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Calcifying panniculitis following subcutaneous injections of nadroparin-calcium in a patient with osteomalacia

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None declared.

Summary

Calcifying panniculitis is a rare form of calcinosis cutis belonging to the spectrum of calciphylaxis that has almost invariably been described in patients with severe renal disturbances. We report a patient with osteomalacia without chronic renal failure, who developed calcifying panniculitis following subcutaneous administration of nadroparin-calcium. Light microscopy studies of biopsy specimens revealed multiple foci of microcalcification within the adipose lobules, in the interadipocyte spaces, in connective tissue septa and in the media of small arteries in the subcutis. The patient had an elevated level of intact parathyroid hormone, whereas the calcium-phosphorus product was normal. The lesions slowly resolved upon discontinuation of nadroparin. We conclude that calcifying panniculitis is a rare complication associated with the subcutaneous administration of nadroparin-calcium that may rarely also occur in the absence of renal disturbances. Low molecular weight calcium-containing heparins should probably be used with caution in the presence of hyperparathyroidism.

Low molecular weight heparins are routinely used for the prevention and treatment of thromboembolic events. Subcutaneous injections of low molecular weight heparins containing calcium or sodium may result in various local side-effects including haematoma, cutaneous induration, urticaria, allergic skin reactions and skin necrosis.[1,2] Rarely, subcutaneous injections with the low molecular weight heparin nadroparin containing calcium salts have led to the development of calcifying panniculitis. Calcifying panniculitis is a peculiar form of calcinosis cutis thought to belong to the spectrum of calciphylaxis and is characterized by calcium deposits confined to the subcutaneous adipose tissue.[3]

Calciphylaxis is a rare life-threatening condition characterized by calcifications and thromboses involving small to medium-sized arteries of the dermis and subcutaneous fat. This disorder occurs almost exclusively in association with an underlying disease associated with a disturbance of the calcium–phosphate balance.[4] We report a middle-aged paraplegic woman who developed calcifying panniculitis at sites of nadroparin-calcium injections. While she had no evidence of an underlying renal disease, she had osteomalacia which most probably predisposed the patient for this unusual complication.

Case report

A 51-year-old African-American woman was admitted to our hospital for management of a depressive state. She had been paraplegic and wheelchair-bound for the previous 10 years because of a traumatic brain injury. Her past history was otherwise unremarkable. During hospitalization, she developed spontaneous bilateral fractures of her tibias. Bone densitometry showed a severe diffuse osteopenia. Laboratory investigations revealed normal levels of calcium (2·29 mmol L^{-1}, normal 2·20–2·52), phosphate (0·89 mmol L^{-1}, normal 0·80–1·50), urea (2·3 mmol L^{-1}, normal 2·8–7·1) and creatinine (44 mmol L^{-1}, normal 35–88). The vitamin D 25-OH-cholecalciferol (12·5 nmol L^{-1}, normal 20–90) level in the serum was decreased, while the intact parathyroid hormone (45·2 pmol L^{-1}, normal 1·2–6·0) was significantly increased.

Based on clinical and laboratory findings, the patient was diagnosed as having osteomalacia with secondary hyperparathyroidism. She was given oral calcium (1 g daily) and vitamin D_3 (2000 IU daily). Furthermore, she received subcutaneous injections of a low molecular weight heparin, nadroparin-calcium, 5700 IU daily, in the abdominal area and in both thighs. After 3 months of hospitalization, she progressively developed painful nodules localized at the sites of injections of nadroparin-calcium. Clinical examination revealed multiple tender, poorly delimited, subcutaneous indurated nodular lesions and plagues, up to 2·5 cm in diameter. Some lesions were crusted and showed a scarring tendency (Fig. 1). Full blood count, serum chemistry, liver function tests and urinalysis were within normal limits. The erythrocyte sedimentation rate was increased to 40 mm in the first hour.

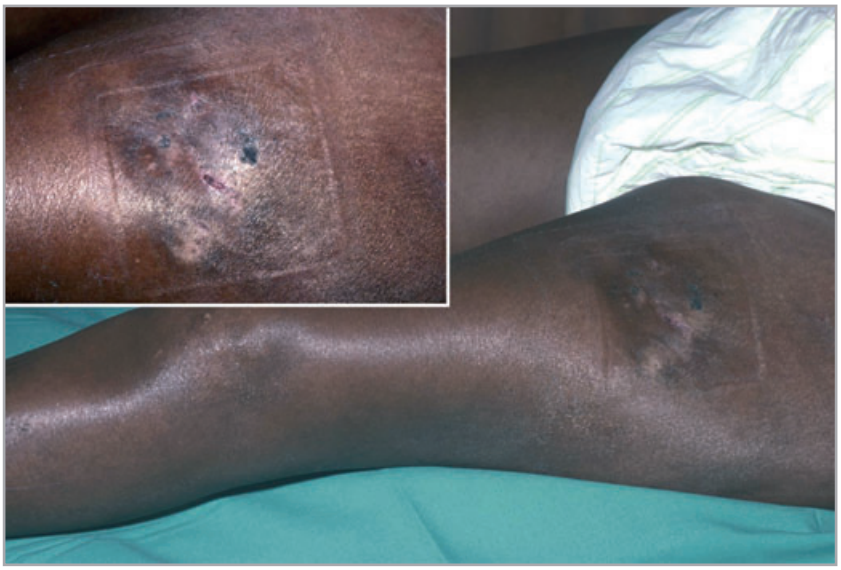

Fig 1. Presence of poorly delimited subcutaneous indurated plaques and nodular lesions with crusts and scarring.

Protein electrophoresis and immunoelectrophoresis showed no evidence for a monoclonal gammopathy. The prothrombin time was 37% (normal 80–120), while the activated partial thromboplastin time was normal at 29·6 s (normal 25–32). A search for antinuclear antibodies, antineutrophil cytoplasmic antibodies and rheumatoid factor was negative. Chest X-ray was normal.

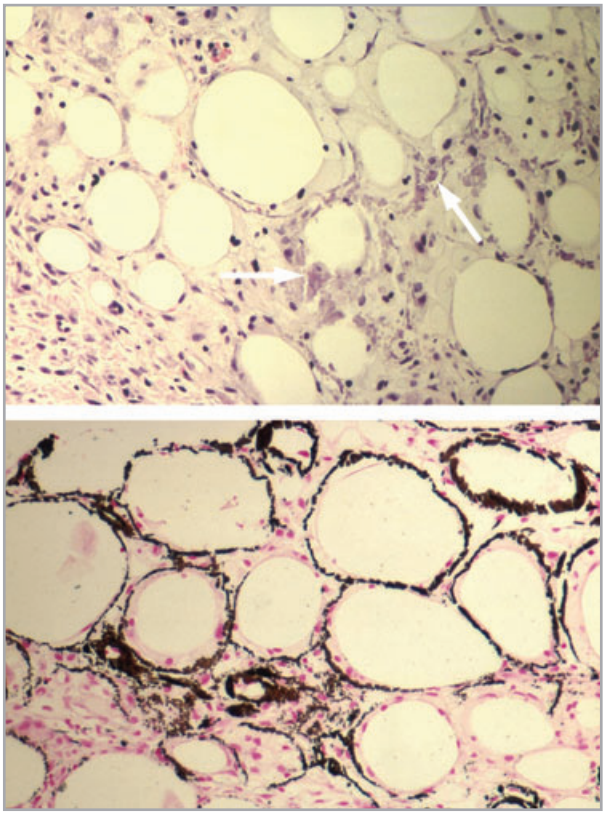

Fig 2. (a) Light microscopy study of a biopsy specimen demonstrates multiple foci of calcification (arrows) within the adipose lobules, in the interadipocyte spaces and in the media of small arteries (haematoxylin and eosin; original magnification ×40). (b) Black-stained calcium deposits localized around the adipocytes, in interadipocyte spaces and in the media of small arteries (von Kossa; original magnification ×40).

Light microscopy studies of a nodule of the left thigh revealed multiple foci of microcalcification within the adipose lobules, in the interadipocyte spaces, in connective tissue septa and in the media of small arteries in the subcutis (Fig. 2a). These foci were positive with von Kossa staining (Fig. 2b). The arteries also showed intimal fibrosis and thickening, while no thrombi were noted. The administration of nadroparin-calcium was stopped and the patient was given oral acenocoumarol. Under this regimen, the skin disease slowly improved with progressive regression of the plaques and cutaneous nodules during a 6-month follow up.

Discussion

Our observation illustrates the potential occurrence of a calcifying panniculitis in association with the use of nadroparin, a low molecular weight heparin containing calcium salts. Our case is unusual in that the skin lesions were widespread and severe and occurred in the context of an osteomalacia without evidence for renal disturbance.

Calcifying panniculitis is an uncommon but severe condition. It is a distinct form of calcinosis cutis thought to belong to the spectrum of calciphylaxis and is characterized by calcium deposits confined to subcutaneous adipose tissue.[3] It presents as painful plaques and subcutaneous nodules, which may undergo necrosis. Lesions predominantly involve regions rich in adipose tissue, such as the abdomen and thighs. Calcifying panniculitis has almost invariably been described in association with an underlying disease resulting in a disturbed calcium–phosphate balance, such as in end-stage renal disease and secondary hyperparathyroidism.[3]

So far, only seven cases of calcinosis subcutis following injections of the low molecular weight heparin nadroparin have been described in the English language literature.[5–7] In all these cases, chronic renal failure was present, parathyroid hormone levels were elevated and the calcium–phosphate product was increased. In contrast, our patient had no evidence of an underlying renal disorder, but showed high parathyroid hormone level due to osteomalacia, with a normal calcium–phosphate product. In affected patients, light microscopy studies have usually disclosed calcium deposits in both dermis and subcutis, whereas in our case calcium deposits were confined to the subcutis. In all cases, the lesions progressively resolved without necrosis or secondary infection after the nadroparin injections were stopped.

Calcifying panniculitis is thought to represent a peculiar form of calciphylaxis involving the subcutaneous adipose tissue without systemic involvement. Calciphylaxis, also known as calcific uraemic arteriolopathy, represents a peculiar type of metastatic cutaneous calcification.[8] It is a small and medium-sized vessel vasculopathy characterized by mural calcification, intimal hypertrophy and thrombosis, that cause tissue ischaemia leading to cutaneous necrosis and ulceration with potential systemic involvement. Calciphylaxis, which carries a high mortality rate, most commonly occurs in patients with end-stage renal disease who are on dialysis or who have undergone kidney transplantation.[9] Calcifying panniculitis should be differentiated from other forms of calcinosis cutis, of which four different forms are recognized:[4] metastatic calcifications, dystrophic calcifications, idiopathic calcinosis cutis and iatrogenic calcification. The first form comprises metastatic calcifications that usually appear in the context of secondary hyperparathyroidism with abnormal calcium and/or phosphate metabolism. Calcifications predominantly affect the cardiovascular system, kidneys, lungs and gastrointestinal tract. Cutaneous metastatic calcifications are uncommon and are localized at periarticular sites and on fingertips.[10] Dystrophic calcifications are the result of calcium salt deposits in previously damaged or diseased tissue without disturbance of calcium or phosphate metabolism. The latter are commonly seen in autoimmune connective tissue diseases such as systemic scleroderma.[4] Idiopathic calcinosis cutis is a uncommon disorder, sporadic or associated with Down syndrome, and appears more often in childhood or adolescence. Finally, iatrogenic calcification is due to the rapid precipitation of calcium salts within the skin after intravenous administration of calcium or phosphate as well as to calcium salt exposure from electroencephalography and electromyographic electrode components.[4]

Selye and Nielsen first used the term 'calciphylaxis' based on experimental observations in an animal model.[11,12] Experimental calciphylaxis was associated with the local or systemic tissue deposition of calcium salts followed by inflammatory necrosis. These deposits were induced by a 'sensitizer', such as bovine parathyroid hormone, vitamin D and analogues, after administration of a 'challenger'. The latter may include metal salts, albumin and physical trauma, as well as nephrectomy and nephrotoxic insults, which act as precipitating factors.

In our patient, it is conceivable that the calcium salts of nadroparin-calcium together with local trauma related to the subcutaneous injections acted as triggers in a sensitized environment with high parathyroid hormone level due to osteomalacia and with exogenous intake of vitamin D_3 and calcium. In analogy to our case, there are reports of patients who developed calcinosis subcutis following nadroparin-calcium injections which regressed spontaneously once this treatment was discontinued.[5,6,7] These patients did not show any reaction following injection of low molecular weight heparins containing sodium salts, an observation implying that the presence of calcium salts in nadroparin was implicated in the development of lesions. Finally, it has been claimed that infections[13] as well as mast cells can also favour pathological calcification.[11,12,14–16] In our case, no mast cells were observed close to the calcium deposits in the adipose tissue.

There is no specific therapy for calcifying panniculitis induced by nadroparin-calcium. All reported cases resolved after discontinuation of nadroparin.

In conclusion, we describe the occurrence of calcifying panniculitis following subcutaneous injections of the heparin nadroparin-calcium in a patient with elevated parathyroid hormone level; clinicians should be aware of this rare complication. Use of low molecular weight calcium-containing heparins should be carefully evaluated in the presence of hyperparathyroidism.

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