week before death [% (*n*)]	24 h before death [% (*n*)]
All patients			
<500 ml/day	44 (100)	48 (109)	62 (139)
500–1000 ml/day	21 (47)	22 (49)	21 (48)
≥1000 ml/day	35 (79)	30 (68)	17 (39)
Hydration group ($n=59$)			
Hydration volume, ml/day [mean ± SD (median)]	1405±479 (1300)	1253±379 (1100)	838±580 (1000)
Continuous administration	63 (37)	66 (39)	61 (36)
Intermittent administration	37 (22)	34 (20)	24 (14)
Via a central vein	76 (45)	75 (44)	61 (36)
Via a peripheral vein	24 (14)	25 (15)	22 (13)
Hyperalimentation	56 (33)	54 (32)	31 (18)

SD, standard deviation.

Pleural effusion and bronchial secretion

The number of the patients whose pleural effusion symptom score increased by one or more point in the final 3 weeks was significantly higher in the hydration group than in the non-hydration group [15% ($n=9$) versus 5.4% ($n=9$); $P=0.016$]. Hydration group was not significantly associated with changes in the pleural effusion symptom score after controlling for covariates and treatment settings (0.22±0.46 3 weeks before death to 0.36±0.61 24 h before death in the hydration group versus 0.27±0.60 to 0.31±0.63 in the non-hydration group; $P=0.76$) (Figure 1).

There was no statistically significant difference in the prevalence of bronchial secretion between the hydration and the non-hydration groups (Table 4).

Communication capacity, agitation and delirium

There were no statistically significant differences in the communication score, agitation score or prevalence of hyperactive

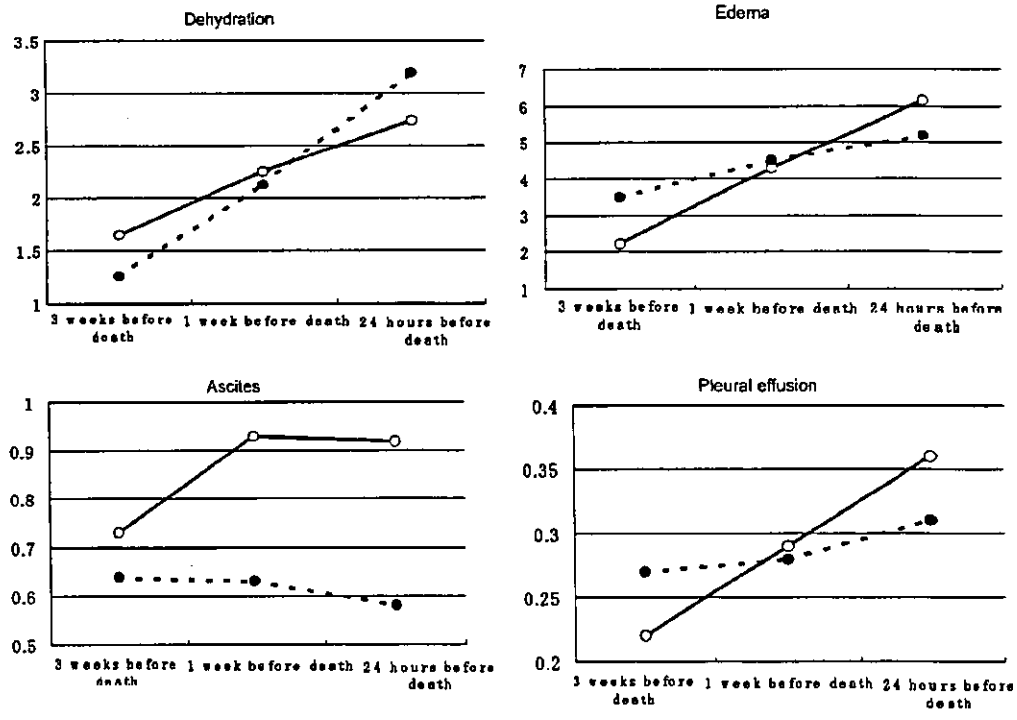

Figure 1. Effects of hydration on dehydration and fluid retention symptoms. Open circles, hydration group ($n=59$); filled circles, non-hydration group ($n=167$).

Table 4. Symptom severity in the last 3 weeks of the patients with and without hydration

	Hydration group ($n=59$)	Non-hydration group ($n=167$)	P
Bronchial secretion[a] [% (n)]	44 (26)	46 (77)	0.79
Severe bronchial secretion[b] [% (n)]	19 (11)	17 (28)	0.74
Communication score[c] (mean ± SD)	3.2 ± 3.0	3.7 ± 3.1	0.30
Agitation score[d] (mean ± SD)	2.1 ± 2.8	2.3 ± 2.7	0.35
Hyperactive delirium[e] [% (n)]	12 (7)	13 (22)	0.80

[a]Defined as audible bronchial secretion, requirement of any anti-muscarinic medications or oral/bronchial suctioning.
[b]Defined as clearly audible bronchial secretion.
[c]The total score of one item from the Memorial Delirium Assessment Scale and two items from the Communication Capacity Scale. Higher scores indicate higher levels of communication capacity.
[d]The total score of four items from the Agitation Distress Scale. Higher scores indicate higher levels of agitation.
[e]Defined as scores of 2 or 3 on the psychomotor activity item of the Memorial Delirium Assessment Scale.

delirium between the hydration and the non-hydration groups (Table 4).

Myoclonus and bedsores

There were no statistically significant differences in the prevalences of myoclonus or bedsores between the hydration and the non-hydration groups [for myoclonus 1.7% ($n=1$) versus 8.4% ($n=14$), $P=0.12$; for bedsores 27% ($n=16$) versus 34% ($n=57$), $P=0.32$].

Patients with peritoneal metastases

The interactions between hydration group and symptom changes in the last 3 weeks were statistically significant in dehydration score (1.7 ± 1.43 weeks before death to 2.9 ± 1.6 24 h before death in the hydration group versus 1.3 ± 1.3 to 3.5 ± 1.4 in the non-hydration group; $P=0.0043$) and pleural effusion score (0.22 ± 0.47 to 0.35 ± 0.60 versus 0.30 ± 0.63 to 0.27 ± 0.57, respectively; $P=0.046$), and marginally significant in ascites score (0.91 ± 0.78 to 1.0 ± 0.87 versus 0.88 ± 0.80 to 0.70 ± 0.75, respectively; $P=0.091$).

Table 5. Fluid retention symptoms in dehydrated patients ($n=149$)

	% (n)
Peripheral edema	
Hands and/or feet	69 (102)
Forearms and/or lower legs	56 (83)
Upper arms and/or thigh	36 (54)
Trunk	26 (39)
Any peripheral edema	73 (108)
Ascites	46 (69)
Pleural effusion	19 (29)
Any fluid retention symptoms	81 (121)

Dehydration was diagnosed as present if the axillary moisture was rated as dry 24 h before death.

Laboratory findings

We obtained paired blood samples taken 3 weeks and 1 week before death from 37 (63%) and 56 (34%) patients in the hydration and non-hydration groups, respectively. The blood urea nitrogen/creatinine levels increased from 34 ± 15 to 44 ± 18 mg/dl in the hydration group in the last 3 weeks, compared with from 31 ± 17 to 39 ± 20 mg/dl in the non-hydration group. The difference between hydration groups was not statistically significant ($P=0.58$).

Comorbidity of dehydration and fluid retention symptoms

Of the 149 dehydrated patients with dry axillary 24 h before death, 73%, 46% and 19% had simultaneous edema, ascites or pleural effusion, respectively; and 81% had some fluid retention symptoms (Table 5).

Discussion

This is, to the best of our knowledge, the largest and the first multicenter observation study to investigate the association between hydration volume and dehydration and fluid retention symptoms in terminally ill cancer patients.

This study revealed that peripheral edema, ascites and pleural effusion in the hydration group were more likely to worsen in the last 3 weeks. The association between hydration group and ascites severity was statistically significant after controlling all covariates and treatment settings, and in a subgroup of patients with peritoneal metastases there was a statistically significant interaction between hydration practice and changes in pleural effusion severity. The underlying mechanisms of fluid retention symptoms include a decrease in colloid osmotic pressure, an increase in membrane permeability, and an increase in hydrostatic pressure [11]. Our findings suggest that overhydration in the terminal phase could deteriorate fluid retention symptoms.

We also found that dehydration scores increased in the last 3 weeks of life regardless of whether patients received artificial hydration or not, although scores increased less in the hydration than in the non-hydration group. The potential interpretations of this finding are that: (i) the instruments for measurement of dehydration used in this study could not differentiate dehydration signs from changes related to progressed cachexia; (ii) current hydration volume was not sufficient to maintain hydration status and more active hydration could alleviate membrane dehydration signs; or (iii) artificial hydration therapy in the terminal stage could not effectively alleviate dehydration even if an appropriate volume was provided due to some pathological mechanisms (e.g. fluid shift from the intravascular components to the third space). The first

interpretation we consider unlikely, because additional analysis of laboratory findings suggested that the blood urea nitrogen/creatinine level, a biological marker of dehydration, increased in the hydration group similar to the non-hydration group. The second interpretation seems also less likely, because a well-conducted open trial and a small randomized controlled trial indicated that artificial hydration therapy had limited beneficial effects in alleviation of thirst sensation for most terminally ill cancer patients [7, 9], and this study suggests that more active hydration would cause more fluid retention symptoms, limiting the use of hydration. On the other hand, the third interpretation is supported by an exploratory study indicating that the main pathophysiology of terminal dehydration is decreased intravenous volume with increased interstitial fluids [11], and this study revealed that many patients simultaneously had both dehydration and fluid retention symptoms. Therefore, it is suggested that while artificial hydration therapy may help alleviate membranous dehydration signs in some patients, the overall benefits of active hydration therapy are limited by the possibility of aggravating fluid retention symptoms [14, 15].

This study did not identify any beneficial effects of artificial hydration therapy on psychiatric symptoms. Previous retrospective, historical control and prospective observational studies have demonstrated that active rehydration could contribute to alleviation of delirium [12, 13, 16], while another historical control study and a small randomized controlled trial found no overall benefit [7, 27]. These conflicting results suggest that the benefits of artificial hydration therapy in alleviating delirium may be applied to a certain group of patients with specific underlying etiologies, such as opioid hyperexcitability syndrome or acute dehydration [5].

This study identified no clear association between hydration volume and the development of bronchial secretion. Of note was that our sample was limited to patients with abdominal malignancies, and hydration volume was relatively small. Therefore, our findings suggested that, for patients with abdominal malignancies receiving moderate level of hydration (e.g. $\leq$1 l/day), bronchial secretion is not influenced by hydration volume. On the other hand, previous observational studies including lung cancer patients have identified pulmonary edema as a significant etiology of severe bronchial secretion [10, 29], and bronchial secretion has multiple etiologies, including respiratory malignancies, infection, pulmonary edema, dysphasia and brain metastases [30, 31]. Thus, the effect of hydration volume on other groups of patients should be examined in future studies.

This study successfully recruited patients with a narrow range of primary tumor sites, enrolled patients from multiple centers, used a comprehensive set of assessments that were sensitive to symptom changes and highly feasible, and prospectively evaluated multiple symptoms. Nonetheless, this study has several limitations. First, this was not an intervention trial. Although we acknowledge that a randomized controlled study is the best research design to scientifically clarify the treatment effects of hydration therapy, the information required for planning controlled trials, such as useful end point measures, their estimated differences and the necessary sample size, is lacking. Therefore, we decided to perform an observation study first. Secondly, the main end points were measured objectively. Therefore, we did not evaluate the effect of hydration volume on patients' subjective well-being, and there was a possibility of under- or overestimation in addition to reporting bias from treating physicians. This is, we believe, a realistic option to minimize selection bias and ensure sufficient sample size, but this flaw should be overcome in the next study. Future studies should adopt a combination of patient-rated well-being and the objective methods successfully used in this study as the primary end points. Thirdly, the reliability and validity of some measurements (i.e. peripheral edema, ascites and pleural effusion) have not been formally tested. We minimized this potential bias by confirming the full agreement of physicians and nurses, and explicitly defining the criteria in rating systems. Fourthly, stomach cancer is one of the most common malignancies in Japan, and was the primary diagnosis in nearly 30% of our subjects. Our findings therefore may not be generalizable to patients from other countries. Fifthly, as only patients who eventually died were analyzed, we did not evaluate the effects of hydration on patient survival. Finally, the result could be influenced by the treatment bias: it is possible that dehydration symptoms in the non-hydration group would have improved if they had received hydration, or that fluid retention symptoms in the hydration group would have been minimized if they had not received hydration.

In conclusion, although artificial hydration therapy might alleviate membranous dehydration signs in terminally ill patients, it could worsen peripheral edema, ascites and pleural effusions. Our findings suggest that the potential benefits of artificial hydration therapy should be balanced with the risk of worsening fluid retention symptoms. Further clinical studies are clearly needed to identify which subgroups of terminally ill patients may or may not benefit from artificial hydration therapy. In the meantime, an individualized treatment based on the comprehensive assessment followed by close monitoring of both dehydration and fluid retention symptoms is strongly recommended.

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References

1. Sarhill N, Walsh D, Nelson K, Davis M. Evaluation and treatment of cancer-related fluid deficits: volume depletion and dehydration. Support Care Cancer 2001; 9: 408–419.
2. Bruera E, Belzile M, Watanabe S, Fainsinger RL. Volume of hydration in terminal cancer patients. Support Care Cancer 1996; 4: 147–150.
3. Morita T, Shima Y, Adachi I, Japan Palliative Oncology Study (J-POS) Group. Attitudes toward terminal dehydration of Japanese physicians: a nationwide survey. J Clin Oncol 2002; 20: 4699–4704.
4. Andrews M, Bell ER, Smith SA et al. Dehydration in terminally ill patients. Is it appropriate palliative care? Postgrad Med J 1993; 93: 201–208.
5. Lawlor PG. Delirium and dehydration: some fluid for thought? Support Care Cancer 2002; 10: 445–454.
6. Burge FL Dehydration symptoms of palliative care cancer patients. J Pain Symptom Manage 1993; 8: 454–464.
7. Cerchietti L, Navigante A, Sauri A, Palazzo F. Hypodermoclysis for control of dehydration in terminal-stage cancer. Int J Palliat Nurs 2000; 6: 370–374.
8. Ellershaw JE, Sutcliffe JM, Saunders CM. Dehydration and the dying patient. J Pain Symptom Manage 1995; 10: 192–197.
9. McCann RM, Hall WJ, Grith-Juncker A. Comfort care for terminally ill patients. The appropriate use of nutrition and hydration. JAMA 1994; 272: 1263–1266.
10. Morita T, Tsunoda J, Inoue S, Chihara S. Risk factors for death rattle in terminally ill cancer patients. A prospective exploratory study. Palliat Med 2002; 14: 19–23.
11. Morita T, Tei Y, Inoue S et al. Fluid status of terminally ill cancer patients with intestinal obstruction: an exploratory observational study. Support Care Cancer 2002; 10: 474–479.
12. Bruera E, Franco J, Maltoni M et al. Changing pattern of agitated impaired mental status in patients with advanced cancer: association with cognitive monitoring, hydration, and opioid rotation. J Pain Symptom Manage 1995; 10: 287–291.
13. Lawlor PG, Ganon B, Mancini IL et al. Occurrences, causes, and outcome of delirium in patients with advanced cancer. A prospective study. Arch Intern Med 2000; 160: 786–794.
14. Mercadante S, Ripamonti C, Casuccio A et al. Comparison of octreotide and hyoscine butylbromide in controlling gastrointestinal symptoms due to malignant inoperable bowel obstruction. Support Care Cancer 2000; 8: 188–191.
15. Morita T, Tsunoda J, Inoue S, Chihara S. Determinants of sensation of thirst in terminally ill cancer patients. Support Care Cancer 2001; 9: 177–186.
16. de Stoutz ND, Bruera E, Suarez-Almazor M. Opioid rotation for toxicity reduction in terminal cancer patients. J Pain Symptom Manage 1995; 10: 378–384.
17. Viola RA, Wells GA, Peterson J. The effects of fluid status and fluid therapy on the dying: a systemic review. J Palliat Care 1997; 13: 41–52.
18. Morita T, Adachi I, Japan Palliative Oncology Study (J-POS) Group. Satisfaction with rehydration therapy for terminally ill cancer patients: concept construction, scale development, and identification of contributing factors. Support Care Cancer 2002; 10: 44–50.
19. Pereira J, Hanson J, Bruera E. The frequency and clinical course of cognitive impairment in patients with terminal cancer. Cancer 1997; 79: 835–842.
20. Stromgren AS, Goldschmidt D, Groenvold M et al. Self-assessment in cancer patients referred to palliative care. A study of feasibility and symptom epidemiology. Cancer 2002; 94: 512–520.
21. Eaton D, Bannister P, Mulley GP, Connolly M. Auxiliary sweating in clinical assessment of dehydration in ill elderly patients. BMJ 1994; 308: 1271.
22. Gross CR, Lindquist RD, Woolley AC et al. Clinical indicators of dehydration severity in elderly patients. J Emerg Med 1992; 10: 267–274.
23. McGee S, Abernethy WB, Simel DL. Is this patient hypovolemic? JAMA 1999; 281: 1022–1029.
24. Back IN, Jenkins K, Blower A, Beckhelling J. A study comparing hyoscine hydrobromide and glycopyrrolate in the treatment of death rattle. Palliat Med 2001; 15: 329–336.
25. Morita T, Tusnoda J, Inoue S et al. Communication Capacity Scale and Agitation Distress Scale to measure the severity of delirium in terminally ill cancer patients: a validation study. Palliat Med 2001; 15: 197–206.
26. Matsuoka Y, Miyake Y, Arakaki H et al. Clinical utility and validation of the Japanese version of Memorial Delirium Assessment Scale in a psychogeriatric inpatient setting. Gen Hosp Psychiatry 2001; 23: 36–40.
27. Morita T, Tei Y, Inoue S. Agitated terminal delirium and association with partial opioid substitution and hydration. J Palliat Med 2003; 6: 557–563.
28. Morita T, Tsunoda J, Inoue S, Chihara S. Contributing factors to physical symptoms in terminally-ill cancer patients. J Pain Symptom Manage 1999; 18: 338–346.
29. Wildiers H, Menten J. Death rattle: prevalence, prevention and treatment. J Pain Symptom Manage 2002; 23: 310–317.
30. Bennett M, Lucas V, Brennan M et al. Using anti-muscarinic drugs in the management of death rattle: evidence-based guidelines for palliative care. Palliat Med 2002; 16: 369–374.
31. Morita T, Hyodo I, Yoshimi T et al. Incidence and underlying etiologies of bronchial secretion in terminally ill cancer patients: a multicenter prospective observation study. J Pain Symptom Manage 2004; 27: 533–539.

Gastritis Cystica Polyposa Concomitant with Gastric Inflammatory Fibroid Polyp Occurring in an Unoperated Stomach

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Gastritis Cystica Polyposa Concomitant with Gastric Inflammatory Fibroid Polyp Occurring in an Unoperated Stomach

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Abstract

The endoscopic examination of a 61-year-old male patient revealed a protruding lesion in the greater curvature of the lower third area of the stomach. The lesion, 17 mm in size, was resected completely with endoscopic submucosal dissection using an insulated-tip diathermic knife (IT-ESD). Histological examination of the protruding lesion revealed proliferation of fibroblasts and infiltration of inflammatory cells in the mucosa and submucosa, and it was diagnosed as an inflammatory fibroid polyp (IFP). Gastritis cystica polyposa (GCP) was presented adjacent to the IFP. This may be the first report of GCP concomitant with gastric IFP occurring in an unoperated stomach.
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Key words: gastric cysts, inflammatory polyp, neoplasm, insulated-tip diathermic knife, endoscopic submucosal dissection

Introduction

Inflammatory fibroid polyp (IFP) is a relatively rare disorder, which is thought to be clinically and histologically benign, and was first described as "polypoid fibroma" in 1920 by Konjetzny (1). Gastritis cystica polyposa (GCP), characterized by polypoid hyperplasia of the gastric mucosa, is an uncommon lesion that develops in patients who have undergone gastroenterostomy with or without gastric resection (2–5). GCP is rarely found in an unoperated stomach (4–6). There have been no previous case reports of gastric IFP concomitant with GCP. Herein, we report a case of GCP concomitant with gastric IFP occurring in an unoperated stomach, and treated by endoscopic submucosal dissection using an insulated-tip diathermic knife (IT-ESD).

Case Report

A 61-year-old man visited our hospital for further evaluation of abnormal radiographic findings of the stomach in a yearly physical checkup on October 13, 2001. No specific family or past medical history was identified. Routine hematological examination and biochemical tests were within normal limits. Serum anti-*Helicobacter pylori* (*H. pylori*) immunoglobulin G (IgG) antibody was positive. Endoscopic examination of the upper digestive tract revealed a protruding lesion, about 20 mm in diameter, in the pyloric gland area, in the greater curvature of the lower third area of the stomach (Fig. 1). The biopsy specimen obtained from the lesion revealed normal gastric mucosa. We had to make a differential diagnosis between a large hyperplastic polyp and a submucosal tumor covered with normal gastric mucosa. Endoscopic ultrasonography (EUS) with a miniature probe of 20 MHz frequency using the water filling method revealed a hypoechoic mass covered with a hyperechoic lesion that had anechoic areas in the second and third layers of the gastric wall (Fig. 2). This protruding lesion was surrounded by intestinal metaplastic mucosa. There were some red patches with erosions in the antrum, however, there was not any diffuse red area in the fundic area. The culture of gastric mucosa propagated the microaerophilic bacteria, *H. pylori*. On the basis of EUS findings, we could not deny that the tumor might be gastric cancer resembling a submucosal tumor or gastric cancer with a mucinous component. We suspected this patient had a submucosal tumor, but the definite diagnosis could not be made. The patient underwent an IT-ESD for histological confirmation. IT-ESD was performed as we previously described (7). The protruding lesion, 17×15×5 mm in size, was resected completely with a safe lateral

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