# Oxalosis

## Report of a Case and Brief Review of Literature*

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Oxalosis, or primary hyperoxaluria, is a rare genetic disorder of glyoxalate metabolism clinically characterized by calcium oxalate urolithiasis, nephrocalcinosis, recurrent urinary tract infections and disseminated extrarenal calcium oxalate deposits.[1] The characteristic pathologic feature of the disease is the deposit of double refractile calcium oxalate crystals in the tissues. As a result of an inborn error of metabolism of glyoxylic acid, a highly endogenous oxalate is formed which is metabolically inert, consequently excreted into the urine (hyperoxaluria) and deposited in the kidney and extra-renal tissues. Calcium oxalate deposition in the kidney results in impairment of renal function and stone formation.[1-6]

The object of this article is to present for the first time in Turkish literature a case of oxalosis in a 20-month-old female and to review briefly the pertinent literature.

### *Case Report*

*Clinical Summary*: A 20-month-old female was seen at Hacettepe Children's Hospital because of swelling of the body, paleness, vomiting and coughing of one month's duration. She was the third child of first cousins, a 28-year-old female and a 30-year-old male. Her three siblings, aged 7 years, 5 years and 4 months, were alive and well. Past history was noncontributory; her growth and development were reported as normal.

*Physical Examination*: Weight was 8,700 grams, height 71 cm, rectal temperature 37°C, pulse 120 and regular, respiration 26 and systolic blood pressure 90 mm Hg. There was pallor of the skin and mucous membranes.

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The face appeared swollen and edematous. Examination of the chest, heart, lungs and other systems revealed no abnormalities. There was two plus pitting edema of the extremities.

*Laboratory Findings*: A complete blood count revealed hemoglobin to be 5.3 grams/100 ml (increased to 12.50 grams/100 ml after transfusion), WBC 5,000 to 6,000 per $mm^3$ with an unremarkable differential, reticulocytes 1 per cent, hematocrit 15 to 25 per cent, and thrombocytes 1 per 144,000/$mm^3$. Peripheral smears showed hypochromia and anisocytosis. There was ertythroid hyperplasia of the bone marrow; no crystals were seen. Repeated urinalysis showed pH 5.8, trace to one plus albumin, abundant leukocytes, few erythrocytes and occasional epithelial cells. Specific gravity ranged from 1.005 to 1.010. Twenty-four hour urine excretion measured 400 cc, the patient having been given 600 to 800 cc of fluid. Urine culture grew abundant E. coli. NPN varied from 110 to 252 mgm/100 ml; total serum protein was 6.1 gm/100 ml with 3.5 gm albumin; chlorides 90 mEq/L; $CO^2$ ranged between 10.04 and 19.9 mEq/L; calcium between 4.8 and 7 mgm/100 ml; phosphorus between 7.2 and 11 mgm/100 ml; sodium and potassium were 136 and 4.25 mEq/L respectively; alkaline phosphatase 4.0 Bodansky units; and uric acid 5.9 mgm/100 ml.

*Roentgenographic Examination*: Roentgenograms of the chest and cranium showed no abnormalities; those of the extremities revealed some osteoporosis. On flat films of the abdomen both kidneys appeared smaller than normal with irregular contours, and several small round bilateral calcific opacities appeared to be confined to the renal parenchyma. Apart from this nephrocalcinosis, no stones were visible within the renal calyces or pelvis.

*Clinical Course*: During hospitalization the patient received I. V. fluids, blood transfusions, vitamins, antibiotics, aluminum hydroxide, calcium lactate and diuretics. Milk and milk products were not given. Despite therapy, the patient died of renal failure on the 65th day after admission. Immediately after death, using the needle biopsy technique, tissue from the kidneys and liver were obtained for microscopic examination. Permission for autopsy was not granted.

*Microscopic Examination:* Hematoxylin and eosin-stained sections of the kidneys were found to contain an average of 15 glomeruli and an abundant number of renal tubules. The glomeruli showed no increased cellularity or thickening of the basement membrane. There was slight thickening of the Bowman's capsule in some of the glomeruli. The tubules were markedly dilated and their lumina and epithelia were filled with unstained, slightly yellowish, ordinary light refractile crystals (Figure 1).

They varied in shape but generally had a broken-plate appearance with some areas having a triangular, needle-like shape. The tips of the crystals were oriented to the lumina and under polarized light showed birefringence (Figures 2 and 3). No crystals were seen within the glomeruli, interstitial tissues or the walls of the vessels. There were foci of a mild mononuclear inflammatory cell infiltrate and slight fibrosis of the interstitial tissues. Sections of the liver were unremarkable and using ordinary and polarized light no crystals were demonstrable.

Histochemical studies were done on kidney tissues. Von Kossa reaction was positive (Figure 4). Solubility tests were done on deparaffinized and unstained sections and the results were as follows: the crystals were soluble in sulfuric and in hydrochloric acid, but insoluble in glacial acetic acid, potassium hydroxide and sodium carbonate. Using Johnson's microincineration method for calcium oxalate, tissue sections[7] were left at 400°C for half an hour and later concentrated sulfuric acid was added. Under direct microscopic observation bubbles of $CO_2$ were seen.

## *Discussion*

Despite the frequency with which oxalates are found in the urine of normal persons and the high proportion of renal stones composed of oxalate, deposition of crystals in the renal parenchyma is rare.[3 8] Davis et al[9] in 1950 published the first description of this unusual condition found in a child with kidney stones, renal parenchymal calcification and calcium oxalate crystals in the kidneys and bones. They suggested that a defect in calcium oxalate metabolism was present. However, the term oxalosis was first used by Chou et al[10] in 1952 who suggested the possibility of an inborn error of metabolism in which oxalic acid is formed in an excessive amount and combined with calcium to form relatively inert compounds. Dunn[11] reviewed a series of 14 cases and concluded that evidence favored a primary disturbance of oxalate metabolism in which deposits of calcium oxalate occurred in kidneys and in some cases in other viscera. Chemical analysis of stones from a patient with oxalosis revealed mostly calcium oxalate monohydrate.[12] X-ray diffraction studies of dried kidney tissue from a patient with oxalosis revealed calcium deposits identified as calcium monohydrate.[13] Archer et al[2] first used the term primary hyperoxaluria in 1957 to describe a condition which exhibits excretions of urinary oxalate ranging from 100 to 400 mgm per 24 hours. (The finding of calcium oxalate in urine and a 10 to 30 mgm excretion of oxalic acid per day in urine is normal.[2 11]) These studies showed no evidence of a high urinary output of oxalic acid resulting from the absorption of an abnormally large portion

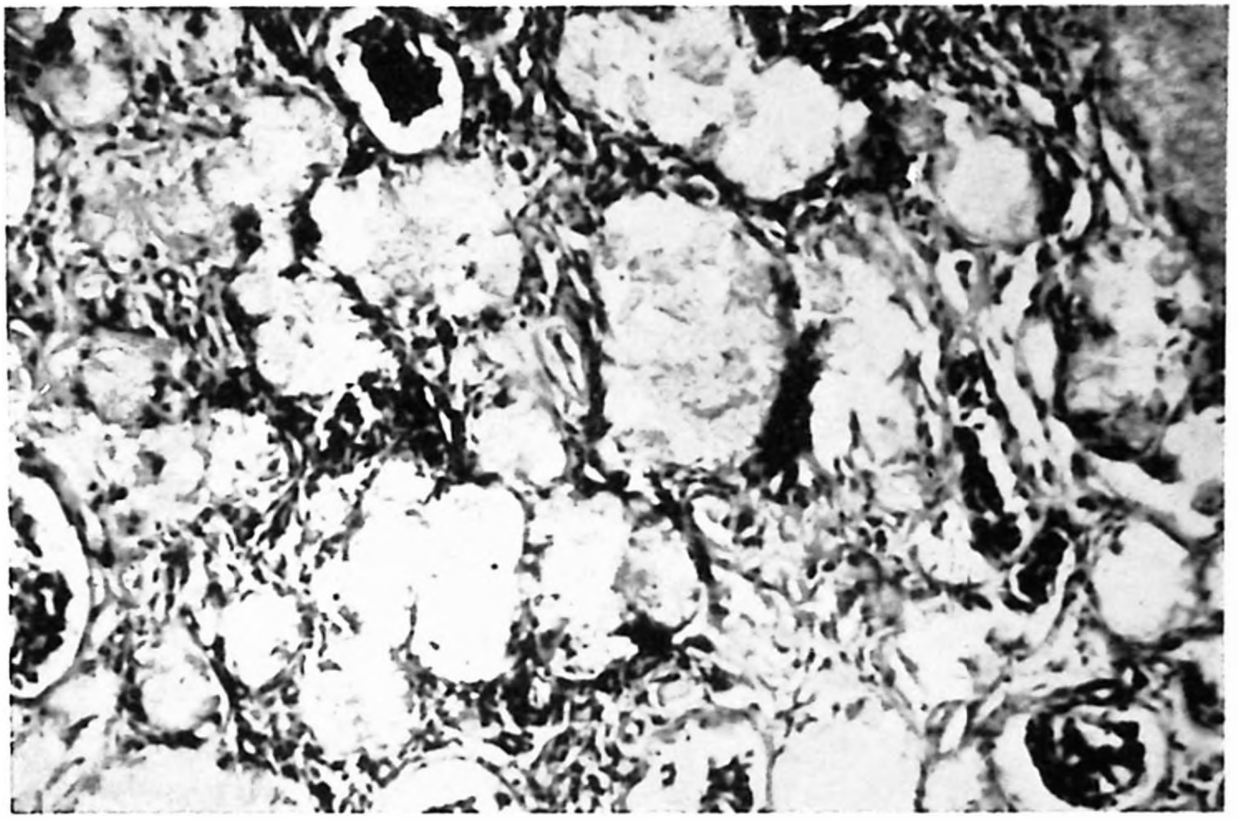

**Figure 1.** H-and E-stained sections under medium power show markedly dilated tubuli filled with crystals. There is mild interstital fibrosis and focal mononuclear cell infiltrate.

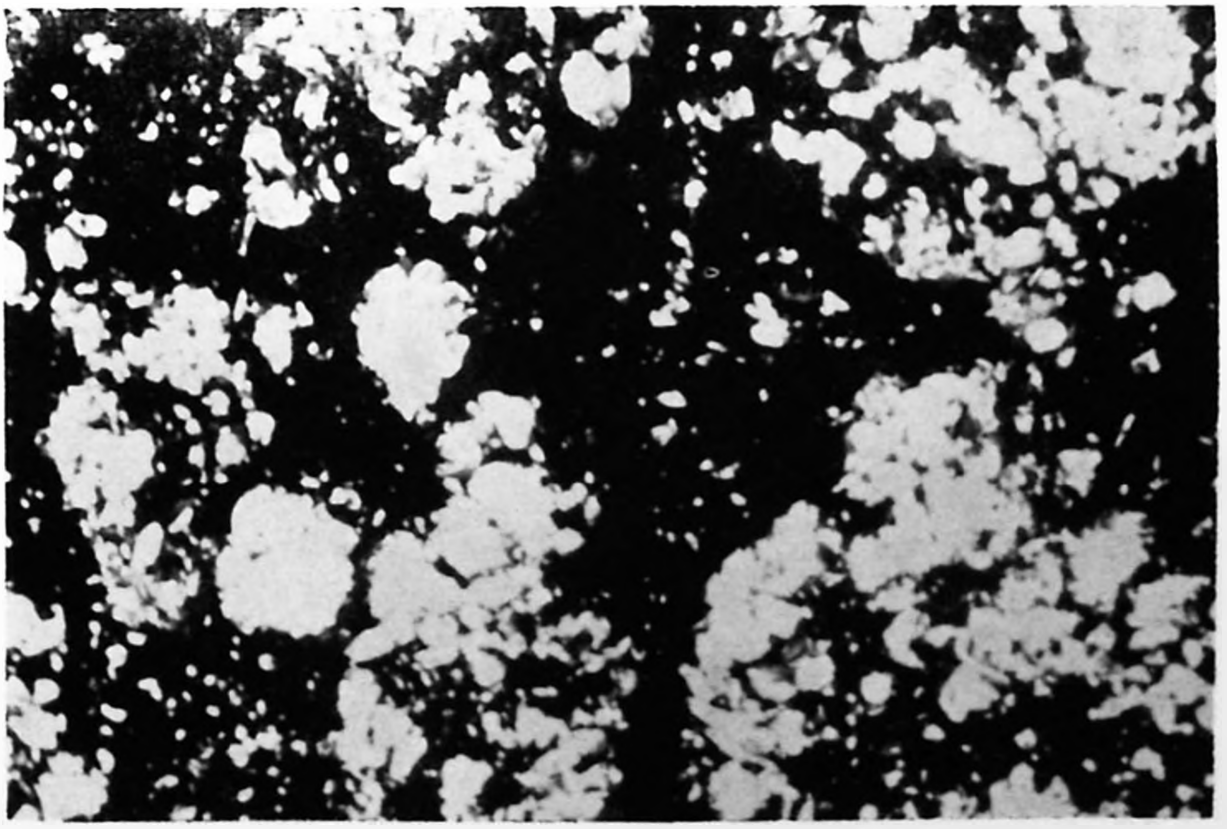

**Figure 2.** Under low power and polarized light only double refractile crystals are seen.

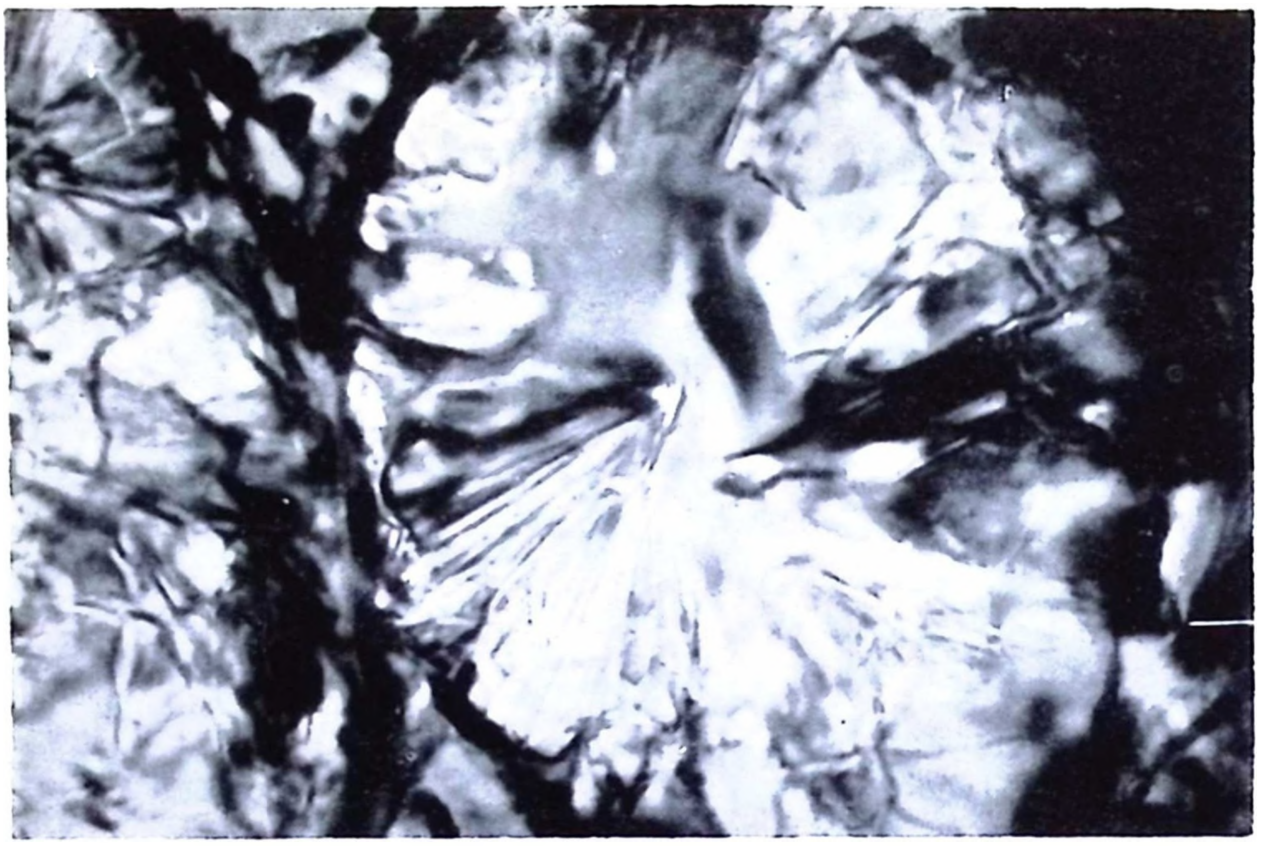

**Figure 3.** Under high power, H-and E-stained sections show crystals of calcium oxalate.

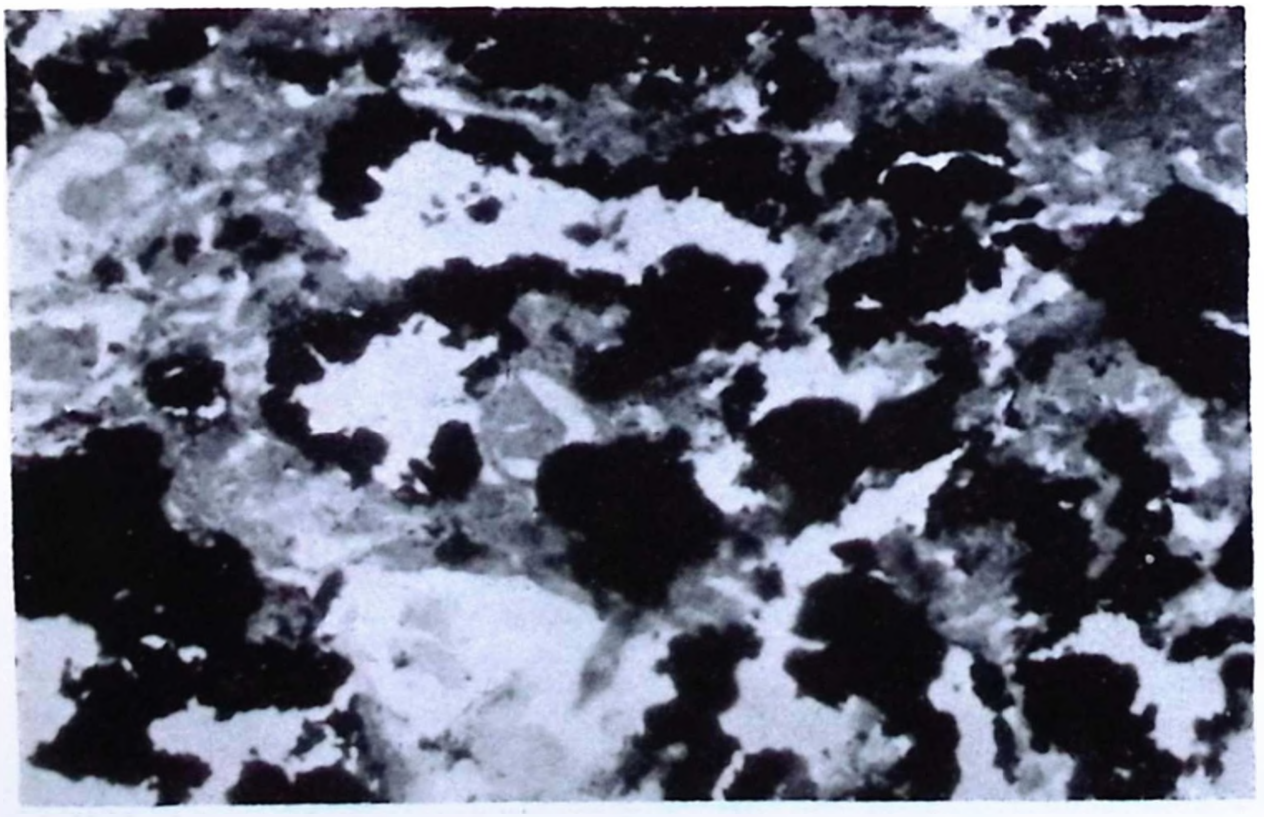

**Figure 4.** Under medium power using Von-Kossa stain, calcium is seen as dark deposits.

of a given dose of oxalate or of a foodstuff containing oxalate. Crawhall et al,[14] using isotopically-labeled carbon in primary hyperoxaluria, have shown that glycine is the precursor of urinary oxalate, probably via glyoxylate. As a result of an inborn error of metabolism involving failure to degrade glyoxylate to formic acid and $CO_2$, an abnormal conversion of glyoxylate to oxalate occurs. Scowen et al[15] reported that administration of sodium benzoate significantly diminishes urinary excretion of oxalate in patients with primary hyperoxaluria and similarly acts on glycine to form hippurate which causes depletion of the pool of available glycine. Recently Frederick et al,[16] using isotopically labelled glyoxylate, demonstrated impairment of metabolism to $CO_2$ and formic acid and also discovered that on the average there was five times the normal amount of glycolic acid in the urine. They suggested the name of primary hyperglycoluria for this metabolic disorder.

*Site of Metabolic Abnormalities*: Previous studies have not shown an abnormality of glyoxylate metabolism in the liver tissue,[17] erythrocytes or leukocytes.[16] Recently, radiochemical methods[5] have shown defective glyoxylate metabolism in kidney tissue from a patient with primary hyperoxaluria. More recent studies[5] have shown two types of defective enzyme activity. One is 2-oxo-glutarate:glyeoxylate carboligase in cytoplasmic extracts of liver, kidney and spleen.[18] The second glyoxylate enzyme defect shown by Williams and Smith[19] is D-glyceric dehydrogenase in leukocyte preparations. They suggested reclassification of oxalosis as type I-glycolic aciduria in which the enzyme 2-oxo-glutarate:glyoxylate carboligase is defective; and type II-L-glyceric aciduria in which D-glyceric dehydrogenase is defective. Both types produce excessive oxalic acid in urine.

The relationship between primary hyperoxaluria and oxalosis is not yet known. Since both are cases of increased secretion of oxalic acid in urine without evidence of calcium oxalate deposition,[20] secondary precipitation of calcium oxalate crystals may occur in a variety of conditions, for example uremia.[21-24] This secondary oxalosis should be differentiated from primary oxalosis. Calcium oxalate crystals have also been found in poisoning from solvents used in industry and freezing-point depressants containing ethylene glycol.[25] Similar crystals, such as cystine and sulfathiazole, are easily differentiated by simple histological methods. Chemical methods, such as the x-ray diffraction technique, may be used but are not necessary for diagnosis.

*Clinical Features*: Oxalosis is a rare disease which can occur at any age, but the majority of cases involve children under 10 years of age, the youngest[13] being four and a half months old. The oldest patient described

was 66 yearsold [4]. The disease, transmitted as an autosomal recessive trait, was most frequently reported in males, and familial occurrence has also been reported.[8 20 27 29]. An interesting feature of our case was the consanguinity of the parents. Consanguinity has been reported in only four cases[6] and its value in the clinical diagnosis of the disease has been mentioned.[1] We feel that its value in diagnosis is complicated by the presence of frequent consanguinous marriages in Turkey.

*Symptoms:* Hematuria, pyelonephritis, hypertension associated with pyelonephritis and kidney stones are the most frequent symptoms of oxalosis. Oxalate stones are common (of the reported kidney stones in the United States, about 30 per cent are of calcium oxalate[1 2]), but oxalosis is rare, the reason for this is unknown. Oxalosis should be considered in the differential diagnosis of clinically demonstrable nephrocalcinosis.[29] Growth and development are disturbed during the terminal phase of the disease.

*Laboratory Findings:* With a few exceptions, x-ray films show nephrolithiasis and nephrocalcinosis. There is increased calcium oxalate, glycolate, glyoxylate and L-glyceric acid excretion in the urine.[2 6 18 19] Low levels of calcium and roentgenographic bone findings eliminate parathyroid hyperplasia,[13] therefore it is suggested that the urine be examined rather than the parathyroid[30] to make the diagnosis. The other serum findings are those associated with uremia. In a few cases, as in ours, increased uric acid levels have been found.[30]

*Treatment:* The most important point in therapy is the control of glyoxylate metabolism. Except for one patient whose urinary oxalate decreased under pyridoxine,[31] no effective treatment for primary hyperoxaluria has been reported.[20] In a recent study[32] the possibility of reducing urinary oxalate excretion in primary hyperoxaluria by giving drugs(Allopurinol, Disulfiram, and Acetomenaphthone) to inhibit enzymes which oxidize aldehydes to carboxylic acid and by restricting protein in the diet, were unsuccessful. Similarly pyridoxine and pyridoxine plus folic acid did not lower urinary oxalate excretion.[32] Williams and Smith[19] suggested that, in the absence of specific therapy, attempts should be made to decrease oxalate excretion and increase calcium oxalate solubility in the urine by such measures as pyridoxine, a high phosphate regimen and magnesium oxide.

The clinical course varies: in some cases, such as ours, the disease is acute and death occurs within a few months; in others the course is chronic with intermittant, symptom-free periods, the longest reported being 22 years.[1] The cause of death is almost always renal failure.

In our case the diagnosis was made on renal tissue obtained by needle biopsy technique immediately after death. Biopsy diagnosis in live patients has been reported.[4 24]

## *Summary*

A case of oxalosis in a 20-month-old female with edema, anemia, pyelonephritis with nephrocalcinosis, acidosis, oliguria and uremia is described for the first time in Turkish literature. Diagnosis was established by examination of renal tissue obtained by immediate post-mortem needle aspiration technique. Clinical and microscopic features, as well as the pathogenesis of the disease and a review of the pertinent literature, are presented. Evidence suggests that this metabolic disorder of glyoxylate metabolism results in the precipitation of calcium oxalate crystals which can easily be demonstrated by kidney biopsy technique and the value of this technique in the diagnosis of the disease is worth emphasizing. Other points of interest are the consanguinity of the parents, which is consistent with the recessive transmission of the disease, and elevated uric acid levels in the serum.

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