Calciphylaxis-Associated Second Renal Graft Failure and Patient Loss: a Case Report and Review of the Literature

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Abstract

Objectives: **Calciphylaxis is a small vessel disease that affects 1% to 4% of patients undergoing dialysis. Only 21 cases of postrenal transplant calciphylaxis have been reported, but none has been associated with primary graft failure or has occurred in a second graft. We present the first case of second renal graft calciphylaxis leading to primary graft failure and death.**

Materials and Methods: **We reviewed the 22 cases, including ours, and assessed risk factors, management, and mortality for these cases.**

Results: **The mean age was 34.2 ± 10.6 years, 11 patients were males (50%), and 13 (57.9%) underwent a deceased-donor renal transplant. The mean pretransplant dialysis period was 35.7 ± 39.3 months, 22 patients (100%) were on steroid therapy, 8 (36.4%) had a rejection, 18 (81.8%) underwent postcalciphylaxis parathyroidectomy, and 11 patients died (50%). Acute graft rejection and its management in the presence of high parathormone and divalent ion levels may be associated with postrenal transplant calciphylaxis.**

Conclusions: **If the high parathormone levels are not adequately suppressed with medical treatment, prerenal transplant preparation should include parathyroidectomy. In addition, steroids and other immunosuppressive medications should be tapered quickly in calciphylaxis patients, especially if a patient's life is at risk.**

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Calciphylaxis is a small vessel disease characterized by intimal proliferation, endovascular fibrosis, and mural calcification resulting in end-organ ischemia and damage (1). Therefore, calciphylaxis is considered as one of the recognized causes of morbidity and mortality in hemodialysis patients (2). The first animal model of calciphylaxis was described by Selye in the early 1960s (3). Although most body organs can be affected by calciphylaxis, its most common manifestations are skin ulcers, acral gangrene, intestinal ischemia, and aortic calcification (4-6). Sudden fatal pulmonary calcification also has been reported after renal transplant (7).

To our knowledge, a total of 21 cases of postrenal transplant calciphylaxis have been published in 13 reports (7-19). However, none of the patients had calciphylaxis after the second renal allograft or has entertained the possibility of calciphylaxis as one of the causes of primary graft failure. In this case report, we present, for the first time, a patient who lost his second renal allograft and subsequently died owing to calciphylaxis. We also pooled and analyzed the previously reported 21 cases, in addition to our case, to draw better conclusions and assess the risk factors, management, and outcomes of this uncommon complication.

Case report:

A 33-year-old patient with end-stage renal disease of an unknown origin had hemodialysis for 3 months in 1988, followed by a commercial, living, nonrelated renal transplant abroad, which failed after 3 years. The histopathology of the first graft, unfortunately, was not provided. He underwent hemodialysis for another 10 years, until he had the second commercial

renal transplant abroad in August 2002. Immediately after surgery, the patient resumed hemodialysis because of delayed graft function. He refused a kidney biopsy and was given antirejection therapy in the form of pulse methylprednisone, antilymphocyte globulin, and daclizumab. The transplanted kidney did not show improvement, and the patient was discharged home on prednisone, mycophenolate, and Rapamune.

Six weeks after the retransplant, the patient was admitted to King Faisal Specialist Hospital & Research Center in an anuric state, and was maintained on hemodialysis. Doppler ultrasound showed patent graft vessels with increased vascular resistance. A renal scan showed good perfusion, but with no excretion. A kidney biopsy showed findings consistent with acute tubular necrosis, and the patient was continued on the same medications. Two days after presentation, he developed a painful violaceous skin rash (Figure 1A) on the trunk and on the medial side of both thighs. Skin biopsy showed only hemorrhagic necrosis of the epidermis. A few days later, the skin rash progressed to necrotic deep ulcers (Figure 1B). The differential diagnoses were panniculitis, vasculitis, and calciphylaxis.

Results of a laboratory work-up for vasculitis was negative. Protein electrophoresis showed low serum albumin and hypogammaglobulinemia. Immunofixation did not show a monoclonal band. The patient's hemoglobin level was 78 g/L, hematocrit, 0.25%; parathyroid hormone (PTH), 1456 ng/L; corrected serum calcium, 2.43 mmol/L; phosphate, 2.43 mmol/L; Mg++, 0.78 mmol/L; alkaline phosphatase, 314 IU/L; urea, 19 mmol/L; serum creatinine, 702 μmol/L; CO_2, 24 mmol/L; albumin, 24 g/L; protein S, 1.33 IU/mL (normal range, 0.67-1.19 IU/mL); protein C, 0.75 IU/mL (normal range, 0.5-1.24); C-reactive protein, 171 mg/L increased to 489 mg/L at the time of the second skin biopsy. An ultrasound scan of the neck showed enlargement of the 4 parathyroid glands (hyperplasia), and a diagnosis of parathyroid adenomas was confirmed by technetium scan. A second skin biopsy showed extensive subepidermal vascular calcification in the media with intimal fibrosis (Figure 2C) consistent with a diagnosis of calciphylaxis.

Ten days after admission, a total parathyroidectomy was done with dissection of the thymus. This led to normalization of the corrected serum calcium, phosphate, and alkaline phosphatase levels, and the parathyroid hormone level remained less than 1.2 ng/L. One week later, the graft showed no signs of improvement. Therefore, another kidney biopsy was done, which showed areas of infarction,

Figure 1. (A) Early stages of calciphylactic skin lesions appear as violaceous macules in the back. (B) Late stages of calciphylactic skin lesions appear as bilateral deep necrotic ulcers in the thighs.

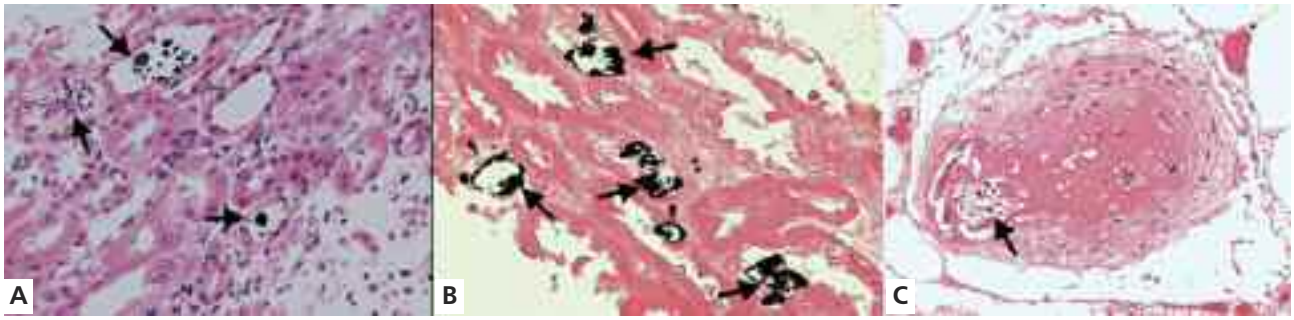

Figure 2. (A) Calcification within the renal tubules and interstitium (H&E; ×200). (B) Renal biopsy in which the deposited calcium stains black within the renal tubules and interstitium (Von Kossa's stain; ×400).(C) Medial calcification and intimal fibrosis of a small subcutaneous artery (H&E; ×400).

Table 1a. Characteristics of patients at the time of calciphylaxis (demographic and renal).

N	R (case)	Age (year)	Time post-tx	Sex	PTH (week)	Dialysis period (month)	Ca++ x P+++	Ca++ (mg/dL)	P+++(mg/dL)
1	7	42	5	M	?	24	34.86	8.3	4.2
2	8	41	12	F	?	13	23.94	11.4	2.1
3	9 (2)	20	44	F	?	5.5	58.00	9.5-10.5	5.8
4	(7)	18	60	M	?	4.5		8.5-10.5	Normal
5	(8)	30	40	M	?	1	39.60	9.3-10.5	3.4 – 4.6
6	(9)	20	56	M	?	7	82.80	9.6-11.1	8
7	(10)	48	156	F	?	6	36.73	10-12.6	2.5-4
8	10 (1)	20	104	F	935 pg/mL**	12	37.98	10.1-11	3.0-4.2
9	(2)	30	130	M	965 pg/mL**	43	33.02	9.1-9.5	3.0-4.1
10	(3)	28	228	M	130 pg/mL	24		11-13	?
11	(4)	42	104	F	40 pg/mL*	36	42.42	10.1	4.2
12	11	42	20	F	1200 μL Eq/mL	15	23.00	9-11	2.3
13	12 (1)	50	8	F	1055 ng/mL†	60	46.42	2.68‡	1.25‡
14	(2)	30	72	M	793 ng/L†	72	58.80	2.5‡	1.9‡
15	13	30	3	F	?	84		High	High
16	14	26	572	M	268 ng/L	?	87.36	9.1	9.6
17	15	43	1092	M	9.1 ng/mL§	22	22.50	9	2.5
18	16	49	104	F	2.4 pmol/L	24	28.34	1.99‡	1.15‡
19	17	50	52	M	6 pmol/L¶	144	39.57	2.35‡	1.36‡
20	18	25	28	F	High	12		2.7‡	Normal
21	19 (2)	36	20	F	?	20	32.55	10.5	3.1
22	Our	33	4	M	1456 ng/L	120	73.09	2.43‡	2.43‡

R, reference. ( ), case number in the reference. M, male. F, female. PTH, parathyroid hormone. ?, unknown. *The normal range in this case was 2-10 μL Eq/mL. **The normal range was 75-675 pg/mL. §this level was 3 years before calciphylaxis. †the normal range was 10-55 ng/L. ¶the normal range in this case was 1-5.5 pmol/L. ‡the unit is mmol/L. C++, calcium. P+++, phosphorus.

rejection (Banff grade 2), and severe intratubular, vascular, and interstitial calcium crystal deposition (Figures 2A and 2B). Pulsed methylprednisone therapy was given and mycophenolic acid was changed to tacrolimus. However, the patient continued to be anuric. Therefore, a decision to withdraw all immunosuppressive medications was made and the patient's corticosteroid therapy was tapered gradually.

A wound culture showed multi–drug-resistant organisms including *Klebsiella pneumonia*, *Escherichia coli*, Gram-positive rods resembling *Propionibacterium* species, *Yeast*, and Gram-negative rods. A blood culture was positive for *Klebsiella*, which was also multidrug resistant. The patient was then maintained on regular hemodialysis, antibiotics, total parenteral nutrition, growth hormone and wound care. However, he continued to deteriorate, developed intractable sepsis, and finally died.

Results of pooled cases

After a thorough PubMed search, from 1969 until 2005, 21 cases of postrenal transplant calciphylaxis were reported in 13 references (7-19). Our case therefore is the 22nd. We have presented the demographic, renal, and immunologic characteristics of these patients, in addition to the interventions given, and mortality data in Tables 1a and 1b. Pooled results of the whole 22 case are presented in Table 2.

Table 1b. Further patients characteristics (transplant, intervention, and mortality).

N	R (case)	Tx Type	PTx	Rejection	DGF	On steroid	Prednisone dosage (mg)	Died
1	7	DD	No	Yes	Yes	Yes	?	Yes
2	8	LR	Yes	No	No	Yes	30	No
3	9 (2)	LR	Yes	Yes	?	Yes	?	No
4	(7)	LR	Yes	Yes	No	Yes	?	No
5	(8)	LR	Yes	?	?	Yes	15	No
6	(9)	LR	Yes	?	?	Yes	?	Yes
7	(10)	DD	Yes	No	No	Yes	20	No
8	10 (1)	LR	Yes	Yes	Yes	Yes	10	Yes
9	(2)	DD	Yes	?	?	Yes	15-20	Yes
10	(3)	LR	Yes	Yes	No	Yes	12.5	Yes
11	(4)	DD	Yes	No	No	Yes	4*	No
12	11	DD	Yes	No	No	Yes	30	No
13	12 (1)	DD	Yes	No	No	Yes	4*	No
14	(2)	DD	Yes	Yes	No	Yes	10*	No
15	13	?	No	?	?	Yes	?	Yes
16	14	LR	No	?	?	Yes	10	No
17	15	DD	Yes**	Yes	?	Yes	?	Yes
18	16	DD	No	?	?	Yes	24*	No
19	17	DD	Yes	No	No	Yes	8	Yes
20	18	DD	Yes	No	Yes	Yes	7.5	Yes
21	19 (2)	DD	Yes	No	No	Yes	20	Yes
22	Our	DD	Yes	Yes	Yes	Yes	17.5	Yes

Abbreviations: R, reference; Tx, transplant; PTx, Parathyroidectomy; DGF, delayed graft function; ?, unknown; DD, deceased donor; LR, Living-related; *, methylprednisone; **, PTx was subtotal and was done 3 months post-Tx and not as a treatment of calciphylaxis.

Briefly, the mean ± SD age at presentation was 34.2 ± 10.6 years, there were 11 males (50%), and 13 (57.9%) underwent deceased-donor renal transplant. The mean ± SD pretransplant dialysis period was 35.7 ± 39.3 months, 22 patients were on steroid therapy, 8 had rejection (36.4%). Calciphylaxis developed after a mean ± SD interval of 132.5 ± 246.8 week postrenal transplant. In 18 patients (81.8%), total parathyroidectomy was performed after the occurrence of calciphylaxis, and mortality was reported in 11 patients (50%) (Table 2).

Table 2. Pooled characteristics of postrenal transplant patients at the time of calciphylaxis (n=22).

Variable	Mean ± SD or n (%)
Age (years)	34.2 ± 10.6
Sex	
M	11 (50.0)
F	11 (50.0)
Dialysis period (months)	35.7 ± 39.3
Transplant type	
Deceased-donor	13 (57.9)
LR	8 (36.8)
Unknown	1 (5.3)
Time post-Tx (weeks)*	132.5 ± 246.8
Serum calcium (mg/dL)	10 ± 1.0
Phosphorus (mg/dL)	4.5 ± 2.1
Calcium phosphorus product	44.5 ± 19.8
DGF	
Yes	8 (36.4)
No	8 (36.4)
Unknown	6 (27.3)
Previous rejection	
Yes	8 (36.4)
No	8 (36.4)
Unknown	6 (27.3)
On steroid	22 (100.0)
Steroid dose (mg/day) **	16 ± 8.0
Parathyroidectomy	
Yes	18 (81.8)
No	4 (18.2)
Mortality	11 (50.0)

Abbreviations: DGF, delayed graft function; LR, Living-related; M, male; F, female; *the median is 54 and the range is 1089 weeks; **after conversion to predinsone; n, number; SD, standard deviation

Discussion

Calciphylaxis is a syndrome that affects between 1% and 4% of all patients undergoing dialysis (20); it leads to vasculopathy (in the form of widespread calcification of blood vessels) with subsequent vessel narrowing and tissue ischemia. Although Virchow was the first to describe soft-tissue calcification associated with renal failure (21), Selye, in early 1960s, produced data from experiments on rats that showed that corticosteroid administration hastens the development of calciphylaxis, especially when given with calcium and parathyroid hormone (22).

Selye postulated "2 steps" for the calciphylaxis to occur. The first is systemic sensitization induced by agents such as parathyroid hormone, vitamin D, phosphates, or calcium salts. The second step, which comes after a period called the critical period, is the exposure of the animal to challenging agents resulting in extensive tissue calcification. These "challengers" include glucocorticoids, egg albumin, iron salt, and local trauma. This hypothesis of a hypersensitivity phenomenon was further supported in other animal studies (23, 24).

A case control study by Mazhar and associates, showed that female sex, hyperphosphatemia, high alkaline phosphatase, and low serum albumin are risk factors for calciphylaxis and mortality in patients with end-stage renal disease (1). Low serum albumin as a risk factor for development of calciphylaxis also was observed by Bleyer and associates, who noticed a 17-fold increase in the risk of developing calciphylaxis with each 1 g/L decrease in serum albumin (25). This observation was supported by Coats and associates, who reported a loss of more than 10% body weight over 6 months preceding the diagnosis of calciphylaxis in 7 out of 16 patients in their series (26). Our patient had low serum albumin at presentation (24 g/L), which dropped further to 18 g/L throughout the course of his illness.

Calciphylaxis may be precipitated by an intravenous injection of iron (27-29) or calcium (7, 8, 12) before or after transplant. Analysis of the pooled 22 reported cases revealed that 3 of the 22 patients (13.4%) had an intravenous calcium injection (7, 8, 12). The effect of glucocorticoids on the pathogenesis of calciphylaxis is still not clear (3).

In some circumstances, glucocorticoids can prevent calciphylaxis, while in others, it may aggravate the disease process. Fader and Kang reported calciphylaxis in a patient with advanced liver disease treated with prednisone and albumin infusion (30). Indeed, in an in vitro study by Mori and associates (31), dexamethasone was found to stimulate a cyclic adenosine monophosphate response to parathyroid hormone, and to produce a dose-dependent enhancement of vascular calcification. Our patient, because of the delayed graft function and rejection, was pulsed twice with high-dose methylprednisone. This high corticosteroid dose was

given in the presence of a very high level of parathyroid hormone. Analysis of the 22 postrenal transplant calciphylaxis patients showed that 100% of the patients were on corticosteroid therapy (Table 2), some of them developed the calciphylaxis immediately after treatment of rejection with pulse steroids (7).

Only 4 cases of postrenal transplant calciphylaxis reported histopathological findings of the allograft, and there results were variable (7, 12, 13). In the case reported by Giacobetti and associates, the graft biopsy showed acute tubular necrosis (7), exactly like the first biopsy obtained in our patient. This may reflect early graft ischemia as a result of calciphylaxis rather than as acute tubular necrosis that is commonly seen in early postrenal transplant. However, there was no histopathological follow-up report of this patient, whose graft was removed on the 45th day after transplant. The 2 cases reported by Wenzel-Seifert and associates, showed calcified microcylinders in the tubules of a transplanted kidney, and chronic rejection with severe calcinosis of the interstitium in a removed kidney (12). The third was an autopsy of the allograft removed 3 weeks after renal transplant, which showed focal calcification of the transplanted kidney (13). The fourth showed intrarenal arteries with myointimal calcification (13). In our patient, the calcification was in the renal tubules and in the interstitium (Figures 2A and 2B).

Patients with calciphylaxis have an 8-fold increased risk of death compared with controls (1). The most common cause of death is infection (32), as occurred with our patient. Indeed, the mortality was reported in 11 of the 22 (50%) reported postrenal transplant calciphylaxis patients (Tables 1b and 2). This high rate of mortality emphasizes the importance of prevention, early detection, and treatment of such cases. Five patients (45.4%) had acute rejection and were treated with pulse steroids, and only 3 of the 11 deceased patients (27.3%) had no history of acute rejection, while the rejection status in the remaining 3 patients (27.3%) was unknown. On the other hand, only 3 of the 11 patients (27.3%) who survived had an acute rejection episode. This may suggest the importance of acute rejection as risk factor for calciphylaxis in the appropriate setting. Eight of the 22 patients (36.4%) had pulse steroid treatments at least once, and in 2 patients, the dosage of oral steroid was increased significantly, just before the diagnosis of calciphylaxis (8, 16). The underlying risk factor among the majority of the patients is the treatment with corticosteroid and an immunosuppressant.

The classic therapy of calciphylaxis involves control of hyperphosphatemia, reduction of calcium phosphorus product to < 55 mg/L, and total parathyroidectomy (2). However, management of postrenal transplant calciphylaxis patients remains a matter of controversy. Subtotal total parathyroidectomy was required only in few cases of persistent postrenal transplant hypercalcemia (33-35). Geis and associates, suggested that posttransplant total parathyroidectomy may improve renal function, especially in patients with high ionized calcium levels and progressive deterioration of renal function (36). Similarly, Perloff and associates, recommend performing a total parathyroidectomy within 1 year of transplant, if parathyroid hormone and serum calcium levels are persistently elevated (10).

Fox and associates, reported healing of the skin lesions after total parathyroidectomy (11). As a consequence, they suggested performing total parathyroidectomy for patients with a functioning graft, and withdrawal of the immunosuppressive agents in patients with nonfunctioning grafts. Revision of the 22 postrenal transplant calciphylaxis patients, all of the patients (100%) who showed improvement had a total parathyroidectomy, while 9 of the 11 patients (81.8%) who died had a total parathyroidectomy. This is similar to what was reported in patients without a renal transplant. Chan and associates, reviewed 47 calciphylaxis cases, and noted that the survival rate of patients who underwent a total parathyroidectomy was similar to those who did not (37). This also is supported by the study of Budisavijevic and associates, in which 50% of the 31 patients who had a total parathyroidectomy performed after calciphylaxis died within 9 weeks of the total parathyroidectomy (38). Thus, the importance of a total parathyroidectomy in the management of postrenal transplant calciphylaxis needs further evaluation. In our patient, a total parathyroidectomy did not stop the progression of the skin ulcers. This may be explained by the continuous challenging effect of corticosteroid given as pulse therapy for rejection. When corticosteroids were discontinued in some patients after graft failure the wounds healed, and the patients were saved (9).

Owing to an organ shortage, some of our patients sought out commercial kidney transplants outside our country (as was the case with this patient). Although we are against this type of transplant from an ethical point of view, we cannot refuse treating these patients when they return home. The complications encountered with such cases attest to the reasons against commercial transplant, not only ethically, but also, about the procedure and its outcomes.

Fetuin-A, an acute phase glycoprotein synthesized by hepatocytes, is a powerful circulating inhibitor of hydroxyapatite formation (39, 40). Low fetuin-A levels have been associated with endothelial dysfunction, increased cardiovascular calcification, and increased morbidity and mortality in patients with chronic kidney disease (41). Also, sevelamer, a non–calcium-based phosphate binder has recently been shown to increase attenuate cardiovascular calcification by increasing fetuin-A levels in nondiabetic patients with stage 4 chronic kidney disease. The role of fetuin-A in postrenal transplant calciphylaxis has not been tested and warrants further investigation (42).

In conclusion, calciphylaxis is not uncommon after renal transplant and may eventually lead to primary graft failure and patient loss. Acute renal graft rejection and its management, especially pulse steroid, represent the main risk factors associated with postrenal transplant calciphylaxis, especially in presence of high concentrations of divalent ions and parathyroid hormone. Therefore, these immunosuppressive therapies should be tapered quickly when the patient's life is at risk. In addition, prerenal transplant may be performed, if parathyroid hormone levels are not adequately suppressed with medical treatment. However, the value of this procedure remains a controversial issue and warrants further evaluation.

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