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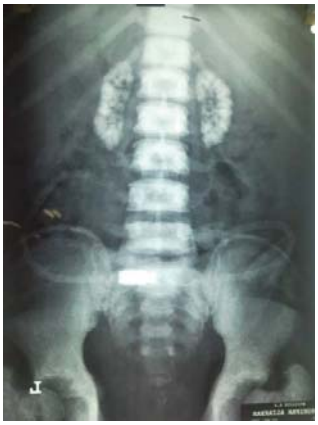

Figure 1. Nephrocalcinosis, small shrunken kidneys with extensive calcium deposits.

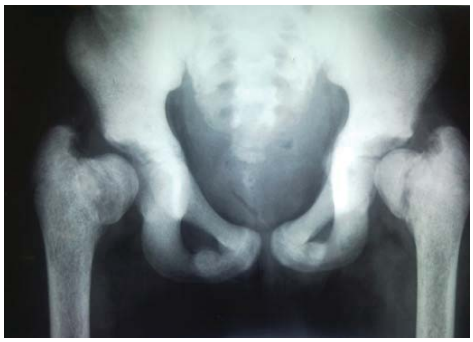

Figure2. Bone changes, generalized osteosclerosis with slipped femoral epiphyses.

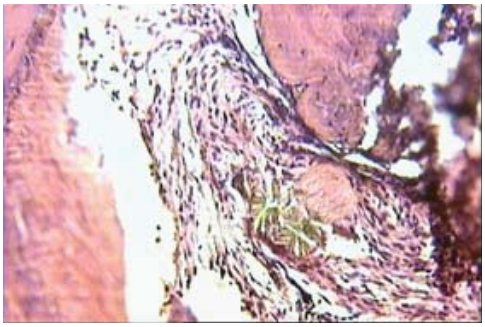

Figure 3. Bone marrow biopsy, severely hypocellular with foreign body granulomas that contain oxalate crystals (H&Ex20)

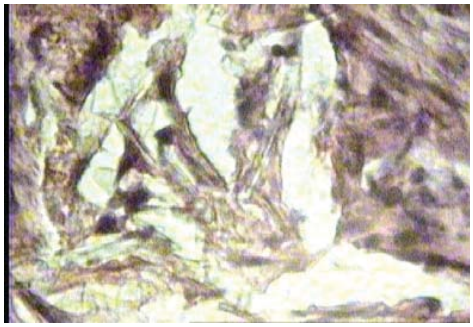

Figure 4. Bone marrow biopsy containing needle like crystals compatible with oxalosis (H&Ex40)

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Our patient was an 18-year-old boy who was the sixth child of his family. His parents were close relatives. A positive history of death before one year of age (infantile death) was present in four of his siblings. At age 8, the first symptoms of his disease including dysuria and flank pain began. In the laboratory evaluation performed, urinary calcium oxalate stones and nephrocalcinosis were detected and diagnosis of bilateral multiple calcium oxalate stones was proposed. In spite of treatment for his renal stones, he showed no improvement and his kidneys gradually became shrunken and renal failure developed with extensive calcium deposition (Figure 1). Unfortunately, the managements were done without performing a renal biopsy. At the age of 10, he was admitted to nephrology department of Mofid Children Hospital for the first time with End Stage Renal Failure (ESRF) while anuric. Since he had no confirmed diagnosis, he underwent renal transplantation. Transplanted kidney failed one year later and since then, he is under peritoneal dialysis. He has been admitted for several times due to pain and swelling in several joints. Splenomegaly and ocular findings (alternative ectropion) were also present. In laboratory evaluation, serum calcium and phosphate levels maintained normal with phosphate binders but PTH level was always markedly elevated most of the times. Serial CBCs showed progressive pancytopenia. Brucella and rheumatologic tests including ANA, RF, P-ANCA and C-ANCA were negative. In radiographies, generalized osteosclerosis (Figure 2), multiple growth arrest lines in distal femur and proximal tibia and fibula with lytic areas in long bone metaphyses were seen. Ehler myer deformity, areas of bone within bone and coxa vara was also detected. All these changes proposed a renal osteodystrophy and oxalosis-induced bone complications. In the last bone marrow examination, severely hypo-cellular bone marrow with oxalate crystals were seen (Figure 3 and Figure 4). The patient is a candidate for a simultaneous liver and kidney transplantation.

What is your diagnosis?
See the Next Page

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Photoclinic Diagnosis: **Primary hyperoxaluria**

Primary hyperoxaluria (PHO) is a rare metabolic disorder with autosomal recessive inheritance which presents with recurrent nephrolithiasis and early end stage renal failure.[1]

The first symptoms occur before one year of age in 15 percent and before 5 years of age in 50 percent of patients.[2]

Affected children, present with symptoms of urolithiasis (renal colic, hematuria, and urinary tract infection) or, in some cases, complete obstruction with acute renal failure. The calcium oxalate stones are bilateral and radiopaque on x-ray examination. Some patients present in adulthood with end-stage renal disease.[1] Serum levels of oxalate do not reflect the total amount of oxalate present within the body, since significant reservoirs of oxalate reside within the bone marrow and soft tissue. Unfortunately, neither haemodialysis nor peritoneal dialysis is effective in reducing total body oxalate stores significantly.[3]

PHO1, in general, has five presentations: 1) an infantile form with early nephrocalcinosis and kidney failure; 2) recurrent urolithiasis and progressive renal failure leading to a diagnosis of PHO1 in childhood or adolescence; 3) a late-onset form with occasional stone passage in adulthood; 4) diagnosis suggested and confirmed only by post-transplantation recurrence and; 5) pre-symptomatic subjects with a family history of PHO1.[4]

Type 1 and 2 PHO disease can be distinguished by assessing the urinary excretion of glycolate and L-glyceric acid:

1. Most patients with type 1 PHO have increased glycolate excretion.
2. Nearly all patients with type 2 diseases have increased excretion of L-glyceric acid.[5]

When the glomerular filtration rate declines to below 25 mL/min per 1.73 m2, the combination of oxalate overproduction and reduced urinary oxalate excretion results in systemic oxalosis with calcium oxalate deposition in many tissues, including the heart, blood vessels, joints, bone, and retina.[6]

Early diagnosis of primary hyperoxaluria is of vital importance so that treatment can be initiated as soon as possible. Yet, due to lack of familiarity with the disease, delays of many years from onset of symptoms to diagnosis are common. Early diagnosis can improve the chance for long term renal function, thereby obviating the need for renal replacement therapy. All the pathological sequelae of the primary hyperoxalurias are related to the increased synthesis and excretion of oxalate. The majority of patients are symptomatic before 10 years of age. Oxalate at high concentrations with calcium in the urine forms crystals that form in the urinary tract leading to stones, and also deposit in kidney tissue causing nephrocalcinosis. Calcium oxalate crystals are also directly injurious to renal cells and incite a granulomatous reaction in the renal interstitium. Over time the effects of such injury, often combined with intermittent obstruction or infection related to stones, lead to kidney failure.[7]

Current approach to PHO 1 consists of measures to increase excretion of oxalate and prevent oxalate crystal formation within the renal tubules and stone formation within the collecting system. Pyridoxine has been found empirically to decrease oxalate production in a significant portion of patients, possibly by increasing the function of abnormal hepatic alanin glyoxylate aminotransferase (AGT).[8] Patients who develop ESRD from PHO 1 have generally had poor long term clinical outcomes.[9]

A liver biopsy is particularly required for a definitive diagnosis prior to hepatic transplantation, except in patients with a known genotype or with a sibling with a definitive diagnosis.[8]

Liver transplantation successfully corrects the underlying AGT enzymatic defect and kidney transplantation replaces lost renal function.[10] Preemptive isolated liver transplantation might be the first-choice treatment in selected patients before advanced chronic renal failure has occurred, at a GFR between 60 and 40 ml/min/1.73m^2 and this may improve renal function.[11] Major advances in biochemistry, enzymology, genetics, and management have been achieved during recent years. Improved knowledge of the disease, early and accurate diagnosis, before renal failure occurs, and aggressive supportive treatment are of critical importance for the prognosis. In (pre)ESRD patients, the greatest experience has been obtained with one-step combined liver-kidney transplantation.[12] Patients may require dialysis support for months in order to deplete the systemic load of oxalate and reduce serum oxalate concentrations to safe levels. Initial results suggest that multi-system complications of oxalate deposition stabilize or clear with a successful combined liver–kidney transplantation.[13]

New insights into potential therapies including the restoration of defective enzymatic activity through the use of chemical chaperones and hepatocyte cell transplantation, or recombinant gene therapy for enzyme replacement provide hope for curative treatments of primary hyperoxalurias in the future.[14,15]

Based on these reports, the planned approach for our patient is combined liver and kidney transplantation.

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