Calcifying panniculitis in a child after renal transplantation

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Introduction

The most important cause of calcium deposits in humans is hyperparathyroidism (primary or secondary) with an elevated calcium phosphate product. Systemic deposition in predisposed organs, i.e. cardiovascular system, lungs, kidney, stomach, and intestines, is the most frequent manifestation. Most cases occur in individuals with chronic renal failure while on renal replacement therapy who suffer from overt hyperparathyroidism [1,2]. Systemic calcium deposits are also described in other conditions such as calciferol intoxication, milk–alkali syndrome, rickets, infantile hypercalcaemia, collagen diseases, leukaemia, lymphoma, and multiple myeloma [2]. Localized calcium precipitation is far less commonly seen and the most frequent presentations are (1) ‘calcifying vasculitis’ with deposits predominantly seen in the vessels with subsequent cutaneous necrosis that may lead to gangrene, and (2) ‘calcifying panniculitis’ when calcium deposits are confined to subcutaneous adipose tissue [2,3]. The latter is the most uncommon form and often results in cutaneous necrosis with secondary infection that may ultimately lead to death.

The present article reports on calcifying panniculitis associated with subcutaneous low-molecular-weight heparin administration in a boy after renal transplantation.

Case report

F.C. developed end-stage renal failure secondary to posterior urethral valves at 13.9 years of age when he received his first renal transplant (pre-emptive, cadaver donor), which was lost 1 month later from arterial thrombosis. Subsequently he was treated with regular haemodialysis for 17 months with several thrombotic episodes of the vascular accesses. At 15.4 years of age he received a second kidney (cadaver donor) and standard triple immunosuppressive therapy. Subcutaneous low-molecular-weight heparin (LMWH) (nadroparin calcium, Fraxiparine, Sanofi Winthrop France, 3075 UI/day) was administered as a prophylactic measure.

Early graft function was adequate and serum creatinine declined from a pretransplant value of 830 mmol/l to 175 mmol/l 10 days after grafting. The patient experienced two episodes of acute rejection; the first occurred on day 17 and was successfully controlled by methylprednisolone pulses and the second occurred on day 43 and was treated with orthoclone OKT3 for 10 days. Shortly after discharge, the patient developed another severe rejection episode due to non-compliance with the immunosuppressive therapy. He therefore required haemodialysis and concomitant methylprednisolone pulses. He did not respond to steroid therapy, and antithymocyte globulin was administered. At this time (day 93), inflammatory subcutaneous nodules were noted in the abdomen, calves, and arms. A technetium 99m bone scan was performed, which showed numerous labelled spots at the same sites where LMWH had been injected. There were no signs of systemic involvement (Figure 1).

Pretransplant calcium–phosphate laboratory values were: total serum calcium 2.70 mmol/l, phosphate 1.10 mmol/l, and intact parathyroid hormone (PTH) 83 pg/ml (normal 20–55). At the time of the bone scan (day 93), the results were: total serum calcium 2.70 mmol/l, phosphate 1.90 mmol/l, and PTH 199 pg/ml. He was then receiving oral calcium carbonate (3 g/day) as a phosphate binder and alfacalcidol (1 mg/day).

After the nodules were discovered, oral calcium carbonate and LMWH were discontinued, which resulted in a progressive reduction of the lesions and finally their complete disappearance. Neither cutaneous necrosis nor secondary infection occurred during the evolution. Graft function progressively improved, and 6 months after transplantation inulin clearance was
Calcium deposits in a child after renal transplantation

Table 1. Calcium × phosphate product

<table>
<thead>
<tr>
<th>Days post-transplantation</th>
<th>Event</th>
<th>Ca × P product (mmol × mmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Transplantation</td>
<td>2.9</td>
</tr>
<tr>
<td>17</td>
<td>1st rejection episode</td>
<td>5.0</td>
</tr>
<tr>
<td>43</td>
<td>2nd rejection episode</td>
<td>2.5</td>
</tr>
<tr>
<td>75</td>
<td>3rd rejection episode</td>
<td>7.9</td>
</tr>
<tr>
<td>80</td>
<td>2 weeks before bone scan</td>
<td>7.0</td>
</tr>
<tr>
<td>93</td>
<td>99mTc bone scan</td>
<td>5.1</td>
</tr>
<tr>
<td>180</td>
<td>Inulin clearance test</td>
<td>2.8</td>
</tr>
</tbody>
</table>

40 ml/min/1.73 m², PTH 79 pg/ml, total serum calcium 2.30 mmol/l, and serum phosphate 1.20 mmol/l. Phosphate binders were no longer needed and low-dose alfalcacidol (0.25 μg/day) was maintained.

Discussion

The exclusive subcutaneous deposition of calcium without systemic or arterial involvement supports the diagnosis of calcifying panniculitis in the reported patient. To our knowledge, isolated calcifying panniculitis has not been described in children so far. In general, tissue calcification has rarely been observed in children with renal disease. Drachman et al. [6] reported that four of 18 children on dialysis had pulmonary calcifications, and Milliner et al. [7] found tissue calcifications at autopsy in 72 of 120 paediatric patients on dialysis or following renal transplantation; 60% of these 72 children had systemic (mainly vessel, lung, kidney, and myocardial) calcifications, while the remaining 40% had localized deposits (tubules of diseased kidneys, vessels, central nervous system, adrenal glands).

The favourable outcome of our patient, along with the absence of skin necrosis contrast with literature reports in adults, since calcifying panniculitis is associated with a high morbidity and mortality rate, even after parathyroidectomy [2–4]. It is impossible to ascertain whether the resolution of the calcium nodules was due to improvement of graft function and subsequent decrease of serum PTH, or whether calcifying panniculitis generally has a better prognosis in children.

Although we do not have definitive histological evidence, the clinical picture of the patient fits with the definition of calciphylaxis. Increased PTH, vitamin D administration, as well as subcutaneous injections have been described in both animals [8] and humans [4,5] in association with this disease. The Ca × P product was not elevated on the day of the bone scan, but it was moderately high 2 weeks before (Table 1).

Subcutaneous LMWH is associated with several cutaneous pathologies, i.e. skin necrosis, subcutaneous haematomas, allergic reactions, and only very rarely with calcified nodules [5,9,10]. In the reported patient, LMWH should be considered as an important precipitating factor, since neither hyperparathyroidism, nor calcium–phosphate product were excessively elevated. For the above-mentioned reasons, subcutaneous heparins should be regarded as high-risk drugs in patients with hyperparathyroidism, since heparin captures calcium salts. This might be dangerous, particularly in the presence of even moderate elevations of PTH and Ca × P product.

We conclude that calcifying panniculitis is a complication that should be considered in the differential diagnosis when children with any form of chronic renal failure develop subcutaneous nodules. This is particularly true for patients who receive subcutaneous heparin preparations.

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