



Calcifying uremic arteriolopathy (calciphylaxis): incidence, clinical features and long-term outcomes

V. Esteve, J. Almirall, J. Luelmo*, A. Sáez**, X. Andreu** and M. García

Departments of Nephrology, Dermatology* and Pathology**. Corporació Sanitària Parc Taulí. Institut Universitari Parc Taulí (UAB). Sabadell.

SUMMARY

*Calcific uraemic arteriolopathy, also named calciphylaxis, is a rare but serious disorder characterized by medial mural calcification of small vessel leading to tissue ischaemia. It most commonly occurs in end stage renal disease patients on dialysis or recently received renal trasplant with chronic nephropathy allograft. The pathogenesis of calciphylaxis is poorly understood. Abnormalities in mineral metabolism are clearly involved, but the specific factors that induces this disorder are not completely known. **Objectives:** Describe the main clinical features, outcomes and follow up of all calciphylaxis cases recorded in our dialysis unit in order to analyse the incidence, the main biologic parameters and the therapeutic background in wich calciphylaxis appeared. **Material and methods:** We performed a descriptive study about all the calciphylaxis cases diagnosed at our dialysis unit beetwen the years 1991 and 2005. **Results:** 8 cases, 6 women. Mean age: 65.3 years. All the patients were on haemodialysis treatment (one previous renal trasplant). Mean time on dialysis was 76.6 months. Cumulative incidence was 1.17%. The principal end stage renal disease aethiology was neprhoangioesclerosis in four patients. Secondary hiperparatyroidism was present in 4 patients and 2 of them had been paratyroidectomized previously. A second cutaneus biopsy was needed for correct diagnosis in 3 patients. Calciphylaxis distal lesions were present in 7 patients. Two cases required urgent paratyroidectomy in order to control calciphylaxis. Only in 2 cases a Ca x P product > 60 mg/dL was present and 3 cases had PTHi values higher than 300 pg/mL. Calcium phospate binders and vitamin D were present in 2 and 4 cases, respectively. One patient with proximal calciphylaxis died due to skin injury infection. **Conclusions:** Calciphylaxis is a rare disorder but not exceptional, related to end stage renal disease patients. The diagnosis requires a high clinical suspicion, beeing sometimes dificult to distinguish from other entities in spite of pathological study. Proximal distribution of calciphylaxis had worst prognostic. Metabolic disorders and therapeutics background were not different from other patients included in dialysis treatment.*

Key words: **Calciphylaxis. Renal disease. Dialysis.**

Correspondence: Vicente Esteve Simó
Consorci Sanitari de Terrassa
Ctra. Torrebonica, s/n
08227 Terrassa (Barcelona)
E-mail: viesi@hotmail.com

ARTERIOLOPATÍA URÉMICA CALCIFICANTE (CALCIFILAXIS): INCIDENCIA, FORMAS DE PRESENTACIÓN Y EVOLUCIÓN

RESUMEN

La arteriopatía urémica calcificante, también conocida como calcifilaxis, es una entidad caracterizada por la presencia de áreas de necrosis isquémica junto con extensas calcificaciones de la capa media de las arteriolas dermoepidérmicas. Fundamentalmente se desarrolla en pacientes con insuficiencia renal en diálisis o trasplantados con disfunción del injerto. Aunque las alteraciones propias del estado urémico y del metabolismo calcio-fósforo son importantes, su etiopatogenia es compleja; siendo los mecanismos desencadenantes poco conocidos. **Objetivos:** Describir las formas de presentación y evolución de los casos de calcifilaxis diagnosticados en nuestra unidad de diálisis. Calcular la incidencia y analizar el contexto biológico y terapéutico previo al episodio de calcifilaxis. **Material y métodos:** Análisis descriptivo de todos los casos de calcifilaxis diagnosticados en nuestra unidad durante el período comprendido entre 1991-2005. **Resultados:** 8 casos, 6 mujeres. Edad media: 65,3 años. Todos los pacientes incluidos en programa de Hemodiálisis (1 trasplante renal previo). Tiempo medio en diálisis de 76,6 meses. La incidencia acumulada fue de 1,17%. La principal etiología de la IRC fue la Nefroangioesclerosis (4 pacientes). Existía antecedentes de hiperparatiroidismo secundario en 4 pacientes, con paratiroidectomía previa en 2 de ellos. En 3 pacientes el diagnóstico requirió una segunda biopsia cutánea. La distribución de las lesiones fue distal en 7 casos. En 2 casos se practicó paratiroidectomía urgente para el control de las lesiones. Tan sólo 2 casos presentaban producto Calcio-fósforo > 60 mg/dL y 3 casos cifras de PTHi > 300 pg/mL. 2 casos tomaban quelantes cálcicos y 4 suplementos de vitamina D. Un paciente con distribución proximal de las lesiones fue exitus por sobreinfección de las mismas. **Conclusiones:** La calcifilaxis es un proceso infrecuente. El diagnóstico requiere de una alta sospecha clínica, siendo en ocasiones difícil de distinguir de otros procesos. La localización a nivel proximal confiere un peor pronóstico a las lesiones. Las alteraciones metabólicas y conductas terapéuticas son indistinguibles de las que presentan el resto de pacientes sometidos a diálisis.

Palabras clave: **Calcifilaxis. Insuficiencia renal. Diálisis.**

INTRODUCTION

La calcifying uremic arteriopathy, also known as calciphylaxis, is a clinical condition characterized by the presence of ischemic necrotic areas together with vast calcifications of the intermediate layer of the dermoepidermal arterioles. It mainly develops in renal failure patients on dialysis or transplanted patients with graft dysfunction.^{1,2} Although the impairments due to the uremic status and the calcium-phosphate metabolism are important, the pathogenesis is complex with little known triggering mechanisms.

There is the impression that in recent times we are witnessing an increase in the number of cases of calciphylaxis, probably in relation to the increase in the therapy with vitamin D analogues and calcium-based

phosphate chelating agents to manage severe hyperparathyroidism.³ In our study, we analyze the incidence, clinical presentation, and progression of calciphylaxis cases diagnosed at our Unit in the period 1991-2005.

MATERIAL AND METHODS

A descriptive analysis was done of all patients included into the dialysis program at our center and that had presented throughout their time on dialysis therapy skin lesions diagnosed as calciphylaxis, during the period comprised between January of 1991 and March of 2005.

We gathered the data on demographics, pathology, associated morbidity, presence of predisposing drugs

Table I. Main demographics, etiology, comorbidity, and predisposing drugs for calciphylaxis

Age	Gender	Etiology	RRT	Months on RRT	Predisposing drugs	Biopsy	Locations	PTX	Lesions course	Follow-up	Cause of death
74	M	NAS	CAPD(9) HD(12)	21	AHT, OAC, PDN	2	1/3 DISTAL LL	NO	HEALED	EXITUS	UK
59	M	NAS	HD	72	HPTH, AHT	1	1/3 DISTAL LL	NO	HEALED	HD	
76	F	NAS	HD CAPD(53)	132	AHT, HPTH (PTX)	1	1/3 DISTAL LL	NO	HEALED	EXITUS	MI
41	F	PCRD	HD(144) RTx(48)	245	AHT, HPTH (PTX)	1	Upper foot I	NO	HEALED	EXITUS	UK
75	F	NAS	HD	48	HPTH	1	1/3 DISTAL LL	YES	HEALED	HD	
54	F	CGN	HD	48	AHT, PDN	1	ABDOMINAL	YES	EXITUS		Sepsis
78	F	Unknown	HD	23		2	1/3 DISTAL LL	NO	HEALED	EXITUS	CVA
66	F	CPN	HD	24	AHT	2	KNEE RLL	NO	HEALED	EXITUS	Sepsis

RRT: Time on renal replacement therapy (months); M: male; F: female; NAS: nephroangiosclerosis, PCRD: polycystic renal disease, CGN: chronic glomerulonephritis, CPN: chronic pyelonephritis, HD: hemodialysis, CAPD: peritoneal dialysis, RTx: renal transplant, OAC: oral anticoagulants, PDN: corticosteroids, HPTH: hyperparathyroidism, PTX: parathyroidectomy, MI: mesenteric ischemia, CVA: Cerebrovascular accident. UK: Unknown.

(corticosteroids, oral anti-coagulants), the features of renal replacement therapy, and the clinical course of the patients. The laboratory data analyzed included biochemical parameters about renal osteodystrophy (serum values of calcium, phosphate, iPTH, alkaline phosphatase, and aluminum), the nutritional status (albumin, proteins), and the main hematological variables. We could not get the data pertaining to the patients' hypercoagulability study (protein C and S, lupus anti-coagulant). The diagnosis was based on the finding of calcifications at the intermediate layer of the dermoepidermal arterioles on the pathological study. The biological and therapeutic settings during which the calciphylaxis episode occurred were considered, as well as further progression of the lesions after implementing treatment.

RESULTS

During the fifteen years analyzed, 8 cases in total were diagnosed as having calciphylaxis. During this time, the number of patients included in the hemodialysis program of our Unit was 680, with a cumulative incidence for calciphylaxis of 1.17% (8 cases/680 dialysis patients). Six (75%) of the cases diagnosed occurred between 1995 and 1999, whereas the remaining cases occurred between 2003 and 2004.

Table I shows in detail the main clinical characteristics of the calciphylaxis cases. Mean age of the cases was 65.3 years, with an average time on dialysis program of 76.6 months. A total of 6 cases (75%) were

women, and the main etiology of renal failure was nephroangiosclerosis that occurred in 4 patients (50%). At the time the calciphylaxis episode occurred, all patients were included in regular dialysis program, although two patients had previously received peritoneal dialysis (CAPD) and one patient had previously received renal transplant from a dead donor. Among the predisposing factors, 2 patients were on regular oral corticosteroid therapy and 1 patient was receiving chronic therapy with oral anti-coagulants due to chronic atrial fibrillation. Four patients (50%) had a personal history of secondary hyperparathyroidism, two of them having required parathyroidectomy before the diagnosis of calciphylaxis was done. In all cases, the diagnosis was made by skin biopsy, and in three cases a second biopsy was required since initial pathological findings posed other differential diagnoses. Seven patients (88%) presented lesions located in the third distal region of the lower limbs, whereas the remaining case had widespread calciphylaxis lesions at the abdomen (fig. 1).

Table II shows the main biochemical parameters analyzed and the treatment used for calcium-phosphate metabolism management before the occurrence of the lesions. In one patient the analytical data were not available when reviewing the clinical chart. Mean serum calcium and phosphate values were 10.17 and 4.54 mg/dL, respectively, with mean calcium-phosphate product of 44.25 mg/dL. The mean value of inhibited parathyroid hormone (iPTH) was 340 pg/mL. Only 2 patients had calcium-phosphate product higher than 60 mg/dL and in three cases the iPTH values were higher than 300 pg/mL.

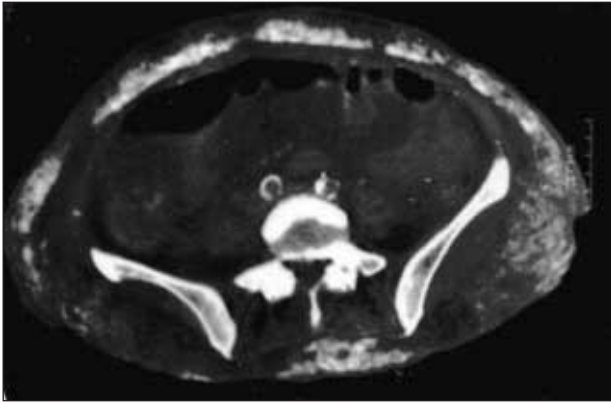


Fig. 1.—Abdominal CT scan: Calciphylaxis with proximal distribution. Widespread distribution of calcium depositions at the abdominal wall.

About patients' therapy before the calciphylaxis episode, 1 patient was on combined triple therapy with oral vitamin D supplements, calcium-based chelating phosphate agents, and aluminum hydroxide; 1 patient was on double combine therapy with vitamin D and calcium-based phosphate chelating agents; 2 cases were treated with calcium carbonate and aluminum hydroxide, and 2 patients received with just one of the drugs previously mentioned. The concentration of the dialysis bath was for all cases 3.5 mmol/L. These therapeutic schedules were not different from those received by the remaining patients on dialysis program.

The clinical course of the calciphylaxis episode was satisfactory in 7 cases after antibiotic coverage and comprehensive local management of the skin lesions. Two patients with a previous history of hyperparathyroidism required urgent parathyroidectomy for controlling the skin lesions. One patient with widespread distribution of the skin lesions at the proximal regions died during the calciphylaxis episode due to poor clinical course and superinfection of the skin lesions with *Pseudomonas aeruginosa*. Later on, five patients that still were on regular hemodialysis program died because of complications associated with their clinical condition of end-stage renal failure, once the calciphylaxis episode had been resolved in a mean time of 19.5 months (1 cerebrovascular accident, 1 massive mesenteric ischemia, 1 septic process, 2 of unknown cause). The remaining two patients still are on hemodialysis program.

DISCUSSION

Calciphylaxis is an entity characterized by the presence of areas of ischemic necrosis together with vast

calcifications of the intermediate layer of dermoepidermal arterioles essentially developing in patients with end-stage renal failure or renal transplanted patients with graft dysfunction, although isolated cases not associated to renal failure have been described.^{1,2,4-6} It was first described by Selye in 1962, while experimentally observing the occurrence of tissue calcifications and local inflammatory signs in rat tissues previously sensitized to drugs such as PTH and vitamin D.⁷

Calciphylaxis is a rare entity, with an estimated annual incidence of about 1% according to the data found in the literature.^{8,9} In our work, the cumulative incidence for calciphylaxis is comparable to that obtained in previous studies and in spite of being a rare condition, there seems to exist a trend to diagnose more cases at the end of the 1990s. This trend may have some relationship with an increase in therapies using vitamin D analogues and calcium-based phosphate chelating agents; however, this increase may have been lessened likely due to better management of severe hyperparathyroidism with new therapeutic agents together with a better knowledge on calcium-phosphate metabolism impairments. After the recent introduction of calcimimetic agents for managing severe hyperparathyroidism, not available at the time of writing this manuscript, it would not be surprising that in the future these drugs may be a novel and beneficial therapeutic armamentarium for managing these skin lesions.

The etiopathogenic mechanism of calciphylaxis is poorly understood. Mineral metabolism impairments such as severe hyperparathyroidism, elevated calcium-phosphate product, and sustained hyperphosphatemia might have an important although insufficient role since there are cases with no mineral metabolism impairments. Thus, there should be other factors explaining facts such as the little presence of calciphylaxis in patients with important associated calcification of the vessel and tissues.^{6,10-12} Among risk factors for developing calciphylaxis female gender, smoking status, diabetes mellitus, peripheral vascular insufficiency, protein-caloric malnourishment, liver cirrhosis, the use of oral anticoagulants, estrogens, vitamin D, and immunosuppressants, and the deficit of specific proteins (protein C, protein S, Fetuin A, anti-thrombin III).¹³⁻¹⁵ In our series, previous comorbid conditions, calcium-phosphate metabolism impairments (2 patients with CaxP product > 60, and 3 patients with iPTH > 300 mg/dL) and the treatment used did not show important differences when compared with the metabolic and mineral profile, as well as the treatments used by the remaining patients in the conventional dialysis program.

Table II. Main analytical parameters in calciphylaxis

Ca (mg/dL)	P (mg/dL)	CaxP (mg/dL)	iPTH (pg/MI)	Alu (ug/L)	AP (U/L)	Alb (g/l)	Treatment	HD bath
9.4	2.7	25.3	74	116	93	23.7	Vit D, ALOH3, CaCO3	3.5
9.8	2.9	28.4	580	60	106	39.3	Vit D, ALOH3	3.5
9.9	3.8	37.6	62	8.3	157	41.4	Vit D, CaCO3	3.5
9.4	4.4	40.5	14	50.9	219	38	ALOH3	3.5
10.6	5.9	62.5	1,026	27	709	48	CaCO3	3.5
8.8	8.1	71.3	489		520	31	Vit D, ALOH3,	3.5
-	-	-	-	-	-	-	-	-
13.5	4	54	128		178			3.5

Ca: calcium, P: phosphate; CaxP: calcium-phosphate product, iPTH: parathyroid hormone; Alu: aluminium, AP: alkaline phosphatase; Alb: albumin.

The clinical manifestations include the presence of lesions, often times triggered by mild trauma, initially as purpura, livedo reticularis, or painful skin nodules that may evolve to ischemic necrotic ulcers and formation of superinfected scars, mainly distributed in areas of abundant cellular subcutaneous tissue, such as muscles, skin folds, and the abdominal wall.^{6,16}

A high clinical suspicion index is required for early diagnosing calciphylaxis, although the definitive diagnosis will be confirmed after the pathological study. The performance of skin biopsies has been a matter of debate due to the risk for superinfection or local dissemination of the ulcer; so for, a conservative approach should be considered in relation to skin biopsy. This will be reserved for those cases posing difficulties in the differential diagnosis with other conditions such as metastatic calcinosis metastásica, disseminated intravascular coagulation, systemic vasculitis, atherothrombotic disease, cryoglobulinemia, anti-phospholipid syndrome, dicoumarinic-induced necrosis, or infectious endocarditis. Deep skin biopsy will show the presence of calcifications in the intermediate layer of the dermoepidermal arterioles, together with local ischemic phenomena in the absence of other signs of vasculitis.^{1,4,16} In some instances, local ischemic phenomena that appear in ulcerated areas contain histological findings similar to those found in systemic vasculitis, such as hematic leakage, polymorphonuclear leukocytic infiltration within the vascular wall, or the presence of fibrinoid necrosis, which renders the diagnosis of calciphylaxis extremely difficult. For this reason, biopsy should be taken from peripheral sites of the lesion and not from the ulcerated lesion itself. On the other hand, since the calcium deposition at dermoepidermal arterioles may be very localized, we should serialize and thoroughly examine the histological sample in order to increase the diagnostic sensitivity of the biopsy. In many cases, the suspicion diagnosis was based on the presence of

compatible skin lesions and, in all cases, histological confirmation was obtained. We should, however, point out that a total of 11 biopsies were taken since in 3 patients a second biopsy was required because the first one posed a differential diagnosis with other chronic inflammatory entities, mainly small-vessel vasculitis. These facts highlight the serious difficulty that entails diagnosing this entity, even for qualified professionals.

From the therapeutic perspective, there is no specific therapy for calciphylaxis. The time elapsed since the onset of the lesions, the proximal location, and the involvement of soft tissues seem to be unfavorable prognostic factors in the course of the lesions.^{16,17} Usually, the prognosis is poor in those wounds with torpid course and superinfection, implicating a high associated mortality rate. Prevention of the lesions, based on analgesic therapy, specific and careful cures of the wounds, and prevention of trauma or local injections, seem to be fundamental measures in further progression of the lesions. The classical measures used include correcting calcium-phosphate metabolism impairments, avoiding the use of vitamin D and calcium-based chelating agents, doing hemodialysis sessions with dialyzate solutions poor in calcium, and even performing urgent parathyroidectomy in those cases needing so.^{2,4,18-20}; however, there are reported cases in which the lesions persisted even months after the parathyroidectomy in spite of having low levels of iPTH. Among the most novel therapies, based on the experience in sporadic cases, we may include, among others, the use of hyperbaric oxygen chambers, diphosphonates, pentoxifylline, use of sterile larvae, and sodium tri-sulfate.²¹⁻²⁴ In this sense, we should not forget the evident improvement in recent years of comorbid conditions such as hyponutrition, as well as the close follow-up of ulcerated lesions and their complications, thus preventing aggressive surgical treatment that would worsen the

vital patient's prognosis. In our series, the clinical course was favorable in most of the cases; this may be likely due to early diagnosis based on high clinical suspicion index, the therapy used (antibiotic therapy, comprehensive and prolonged debridements, urgent parathyroidectomy in two cases), and the distal location of the lesion, although one patient with vast involvement of the abdominal wall died because of wound superinfection, confirming the poor prognosis in extent lesions at proximal sites.

In summary, we present our experience through a long period of time in managing a rare condition; we would like to highlight the need for a high suspicion index for its diagnosis in spite of the typical presentation since the metabolic impairments and therapeutic approaches used in these patients are undistinguishable from those existing in other dialysis patients, as well as the fact that, once the diagnosis has been established, a comprehensive multidisciplinary therapeutic approach is required for managing the lesions and preventing wound superinfection.

REFERENCES

- Coates T, Kirkland GS, Dymock RB et al.: Cutaneous necrosis from calcific uremic arteriopathy. *Am J Kidney Dis* 32: 384-91, 1998.
- Janigan DT, Hirsch DJ, Klassen GA, Mac Donald AS: Calcified subcutaneous arterioles with infarct of the subcutis and skin (calciophylaxis) in chronic renal failure. *Am J Kidney Dis* 35: 588-97, 2000.
- Fine A, Zacharias J: Calciophylaxis is usually non-ulcerating: Risk factors, outcome and therapy. *Kidney Int* 61: 2210-7, 2002.
- Gipstein RM, Coburn JW, Adams DA et al.: calciophylaxis in man: a syndrome of tissue necrosis and vascular calcification in 11 patients with chronic renal failure. *Arch Intern Med* 136: 1273-80, 1976.
- Fader DJ, Kang S: Calciophylaxis without renal failure. *Arch Dermatol* 132, 837-8, 1996.
- Budisavljevic MN, Cheek D, Ploth DW: Calciophylaxis in chronic renal failure. *J Am Soc Nephrol* 7: 978-82, 1996.
- Seyle H, Gabbiani G, Strebel R: Sensitization to calciophylaxis by endogenous parathyroid hormone. *Endocrinology* 71: 554-59, 1962.
- Angelis M, Wong LL, Myers SA, Wong LM: Calciophylaxis in patients on hemodialysis: a prevalence study. *Surgery* 122: 1083-9, 1997.
- Levin A, Metha RL, Goldstein MB: Mathematical formulation to help identify the patient at risk of ischemic tissue necrosis—a potentially lethal complication of chronic renal failure. *Am J Nephrol* 13: 448-53, 1993.
- Llach F: Calcific uremic arteriopathy (calciophylaxis): an evolving entity? *Am J Kidney Dis* 32: 514-8, 1998.
- Mazhar AR, Johnson RJ, Gillen D, Stivelman JC, Ryan MJ, Davis CL, Steham-Breen CO: Risk factors and mortality associated with calciophylaxis in end stage renal disease. *Kidney Int* 60 (1): 324-32, 2001.
- Easary LR, Wick MR: Cutaneous calciophylaxis. An underrecognized clinicopathologic entity. *Am J Clin Pathol* 113 (2): 280-7, 2000.
- Mehta RL, Scott G, Sloand JA, Francis CW: Skin necrosis associated with acquired protein C deficiency in patients with renal failure and calciophylaxis. *Am J Med* 88 (3): 252-57, 1990.
- Schafer C, Heiss A, Schwarz A et al.: The serum protein alpha 2-Heremans-Schmid glycoprotein/fetuin A is a systematically acting inhibitor of ectopic calcification. *J Clin Invest* 112 (3): 357-66, 2003.
- Pérez Mijares R, Guzmán Zamudio JL, Payán López J, Rodríguez Fernández A, Gómez Fernández P, Almaraz Jiménez J. Calciophylaxis in a haemodialysis patient: functional protein S deficiency? *Nephrol Dial Transplant* 11 (9): 1856-9, 1996.
- Roe SM, Graham LD, Brock WB, Barker DE: Calciophylaxis: early recognition and management. *Am Surg* 60: 81-6, 1994.
- Chan YI, Mahony JF, Turner JJ, Possen S: The vascular association with skin necrosis in renal disease. *BR J Dermatol* 109: 85-95, 1983.
- Campistol JM, Almirall J, Martin E, Torras A, Revert L: Calcium—carbonate—induced calciophylaxis. *Nephron* 51; 549-50, 1989.
- Duh QY, Lim RC, Clark OH: Calciophylaxis in secondary hyperparathyroidism. Diagnosis and parathyroidectomy. *Arch Surg* 126: 128-19, 1991.
- Don BR, Chin Ai: A strategy for the treatment of calcific uremic arteriopathy (calciophylaxis) employing a combination of therapies. *Clin Nephrol* 59(6): 463-70, 2003.
- Vassa N, Twardowski ZJ, Campbell J: Hyperbaric oxygen therapy in calciophylaxis—induced skin necrosis in peritoneal dialysis patient. *Am J Kidney Dis* 23: 878-81, 1994.
- Cicone JS, Petronis JB, Embert CD: Successful treatment of calciophylaxis with intravenous sodium thiosulfate. *Am J Kidney Dis* 43: 1104-5, 2004.
- Picazo M, Bover J, De la Fuente J, Sans R, Cuxart M, Matas M: Sterile maggots as adjuvant procedure for local treatment in a patient with proximal calciophylaxis. *Nefrología* 25 (5): 559-62, 2005.
- Monney P, Nguyen QV, Perroud H, Descombes E: Rapid improvement of calciophylaxis after intravenous pamidronate therapy in a patient with chronic renal failure. *Nephrol Dial Transplant* 19 (8): 2130-2, 2004.