研究で，カルシフィラキシーの発症に核因子-κBリガンドの可溶性受容体アクチベーター(receptor activator of nuclear factor-κB ligand：RANKL)が関与しているといわれている．RANKLは破骨細胞の分化と骨吸収機能を誘導し，心血管系の石灰化に関与すると推測されている．副甲状腺ホルモン，コルチコステロイド，アルミニウム，肝疾患，炎症性疾患はRANK分子の発現を増強させることがわかっており，calciphylaxis発症の誘発因子になりうるのではないかと推測されている．

Calciphylaxis発症の危険因子として，

・Ca×P　70 m^2/dl^2以上
・Ca　　10.5mg/dl以上
・IP　　5.0mg/dl以上

との報告がある[3]．またcalciphylaxisの誘発因子としては，低アルブミン血症，肥満(BMI>30)[4]，急激な体重減少，ワーファリン投与[5]，局所の外傷，プロテインC低下[6]，プロテインS低下[7]などがあげられる．自験例のcalciphylaxis発症のリスク因子をあげると，IP 5.0mg/dl以上，低アルブミン血症，ワーファリン投与歴，プロテインS低下である．カルシウム・リン代謝に着目すると，血清リン値は初診時高値であったものの，血液透析導入後から経過中，血中カルシウム・リン値，副甲状腺ホルモンのコントロールは比較的良好であった．Ca×Pは70m^2/dl^2以下を推移しており，リン値は軽度上昇を認めていたが，カルシウム値は正常範囲内であった．コントロール良好であったにもかかわらずcalciphylaxisを発症しており，発症機序としてカルシウムリン代謝のみならず，複合的な要因の関与が考えられる．

Calciphylaxisの治療として確立された治療法はいまだないのが現状である．創部ケア(外用，デブリドマン)，疼痛コントロール(硬膜外麻酔，麻薬など)，血中カルシウム・リン値の補正，塩酸セベラマーの投与，大量ビスフォスフォネート投与，チオ硫酸ナトリウム投与，高圧酸素療法，副甲状腺ホルモン値高値の場合には副甲状腺摘出術などが試みられている．Rogerら[4]は，64名のカルシフィラキシーの患者のレトロスペクティブ調査で，唯一外科的デブリドマンが生存率の延長に寄与したと述べている．副甲状腺摘出術に関しては有効とする論文が散見されるが，この調査では，摘出術施行群，未施行群の間で生存率に有意差はなく，重篤な続発性副甲状腺機能亢進症が証明された場合のみに施行するべきであるとしている．自験例では，高酸素療法を施行するもその前後での変化はほとんどなく，むしろ皮疹は新生した．3度にわたる外科的デブリドマンが有効であったと考えている．

Calciphylaxisの発症部位は生存率の違いに関与しないとする論文もあるものの[4]，躯幹，臀部，大腿などの中枢側に生じると致死率80%[8]といわれており，致死率が高い．中枢側の潰瘍の出現が予後を大きく左右すると考えられている．本邦でも中枢側に広範囲に潰瘍を生じ，十分にデブリドマンを施行できず，死亡した症例の報告が散見される[9,10]．自験例は難治性であったが，デブリドマン後徐々に潰瘍は上皮化し，生存しえた．自験例で良好な予後が得られた理由として，1)遠位側に発症したこと，2)血液透析導入後から経過中，血中カルシウム・リン値，副甲状腺ホルモンのコントロールは比較的良好であり，心弁膜などの内臓の石灰化を生じなかったこと，3)疼痛コントロール下で複数回デブリドマンを施行したことで，潰瘍局所の感染をコントロールでき，敗血症などへの発展を予防しえたことがあげられる．本症は予後不良な疾患とされるが，下腿のような末梢側のみに発症した場合，早期に診断し，加療することにより生存しうる．慢性腎不全患者の有痛性紫斑，難治性潰瘍をみたときには，本症を鑑別診断の1つに入れ，生検により確定診断し，外科的デブリドマンを含めた早急な対応をすることが望まれる．

本論文の要旨は，第106回日本皮膚科学会総会にて報告した．

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＜症例報告＞

静脈うっ滞により顕在化したと考えられたCalciphylaxisの1例

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Key Words：calciphylaxis，静脈うっ滞，慢性腎不全，人工透析，二次性副甲状腺機能亢進症

はじめに

Calciphylaxisは1962年にSelyeらによってはじめて報告されており[1]，中小動脈に進行性の石灰沈着を起こし，虚血や皮膚壊死を生じる現象と定義されている[2]。透析患者の約1％に発症する比較的まれな疾患であり[2,3]，わが国では2006年までに約50例が報告されているにすぎない[3～5]。今回われわれは，静脈うっ滞を契機に顕在化したと考えられるcalciphylaxisによる下腿潰瘍の1例を経験したので，若干の文献的考察を加えて報告する。

症　例

患者：55歳，女性。

主訴：右下腿，足背の疼痛。

既往歴：1981年，妊娠腎との診断を受けた。1993年，維持透析を導入された。1993年～2000年，両側上肢でシャント形成，閉塞を繰り返す。2000年，左下肢シャント形成術を施行された。

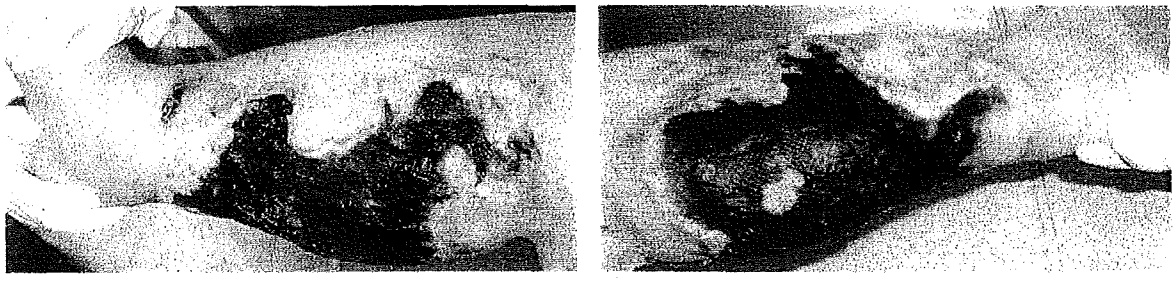
家族歴：特記すべき事項なし。

現病歴：2007年1月，右大腿部にAVシャント形成後より右下肢下垂に伴う疼痛が出現した。このとき右下肢全体が腫脹したが発赤はなく，明らかな蜂窩織炎は認めなかった。2月上旬になり，右下腿屈側と右足背に水疱が出現した。このため右大腿部のシャントの使用を中止し，以後左内頸静脈に留置したWルーメンカテーテルより維持透析を施行された。

その後保存的治療を行われるも増悪し，3月上旬には右下腿屈側と右足背に黒色壊死組織が出現した。このときの検査データではWBC 23,600/μl，CRP 35mg/dlと著明な炎症反応を認めた。3月中旬に行われた静脈造影では，右外腸骨静脈の閉塞と静脈圧の上昇を認めた。その後も保存的治療を継続されたが改善せず，4月上旬に当科紹介入院となった。

入院時現症：右下腿の膝窩よりやや末梢から足関節にかけて，右下腿屈側ほぼ半周性に中心部に黒色壊死組織を有した地図状の潰瘍を認めた（**図1a，b**）。また，右第2，3趾背側にはMP関節からDIP関節にかけて境界明瞭な楕円形の潰瘍を認め，右下腿と同様に黒色壊死組織を有していた（**図2**）。また足背動脈，後脛骨動脈の拍動は，左右とも同様に触知した。なお，この時点で右下肢全体の腫脹は軽快していた。

血液検査所見：炎症反応は3月の前医での所見にくらべやや低下していた。またPTHと血中カルシウム，リン濃度が高値で，長期の維持透析による二次性副甲状腺機能亢進症が存在すると考えられた。免疫学的血



(a)　(b)

図1　右下腿の入院時現症
右下腿の膝窩よりやや末梢から足関節にかけて，内側（a）から屈側および外側（b）に及ぶ地図状の潰瘍を認め，中心部に黒色壊死組織が付着していた。

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表1　入院時血液検査所見
PTHと血中カルシウム，リン濃度，Ig-G，CH_{50}，抗核抗体の高値を認めた。

WBC 5,600/μl	RBC 2.84 × 10^6/ml	PLT 200 × 10^3/μl	Hb 8.0 g/dl
HbA_{1c} 4.19 %	T-Pro 6.15 g/dl	Alb 2.49 g/dl	T-BIL 0.59 mg/dl
ALT 12.4 IU/l	AST 4.6 IU/l	ALP 465 IU/l	γ-GTP 44.8 IU/l
CK 29 IU/l	CRP 4.26 mg/dl	BUN 22.31 g/dl	Cr 5.36 mg/dl
Na 138.6 mEq/l	K 3.14 mEq/l	Cl 106.7 mEq/l	Ca 12.43 mg/dl
P 3.63 mg/dl	PTH 100 Pg/ml	Ig-G 2,210 mg/dl	Ig-A 254 mg/dl
Ig-M 54 mg/dl	C_3 100 mg/dl	C_4 32 mg/dl	CH_{50} 62.6 U/ml
ANA 80倍	DS-DNA 4.1 U/ml	SS-DNA74.3 AU/ml	抗SS-A抗体 <5
抗SS-B抗体 17.1	クリオGlob（－）	抗β-2GPIカルジオリピン複合体抗体 <1.2 U/ml	
ループスAC 0.96	Protein-C活性 60	Protein-S活性 151.3	

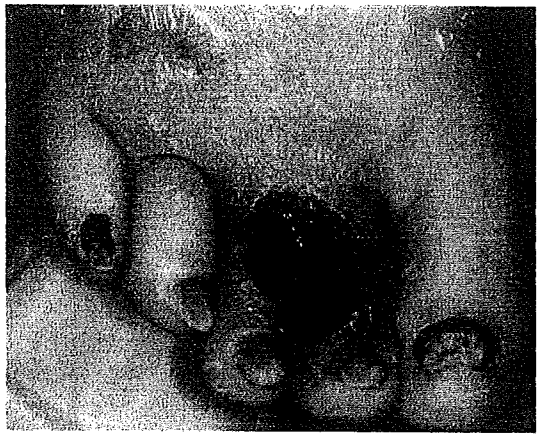

図2　右第2，3趾の入院時現症
右第2，3趾背側にはMP関節からDIP関節にかけて境界明瞭な楕円形の潰瘍を認め，右下腿と同様に黒色壊死組織が付着していた。

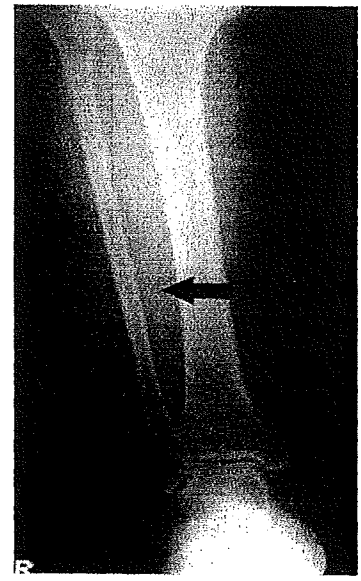

図3　右下腿の単純X線写真
右下腿では前脛骨動脈の石灰化を認めたが（矢印），明らかな体表近くの細動脈の石灰化は認めなかった。

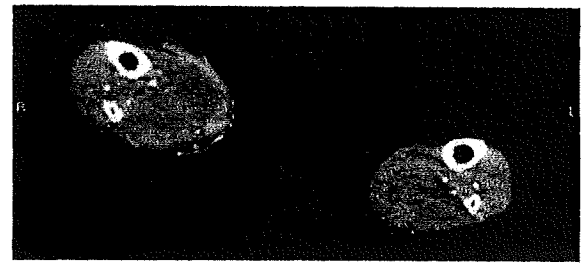

図4　右下腿造影CT
右下腿は左下腿に比べて腫大しており，筋膜および筋内に淡い造影効果を認める部位が存在し，蜂窩織炎，腱膜・筋膜炎に伴う変化と考えられた。

液検査所見ではIg-G，CH_{50}，抗核抗体の高値を認めた（**表1**）。

単純X線：右下腿では前脛骨動脈の石灰化を認めたが，明らかな体表近くの細動脈の石灰化は認めなかった（**図3**）。また右第2，3趾については，明らかな骨壊死は認めず，潰瘍周囲の中小動脈の石灰化も認めなかった。

CT所見：右下腿の筋膜および筋内に淡い造影効果を認める部位が存在し（**図4**），蜂窩織炎，腱膜・筋膜炎に伴う変化が疑われた。CT angiographyでは右浅大腿動脈の狭窄（起始部：50％）と両側前脛骨・腓骨動脈の末梢での途絶を認めた（**図5**）。また，単純CT検査では両側気管支壁および甲状腺左葉外側に異所性石灰化を認めた。造影CT検査では右下肢の明らかな静脈内血栓は指摘できなかった。

エコー所見：ドップラーエコーでは，右大腿静脈から右膝窩静脈までの血栓や血液の逆流現象は指摘できなかった。また，吸気に伴う右大腿静脈の拡張を認めた。

治療と経過（1）：以上の検査所見より右下肢潰瘍の原因としてPAD（peripheral arterial desease），静脈うっ滞性潰瘍，calciphylaxisを考え，2007年4月中

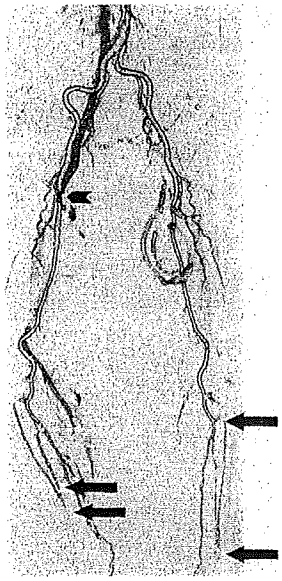

図5　CT angiography
右浅大腿動脈起始部の50％の狭窄（羽根印）と，両側前脛骨・腓骨動脈の末梢での途絶（矢印）を認めた。

旬，感染コントロールと診断確定のため，デブリードマンと潰瘍周堤皮膚の生検を施行した。デブリードマン後は創面全体を人工真皮で被覆した。なお，前医より二次性副甲状腺機能亢進症の治療目的にて処方されていたカルシウム製剤は，血中カルシウム濃度高値のため投与を中止した。

病理組織学的検査所見：真皮下層に存在する動脈の中膜に石灰化を認め，血管内腔は閉塞し，再開通も認められた（**図6**）。また，標本内の動脈周囲に明らかな炎症反応は認めなかった。

診断：本症例は慢性腎不全，それに伴う副甲状腺機能亢進症が基礎疾患として存在しており，潰瘍周堤の生検所見では動脈の石灰化像も認めた。これによる虚血性変化として右下肢潰瘍が出現したと考え，calciphylaxis に伴う右下肢潰瘍と診断した。また，潰瘍形成後の静脈造影では右外腸骨静脈の閉塞を認めており，これとシャント形成による右下肢の静脈うっ滞は潰瘍形成に無関係ではなく，その発症に関与したと考えられた。

治療と経過（2）：デブリードマン，生検後は塩酸セベラマー投与による血中リン濃度のコントロールと創部の保存的療法にて順調に経過した。6月上旬に腓腹筋腱露出部以外の右下腿に分層植皮術を施行し，7月上旬に軽快退院となった。その後近医にて保存的療法と高気圧酸素療法を施行した結果，腓腹筋露出部に肉芽の増生を認めたため，10月下旬に同部位の分層植皮術を施行した。現在術後3ヵ月であるが，良好な移植皮片の生着を認めている（**図7**）。

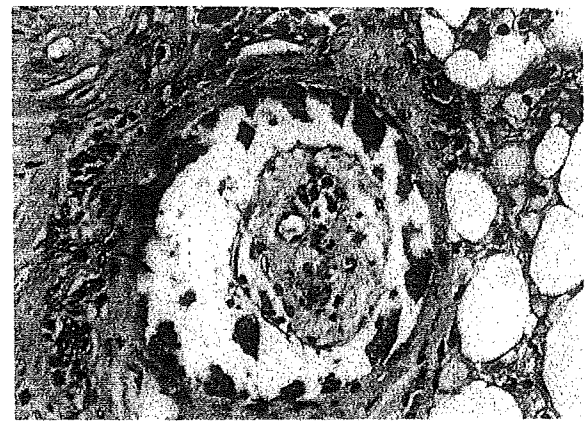

図6　病理組織学的検査所見
真皮下層に存在する動脈の中膜に石灰化を認め，血管内腔は閉塞し，再開通も認められた。

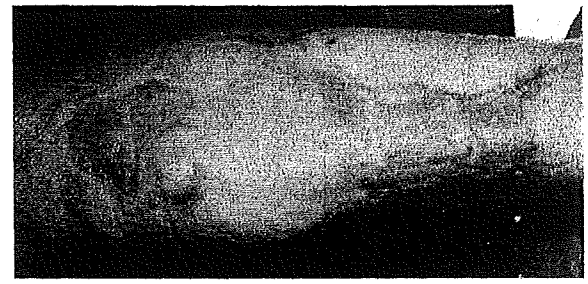

図7　分層植皮後3ヵ月の右下腿

また，術後6週で両側下肢のSPP（皮膚灌流圧）を測定したところ，右足背67mmHg，右足底74mmHg，右足関節69mmHg，右下腿86mmHg，左足背84mmHg，左足底12mmHg，左足関節68mmHg，左下腿46mmHgであった。なお，全経過を通じて血中カルシウム濃度とリン濃度の積が70（mg/dl）[2]をこえることはなかった。

考　察

Calciphylaxisは透析患者の約1％に発症し[2,3]，発症年齢は48歳前後で，男女比は1：3と中年女性に多いとされている[3]。その皮膚症状は四肢近位や体幹部に強い疼痛をもった細網状紫斑が出現し，急速に進行して6ヵ月以内に皮膚壊死，潰瘍形成にいたる[5,6]。内臓虚血を合併するsystemic calciphylaxisと皮膚，皮下組織の虚血に伴う皮膚症状のみのtopical calciphylaxisとに分類されており，topical calciphylaxisはさらに体幹，四肢近位に皮膚症状を呈するproximal typeと，四肢末端に皮膚症状を呈するdistal typeに分類される[2,4]。いずれも予後は不良であり，特にproximal typeでは急速に潰瘍が進行し，敗血症によって死亡する例が多い[5]。過去の統計では，

proximal typeの死亡率は63％，distal typeの死亡率は23％と報告されている[3,7]。病理組織学的には，真皮，皮下組織に存在する細動脈の中膜への石灰沈着が特徴的である[5]。なお，今回われわれが調べえた限り，明確で定量的なcalciphylaxisの診断基準は存在しなかった。

Calciphylaxis発症例においては，その基礎疾患として腎不全に伴う二次性副甲状腺機能亢進症の存在が広く知られている。慢性腎不全では活性化ビタミンDが欠乏し，経口摂取されたカルシウムの吸収が低下し，低カルシウム血症となる。ビタミンD非依存性であるリンは吸収され，また腎排泄量が低下し，高リン血症となる。血中カルシウム濃度とリン濃度の値を一定にするためさらに低カルシウム血症となり，副甲状腺ホルモンの分泌が刺激され，二次性副甲状腺機能亢進症が発症し，その結果動脈の石灰化など異所性石灰化を生じることとなる。

この異所性石灰化は血中カルシウム濃度とリン濃度の積が70（mg/dl)^{2}以上になると促進されるといわれており[2,3,5]，calciphylaxisにおいても血中カルシウム濃度とリン濃度のコントロールが重要と考えられている。しかし，血中カルシウム濃度とリン濃度が正常値にもかかわらずcalciphylaxisを発症した例や，二次性副甲状腺機能亢進症の治療として副甲状腺摘出術を施行しそれらを正常化させたにもかかわらず，皮膚症状が増悪した例も存在する[2,3,5]。したがって，calciphylaxisの発症には血中カルシウム濃度，リン濃度以外の因子が関与している可能性は否定できない。そのほか，二次性副甲状腺機能亢進症以外に皮下注射等の局所刺激，ワーファリン投与，糖質コルチコイド，免疫抑制薬の投与やprotein Sの低下等が発症の危険因子とされているが，その詳細な発症機序は不明である[7]。

本症例には二次性副甲状腺機能亢進症以外の上述した危険因子は存在せず，下肢にシャントを形成直後に水疱，潰瘍が出現しており，潰瘍形成後の静脈造影では右外腸骨静脈の閉塞と静脈圧の上昇を認めている。したがって，本症例の潰瘍は静脈うっ滞を契機に発症したものと考えられた。つまり，細動脈の石灰沈着に伴う皮膚の虚血状態が基礎にあり，そこに静脈うっ滞や動脈閉塞が加わり難治性の潰瘍を形成したと考えられる。右下肢の腫脹が軽快後，2回の分層植皮が比較的スムーズに生着したこともこの推定を支持しているといえる。われわれが調べえた限りこのような報告例はこれまでになく，今後同様の症例の集積が待たれる。また，本症例の病理組織学的所見において細動脈の石灰化は過去の報告例と比較して多くなく[7]，標本内に数個認めるのみであったことも，本症例のcalciphylaxisの程度が軽く，可逆性であったことを示唆している。さらに右第2，3趾の潰瘍がデブリードマンにより順調に治癒したのも，足趾末梢の単純X線で動脈に沿った石灰化がみられなかったことも，本症例のcalciphylaxisの病期に関連していた可能性があり，興味深い。

Calciphylaxisによる潰瘍の治療としては，創部のデブリードマンや保存的療法，高気圧酸素療法，副甲状腺摘出術，透析回数の増加のほかに，ヘパリンやt-PA（tissue plasminogen activator）の低容量投与が行われている。これはcalciphylaxisには凝固能が亢進する場合があるためであり，過去の報告例では比較的良好な治療結果が得られている。本症例では明らかな凝固能の亢進は認めなかったため施行しなかったが，病理組織学的所見では皮下組織レベルでの静脈内血栓を認めており，もしヘパリンやt-PAの低容量投与を行ったとすれば，それが奏効した可能性は否定できない。また，この抗凝固療法は危険因子の一つであるワーファリンの投与と一見矛盾しているようであるが，ワーファリンの投与が危険因子とされているのは，それによりビタミンK依存性抗凝固物質であるprotein Cやprotein Sの血中濃度の低下が起こるためで，抗凝固作用そのものが危険因子となるわけではないとされている[8]。

まとめ

Calciphylaxisを伴う下肢潰瘍の1例を経験した。長期維持透析患者に皮膚潰瘍が生じた場合，calciphylaxisは想起すべき重要な疾患と考えられた。

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Case Report

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Successful management of critical limb ischemia with intravenous sodium thiosulfate in a chronic hemodialysis patient

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Key words
sodium thiosulfate – vascular calcification – calciphylaxis – hemodialysis – hyperparathyroidism

Abstract. Vascular calcification is common among hemodialysis (HD) patients and contributes to the development of peripheral arterial disease. A 57-year-old Japanese man who had been on HD for 30 years was referred to us for severe pain with multiple ulcers on his toes and fingers. He was an ex-smoker and had no diabetes mellitus. On admission, he had ulcers on his big toes bilaterally and right 2nd – 4th fingers. Peripheral pulses were strong and his ankle-brachial pressure index was above 1.3. Laboratory data were as follows: calcium 9.9 mg/dl, albumin 3.3 g/dl, phosphate 3.0 mg/dl, Ca × P product 30, and parathyroid hormone 98 pg/ml. He had a parathyroidectomy in 1998 and 1999. X-rays of his hands and legs showed diffuse subcutaneous arteriolar calcification. Angiography revealed no local stenotic lesions. Despite intensive therapies including hyperbaric oxygen therapy, painful gangrene developed on his right big toe and the pain was so intense that he could not go to sleep in a supine position. We infused intravenous sodium thiosulfate (20 g) 3 times weekly, based on previous reports. Within 4 – 5 days, he experienced rapid and dramatic symptom relief. The score of the visual analogue pain scale improved from 10/10 – 2/10. The signs of ischemia, measured by transcutaneous partial oxygen pressure and thermography, improved significantly. During the infusion of sodium thiosulfate, the patient complained of nausea, vomiting and hyperosmia. These adverse symptoms were resolved after discontinuation of the infusion. Pain relief was sustained and he could walk after 2 weeks of infusion. Our case supports the use of sodium thiosulfate as a novel therapeutic choice for critical limb ischemia with severe vascular calcification in chronic HD patients.

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Introduction

Vascular calcification is common among hemodialysis (HD) patients. Recent reports emphasize the multidisciplinary therapeutic approach focusing on correction of the underlying abnormalities of serum calcium and phosphorus levels using non-calcium-containing phosphate binders. Local wound care with debridement of necrotic tissues and aggressive treatment of infectious complications is also required [Budisavljevic et al. 1996]. The usefulness of parathyroidectomy and hyperbaric oxygen therapy remains controversial [Basle 2000, Budisavljevic et al. 1996], thus, newer therapeutic modalities need to be explored. Intravenous sodium thiosulfate, which is currently used as an antidote for the treatment of cyanide poisoning and the prevention of toxicity due to cisplatin cancer therapies, might be an alternative treatment choice in such conditions [Cicone et al. 2004].

We report a patient on long-term HD with severe pain and peripheral vascular calcification who responded dramatically to sodium thiosulfate infusion. We describe the details of the clinical course and the side effects of the treatment.

Case report

A 57-year-old Japanese man on chronic HD due to chronic glomerulonephritis was referred for multiple ulcers on his big toes bilaterally and fingers on his right hand with severe pain. He has been on HD 4 hours 3 times per week since 1975. He was an ex-smoker, 20 cigarettes/day for 25 years, and had no history of diabetes mellitus. He denied preceding warfarin treatment.

Skin ulcers progressed gradually despite several conventional therapies such as local wound care and infusion of vasodilating pro-

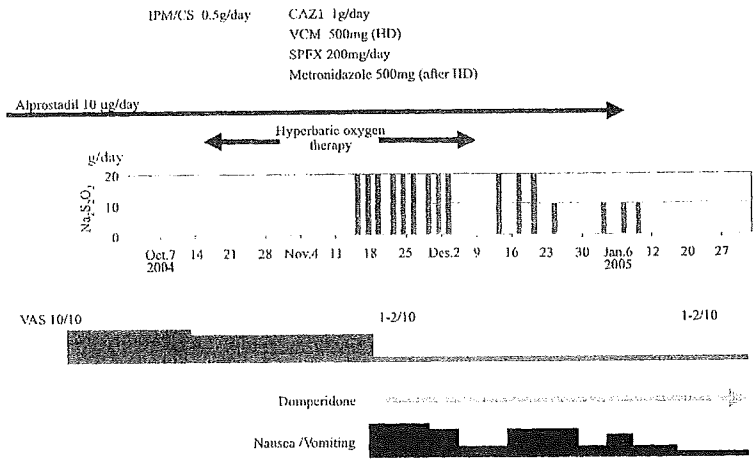

Figure 1. Clinical course of the patient. CAZ ceftazidime, VCM vancomycin, SPFX sparfloxacin, IPM/CS imipenem, HD hemodialysis, VAS visual analogue scale.

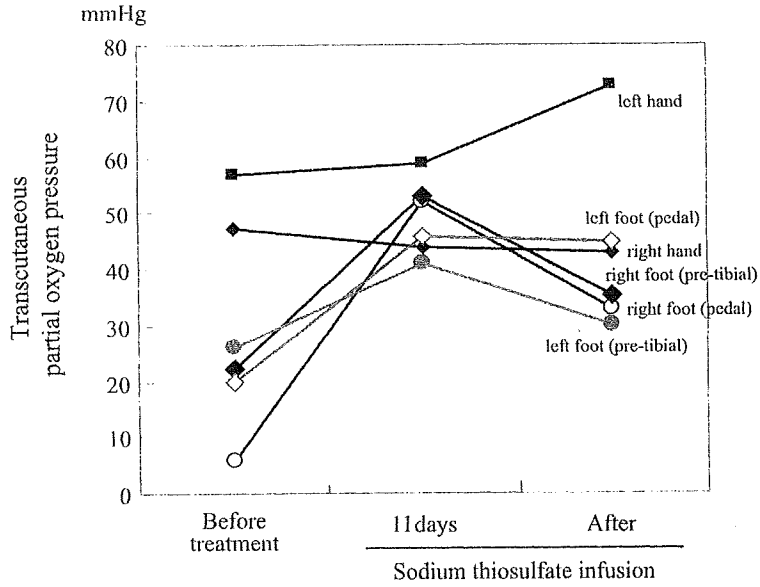

Figure 2. Changes in subcutaneous partial oxygen pressure.

staglandins. Intact parathyroid hormone (PTH) levels were consistently low because of parathyroidectomy in 1998 and 1999. He received many drugs such as alprostadil, beraprost, cilostazol, tocopherol nicotinate, calcium carbonate and maxacalcitol during each hemodialysis session and also required other analgesics when he was admitted to our hospital. His skin ulcers developed gradually and vascular calcification was noted in the distal extremities several months before admission.

Upon admission (height 172 cm, weight 68.0 kg), his blood pressure was 112/58 mmHg, pulse rate was 70 beats per minutes and body temperature was 36.9 °C. He had ulcers on his big toes bilaterally and right 2nd – 4th fingers. The skin of his distal extremities was violaceous. Peripheral pulses were palpable and equal bilaterally. Using the pain scale from 0 – 10 (Visual Analogue Scale, VAS), he rated his pain as most severe (10/10). Laboratory findings were as follows: hemoglobin 11.8 g/dl, white blood cell count 8,000/μl, platelet 33.3 × 10^4/μl, blood urea nitrogen 60 mg/dl, creatinine 13 mg/dl, total protein 5.8 g/dl, albumin, 3.7 g/dl, sodium 140 mEq/l, potassium 4.3 mEq/l, uric acid 8.4 mg/dl, calcium 9.9 mg/dl, phosphate 3.0 mg/dl, Ca × P product 30, C-reactive protein 1.2 mg/dl, glucose 60 mg/dl, total cholesterol 168 mg/dl, triglyceride 166 mg/dl and intact PTH 98 pg/ml. His ankle-brachial index was 1.40 (right) and 1.37 (left). The pulse wave velocity was 2,100 cm/s (right) and 1,933 cm/s (left). X-rays of his hands and legs showed diffuse arteriolar calcification. However, there was no evidence of stenotic lesion in large arteries.

The ulcers progressed in size and became deeper. Due to his severe pain and ulceration, skin biopsy was not performed. Angiographic findings showed diffuse arteriolar calcifications from the femoral artery to below the joint of foot, but there were no local stenotic lesions of the iliac aorta. Bone scan (technetium 99 methylane diphosphonate) showed no areas of increased radio-tracer activity corresponding to the subcutaneous calcified plaques characteristic of calciphylaxis.

Clinical course (Figure 1)

Despite intensive therapies with multiple drug regimens and hyperbaric oxygen therapy, painful gangrene developed on his right big toe and the pain was so intense that he could not go to sleep in the supine position. We tried therapy with 20 g sodium thiosulfate infusion, 3 times per week after each HD session beginning in November 2004. On the 5th day after starting this treatment, his pain had decreased from a VAS of 10/10 – 2/10. Laboratory data revealed no significant changes after the infusion. Pain relief was sustained and he could walk 2 weeks after the infusion. All pain and tenderness had disappeared after 16 infusions, and subcutaneous plaques became smaller and more mobile. He became

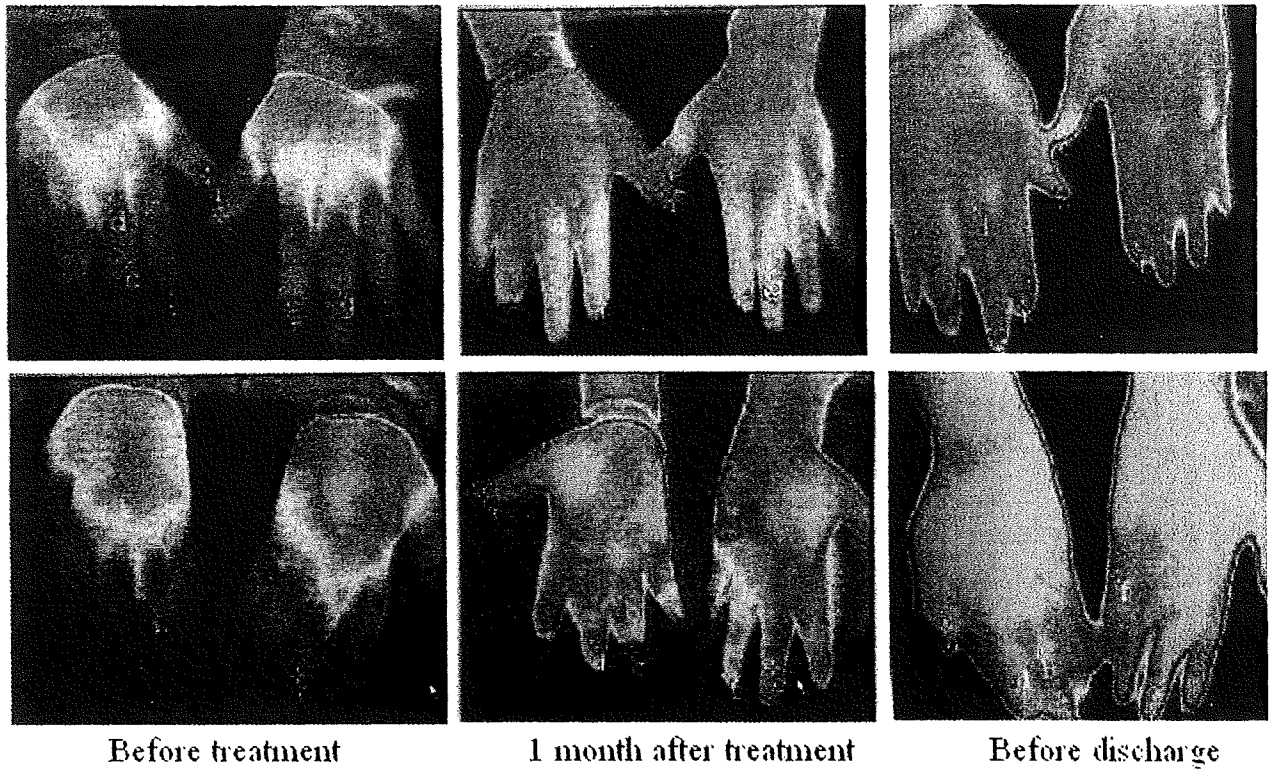

Figure 3. Thermography of the hands before and after the infusion of sodium thiosulfate.

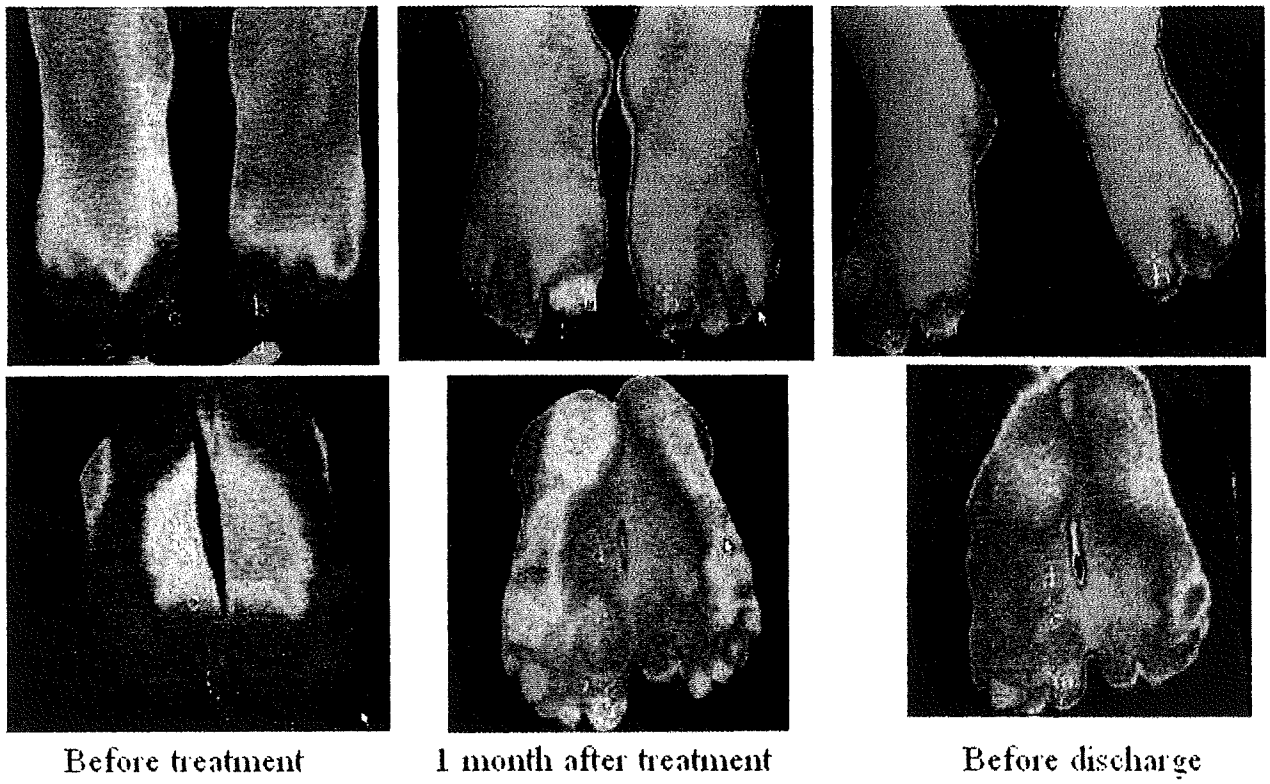

Figure 4. Thermography of the feet before and after the infusion of sodium thiosulfate.

ambulatory and did not require analgesics. The transcutaneous partial oxygen pressure monitor ($tcPO_2$, TCM 400, Radiometer KK, Tokyo, Japan, Figure 2) and thermography (Figures 3, 4) confirmed the relief of the symptoms. He complained of nausea and occasional vomiting, however, during the infusion he had hypersensitivity to food smells

and a loss of appetite. We reduced the dose of sodium thiosulfate to half.

Comments

Our patient had debilitating calciphylaxis-like symptoms, but few putative risk factors of calciphylaxis [Budisavljevic et al. 1996]. Syndromes resembling calciphylaxis have been reported in individuals without such risk factors [Kane et al. 1996, Llach 2003, Wilmer et al. 2002]. His symptoms started after parathyroidectomy and developed despite maintaining normal levels of serum calcium, phosphate and PTH. Calciphylaxis is usually non-ulcerating and shows nodular or plaque-like subcutaneous calcifications [Llach 2003]. The clinical diagnosis of calciphylaxis (calcific uremic arteriopathy) is confirmed by biopsy of a cutaneous lesion [Fine et al. 2002]. Skin biopsy was not performed in our case, however, because it might precipitate ulceration and induce infection.

He has been on long-term HD for 30 years without a history of renal transplantation. Because of the limited number of renal transplantations in Japan, more than 9,000 patients are on chronic dialysis for more than 20 years [Iseki et al. 2005]. To our knowledge, however, this is the first Japanese patient who was treated with thiosulfate infusion. Vascular calcification, including that of the coronary artery, is common in such patients. Peripheral vascular disease is one of the leading causes of loss of extremities and mortality. Tumoral calcification, which is similar to calciphylaxis, is treated with sodium thiosulfate. Cicone et al. [2004] reported the use of sodium thiosulfate to treat a peritoneal dialysis patient with calciphylaxis, without any modifications to the dialysis prescription. They noted significant improvement within 2 weeks of sodium thiosulfate infusion. Lesions were greatly reduced and pain completely disappeared after 8 months of infusion. During the infusion of sodium thiosulfate, our patient complained of nausea, vomiting, and hyperosmia. These adverse symptoms were resolved after discontinuation of the infusion. Sodium thiosulfate has been used therapeutically as an antidote for acute cyanide poisoning and as a topical chemoprotectant against cisplatin. Although it is considered to have low toxicity, it is usually excreted unchanged in the urine. Therefore, it might accumulate in the plasma of HD patients. The dialyzability of sodium thiosulfate is not known, but might be low as it has a molecular weight of 248 Daltons [Brucculeri et al. 2005]. To our knowledge, this is the first case of sodium thiosulfate treatment of limb ischemia in Japanese and probably also in Asian patients.

In summary, we report a case of a patient on long-term HD who had an atypical clinical presentation of severe vascular calcifications confirmed by X-ray and angiography findings. The intravenous sodium thiosulfate (20 g, 3 times per week) effectively achieved rapid and dramatic relief of symptoms and improvement, as indicated by thermography and $TcPO_2$. Sodium thiosulfate infusion is warranted in patients who are unresponsive to conventional treatment.

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Successful Treatment of a Patient With Severe Calcific Uremic Arteriolopathy (Calciphylaxis) by Etidronate Disodium

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A 59-year-old woman with a 10-year history of hemodialysis was admitted to our hospital for painful skin ulcers on her right thigh, right calf, and left upper arm. A whole-body plain computed tomographic scan showed diffuse calcification of the uterus and marked calcification of the mitral valve. Skin biopsy specimens from the left thigh showed calcium deposition in numerous small blood vessels in the dermis and fat, leading to a diagnosis of calcific uremic arteriolopathy (CUA). Despite antibiotic therapy and aggressive wound care for 2 months, the skin ulcers enlarged and the patient's general condition worsened. Surprisingly, oral administration of etidronate disodium (200 mg/d) strikingly improved the focal infection and decreased the size of the skin ulcers within several days. She was discharged from the hospital 2 months later, when epithelialization of the ulcers was almost complete. We report a case of CUA that was improved dramatically by treatment with etidronate. Etidronate therapy should be considered for refractory CUA. *Am J Kidney Dis* 48:151-154.

INDEX WORDS: Calcemic uremic arteriolopathy (CUA); calciphylaxis; etidronate; bisphosphonate; hemodialysis (HD); sevelamer hydrochloride; renal failure.

CALCIFIC UREMIC arteriolopathy (CUA; calcifylaxis) is a life-threatening disease that causes severe and progressive ischemic necrosis of the skin. CUA is characterized by calcium-phosphorus deposition in the media of small vessels. However, its pathogenesis is still unclear. Although CUA is seen primarily in patients with end-stage renal disease, other risk factors contribute, including obesity, female sex, diabetes, hypercalcemia, hyperphosphatemia with concomitant elevation in calcium-phosphorus (Ca × P) product, hypoalbuminemia, hyperparathyroidism, warfarin therapy, and protein C deficiency.[1,2] Despite a number of recommended therapies, including parathyroidectomy, noncalcium phosphate binders, low-calcium dialysis, and hyperbaric oxygen therapy, the prognosis of CUA is still very poor. The mortality rate of patients with CUA with skin ulcers at 6 months was reported to be 80%, and the main cause of death was sepsis.[3] In this report, we describe a patient with severe CUA that was refractory to common therapies for CUA that improved dramatically with etidronate therapy.

CASE REPORT

A 59-year-old woman with a 10-year history of hemodialysis had had painful erythema on her legs since January 2003. Despite careful local wound care, skin lesions worsened and ulcerations developed. She was admitted to our hospital on May 16, 2003. Upon admission, multiple irregular-shaped dark red lesions with necrosis were observed on her right thigh, right calf, and left upper arm (Fig 1A). All lesions were extremely tender. Body temperature was 37.5°C, and blood pressure was 162/86 mm Hg. Body mass index was 17.7 kg/m^2. A systolic murmur was audible around the cardiac apex on auscultation. Peripheral pulses were easily palpable. Blood tests showed the following values: white blood cell count, 10 × 10^3/μL (× 10^9/L); hemoglobin, 8.2 g/dL (82 g/L); platelets, 338 × 10^3/μL (× 10^9/L); albumin, 3.9 g/dL (39 g/L); calcium, 10.2 mg/dL (2.54 mmol/L); phosphate, 8.8 mg/dL (2.84 mmol/L); Ca × P product, 89.8 mg^2/dL^2 (7.21 mmol^2/L^2); potassium, 4.4 mEq/L (4.4 mmol/L); total cholesterol, 197 mg/dL (5.09 mmol/L); glucose, 103 mg/dL (5.7 mmol/L); and C-reactive protein, 161 mg/L (normal range, <3 mg/L). Intact parathyroid hormone level was 34 pg/mL (34 ng/L; normal range, 10 to 50 pg/mL), and bone-specific alkaline phosphatase level was 21.4 U/L (normal range, 9.6 to 35.4 U/L). Antinuclear antibody, myeloperoxidase antineutrophil cytoplasmic antibody, and lupus anticoagulant were all negative. Protein C level was in the

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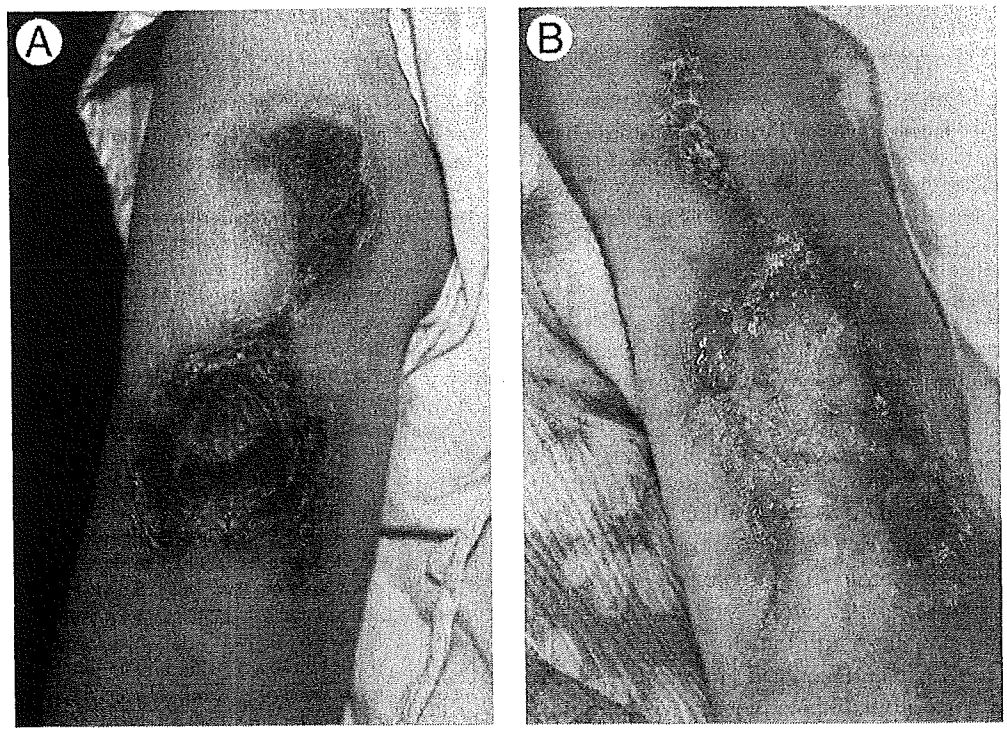

Fig 1. Photographs of the left upper arm on (A) admission and (B) discharge showing dramatic improvement in skin ulcers with etidronate disodium treatment.

normal range. A whole-body plain computed tomographic scan showed diffuse calcification of the uterus and marked calcification of the mitral valve.

Although 3.5 g/d of calcium carbonate was prescribed before admission, serum phosphate level and Ca × P product were high (70 to 90 mg^2/dL^2 [5.6 to 7.2 $mmol^2/L^2$]). After admission, the patient was treated with intravenous antibiotics and underwent daily wound care using local antibiotic ointment and enzymatic débridement agents. Skin biopsy specimens from the left thigh showed calcium deposition in numerous small blood vessels in the dermis and fat, leading to a diagnosis of CUA. Five weeks after admission, serum phosphate and Ca × P product values decreased to 5 to 5.5 mg/dL (1.6 to 1.8 mmol/L) and 50 mg^2/dL^2 (4 $mmol^2/L^2$), respectively. Antibiotics were changed according to culture results from swabs of the skin ulcers, and repeated surgical débridement was performed (Fig 2). However, skin ulcers enlarged and local infection continued.

In July, spiking fevers, general fatigue, appetite loss, and hypotension developed and worsened. We decided to start oral administration of etidronate disodium (200 mg/d for 14 days) on July 21 because the effectiveness of bisphosphonate therapy was shown for the treatment of calciphylaxis in rat models. Surprisingly, within several days, the skin ulcer infection started to improve. Moreover, fever disappeared and C-reactive protein values decreased rapidly. Ten days after the beginning of etidronate therapy, on August 1, the size of the skin ulcers decreased significantly, and necrotic tissue was almost completely eliminated. To obtain an additional decrease in serum calcium level and Ca × P product, sevelamer was prescribed instead of calcium carbonate on August 2. Because epithelialization of the ulcers was almost complete (Fig 1B), the patient was discharged from our hospital on September 24.

DISCUSSION

Bisphosphonates, synthetic compounds characterized by a P-C-P group, have been used mainly to inhibit bone resorption in patients with such diseases as osteoporosis, Paget disease, and hypercalcemia associated with malignancy. This suppression of bone resorption is believed to be caused by a cellular effect involving both apoptosis of osteoclasts and destruction of the osteoclastic cytoskeleton, thus inducing a decrease in osteoclast activity.[4] However, because of an additional property of inhibiting calcium phosphate crystal formation, bisphosphonates were used as inhibitors of ectopic calcification, such as fibrodysplasia ossificans progressiva, and heterotopic ossification after spinal cord injury and total hip replacement since the 1960s. In addition, the efficacy of bisphosphonates to inhibit calcification in 2 different types of vascular disease, atherosclerosis[5] and calciphylaxis,[6-8] also was

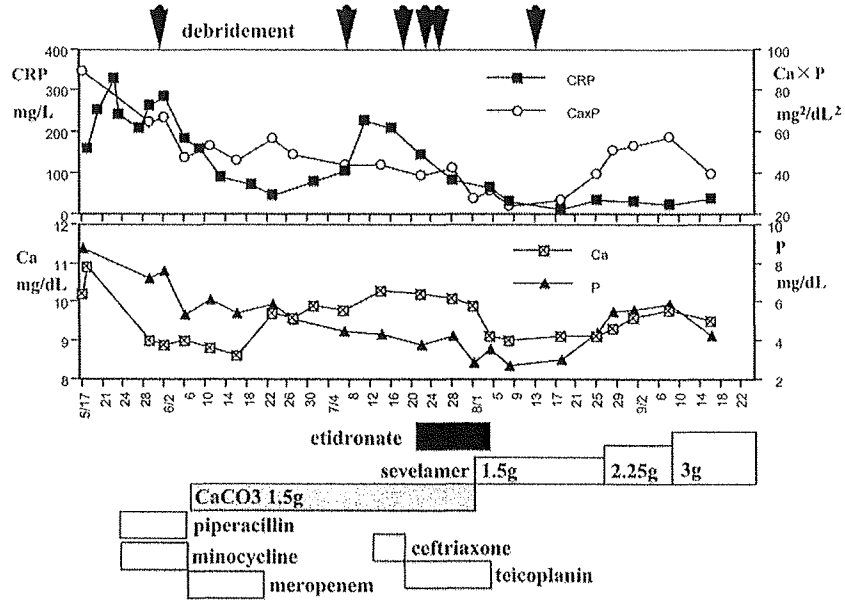

Fig 2. Schematic representation of the patient's clinical course. To convert calcium in mg/dL to mmol/L, multiply by 0.2495; phosphate in mg/dL to mmol/L, multiply by 0.3229; Ca × P product in mg^2/dL^2 to $mmol^2/L^2$, multiply by 0.0806.

shown in animal models. When this patient presented to us, no reports were available regarding the treatment of human CUA by using bisphosphonates. Although several differences were found between calciphylaxis in animal models and human CUA,[9] we expected that bisphosphonates also might have a favorable effect on human CUA.

Several bisphosphonates have been developed to date, and they can be divided into 3 groups according to the structure of their side chains and their potency to inhibit bone resorption.[4] The second- and third-generation compounds are 1 to 10,000 times more powerful than the first-generation compounds in preventing bone resorption, but are relatively less potent in inhibition of calcium phosphate crystal formation. We chose etidronate, which belongs to the first generation, because of its strong inhibitory effect on calcification.

After orally administered etidronate is absorbed in the body, some is taken up by bone and the rest is excreted unchanged in urine. Therefore, accumulation of etidronate in patients with renal insufficiency is anticipated.[10] Thus, we administered etidronate, 200 mg/d, for 14 days to this patient according to the regimen used for treatment of osteoporosis in our country. Surprisingly, dramatic clinical effects were observed within several days, and oral administration of etidronate was discontinued as scheduled. The effect of etidronate appeared to continue after it was stopped. No apparent adverse effects were observed. Very recently, inhibition of coronary artery and aortic calcification in hemodialysis patients was reported by using etidronate.[11,12] Although 200 mg of etidronate was administered to 35 patients for 14 days and this cycle was repeated 3 times every 90 days in the former report, the same amount of etidronate was administered to 18 patients 3 times a week when dialysis was conducted for 6 months in the later report. No adverse effects were observed in either study.

Because beneficial effects of orally administered etidronate in this patient were observed within several days, it is unlikely that this effect was a result of the changes in serum calcium or phosphate values. Phanish et al[13] reported rapid improvement in systemic inflammatory response and pain accompanied by ectopic calcification within several days by using bisphosphonate. In addition, after we treated this patient, a case report of successful pamidronate therapy for human CUA was published.[14] In this report, 30 mg of pamidronate was administered intravenously several times, and significant improvements in pain and C-reactive protein levels were observed 48 hours after the first injection. The pathogenesis of CUA still is not clear. However, it is speculated that inflammatory changes might contribute to the development of CUA to some

extent.[15] Because several studies showed that bisphosphonates have inhibitory effects on macrophage activity and local proinflammatory cytokine production,[16,17] this anti-inflammatory effect may have had an important role in the rapid improvement in clinical condition in our patient.

In this report, we describe a case of severe CUA that was resistant to aggressive wound care and administration of antibiotics, but that dramatically improved with etidronate therapy. Although only 1 report is available regarding the treatment of human CUA by bisphosphonates to date, this case suggests that bisphosphonates may be an effective treatment in some cases of CUA. Additional studies are required to investigate the efficacy of different types of bisphosphonates and determine appropriate doses and duration of administration of bisphosphonates for the treatment of patients with CUA.

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Intractable wounds caused by calcific uremic arteriolopathy treated with bisphosphonates

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Background: Calcific uremic arteriolopathy (calciphylaxis) is a calcification syndrome that predominantly affects relatively small vessels and is a life-threatening entity usually seen in patients with end-stage renal disease. Intractable skin necrosis sometimes causes lethal sepsis because it progresses rapidly as a result of mechanical stress.

Objective: We sought to investigate the efficacy of etidronate disodium (bisphosphonates) in treating intractable ulcers occurred in a patient on hemodialysis accompanied with calcific uremic arteriolopathy.

Methods and Results: A 53-year-old patient receiving hemodialysis with chronic renal failure accompanied with calciphylaxis had bilateral leg ulcers caused by minor trauma. The aggressive debridement worsened his skin condition as is usually seen in pyoderma gangrenosum. It eventually healed by lowering calcium-phosphorus levels with the administration of bisphosphonates and with the continuous use of sevelamer hydrochloride.

Limitations: This study reporting a single case limits the interpretation of results.

Conclusion: Bisphosphonates may be effective in treating calciphylaxis and arteriosclerosis obliterans by reducing the formation of ectopic calcification around blood vessels. (J Am Acad Dermatol 2007;57:1021-5.)

Patients with chronic renal failure receiving hemodialysis (HD) usually have other serious disorders including diabetes mellitus, arteriosclerosis obliterans, and calcific uremic arteriolopathy (CUA) (calciphylaxis). Extreme care is necessary to avoid skin ulcerations because amputation of lower extremities can be observed as a result of the intractability of the wounds.

CUA (calciphylaxis) is a calcification syndrome that predominantly affects relatively small vessels and is a life-threatening entity usually seen in patients with end-stage renal disease.[1,2] The cutaneous manifestation of CUA begins as a painful, purplish, mottled lesion similar to livedo reticularis that eventually becomes an ischemic necrosis with gray-black eschars and gangrene of the surrounding tissues.[3] Although wide local excision has been reported to successfully treat CUA,[4] the role of debridement is controversial.[2] It has been suggested that debridement is contraindicated for wounds covered with dry, noninfected eschars.[5] Minor local tissue injury triggers the development of skin lesions at the injection sites including insulin.[6]

CASE REPORT

A 53-year-old Japanese man with chronic renal failure caused by diabetic nephropathy had been on HD for 4 years. The patient had a history of mitral valve replacement performed in 2003. The patient stated that the ulcers on the lower aspect of his right leg appeared because of an abraded wound after he removed a piece of adhesive tape in February 2006. A bruise of his left leg had triggered the formation of the new ulcers in May 2006. The intractable ulcers had been diagnosed as pyoderma gangrenosum in another hospital because minor trauma triggered

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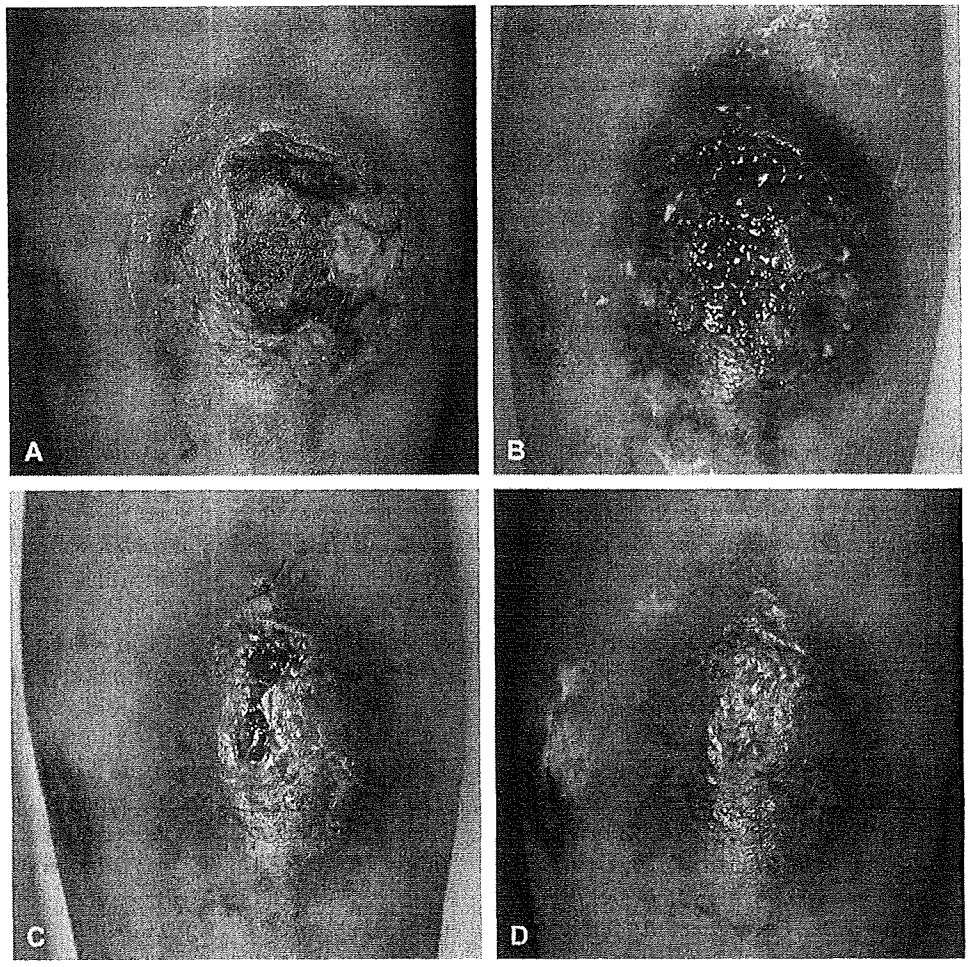

Fig 1. Lower back aspect of left leg of 53-year-old man on hemodialysis with calcific uremic arteriolopathy. **A**, Day 1 after admission; before treatment. **B**, Day 10; after debridement. **C**, Day 20; 1 week after administration of etidronate disodium (bisphosphonates). **D**, Day 33; before hospital discharge.

their generation and the patient was referred to us in May 2006.

On admission, each back region of his bilateral lower legs had ulcers with necrotic tissue, a yellowish discharge, and surrounding erythema and infiltration (Fig 1, *A*). The culture revealed no bacterial infection. The results of his laboratory examination revealed: white blood cell count, $7.4 \times 10^3/\mu L$ (3.3-9.4 $\times$ $10^3/\mu L$); hemoglobin, 11.7 g/dL (13.8-17.0 g/dL); platelet, $2.0 \times 10^3/\mu L$ (1.3-3.2 $\times$ $10^3/\mu L$); C-reactive protein, 25 mg/L (0-2 mg/L); calcium, 8.4 mg/dL (8.4-10.0 mg/dL); inorganic phosphate, 10.4 mg/dL (2.9-4.8 mg/dL); Ca x IP product 87.4 mg^2/dL^2 (24.4-48.0 mg^2/dL^2); hemoglobin A1c, 5.1% (4.3%-5.8%); immunoglobulin, 1420 mg/dL (870-1700 mg/dL); IgA, 379 mg/dL (110-410 mg/dL); IgM, 45 mg/dL (35-220 mg/dL); and parathyroid hormone, 224.6 pg/mL (10-60 pg/mL). Each parenthesis indicates normal values. Test results were all negative for antinuclear antibody, p-ANCA, c-ANCA, anticardiolipin antibody, anti Sjoögren's syndrome antibody-A, -B, antiphospholipid antibody, ACL-β2, and anti-DNA antibody. Systemic plain computerized tomography and radiographs revealed a severe calcification of his major blood vessels including the aorta and coronary arteries and of the peripheral arteries of his bilateral lower legs, toes, and forearms (data not shown). A skin biopsy specimen from the lower back aspect of his left leg ulcer revealed calcification of small veins in the dermis and calcium deposits in the subcutaneous adipose tissue as determined by hemotoxylin-eosin and von Kossa's staining (Fig 2).

We gave the patient the diagnosis of CUA from his condition with chronic renal failure on HD. We debrided the necrotic tissue with a scalpel under local anesthesia quite aggressively and the debridement triggered an exacerbation of all the debrided ulcers (Fig 1, *B*). We then applied a mild debridement

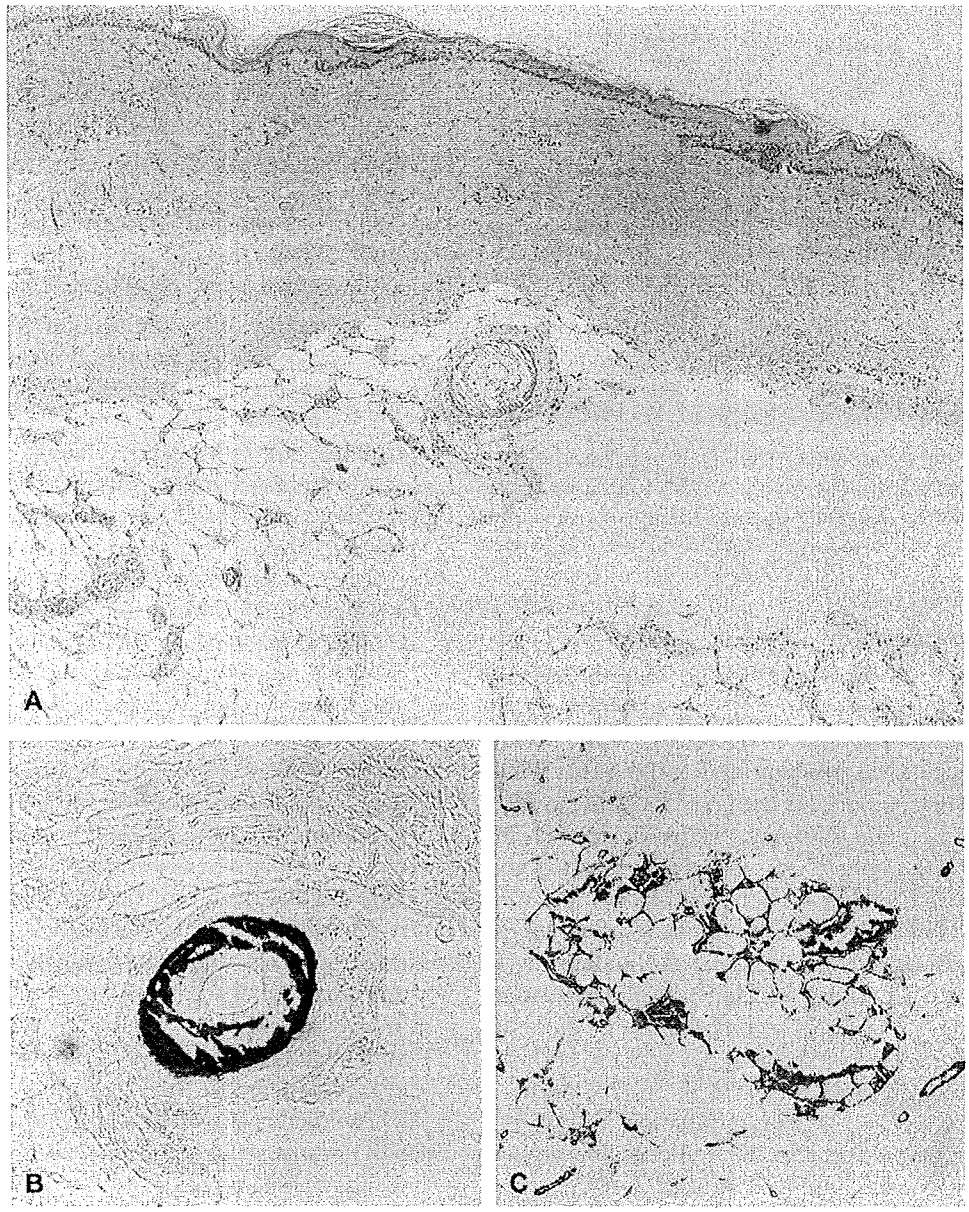

Fig 2. Histology of biopsy specimen from ulcer on lower back aspect of left leg. **A**, Hemotoxylin-eosin staining indicates calcium-phosphorus deposits on basophilic vascular wall. (Original magnification: ×40.) von Kossa's staining revealed blackish calcium-phosphorus deposits in vascular wall (**B**) and subcutaneous fat (**C**). (**B** and **C**, Original magnifications: **B**, ×100; **C** ×40.)

technique with local wound care using sulfadiazine silver. We tried lowering the calcium-phosphorus levels according to recent reports (Fig 3).[2,3,7] At first, we increased the dialyzer size and extended the dialysis time and increased the dosage of sevelamer hydrochloride from 5 to 9 g/d to absorb phosphorus. We administered cathartics to promote phosphorus discharge. Finally, we used etidronate disodium (200 mg/d for 14 days)[8-11] after informed consent was obtained. Informed consent was necessary because the renal clearance of risedronate, another type of bisphosphonate, is related to a decrease in renal function.[12] These therapies effectively lowered the calcium-phosphorus levels and all leg ulcers immediately decreased in sizes especially after the use of bisphosphonates (Fig 1, *C*). The value of parathyroid hormone did not change remarkably. All of his wounds had re-epithelialized completely by the time of his hospital discharge on August 4, 2006 (Fig 1, *D*).

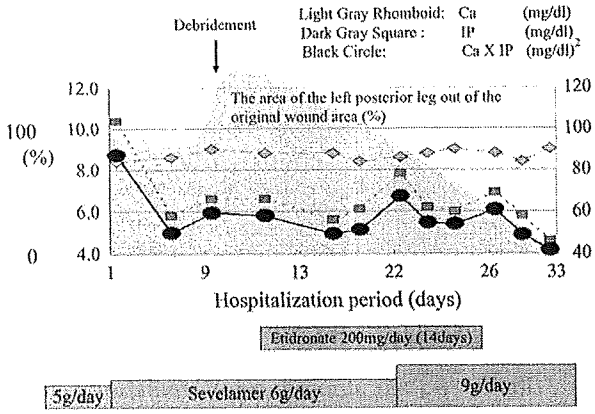

Fig 3. Clinical time course. The x-axis indicates the days after hospitalization. The y-axis indicates the area of the left posterior leg out of the original wound area (0-120%), serum calcium (Ca) and inorganic phosphates (IP) (0-12.0 mg/dl), and Ca × IP (0-120 mg^2/dl^2).

DISCUSSION

CUA is a devastating limb- and life-threatening condition with progressive and intractable necrosis that occurs in patients with chronic renal failure. Patients with CUA are reported to be at an 8-fold increased risk of mortality compared with the general population on HD, the major cause of death being infection and sepsis.[13] Russell et al[7] reported that lowering of elevated serum phosphorus, calcium, and Ca x IP levels, together with aggressive wound care, contributes to the successful outcome of patients with CUA. Don and Chin[3] developed a treatment strategy that used a combination of therapies based on reducing the known risk factors for development of CUA and the use of the following treatment modalities: (1) discontinuation of all oral calcium supplements and calcium-containing phosphate binders; (2) administration of a noncalcium-, nonaluminum-containing phosphate binder; (3) sequential lowering of the calcium concentration in the dialysate to 1.5 to 1.0 mEq/L as tolerated with close monitoring of serum calcium levels predialysis and postdialysis; (4) increase of the frequency of dialysis sessions to 5 to 6 treatments per week; (5) enrollment of the patient in a hyperbaric oxygen treatment program; (6) reservation of parathyroidectomy only for patients with markedly elevated parathyroid hormone levels; (7) consideration of treatment with an intravenous vitamin D analog in patients with markedly elevated parathyroid hormone levels who have contraindications for parathyroidectomy; and (8) not aggressive but gentle wound debridement with local wound care. We have followed modalities 1, 2, 3, and 8 without parathyroidectomy or intravenous treatment with a vitamin D analog. We are in favor of mild debridement of necrotic tissue by CUA according to our experience treating this patient and others.

In addition we have used etidronate disodium treatment because bisphosphonates (diphosphonates) are reported to be effective for removing calcification of the carotid artery in type 2 diabetes mellitus,[14] coronary arteries,[8] and CUA. Although recent reviews also recommend bisphosphonates for treating vascular calcification, to our knowledge, this report describes only the second patient with CUA, who had remarkably improved ulcers within several days after the oral administration of etidronate disodium (200 mg/d for 14 days).[11] Etidronate disodium, an antiresorptive agent, has been established as a first-line drug for treating osteoporosis by blocking osteoclastic function. Moreover, bisphosphonates have been reported to inhibit various enzymes involved in cholesterol biosynthesis and to suppress macrophages in atheromatous lesions.[9] Bisphosphonates may inhibit ectopic calcification through a mechanism associated with the enhanced production of parathyroid hormone–related peptide from vascular smooth-muscle cells, which inhibits calcification by decreasing alkaline phosphatase activity.[15] Its suppressive effect on calcification can also be explained by the inhibition of phosphate transport by a sodium-dependent phosphate cotransporter, which leads to the increased expression of core-binding factor α subunit 1, a bone-specific transcription factor, and the subsequent elaboration of a promineralizing matrix that contains osteopontin and osteocalcin.[16] Although these mechanisms encourage the use of bisphosphonates, we must take into consideration that the administration of bisphosphonates is usually contraindicated in patients with chronic renal failure on HD.[12]

Intractable wounds result from multifactorial causes including CUA in patients on HD. As the number of patients with chronic renal failure increases, the number of leg ulcers refractory to conventional therapies is increasing. In summary, the administration of etidronate disodium (200 mg/d for 14 days) was effective in treating wounds in a patient on HD accompanied with CUA. The use of etidronate disodium may be effective in treating wounds accompanied with calcification of the artery walls including not only CUA but also arteriosclerosis obliterans. In the future, randomized controlled studies are necessary to establish the standard therapy regimen for CUA, but this option seems promising.

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研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Sugi O, Kimata N, Miwa N, Otsubo S, Nitta K, Akiba T.	Successful cinacalcet treatment of refractory secondary hyperparathyroidism due to multiple lung parathyroid adenomas	Nephrology Dialysis Transplantation Plus	3(1)	60–63	2010.
Fujii H, Kono K, Goto S, Onishi T, Kawai H, Hirata K, Hattori K, Nakamura K, Endo F, Fukagawa M.	Prevalence and cardiovascular features of Japanese hemodialysis patients with Fabry disease.	Am J Nephrol	30(6)	527-535	2009
Yokoyama K, Matsuba D, Adachi-Akahane S, Takeyama H, Tabei I, SuzukiA, Shibasaki T, Iida R, Ohkido I, Hosoya T, Suda N	Dihydropyridine- and voltage-sensitive Ca^{2+} entry in human parathyroid cells.	Experimental Physiology	94(7)	847-855	2009
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Yokoyama K,Yoshida H, Maruyama Y, Ozaki A, Yamamoto H, Hosoya T	Should the targeted value of the phosphate be reviewed lower to normal range from the viewpoint of vascular calcification?	Kidney International	(in Press)		
Ohkido I, Yokoyama K, Kagami S, Hosoya T	The hypothesis that bone turnover influenced FGF23 secretion.	Kidney International	(in Press)		
Yokoyama K, Urashima M, Ohkido I, Kono T, Yoshida T, Muramatsu M, Niu T, Hosoya T	L-type voltage-dependent calcium channel alpha subunit 1C is a novel candidate gene associated with secondary hyperparathyroidism:an application of haplotype-based analysis for multiple linked single-nucleotide polymorphisms.	Nephron Clincal Practice	(in Press)		