Crippling bone disease in a 15-year-old girl treated by haemodialysis

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Case history

Born in 1973, this 15-year-old girl was evaluated for kidney transplantation (KTx) in May 1988. A long history of urolithiasis started at the age of 6 months. At age 11 years, she was admitted for regular haemodialysis and submitted to binephrectomy 6 months later. Microscopic examination of the kidneys showed massive calcium oxalate deposition. After 3 years on dialysis, the patient developed increasing proximal bone pain (hips, shoulders, knees, and lumbar spine). At 15 years, walking and standing were impossible and she soon became bedridden. Intact PTH serum levels had persistently been normal since the initiation of dialyses.

On admission, radiological survey of the skeleton demonstrated widespread increase in bone density with coarsening of the trabecular pattern (Figures 1A and 2A). The usual changes of hyperparathyroidism as well as soft tissue calcifications were lacking. The pelvis (Figure 1A) displayed bilateral fractures of the femoral neck, and similar lesions were also present in the upper end of both humeri. Metaphyses of the tubular bones (Figure 2A) showed a wide transversal translucent band, with two thin transversal radiodense lines separating the clear band from the diaphysis and from the growth plate. Typical aspects of 'bone in bone' were clearly visible.

Iliac crest biopsy (Figure 3A) demonstrated irregularly woven and severely lacerated bone structure with numerous broken trabeculae and enlarged haversian system. Large areas of bone marrow were massively invaded with granulomata. Each granuloma consisted of numerous multinucleated macrophagic giant cells and was centered on a large oxalate crystal rosette-shaped edifice. Granulomata were actually disrupting bone trabeculae in some places. Resorption lacunae were present at some distance from granulomata. Severe osteomalacia was demonstrated by the abundance of unmineralised osteoid tissue.

Predialytic plasma oxalate levels ranged from 120 to 150 \( \mu \text{mol/l} \) (normal: 1–3 \( \mu \text{mol/l} \); usual dialysis population: 10–70 \( \mu \text{mol/l} \)).

The diagnosis of primary hyperoxaluria type 1 (PH1) was strongly suggested by the long history of urolithiasis, the extremely high plasma oxalate levels and the massive deposition of oxalate in kidney and
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Therefore, the patient was subjected to combined liver-kidney transplantation (LKTx) in August 1988. PH1 diagnosis was postoperatively confirmed by the considerable decrease of alanine:glyoxylate aminotransférase (AGT) activity measured in the removed liver [2]. Immunosuppression consisted of OKT3-azathioprine-prednisolone, soon followed by cyclosporine-azathioprine-prednisolone.

After an initial acute tubular necrosis requiring the continuance of dialyses for 2 months, the ensuing course was marked by: (i) early dissipation of bone pains (at 4 months, standing was possible and a wheelchair could be used), (ii) steadily increasing creatinine clearance, (iii) hyperoxaluria persisting for 4–5 years, with calculi demonstrated by ultrasound examinations of the kidney graft from 4 months to 5 years after LKTx [3].

Both hips were replaced at 3 and 3.5 years after LKTx, allowing the patient to resume normal physical activities at the age of 19 years. At this time, creatinine clearance was 90 ml/min/1.73 m², oxaluria was 7 μmol/kg/day (normal 5–10 μmol/kg/day), and plasma oxalate concentration was 2 μmol/l.

Figures 1B and 2B demonstrate the disappearance of the radiological bone changes observed prior to LKTx whereas Figure 3B shows the complete disappearance of the medullary granuloma seen in previous bone biopsy, only a few isolated crystals remaining (this is an area particularly rich in oxalate deposits). Irregular woven bone is replaced by normal lamellar bone. Unmineralised osteoid tissue persis in some places.

Comment

Oxalate bone disease has been known since 1955 [4], and its radiological and histopathological aspects have been thoroughly described [5–7]. Most observers considered the bone changes to be due to both oxalate accumulation and secondary hyperparathyroidism, although it was soon recognised that parathyroidectomy was not beneficial. In our patient, serum PTH levels were not increased, and we believe that the bone changes of oxalate osteopathy is mainly due to the granulomatous inflammation generated by massive calcium oxalate deposition within the medullary space. In some places, granulomata may disrupt bone trabeculae. In others, resorption lacunae, mimicking hyperparathyroidism, may possibly result from enhanced osteoclastic activity induced by the cytokines, such as interleukin-1, actively secreted by the macrophages constituting the granulomata.

The anatomical and radiological changes in tubular bones were carefully analysed by Lagier et al. [7]. Oxalate deposits constitute three transversal radiodense lines: (i) one in the metaphysis, (ii) one adjacent to the growth plate, (iii) one parallel with the articular surface. Only the first two are clearly visible in Figure 2A. Oxalate is thus found in active ossification sites where the blood supply is particularly abundant. The translucent band situated between the first two radiodense lines is made up of transversally arranged thickened sclerotic bone trabeculae.

Our patient also illustrates the strategy to be presently recommended for treating end-stage renal failure (ESRF) due to pyridoxine-unresponsive PH1. As discussed elsewhere [8], those patients should not be admitted to long-term dialysis programs since dialyses fail to efficiently extract oxalate. On the other hand, the frequent recurrence of oxalosis within the graft makes KTx particularly inappropriate in this situation since, according to the EDTA Registry [9], graft survival rates are 40% after 1 year and 21% after 3
years in primary oxalosis. Since PH1 is actually caused by the deficiency of the liver-specific peroxisomal enzyme AGT [10], ESRF due to PH1 should actually be treated by LKTx [8]. From 1984 to 1994, 57 such patients were submitted to LKTx in Europe, and current 3-year and 5-year graft survival rates are 78% and 74%, respectively (N. V. Jamieson, data from the European Registry on Primary Hyperoxaluria, 1994). The favourable outcome of our patient also demonstrates that LKTx may completely cure severe oxalate bone disease.

Teaching point

Finally, in the renal stone patient ending in kidney failure, resorptive bone lesions not explained by hyperparathyroidism should strongly suggest primary oxalosis.

References

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