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Case Report

Penile gangrene due to calcific uremic arteriopathy

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Abstract

Calcific uremic arteriopathy (CUA) is a rare but potentially life-threatening complication of end-stage renal disease (ESRD) and secondary hyperparathyroidism. It typically presents with ischemic necrosis involving areas of adiposity in the body mainly the trunk, buttocks, or proximal extremity. Patients can also present with digital ischemia and more rarely penile gangrene. The pathogenesis of CUA is not yet clear but several putative factors, mainly hyperparathyroidism and related metabolic abnormalities are implicated. A number of conditions can mimic CUA clinically and should be differentiated from it. We present in the current study, a patient who presented with progressive penile gangrene and skin necrosis due to CUA. We review the current understanding of the pathogenesis, diagnosis/differential diagnosis, and management of this rare but potentially life-threatening complication of ESRD.

Keywords: Calcific uremic arteriopathy, calciphylaxis, end-stage renal disease

Résumé

Calcifiée arteriopathie urémique (CUA) est une complication rare mais potentiellement mortelle de rénale terminale maladie (IRT) et l'hyperparathyroïdie secondaire. Elle présente généralement avec une nécrose ischémique impliquant des zones l'adiposité dans le corps principalement le tronc, fesses ou extrémité proximale. Les patients peuvent également présenter des digital l'ischémie et la gangrène plus rarement du pénis. La pathogenèse de la CUA n'est pas encore clair mais plusieurs facteurs putatifs, principalement des hyperparathyroïdie et des anomalies métaboliques connexes sont impliqués. Un certain nombre de conditions peut imiter. CUA cliniquement et devrait être distinguée sur elle. Nous présentons dans cette étude, un patient qui a présenté avec progressif gangrène du pénis et nécrose de la peau en raison de la CUA. Nous passons en revue la compréhension actuelle de la pathogenèse, diagnostic de diagnostic/prime et la gestion de cette complication rare mais potentiellement mortelle d'insuffisance rénale terminale.

Mots clés: Calcifi c urémique arteriopathie, calciphylaxis, maladie rénale terminale

Introduction

Calcific uremic arteriopathy (CUA) is a rare complication of end-stage renal disease (ESRD) which has a high morbidity and mortality.[1] It is also called calciphylaxis or the most recent functional term, vascular calcification-cutaneous necrosis syndrome.[2] The condition is confined almost exclusively to patients on dialysis therapy, although it has been reported to occur in clinical conditions such as malignancies, alcoholic liver cirrhosis, rheumatoid arthritis, and systemic lupus erythematosus.[1] It is characterized by widespread dystrophic calcification of small and intermediate size blood vessels, predominantly of skin and subcutaneous tissues.[3] A high index of suspicion is necessary for early diagnosis and treatment.

Case Report

A 72-year-old man, known to have ESRD on hemodialysis for 12 years, presented with complaints of severe pain and progressive black discoloration of glans penis of one-week duration. The patient had history of long-standing diabetes mellitus, hypertension, dyslipidemia, and hepatitis C virus-related chronic liver disease. He had his left forefoot amputated for gangrenous toes around 4 years before presentation. On examination the patient was pale, confused febrile (38.6°C), and tachycardic (pulse rate, 124 per minute). Blood pressure from right brachial artery in supine position was 160/94 mm/Hg and body mass index was 25.2 Kg/m^2. Dorsalis pedis and posterior tibial artery pulses were normal bilaterally. There were multiple ulcerations and eschars over trunk and limbs [Figure 1]. A hard black eschar was noticed over the glans penis [Figure 2]. Foul smelling discharge was coming out of urethra and undersurface of penile lesion. Laboratory investigations at admission revealed polymorpholeukocytosis (white cell count, 17.5 x 10^9/μL with 85.2% neutrophils) and normocytic anemia (Hb, 5.3 gm/dl and mean corpuscular volume, MCV, 90 fL), elevated sedimentation rate (120 mm/H [normal 0 – 10 mm/H]) and C reactive proteins, 125 mgs/l (normal, 0 – 6 mgs/l). Random blood glucose was 8.4 mmols/l. Renal function tests revealed urea of 47.2 mmols/l, creatinine of 674 μmols/l, and bicarbonate of 18 mmols/l. Other serum electrolytes were normal. His liver function tests were normal except for low albumin (12 g/l). His corrected serum calcium was 2.4 mmols/l (normal range, 2.22 – 2.59 mmols/l) and phosphate was elevated (2.36 mmols/l [normal range, 0.81 – 1.58]). Serum calcium-phosphate product was elevated, 5.7 mmols^2/l^2 (normal values, less than 4.4 mmols^2/l^2) as well as serum parathyroid hormone was 33.43 pmols/l (normal 1.6 – 6.9 pmols/l). Cultures from the urethral discharge grew *Citrobacter freundii* and *Pseudomonas aeruginosa*. Immunologic tests including antinuclear antibodies, anti ds-DNA, antineutrophil cytoplasmic antibodies, and cryoglobulins were negative. Noncontrast computed tomography scan of pelvis revealed widespread vascular calcification [Figure 3]. The patient was started on piperacillin-tazobactam and later switched to ciprofloxacin as per the antibiotic susceptibility reports. Urologist suggested local wound while he was continued on maintenance hemodialysis. Over a few days on admission, the penile gangrene progressed up to midshaft with excruciating pain, requiring increasing doses of opioids. The patient declined penectomy as suggested by the urology team and local debridement was performed. Two days later, the patient left against medical advice.

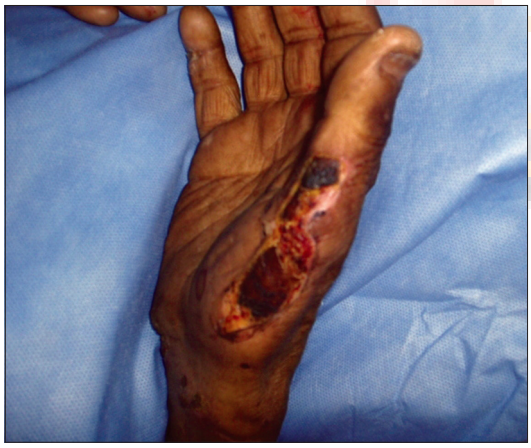

Figure 1: Ulcerations and eschars in the limbs

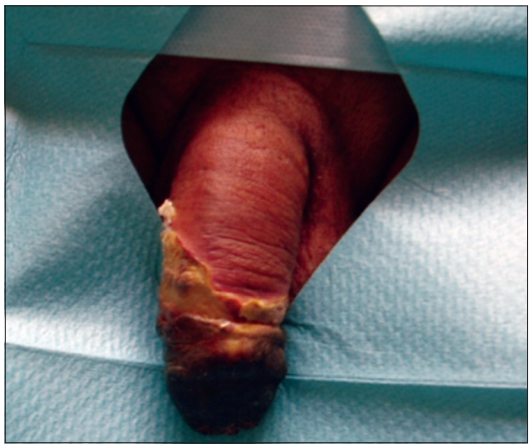

Figure 2: Gangrenous glans penis

Discussion

CUA typically presents with ischemic necrosis predominantly involving areas of adiposity in the body such as the trunk, buttocks, or proximal extremity. However, non-adipose areas can be involved and patients can present with digital

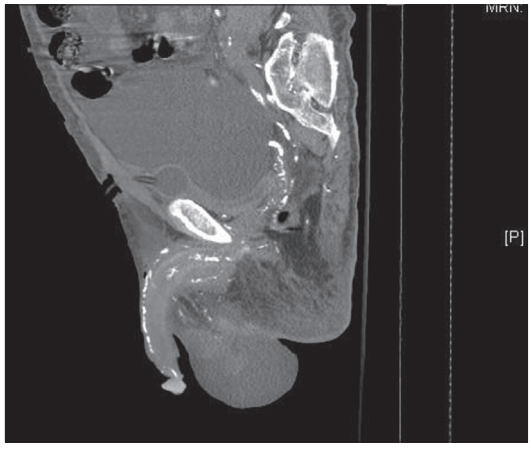

Figure 3: CT-scan showing extensive vascular calcifications, particularly the dorsal penile vessels

ischemia and more rarely penile gangrene as is the case with this patient.

Although the pathogenesis of CUA is still poorly understood, secondary hyperparathyroidism, persistent elevation of serum phosphorus, and consequent increased calcium-phosphorus product has been postulated to play a role in vascular calcification and CUA.[1] However, most patients with hyperparathyroidism do not have skin necrosis and many patients with CUA do not have hyperparathyroidism.[1] The patient presented in the present study had elevated calcium phosphate product and serum parathyroid hormone (PTH) level marginally above the recommended limit of 33 pmoles/l.[4] Many other factors have been implicated in the pathogenesis of CUA, but there is no correlation between the severity of any of these factors and the development of CUA.[1] Patients with calciphylaxis have been shown to have increased expression of osteopontin (bone matrix protein) by vascular smooth muscle cells that might trigger and/or enhance vascular calcification.[5]

CUA is more likely a result of interplay of many pathogenic factors. Risk factors apart from prolonged dialysis that predispose ESRD patients to calciphylaxis include Caucasian race, female gender, insulin-dependent diabetes mellitus, Warfarin therapy, and obesity.

Clinically, patients with CUA present with severe livedo reticularis that progress to excruciatingly painful ischemic ulceration of skin (triggered by superimposed thrombosis of involved blood vessels) that ultimately forms large areas of eschar within days. Most often these lesions have acral distribution (toes and fingers) and may be mistaken for vasculitis and atherosclerotic peripheral vascular disease. Gangrene of penis, secondary to calciphylaxis, has been reported to carry high mortality rate.[6] Bacteria can proliferate under eschar, causing wound infection and sepsis which account for high mortality rate (60 – 80%) associated with the condition.[7] Demonstration of widespread calcification of vascular smooth muscles and fibrinous thrombi occluding vessel lumina in absence of inflammation confirms the diagnosis.[8] Radiological studies show vascular calcification that may alternatively suggest diagnosis as is the case in this patient. Early recognition of the condition together with liberal pain control and prevention and/or treatment of infection (local wound care and appropriate antibiotics) are critical to allow wound healing and decrease morbidity and mortality in these patients. Debridement of the wound is a controversial issue and in general should not be performed unless the eschar is unstable (wet and infected) and perfusion status of the skin (which could be assessed by transcutaneous oxygen pressure measurement) is adequate.[9] Many patients end up with amputation of the gangrenous part for controlling pain and infection. Although parathyroidectomy (to control hyperparathyroidism) may have important long-term advantages in patients with calciphylaxis, it does not appear to affect outcome in these advanced cases. Sodium thiosulphate has also been used with varying degrees of success, but lack of prospective studies precludes its use as a standard treatment for CUA.[1] Therefore, this was not used in this patient. More recently, there are reports of the successful treatment of calciphylaxis with the calcimimetic drug Cinacalcet.[10] However, this was not used in this patient as reports are still anecdotal and the patient's PTH level was just marginally above the recommended limit of 33 pmoles/l.[4]

CUA should be differentiated from the diseases that could have similar clinical presentations such as Warfarin skin necrosis, cryoglobulinemia, vasculitides, cellulitis, nephrogenic fibrosing dermopathy, and cholesterol embolization, which are all unlikely in the patient presented here based on history of physical examination and the laboratory results.

In conclusion, CUA is a relatively rare complication of ESRD with high morbidity and mortality. The exact etiopathogenesis has not yet been fully elucidated, but many putative factors have been implicated. Various modalities of treatment are currently used, but there is a dire need to find a more clear cut etiopathogenesis in order to develop a definitive treatment of this crippling condition which otherwise confers a very high mortality risk.

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