A RARE CLINICAL PRESENTATION: A PATIENT WITH CHRONIC RENAL FAILURE, SECONDARY HYPERPARATHYROIDISM AND CALCIPHYLAXIS

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Abstract

Calciophylaxis, also known as calcific uremic arteriolopathy (CUA), is usually observed in women and it is a serious complication of hyperparathyroidism secondary to chronic renal failure. CUA is characterized by ischemic tissue loss secondary to progressive vascular degeneration. Although it is rare, it may end up with sepsis and organ failure and can be fatal. Its pathogenesis is not fully understood, but it is thought that it occurs secondary to increased calcification activators such as oxidized LDL, TNF- α , calcitriol, fibronectin, collagen-I, and TGF- 1α . The most effective treatment is managing underlying pathology and decreasing serum calcium and phosphorus levels. In this report, we aimed to present an end stage renal failure case with coexisting hyperparathyroidism, hyperthyroidism and calciophylaxis in whom cutaneous manifestations were healed 6 months after parathyroidectomy.

Key words: Calciophylaxis, chronic renal failure, hyperparathyroidism, hyperthyroidism.

INTRODUCTION

Chronic renal failure has various cutaneous manifestations including pigment changes, xerosis, ichthyosis, excoriation secondary to uremic pruritus, perforating dermatosis, bullous dermatosis, nephrogenic fibrosing dermopathy and a specific cutaneous manifestation called calciophylaxis (1). Some of the proposed mechanisms for cutaneous manifestations are accumulated toxic substances, drugs used and immune damage. Calciophylaxis or calcific uremic arteriolopathy is characterized by progressive vascular calcification, soft tissue calcification and ischemic tissue necrosis. This condition is usually seen in advanced chronic renal failure and has a poor prognosis. In this report, we presented an end stage renal failure patient with

coexisting hyperparathyroidism, hyperthyroidism and calciophylaxis accompanied by treatment strategy.

CASE

A 32-year old male patient was admitted to outpatient clinic with complaints of weakness and painful lesions on hand and foot fingers. He was diagnosed with nephrotic syndrome in 1992, dialysis treatment was commenced in 2002 and he underwent renal transplantation in 2013. He has been still on hemodialysis treatment 3 days a week, due to tissue rejection occurred 12 months after transplantation. The patient has been diagnosed with hyperthyroidism and prescribed propylthiouracil (300 mg/day), but he voluntarily stopped the treatment shortly after. At the time of admission, he has been using cinacalcet 180 mg/day and calcitriol 0.5 mcg/day. His family history revealed nothing pathological. Vital signs were as follows: BP: 120/80 mm/Hg, pulse: 120/min and body temperature: 37°C. On physical examination, thyroid gland was soft, enlarged and a nodular lesion 1-2 cm in size on the right lower lobe and few nodular lesions on the left lower lobe which were not well-bordered were palpated. A painful, ulcerated and necrotic lesion placed under right toe nail (Fig. 1), 3 mm in size, ecchymotic and poorly circumscribed cutaneous lesion under left toe (Fig. 2) and a skin lesion with a necrotic focus originating under 3rd finger nail of left hand (Fig. 3) were present. ECG revealed sinus tachycardia. On laboratory examination, urea: 119 mg/dL (19-50mg/dL), creatinine:8mg/dL (0.7-1.3 mg/dL), Na: 134 mmol/L (132-146 mmol/L), K: 5 mmol/L (3.5-5.5 mmol/L), Ca: 10.2 mg/dL (8.6-10.2 mg/dL), P: 2.4 mg/dL (2.4-5.1 mg/dL), albumin: 4.2 g/L (3.2-4.8 g/L), ALP: 359 U/L (45-129 U/L), iPTH: 2485 pg/mL (15-68 pg/mL), TSH: 0.0001 IU/mL (0.35-4.94 mIU/

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Figure 1. Pre-treatment: Necrotic, ulcerated, painful lesion originating under right toe nail (1A), lesion subsided after treatment (1B).

Figure 2. Pre-treatment: Ecchymotic, poorly circumscribed skin lesion under left toe (2A), lesion subsided after treatment (2B).

mL), FT4: 1.5 ng/dL (0.7-1.48 ng/dL), FT3: 4.27 pg/ml (1.71-3.81 pg/mL), anti-TPO:(-), anti-Tg:(-). Kt/V ratio was 1.3. The neck USG demonstrated enlarged thyroid gland with conglomerated, heterogeneous and hypoechogenic solid nodular lesions which had calcified and cystic degenerated areas, the biggest one being 61×37 mm in size. In addition, there was a 17×15 mm heterogeneous, hypoechogenic solid nodular lesion near the right lower pole. This lesion was reported as suspicious for parathyroid adenoma. Technetium scintigraphy showed heterogenic activity uptake and hyperactive nodules on both thyroid lobes. Parathyroid MIBI scintigraphy demonstrated an increased focal activity uptake on the right lower thyroid lobe on early and late images, which was

reported as parathyroid adenoma. Dermatologic examination revealed signs of calciphylaxis and skin biopsy was performed. Histologically, epidermal hyperplasia, significant hypergranulosis, dermal fibrosis and mild perivascular chronic inflammatory infiltration were seen in hematoxylin and eosin stained slides. There was no calcium deposition in the dermis or in the walls of the vessels (Fig. 4A). Histochemical studies with Von Kossa, which were performed based on the clinical suspicion of calcium deposition, exhibited mural calcification in the large vessels of dermis (Fig. 4B-D). Propylthiouracil 300 mg/day and propranolol 40 mg/day treatment was commenced to control hyperthyroidism. When the patient became euthyroid on follow-up, total thyroidectomy and

Figure 3. Pre-treatment: Skin lesion with a necrotic focus originating under left hand 3rd finger nail (3A), lesion subsided after treatment (3B).

Figure 4. In Hematoxylin and eosin stained slides, there was no visible calcium deposition in dermis or vessel walls (4A:H&EX100). Von Kossa stained slides revealed mural calcification in large vessels (arrows) (4B; Von Kossa X 40, 4C; Von Kossa X 100, 4D; Von Kossa X 200).

parathyroidectomy was performed. On pathological examination, abnormal lobular enlargement of 3 parathyroid glands was reported as nodular parathyroid hyperplasia. The final histopathology of thyroid gland was reported as nodular hyperplasia with cystic degeneration. Postoperative laboratory examination revealed iPTH: 1.3 pg/mL, Ca: 6.7 mg/dL, phosphorus: 4.2 mg/dL, and albumin: 4 g/L. Ca replacement was commenced for hypocalcaemia and

L-thyroxin was given for hypothyroidism. Patient was discharged on postoperative sixth day and referred to outpatient clinic follow-up. During follow-up period, the patient received 3/7 days dialysis treatment and cutaneous manifestations subsided within 6 months (Figs 1B, 2B, 3B).

DISCUSSION

Calciphylaxis was first described in 1898 by Bryant and White and the term 'calciphylaxis' was first used in 1962 by Selye (2-4). It is seen in 1-4% of patients with chronic renal failure. It is 3 times more common in females. It affects patients of all ages. It was shown to be closely related to increased morbidity and mortality (5-7).

The pathophysiology of calciphylaxis is not fully understood. Vascular calcification and soft tissue necrosis of the skin may cause calciphylaxis. Several studies have shown that the balance between calcification activators (oxidized LDL, TNF- α , calcitriol, fibronectin, collagen-I, TGF-1 α eg.) and inhibitors (fetuin-A, matrix gla protein, osteoprotegerin, osteopontine, eg.) was lost in favour of activators. Calciphylaxis mainly occurs in small and medium sized venules and arterioles and the places where adipose tissue is thick. Intravascular calcium accumulation takes place in these areas. Histopathologically, various degrees of intravascular calcium deposition in media of dermal and subcutaneous arterioles may be seen (8). Subcutaneous tissue biopsy is required to identify pannicular or dermal arteriolar thrombosis. The

most common histopathological change is cutaneous necrosis. Right toe incisional biopsy of our case showed hyperkeratosis, epithelial hyperplasia and papillomatosis. We also showed calcium deposition presenting as the mural calcification in large vessels of dermis by histochemical studies with Von Kossa.

Risk factors for the development of calciphylaxis are female gender, presence of diabetes, white race, obesity, chronic renal failure, secondary hyperparathyroidism, hyperphosphatemia, hypercalcemia, improper use of vitamin D and calcium based phosphorus binders, calcium x phosphorus > 70 mg²/dL², long term dialysis treatment, increased ALP level, protein C and/or S deficiency, corticosteroid, ferrum dextran and erythropoietin use, Gla deficiency induced by dicoumarinic anticoagulants or by vitamin K deficiency (9-12). In the present case, risk factors for the development of calciphylaxis were chronic renal failure, secondary hyperparathyroidism and long term dialysis. Thyroid hormones could play a role in vascular calcification. Our patient had hyperthyroidism, which is not included in the classical risk factors for calciphylaxis. On the contrary, a study by Sato *et al.* showed that thyroid hormones prevent *in vitro* vascular calcification, hyperthyroidism decreases tissue calcium content by increasing excretion and production of matrix Gla protein, bone morphogenic protein and osteopontin. Thus, it is possible that hypothyroidism might induce calciphylaxis by reducing the expression of critical inhibitors of vascular calcification, causing vascular stenosis and even sudden death, but further clinical studies are needed to clarify this relation and, eventually, to allow inclusion of hypothyroidism among the non-classical risk factors for calciphylaxis (13). For this reason, it may be useful to consider measuring thyroid hormone levels while evaluating risk factors for the development of calciphylaxis in patients who are on long term dialysis for chronic renal failure.

Calciphylaxis lesions are usually seen as chronic, painful and symmetrical yellowish discolorations which are necrotic, gangrenous and poorly circumscribed. Weenig *et al.* (6) studied 64 patients with calciphylaxis and found that the most common localizations were lower extremity (92%), trunk (30%), thigh, upper extremity and genital area. Our patient's lesions were also mainly located on lower extremity.

Detection of calciphylaxis lesions on inspection is diagnostic. Systemic vasculitis,

peripheral artery disease, atheroemboli, cryoglobulinemia, warfarin induced cutaneous necrosis and systemic oxalosis should be considered in the differential diagnosis. Biopsy, measurement of transcutaneous oxygen saturation, bone scintigraphy and xeroradiography are helpful methods in the differential diagnosis (14).

The most important point in the treatment is successful clinical management of underlying condition. It is important that treatment schema should be in a multidisciplinary manner. Although these lesions are reversible, extremity loss may occur in some cases. Use of unnecessary calcium and vitamin D should be avoided. Use of calcium based phosphorus binders in appropriate doses, low phosphorus diet, low calcium dialyzate, wound care, hyperbaric oxygen treatment, debridement of necrotic tissues, wide spectrum antibiotherapy in case of infection and intravenous sodium thiosulphate are treatment of choices (15). Positive effects of parathyroidectomy on survival were also shown (16).

In conclusion, although calciphylaxis is a rare complication of chronic renal failure, it is related to high mortality and morbidity. Therefore, we suggest that risk factors for calciphylaxis should be revised, treatment schema and follow-up should be established in a multidisciplinary manner.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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