A painful skin rash in a patient with Stage V chronic kidney disease

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Introduction

Skin rashes are common in patients with chronic kidney disease (CKD), many of whom have multi-system pathology and are receiving multiple medications. While most rashes are self-limiting, some may signify serious pathology. As this case demonstrates, the formulation of an accurate differential diagnosis is an important first step in the management of skin pathology.

Case history

A 74-year-old Caucasian woman presented with deteriorating renal function. She had a 13-year history of non-insulin-dependent diabetes and had just started insulin due to a rising HbA1C. She also had a 2-year history of hypertension and a remote history of duodenal ulceration. Her creatinine at presentation was 285 μmol/L and her estimated glomerular filtration rate (eGFR) was 14 mL/min.

Her blood pressure and cardiovascular risk factors were optimized and she was started on alfacalcidol for prophylaxis against renal bone disease. A left brachiocephalic fistula was created in preparation for dialysis. Six months later she developed acute cholangitis requiring an endoscopic retrograde cholangiopancreatogram for removal of gallstones, followed by a cerebrovascular accident presenting with left-sided weakness and dysphasia from which she made a good recovery. A computed tomography (CT) scan showed multiple cerebral infarcts and carotid Dopplers showed stenosis of the right internal carotid artery but not of a severity to require endarterectomy. She was started on warfarin with a target international normalized ratio of two to three.

Five months after the above, she presented with painful erythematous lesions on the posterior areas of both calves, which were initially thought to represent phlebitis. Her renal function was unchanged. She was prescribed a course of oral fluocoxacinil. Within 3 weeks, the lesions became purplish, maculopapular and indurated (Figure 1). She had no fever, other rash, arthralgia, history of foreign travel or trauma. The lesions gradually increased in size and became more painful, eventually leading to ulceration and central areas of necrosis (Figure 2).

She was admitted for assessment. Her medication on admission comprised insulin, warfarin, alfacalcidol 0.75 μg once daily, atorvastatin 40 mg once daily, enalapril 20 mg twice daily and erythropoietin alpha 3000 U twice weekly.

On examination, there was no evidence of trauma or nail bed infarcts and she had warm peripheries with no ankle oedema. Longstanding varicose veins were present. The ulcers now affected both proximal and distal limbs but did not affect the extremities of her toes.

Results of clinical chemistry investigations are shown in Table 1.

Liver function tests were normal and hepatitis serology was negative. Creatine kinase levels were within normal limits. The C-reactive protein was raised at 55 mg/L and the total white cell count was 13.1 × 10^9/L, but there was no eosinophilia. Immunological results showed normal immunoglobulins with a minor IgG kappa band of uncertain significance, negative anti-nuclear factor and anti-neutrophil cytoplasmic factor serology, no cryoglobulins and a weak positive smooth muscle antibody. Assays of protein C and protein S were within normal limits.

In the light of diagnostic uncertainty, two skin biopsies were undertaken. The first showed necrotic tissue with a dense polymorphonuclear cell infiltrate and acute inflammatory cells present within vessel walls beneath an acute ulcer bed. The findings were not diagnostic. The second biopsy, taken 3 days later, was a deeper biopsy including areas of macroscopically normal tissue.

Question: What is the diagnosis and how would you distinguish between the differential diagnoses?

Discussion

Possible differential diagnoses are shown in Box 1. Arterial ulceration is unlikely considering the position and nature of the ulceration, as this would predominantly affect the distal extremities of the limbs. Venous ulceration tends to occur...
distally and at areas of maximal dependency and is often associated with peripheral oedema, making this diagnosis also unlikely. Both could be assessed by Doppler studies. The size of ulceration and their limitation to the soft tissue of the thigh and calf argues against a diagnosis of vasculitis, as vasculitic ulcers tend to be more widespread, with smaller areas affected by inflammatory infiltration of small vessels. Similarly, the pattern of ulceration is not typical for a drug-induced vasculitis, which would also be more likely if there were an eosinophilia.

The pattern, appearance and time course of ulceration is consistent with underlying cryoglobulinaemia, but this is usually associated with myeloma or abnormal liver function caused by hepatitis C infection. Similarly, while pyoderma gangrenosum is a possibility, pyoderma lesions are usually described as having a raised purple edge, and there is no history of associated disease such as inflammatory bowel disease or myeloma.

A recent review of diabetic muscle infarction has again raised the awareness of this condition, which is often overlooked and may occur in the thigh or calf, but this is usually associated with limb swelling rather than superficial ulceration [1]. If present, magnetic resonance imaging of the affected area would be the investigation of choice and would show myositis and muscle necrosis. Another differential to consider in a woman receiving warfarin with this pattern of rash is with skin necrosis secondary to protein C deficiency, but the time course would be unusual [2]. Appropriate haematology assessment would be indicated. Another alternative is calciphylaxis, although this is rare in pre-dialysis patients and more commonly considered in the context of severe hyperparathyroidism.

In this case, the second biopsy showed acute inflammation, but no blood vessels were identified to assess for the typical calcification and inflammation found in calciphylaxis. This is a common problem and illustrates the difficulty of making a histological diagnosis of calciphylaxis in such patients and the clinical dilemma of whether to request further biopsies to establish an unequivocal histological diagnosis, balanced against subjecting the patient to further trauma in areas subject to poor wound healing and potential infection. Indeed, some authors have suggested that that skin biopsy should not be undertaken to confirm the diagnosis [3].

Subsequent Doppler ultrasound of the legs showed only mild disease of the left crural artery, while plain radiology of the legs was unremarkable. CT of the legs showed a pattern of dense micro-calcification of the peripheral arterial tree with localized tissue necrosis. The final clinical diagnosis was that of calciphylaxis.

Calciphylaxis, or calcific uraemic arteriopathy, was first described in 1898 and since the advent of dialysis in the 1960s, it has been strongly associated with end-stage renal
failure [4]. It is a very serious condition with a reported mortality of 45–65%, this being higher for patients with more proximal lesions [4]. Death usually results from sepsis arising from superinfection of the necrotic ulcers.

Calciphylaxis is characterized histopathologically by medial calcification of the small arteries and by intimal hyperplasia, with subsequent ischaemia of the subcutaneous fat and skin (Figure 3) [3]. It is more prevalent in Caucasian women and those with a raised body mass index; although not all case series agree, it also appears to be more common in patients with diabetes [5]. It usually presents with erythematous, indurated, painful nodules with associated livedo reticularis. These areas rapidly become black and necrotic, remaining exquisitely painful.

Although calciphylaxis is associated with varying degrees of medial calcification, there is no consistent association with calcium, phosphate, calcium–phosphate product or parathyroid hormone (PTH) levels at the time of presentation [5]. This is an important point, in that early reports suggested that it was invariably a complication of severe hyperparathyroidism [6]. In this patient, it may be relevant that the dose of prescribed alfacalcidol had been sequentially increased over the previous 6 months, despite the serum calcium remaining within the normal range and with minimal elevation of PTH. It is recognized that patients with diabetes and relative hypoparathyroidism may have more rapid calcification of their vascular system when calcium loaded due to the development of adynamic bone disease and a subsequent loss of calcium buffering [7]. However, there have been no large studies to date that have correlated these biochemical variables with the total dose of elemental calcium administered by calcium-based phosphate binders in the preceding months or years or by vitamin D dose.

The diagnosis of calciphylaxis is essentially a clinical one and it can therefore be delayed by inappropriate investigation. The diagnostic test is a good quality biopsy, which will show the characteristic picture of medial calcification with secondary inflammatory infiltration. It is important that deep tissue biopsies are obtained as the findings are otherwise often non-specific, as in this case. Both plain X-rays and CT scans may show arterial calcification, but it may be difficult to distinguish the pathological pattern from the normal variation seen in patients with CKD.

Various treatments have been advocated, mainly aimed at addressing the biochemical abnormalities present at the time of presentation. These include surgical parathyroidectomy [3] or cinacalcet to produce a ‘medical parathyroidectomy’ for treatment of concurrent hypercalcaemia and hyperparathyroidism [8]. Case reports have described the use of biphosphonates [9] and of hyperbaric oxygen, the latter to improve oxygen delivery to ischaemic tissue. Perhaps the most promising agent is sodium thiosulphate, which has been reported to produce significant improvement in a number of case reports and small reviews [3, 10]. However, as is often the case when a number of different treatments for a condition have been tried, there is no good evidence of efficacy and further data are required before any specific combination of therapies may be recommended. In addition, as sodium thiosulphate is excreted by the kidneys, use of this agent is problematic in the pre-dialysis patient. High-dose steroid therapy may be useful to reduce the intense pain and tissue inflammation found in this condition, but there is an increased risk of sepsis and no evidence of improved outcome. As infection is the terminal

**Box 1**

| Differential diagnosis     | Common clinical features                                      |
|----------------------------|---------------------------------------------------------------|
| Arterial insufficiency      | Distal, other signs of atherosclerosis                        |
| Calciphylaxis               | Any area, very painful, often abnormal bone chemistry         |
| Cryoglobulinaemia           | Distal, abnormal LFTs, underlying pathology                   |
| Diabetic muscle infarction  | Limb swelling, pain, underlying diabetes                      |
| Drug reaction               | Widespread distribution, recent drug history, eosinophilia    |
| Pyoderma gangrenosum        | Raised purple edge, underlying pathology                      |
| Skin vasculitis             | Extensor surfaces, systemic features                          |
| Venous ulceration           | Distal, dependent areas, venous insufficiency                 |
| Warfarin-induced skin necrosis | 3–10 days after starting warfarin                            |

**Table 1.** Results of clinical chemistry investigations.

| Time                        | Calcium (mmol/L) | Phosphate (mmol/L) | Calcium–phosphate product (mmol²/L²) | Haemoglobin (g/dL) | eGFR (mL/min) | PTH (ng/mL) | HbA1C (%) |
|-----------------------------|------------------|--------------------|--------------------------------------|--------------------|--------------|-------------|-----------|
| Three months before rash    | 2.11             | 1.87               | 3.94                                 | 9.0                | 15           | 11.4        | 7.4       |
| Time of initial rash (Figure 1) | 2.19             | 1.49               | 3.26                                 | 11.1               | 14           | 13.5        | -         |
| 4 weeks after initial rash (Figure 2) | 2.16             | 1.33               | 2.87                                 | 10.4               | 13           | 6.0         | 7.8       |

Fig. 3. Histology of deep tissue biopsy showing dense calcification of small arteriolar blood vessel walls (arrow) accompanied by neutrophil infiltration of adjacent tissue and tissue necrosis.
event in most patients, antibiotics are also widely used. However, by the time of presentation, the treatment of necrotic, poorly perfused tissue is rarely successful. The mainstay of therapy is to provide adequate analgesia and to exclude any coincident pathology; for peripheral lesions, amputation may be necessary. For the future, focussing on prevention of the medial calcification may help reduce the high mortality seen in this condition.

Clinical course

The patient was aggressively treated with intravenous antibiotics and sodium pamidronate. In view of her exaggerated vascular microcalcification, she was started on cinacalcet, despite her relatively normal bone biochemistry. She was prescribed oral steroids in an attempt to reduce the inflammation seen in the biopsy sample, and her pain was treated with opiate analgesia. As her eGFR was only 14 mL/min, she underwent a trial of dialysis, although this did not seem to make any difference to her overall condition. Unfortunately, her ulcers became infected and despite aggressive local treatment and intravenous antibiotics, she succumbed to sepsis 4 weeks after tissue biopsy.

Summary

This case highlights the importance of early identification of skin lesions in patients with Stage V CKD, whether on dialysis or not. It illustrates the relevant differential diagnosis and the investigations required to establish a diagnosis. Most importantly, it illustrates that calciphylaxis may occur in a pre-dialysis patient with normal levels of calcium and phosphate and minimal elevation of PTH levels, a combination that is poorly recognized in the literature. Although the management of calciphylaxis is largely supportive, with little evidence of benefit from medical or surgical therapy, it is likely that outcome will be improved by earlier diagnosis.

An International Calciphylaxis Registry has been established to increase knowledge and data collection in this condition, to create a tissue bank comprising of blood, tissue and DNA from patients with calciphylaxis and to support future research. This may be accessed at http://www.calciphylaxis.org.uk/.

Learning points

(1) Calciphylaxis is a painful, slowly progressive necrotizing skin lesion.
(2) Calciphylaxis occurs most commonly in patients on haemodialysis but complicate Stage V CKD before renal replacement therapy.
(3) Although most commonly associated with severe hypoparathyroidism, calciphylaxis may occur with minimal abnormalities of bone biochemistry.
(4) The diagnostic investigation is a deep skin biopsy including normal tissue, which characteristically shows dense calcification of arteriolar walls.

Conflict of interest statement. We confirm that the results presented in this paper have not been published previously in whole or part. The authors declare no conflicts of interest.

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