CASE REPORT

Calcific uraemic arteriolopathy

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Accepted 14 August 2015

SUMMARY

A 37-year-old African-American woman with end-stage renal disease presumed to be secondary to diabetes mellitus type 2, on daily peritoneal dialysis, was admitted for a painful left lower extremity lesion. Examination revealed a large, dusky, tender region over the left lateral thigh. She was on warfarin for mechanical heart valves. Despite discontinuation of warfarin and placement on heparin, the lesion progressed to extend to the medial left thigh and medial and lateral right thigh. CT scan demonstrated arteriolar medial calcification and vascular calcification of the small subcutaneous vessels, without evidence of abscess or haematoma. The patient declined punch biopsy. Given the known risk factors of high calcium-phosphate and radiological findings, a diagnosis of calcific uraemic arteriolopathy was made. Phosphate-binder therapy was optimised. She was transitioned to daily haemodialysis, and sodium thiosulfate was initiated. Skin lesions demonstrated improvement at her 5 weeks posthospitalisation follow-up.

CASE PRESENTATION

In late 2013, a 37-year-old African-American woman with end-stage renal disease presumed to be secondary to diabetes mellitus type 2 (not biopsy proven), dependent on daily peritoneal dialysis since 2009, presented with epistaxis, left lower extremity pain and non-healing left leg ulcers (figure 1). Her history was significant for insulin-requiring diabetes mellitus type 2, mechanical aortic and mitral heart valve replacements on chronic warfarin anticoagulation, multiple sclerosis, hypertension and hypothyroidism. She was a lifetime non-smoker and did not consume alcohol. Family history was significant for a maternal grandmother with diabetes mellitus type 2. She had no family history of kidney disease. Laboratory values on admission: blood urea nitrogen 72 mg/dL, creatinine 13.9 mg/dL, serum calcium 6.3 mg/dL, serum albumin 2.5 g/dL, inorganic phosphorus 7.6 mg/dL, glycated haemoglobin 6.9%, international normalised ratio 6.3, white cell count $13.5 \times 10^9/L$, platelets $458 \times 10^9/L$, parathyroid hormone 126.3 pg/mL, iron 23 µg/dL, total iron-binding capacity 131 µg/dL and iron saturation 18%. The maximum calcium phosphate product in the

BACKGROUND

Calcific uraemic arteriolopathy (CUA) is a rare but serious condition requiring prompt management, as it carries a high risk of mortality and complications. CUA is seen in patients with end-stage renal disease. We felt it was important to highlight traditional and alternative diagnostic criteria, as well as therapeutic options and differential diagnoses to be considered. The gold standard for establishing the diagnosis is skin biopsy, but it is often deferred because of the high risk of non-healing and subsequent infection.¹ In our case, even without a biopsy, the diagnosis of CUA was considered given the presence of risk factors and radiological findings demonstrating arteriolar medial calcification and vascular calcification of the small subcutaneous vessels. As a result, empiric therapy was instituted. The risk factors for CUA present in our patient included: female gender, diabetes mellitus, obesity, hyperphosphatemia and medications including calcium-based phosphate binder, vitamin D, ferrous sulfate and warfarin.

Therapeutic options include pain management and wound care of the lesion, instituting aggressive renal support with daily haemodialysis, optimising phosphate-binder medication to lower calcium phosphorus product and instituting sodium thiosulfate. The mechanism of action of sodium thiosulfate is not fully elucidated. It is believed to enhance the aqueous solubility of the calcium deposits and aid in mobilisation and clearance of vascular deposits; its antioxidant properties are proposed to restore vascular wall integrity.^{2,3}

Figure 1 Lesion of the right upper thigh, demonstrating the infarcts of the subcutaneous tissue and skin.

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To cite: Disbrow MB, Qaqish I, Kransdorf M, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-207935

preadmission period was $79.19 \text{ mg}^2/\text{dL}^2$, based on corrected total serum calcium 10.42 mg/dL and phosphorus 7.6 mg/dL .

INVESTIGATIONS

Radiological investigations:

- A. A CT of the left lower extremity had been performed approximately 1 month prior to presentation for similar left lower extremity pain. It demonstrated diffuse anasarca with soft tissue swelling of the left thigh and significant calcific atherosclerosis without focal stenosis. There was no evidence of necrotising fasciitis, abscess, or osteomyelitis (figure 2A, B).
- B. A technetium ($^{99\text{m}}\text{Tc}$) medronic acid three-phase bone scan showed areas of increased tracer accumulation in superficial soft tissues, most prominently in the lateral aspect of the left

thigh (large short arrows) corresponding to the abnormalities seen on CT scan. There was also faint visualisation of the renal outlines (small long arrows) with no significant bladder activity, consistent with end-stage renal disease (figure 3).

- C. Left lower extremity angiography showed patent major arteries without significant atherosclerotic disease.

Owing to concerns of poor wound healing frequently associated with CUA, both the patient and the consulting services were hesitant to proceed with biopsy. Thus, biopsy of the skin lesion was not performed. If non-invasive radiological tests can support the clinical diagnosis of CUA, unnecessary biopsies and associated complications can be avoided.

DIFFERENTIAL DIAGNOSIS

In patients with end-stage renal disease, lower extremity ulcers are not uncommon. We considered several possibilities during our initial consultation with the patient, including:

- A. Arterial ulcer: The patient underwent an angiogram, which essentially ruled out an arterial ulcer, as all the major arteries were patent without significant atherosclerotic disease.

Figure 2 Non-contrast axial (A) and coronal (B) images of the proximal left thigh. CT of the left lower extremity demonstrating diffuse skin thickening in the region of clinical discolouration and tenderness (large arrows). Extensive arteriosclerotic vascular calcification is seen in the left groin ((A) arrowhead), in the left femoral artery. Notably, the most prominent calcifications of the small subcutaneous vessels are readily seen (small arrows).

Figure 3 Technetium-99m methylene diphosphate bone scan showing areas of increased tracer accumulation in superficial soft tissues, most prominently in the lateral aspect of the left thigh (large short arrows) corresponding with the abnormalities seen on the CT scan. Also note very faint visualisation of the renal outlines (small long arrows) with no significant bladder activity consistent with end-stage renal disease.

- B. Warfarin-induced skin ulcer: We did consider warfarin-induced skin necrosis, but as the patient had been on warfarin for several months preceding presentation, this was thought to be less likely, as warfarin-induced cutaneous lesions typically appear within 3–10 days of initiating warfarin.
- C. Calcinosis cutis: This was thought to be unlikely given the lack of its usual presentation, which is usually a periarticular, painless plaque.
- D. Infectious ulcer: Infectious causes were considered given the patient's diabetic history. Infection was evaluated with several different imaging modalities including a three-phase bone scan, which showed diffuse tracer uptake throughout the body related to diffuse tissue oedema without focal evidence of osteomyelitis. Additionally, CT of the left lower extremity, performed approximately 1 month prior to admission for similar left lower extremity pain, demonstrated diffuse anasarca with soft tissue swelling of the left thigh. There was no evidence of necrotising fasciitis, abscess or osteomyelitis. The patient remained afebrile throughout the hospitalisation and there was no growth on blood cultures.

CT scan identified significant calcific atherosclerosis without focal stenosis. This radiological finding of vascular calcification of the small subcutaneous vessels has been described in cases of CUA, and when combining this with the patient's known risk factors, CUA was our top differential.

TREATMENT

To improve renal clearance and further decrease the calcium and phosphate product, the patient was transitioned to daily haemodialysis, and phosphate-binder therapy was optimised. Additionally, she was initiated on sodium thiosulfate infusions during haemodialysis.

OUTCOME AND FOLLOW-UP

Although formal diagnosis through biopsy was not substantiated, given her clinical presentation, radiological findings, and numerous risk factors, the patient was treated empirically for CUA. She was discharged to a long-term care facility on heparin for anticoagulation, with ongoing haemodialysis and with the goal of rehabilitation and transition home. Subsequently, she was discharged home and 5 months posthospitalisation, she reported complete resolution of the painful induration with minimal residual skin discolouration.

DISCUSSION

CUA has been associated with a high risk of morbidity and mortality in patients with chronic kidney disease on dialysis. CUA is a rare, serious condition characterised by extraosseous calcification of the soft tissues.⁴ It occurs in 1–4% of end-stage renal disease patients on maintenance dialysis, carrying a 1-year mortality rate of 45–80%.^{5 6} It is a syndrome of vascular calcification, thrombosis and skin necrosis. The primary lesion is characterised by calcium salts accumulating in the media of small arteries, causing the artery lumen to narrow. This, in turn, causes reduced arteriolar blood flow, which leads to ischaemia. Lesions develop in areas of greatest adiposity, and it is theorised that the excess weight results in focally dystrophic calcifications via the increased stress on dermal arterioles.^{7 8} The clinical manifestations of the syndrome are the secondary lesions, which are comprised of the infarcts seen in the soft tissues.

Given the high morbidity and mortality, early identification of risk factors and diagnosis is critical. The mainstays of therapy are supportive, with appropriate wound care and pain

management. Additionally, switching calcium-based phosphate binders to non-calcium-based phosphate binders to lower the calcium-phosphate product and initiating sodium thiosulfate is considered beneficial. Sodium thiosulfate is thought to enhance the aqueous solubility of the calcium deposits and aid in mobilisation and clearance of these vascular deposits.

Patient's perspective

I am most definitely better. It has been night and day (regarding pain and thigh wound). Last August I was in a wheelchair and now I am able to walk. The pain has completely gone and I haven't needed pain medications since November. I have come a long way and am very thankful for all of the care.

Learning points

- ▶ In calcific uraemic arteriolopathy, the primary lesion is the calcification of the small subcutaneous arteries/arterioles; the resultant infarction of the adjacent subcutaneous tissue and skin comprises the secondary lesion. On biopsy, calcium deposits are seen in media of small-sized and medium-sized arteries.
- ▶ Patient risk factors include: a high calcium-phosphate product, end-stage renal disease on renal replacement therapy, body mass index >30 kg/m², female gender and use of warfarin or systemic corticosteroids.
- ▶ Diagnostic radiological criteria include: arteriolar calcifications of the small subcutaneous vessels.
- ▶ Therapy includes: supportive care with pain control and wound care management; aggressive dialysis with consideration for longer dialysis sessions to improve clearance; lowering the calcium phosphorus product by optimising phosphate binders and switching calcium-based phosphate binders to non-calcium bases such as sevelamer.
- ▶ Clinicians should consider empiric treatment with sodium thiosulfate if there is a strong index of suspicion for calcific uraemic arteriolopathy.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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