Immune thrombocytopenic purpura masking the fatal potential of calciphylaxis in a haemodialysis patient

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Abstract Calciphylaxis on the background of immune thrombocytopenic purpura (ITP) has never been described. The pathogenesis of calciphylaxis is complex and not fully understood as yet. ITP has a complex pathogenesis that leads to bleeding or thrombotic events. Although ITP is treatable and reversible, calciphylaxis on the other hand, responds poorly to treatment and carries high mortality and morbidity. We present a case of a 56-year-old lady with end-stage renal disease with ITP, who complained of 1-month history of painful necrotic patches over the thighs. Due to delayed diagnosis, the patient deteriorated and passed away despite aggressive multidisciplinary approach. This case highlights the importance of early recognition of the increased thrombotic risk in an end-stage renal failure patient with poor phosphate control and ITP.

Keywords Calciphylaxis · Calcification · Necrosis · End-stage renal failure · Immune thrombocytopenic purpura

Introduction

Calciphylaxis, or calcific uremic arteriolopathy (CUA), is a rare but potentially fatal disorder that primarily happens in patients with end-stage renal failure (ESRF). It is characterized by systemic medial calcification of the arterioles that causes vascular thrombosis and cutaneous necrosis.

Patients who are suffering from calciphylaxis typically present with painful violaceous or black nodules/plaques over the extremities, buttock, trunk or rarely the face, which may be indistinguishable from ITP lesions. The lesions then progress to show ischaemic changes, which are similar to livedo reticularis. Subsequently, necrotic ulcers with eschars will be formed when the vascular thrombosis advances. In this case, we report a case of ESRF patient who is with the history of ITP and thrombotic event that masked the presentation of calciphylaxis.

Case presentation

A 56-year-old lady with ESRF who had been on regular haemodialysis for 6 years, was admitted with the problem of intra-dialytic hypotension. She also complained of 1-month history of painful skin lesions over her thighs. Patient had background history of hypertension, type 2 diabetes mellitus, left below-elbow amputation from thrombotic left radial and ulna arteries secondary to ITP for which she had received high-dose prednisolone and a course of intravenous immunoglobulin (IVIG) 8 months prior to the current admission.

Her calcium and phosphate were relatively not well controlled during her follow-ups with calcium 1.74 mmol/L, phosphate 1.81 mmol/L, albumin 35 g/L, ALP 208 U/L and iPTH 179.4 pmol/L. The dose of vitamin D was increased from 0.25 mcg daily to 0.5 mcg daily in an attempt to treat the renal bone disease. Four months later, she started to have discoloration of her left thigh which was associated with mild discomfort. Unfortunately, the rashes were mistaken to be bruises due to concurrent low platelet level from ITP flares (Fig. 1). Her skin lesions progressed to necrotic patches and worsened rapidly (Fig. 2).

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Fig. 1 Bruises that were mistaken with ITP

Fig. 2 Severe eschar formation

During physical examination upon admission, she was Cushingoid. There was extensive ill-defined dusky red to violaceous patches over her both thighs. Some lesions progressed to blisters with erosions and cutaneous necrosis.

Laboratory investigations revealed the following: haemoglobin 8.1 g/dL, white cells $7.5 \times 10^9/L$, platelet $45 \times 10^9/L$, urea 9.6 mmol/L, creatinine 285 $\mu\text{mol/L}$, serum calcium 1.74 mmol/L, phosphate 1.06 mmol/L, albumin 22 g/L, alkaline phosphatase 132 U/L, creatine kinase 100 U/L.

Her medications included prednisolone 15 mg om, amlodipine 5 mg om, ferrous fumarate 200 mg bd, folic acid 5 mg om, mecobalamin 500 mcg tds, vitamin B complex one tab om, lovastatin 20 mg on, s/c actrapid 26 iu tds, insulatard 28 iu on, calcium 500 mg bd, and alfacalcidol 0.5 mcg daily.

Provisional diagnoses of either diffuse thrombosis from ITP or calciphylaxis were made. An urgent skin biopsy done confirmed the diagnosis of calciphylaxis (Figs. 3, 4). Patient was given morphine as for pain relief. Intensified daily dialysis with low-calcium dialysate was introduced. Calcium carbonate and vitamin D were ceased and replaced with non-calcium-based phosphate binders. Patient's nutritional status was supplemented with total

Fig. 3 Calcium deposits are highlighted with Von Kossa stain (black)

Fig. 4 Fibrin thrombi are noted within the vascular channels (arrow) with panniculitis and degenerated adipocytes

parenteral nutrition. However, she developed persistent febrile illness in the ward, despite escalation of antibiotics. Her skin lesions continued to worsen rapidly despite intensification of dialysis regimes. She developed severe sepsis and upper gastrointestinal bleeding and passed away 3 weeks after admission.

Discussions

The pathogenesis of calciphylaxis is complex and not fully understood. Abnormalities in mineral metabolism and uraemia were thought to predispose patients to vascular and soft tissue calcifications [1]. However, no particular laboratory abnormality can predict the development of this condition. Indeed, back in 1962, calciphylaxis was first described in an animal model as a two-step systemic anaphylactic reaction, involving an initial sensitization (e.g. excess vitamin D) and challengers (e.g. local skin trauma) [2]. It is the interaction of sensitizers and challengers that cause abnormal calcification of the vessels. Identified risk factors associated with this disorder include female gender,

obesity (BMI >30), Caucasian race, diabetes, protein malnutrition, chronic inflammatory disorders, hypercoagulable states, use of medications such as warfarin, systemic corticosteroids or vitamin D analogues [1, 3].

Diagnosis of calciphylaxis is often made based on physical examinations, with high index of suspicion. Skin biopsy is usually performed in the absence of contraindications such as active infection. The suggestive features in making histological diagnosis are medial arteriolar calcification, intimal fibrosis and hyperplasia, calcifying septal panniculitis and vascular thrombosis.

Calciphylaxis leads to high morbidity and mortality. The overall 1-year survival is 45 % and the 5-year survival is 35 % [3]. Infection is the primary cause of death. Prevention and early diagnosis is mandatory as it is often difficult to treat. Management of patients with calciphylaxis is mainly supportive and multidisciplinary. Calcium and phosphate products should be reduced by increasing the frequency of dialysis, usage of calcium-free phosphate binders and low-calcium dialysate [2]. Experimental therapies include hyperbaric oxygen and biphosphonates. There are successful reports of using sodium thiosulphate (25 g given intravenously at the end of dialysis session) as an adjunctive therapy in patients with calciphylaxis. Sodium thiosulphate enhances solubility of calcium deposits, reduces pain and improves healing [4]. Aggressive wound care and administration of antibiotics are necessary to control the sepsis. The role of surgical wound debridement of the infected tissue remains debatable [3].

On the other hand, the complex pathogenesis of ITP has only recently begun to be understood in detail [5]. The most common clinical presentation of ITP is bleeding, the severity of which correlates with the degree of thrombocytopenia. However, not many patients with ITP have bleeding complications even with very low platelet counts, an observation that may be related to the presence of young, highly functional platelets or other factors. Contrary to popular belief of ITP only lead to increase bleeding tendency, recent studies have also demonstrated that patients with ITP have an increased risk of thrombosis [6]. The mechanism underlying this paradoxical development of thrombosis in patients with ITP has not been defined as yet. Factors postulated include elevated levels of platelet-derived microparticles [7], elevated antiphospholipid antibodies and complement activation on antibody-coated platelets [8]. Whether the presence of ITP will enhance the severity of calciphylaxis remains unknown.

We found no other case report on the occurrence of thrombotic event from the co-existence of calciphylaxis and ITP. Chronic inflammatory states such as connective tissue disease, Crohn's disease and systemic lupus erythematosus (SLE) are some of the most common clinical features of patients with calciphylaxis [9]. Fetuin-A levels,

a glycoprotein that is present in our bodies to chelate the calcium and phosphate excess, are found to be low in haemodialysis patients who has chronic inflammatory conditions [10]. Fetuin-A limits organ and soft tissue calcification, including vascular calcium deposition in animal model [11]. It is possible that ITP, being a chronic inflammatory condition, reduces the fetuin level and enhances or hastens the development of calciphylaxis in our patient.

In this case, there were several factors leading to the patient mortality. Besides her thrombotic risk from calciphylaxis and ITP, her other risk factors include diabetes, hypertension and ESRF.

Conclusions

Calciphylaxis is devastating and life threatening. Prevention remains the key management. Physicians or nephrologists should actively report similar cases, as well as contribute to the on-going calciphylaxis registries in their countries [2]. This case highlights the importance of early recognition of the disease in patients at risk. As far as we are aware, this is the first case report that reports concurrent calciphylaxis in a patient with ITP.

Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest or conflict of interest.

Informed consent Informed consent was obtained from patient's next of kin.

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