Cystinosis with Sclerotic Bone Lesions

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Received: 31 May 2013 / Revised: 15 July 2013 / Accepted: 30 July 2013 / Published online: 6 October 2013
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Abstract A 26-year-old male with nephropathic cystinosis treated with cysteamine and renal transplantation presented for evaluation of multiple sclerotic bone lesions, which were an incidental finding on chest computerized tomography. These lesions were in a pattern consistent with osteoblastic metastases. He did not have a history of clinically significant hyperparathyroidism or cytopenias either preceding or following his transplant. Bone and tumor markers (including alkaline phosphatase and calcium) were all normal. A percutaneous bone biopsy of the lesions showed changes compatible with cystine deposition. Our case demonstrates that sclerotic bone lesions can be a feature of cystinosis in patients with normal parathyroid function and that significant

bone marrow infiltration with cystine can be present even in the absence of cytopenias.

Nephropathic cystinosis (OMIM 219800) is an autosomal recessive disorder caused by defects in the gene coding for the lysosomal cystine carrier cystinosis (CTNS). Cystinosis causes multiorgan manifestations, including renal insufficiency, eye disease, endocrinopathies, myopathy, and pulmonary involvement (Gahl et al. 2007). Many bone manifestations of cystinosis have been reported, including osteopenia and fractures (Zimakas et al. 2003), renal osteodystrophy, short stature, and hypophosphatemic rickets (Gahl et al. 2007). Bone marrow involvement with deposits of cystine crystals has also been reported in patients presenting with cytopenias (Busuttil and Liu Yin 2000; Quinn et al. 2004; Bigley et al. 2006). We present a case with bone marrow involvement from cystinosis presenting with multifocal osteosclerotic lesions mimicking osteoblastic bone metastases in a patient with normal parathyroid function and no cytopenias.

Communicated by: Eva Morava, MD PhD

Competing interests: None declared

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Case Report

The patient is a 26-year-old male who was diagnosed with cystinosis when he was evaluated at the age of 10 months for bowing of his legs, renal Fanconi syndrome, and corneal crystal deposition. He was placed on oral cysteamine therapy and WBC cystine levels were initially within the target of <1 nmol/mg protein. However, his compliance with therapy as an adult was limited. He went on to develop end-stage renal disease and received a related live donor renal allograft at the age of 14. He did not have significant parathyroid hormone abnormalities

Table 1 Biochemical parameters including tumor markers at the time of evaluation for osteosclerotic bone lesions and parathyroid hormone status pre- and post-transplant

Parameter	Patient values	Normal or target range
Parameters prior to the development of bone lesions		
PTH pre transplant ^a (mean; range)	31.5 pmol/L (14.2–63.3)	16.5–33 pmol/L ^b
PTH post-transplant ^c (mean; range)	5.7 pmol/L (2.1–8.3)	
WBC cystine levels (mean; range for 2 years prior to evaluation for osteosclerotic bone lesions)	1.34 (0.91–2.23) nmol/2Cys/mg pr	<1 (optimal) <2 (still beneficial)
Parameters at the time of evaluation for osteosclerotic bone lesions		
Serum creatinine	110 umol/L	45–110
eGFR	70 mL/min/1.73 m ²	>59
PTH	7.6 pmol/L	1.5–7.6
Total calcium	2.38 mmol/L	2.10–2.60
Alkaline phosphatase	104 U/L	40–145
LDH	179 U/L	90–240
Hemoglobin	143 g/L	135–170
WBC	5.0 giga/L	4.0–11
Platelet count	145 giga/L	150–400
Serum/urine protein electrophoresis	Normal pattern	–
Alpha fetoprotein	4.0 ug/L	<8
Human chorionic gonadotropin	<2.0 IU/L	<10
Prostate-specific antigen	0.37 ug/L	<2.5
Carcinoembryonic antigen	1.2 ug/L	<5

^a Values are in the 15 months prior to live donor renal transplantation. In this time interval, his glomerular filtration rate declined from 21.7 to 7.8 mL/min/1.73m². He was on intermittent hemodialysis for 6 weeks prior to transplantation

^b Target parathyroid hormone level for children with chronic kidney disease (National Kidney Foundation Kidney Disease Outcomes Quality Improvement Guidelines)

^c Values are for the 12 years following live donor renal transplantation. In this time interval, his renal function was normal

prior to or after his transplant (Table 1). Chest X-rays done around the time of his transplant showed vertebral osteopenia but no compression fractures and no other abnormalities.

He underwent regular assessment of his pulmonary function as is recommended in patients with cystinosis (Anikster et al. 2001) and a progressive reduction in his diffusing capacity to 67% of the predicted value with preserved lung volumes was noted over serial pulmonary function tests done over 3 years. This pattern was not suggestive of myopathic pulmonary dysfunction (Anikster et al. 2001) but was more suggestive of possible interstitial lung disease, and he underwent computerized tomography as is recommended in the evaluation of patients with possible interstitial lung disease (Behr 2012) at the age of 26. Although the chest CT showed no evidence of involvement of his lung parenchyma, multiple sclerotic lesions were noted in his vertebral bodies (Fig. 1a and b), which were confirmed by MRI (Fig. 1c). The low signal intensity on T1W and T2W MRI (Fig. 1c) and increased uptake on bone scan was suggestive of osteoblastic metastases (Fig. 1d).

The patient at this time was clinically well and had no symptoms of fevers, night sweats, or weight loss. Blood work, including calcium, alkaline phosphatase, tumor markers, and hematologic parameters, was all normal (Table 1). CT of his neck, abdomen, and pelvis did not show lymphadenopathy or organomegaly.

In this patient with a history of renal transplantation, the clinical index of suspicion for malignancy was high and so a percutaneous biopsy (Fig. 1a) of one of the sclerotic lesions in his right anterior superior iliac crest was performed. This biopsy (Fig. 2a–c) showed thickened benign trabecular bone with scattered aggregates of histiocytes and admixed hematopoietic elements in the marrow space. There was trilineage hematopoiesis present, but the overall cellularity was decreased. These aggregates of histiocytes were found to be CD68 positive and S100 negative immunohistochemically, which further confirms their nature as histiocytes. They contained abundant pale clear cytoplasm, which was filled with variably sized angular vacuolated spaces, in contrast to the small uniform

Fig. 1 Radiologic findings showing osteosclerotic bone lesions. (a) Axial CT scan of the lumbar spine demonstrating multiple well-defined sclerotic lesions in the vertebral bodies and pelvis. The biopsy needle can be seen entering a lesion at the anterior superior aspect of the right iliac blade. (b) Sagittal CT view of the lumbar spine showing the sclerotic lesions. (c) T1 and T2 weighted images MRI of the

lumbar spine demonstrating lesions of low signal intensity on T1W and T2W imaging within the vertebral bodies and posterior elements. Appearances correlate with the sclerotic nature of the lesions on CT. (d) Technetium 99m-labeled bone scan showing multiple areas of uptake in the spine, pelvis, and proximal tibia corresponding to the lesions seen on CT and MRI

round vacuoles that are sometimes seen within the cytoplasm of histiocytes present in reactive processes like fat necrosis. The appearance of these vacuolated intracytoplasmic spaces within the histiocytes was unusual compared to typical foamy appearance previously documented in hereditary cystinosis (Gebrail et al. 2002). This was a highly unexpected finding as, given the sclerotic appearance on the imaging, crystalline deposits were not considered in the differential diagnosis prior to the biopsy, which was subjected to aqueous tissue processing as is standard in our institution. While no polarizable crystal material was identified, the aqueous tissue processing would have completely dissolved the putative cystine crystals, leaving behind only the “ghost” outline of these angulated clear intracytoplasmic spaces. This was therefore

interpreted, in the present clinical context, as being consistent with cystine accumulation in the histiocytes.

Follow-up MR imaging of these lesions performed 6 months later was unchanged.

Discussion

This case is interesting for three reasons. Firstly, this patient demonstrated a marked osteosclerotic response without parathyroid hormone abnormality. It is unclear whether there is a relation between the cystine accumulation in marrow histiocytic aggregates and the osteoclerotic changes, as cystinosis presents more often with osteopenia (Zimakas et al. 2003). Sclerotic lesions in bone are most often related to metastatic disease (Leffler and Chew 1999).

Fig. 2 Histological findings of right iliac core biopsy. (a) Low power magnification (4× objective) showing thickened trabecular bone and clusters of histiocytes in the marrow space. (b) Intermediate magnification (10× objective) showing clusters of histiocytes with clear/vacuolated cytoplasm intermixed with hematopoietic marrow. (c) High magnification (40× objective) shows aggregates of histiocytes that show clear vacuolated cytoplasm with angulated ghost outline of crystals dissolved by aqueous tissue processing

Hematologic disorders, including systemic mastocytosis (Fritz et al. 2012), Langerhans cell histiocytosis, and Erdheim-Chester disease (Wilejto and Abala 2012), can also present with sclerotic bone changes, although there are usually other features on history of imaging to suggest these and the negative S100 immunostaining of the histiocytes from the biopsy exclude Langerhans cell histiocytosis. Nonmalignant causes of sclerotic bone lesions include Paget's disease, osteopoikilosis (Woyciechowsky et al. 2012), and parathyroid-related bone disease. There is a single case (Quinn et al. 2004) where marrow involvement with cystine crystals was accompanied by changes suggestive of parathyroid-related bone disease in a patient with marked elevation (20-fold upper limit of normal) of parathyroid hormone levels. We do not believe that the sclerotic lesions we are seeing in our case are related to parathyroid bone disease for several reasons:

1. His parathyroid hormone levels (Table 1) were controlled within suggested targets (National Kidney Foundation 2003) for end-stage renal disease prior to transplantation.
2. Parathyroid hormone levels have been normal post-transplantation.
3. The bone lesions were clearly not present on imaging done prior to the transplant when his parathyroid hormone levels were highest.
4. The radiologic finding of multiple discrete sclerotic lesions (and reduced bone mineral density is not typical for parathyroid related bone disease in patients with renal disease where the sclerosis is more often diffuse (Burnstein et al. 1985).

This case is also unique because the patient did not have significant cytopenias. Bone marrow involvement with cystine crystals has been documented by other authors (Busuttill and Liu Yin 2000; Quinn et al. 2004; Bigley et al. 2006), but all patients presented with refractory anemia and, in some cases (Busuttill and Liu Yin 2000; Quinn et al. 2004), other cytopenias.

Conclusion

Our case shows that cystine accumulation in histiocytes can occur in cystinosis patients prior to the onset of cytopenia. It also documents multifocal osteoclerotic changes of the bone in a cystinosis patient without parathyroid hormone abnormalities.

Conflict of Interest

Sandra Sirrs, Peter Munk, Paul Mallinson, Hugue Ouellette, Gabriella Horvath, Susan Cooper, Gerald Da Roza, Debbie Rosenbaum, Margaret O'Riley, Gary Nussbaumer, Lien

Hoang, and Cheng Lee have no disclosures related to this manuscript.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Contributions of the Individual Authors

All authors contributing to the planning, conduct, and reporting of the work described in this article and all authors have approved the manuscript. Radiologic images were analyzed and provided by Drs. Munk, Mallinson, and Oulette. Histology images were analyzed and provided by Drs. Hoang and Lee. Clinical information about the patient (before and after his transplant) was provided by Drs. Sirrs, Rosenbaum, Cooper, Horvath, Da Roza, Nussbaumer, and Ms. O'Riley. Dr. Sirrs serves as guarantor of the work.

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