Primary Oxalosis with Pan-Conduction Cardiac Disease: Electrophysiologic and Anatomic Correlation

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SUMMARY A 27-year-old man with primary oxalosis and extensive visceral involvement was maintained on long-term chronic hemodialysis. He had an episode of presyncope associated with electrocardiographic findings of an erratic atrial rhythm, atrioventricular dissociation due to an accelerated junctional rhythm and right bundle branch block. Electrophysiologic studies showed irregular atrial depolarizations probably associated with multiple atrial pacemakers, atrial inexcitability, atrioventricular dissociation and infranodal conduction delay. These findings correlated well with extensive oxalate infiltration of the sinoatrial node and its approaches, the atrial preferential pathways, the approaches to the atrioventricular node, the atrioventricular node, and the His bundle and bundle branches. This is the first reported case of cardiac electrophysiologic abnormalities due to oxalate infiltration in a patient with primary oxalosis.

PRIMARY OXALOSIS is a rare hereditary metabolic disorder in which there is excessive accumulation of calcium oxalate in tissues and formation of calcium oxalate renal calculi.1 2 This disorder usually manifests in childhood with hematuria or renal stones and progresses to renal insufficiency and death before or during early adulthood. Although the clinical presentation of oxalosis is dominated by its renal manifestations, accumulation of calcium oxalate crystals has occurred in many other tissues,1 8 including the heart.4 12

We report the case of a 27-year-old man with longstanding oxalosis who developed evidence of cardiac pan-conduction system disease. Electrophysiologic studies were performed to determine the nature of the conduction disturbances. Postmortem studies enabled detailed evaluation of the conduction system. This is the first case of clinical-electrophysiologic-pathologic correlation in a patient with oxalosis and may provide some insight into the pathophysiology of other infiltrative processes that involve the heart.

Case Report

Clinical Summary

A 27-year-old white male patient with longstanding oxalosis was admitted to the Veterans Administration Hospital, San Francisco, on May 17, 1979 because of progressive dyspnea and palpitations. Sixteen years earlier the patient had passed a calcium oxalate stone after an episode of flank pain and hematuria. He was asymptomatic until age 18 years, when he again passed several stones. During the next 5 years, he had recurrent renal calculi, multiple episodes of pyelonephritis, and progressive renal insufficiency. The left kidney was removed when the patient was 20 years old and the right kidney was resected 4 years later; at this time the diagnosis of oxalosis was first made based on pathologic examination of the kidney and bone marrow. Careful questioning revealed a maternal grandfather with a history of multiple kidney stones. After a year of hemodialysis, a cadaveric kidney was transplanted but became calcified and was removed. Eighteen months before admission, partial parathyroidectomy was performed for treatment of severe renal osteodystrophy. In April and May 1979 the patient deteriorated rapidly: He lost 20 pounds and began to experience severe bone pain and generalized fatigue. Chronic home peritoneal dialysis was instituted in place of hemodialysis, but this produced little change in his clinical course. Progressive dyspnea and an episode of near-syncope developed and the patient was admitted to the hospital.

On physical examination, the patient was cachectic but alert and in no acute distress. He had an occasionally irregular pulse at a rate of 90 beats/min, a blood pressure of 90/60 mm Hg, and was afebrile. Positive findings were dullness and decreased breath sounds over the left lower lung field, a parasternal lift, a loud P2 and a grade 2/6 systolic ejection murmur at the left sternal border. The abdomen was distended and slightly tender, but with normal bowel sounds.

Pertinent laboratory results were as follows: blood urea nitrogen 64 mg/dl, creatinine 10.6 mg/dl, normal serum electrolytes, calcium 7.3 mg/dl, phosphate 7.7 mg/dl, alkaline phosphatase 300 mU/ml, uric acid 8.1 mg/dl, hemoglobin 6.9 g/dl, and hematocrit 20%. The chest roentgenogram showed a large left pleural effu-
sion, which on thoracentesis contained sterile serosanguineous fluid. The ECG showed a generally regular ventricular rhythm at a rate of 74 beats/min with a right bundle branch block configuration, but occasional beats occurred early and appeared to be preceded by P waves (fig. 1). No atrial activity was apparent on most tracings. The last previous electrocardiographic tracing, from a year earlier, had shown normal sinus rhythm and a minor right ventricular conduction defect.

Electrophysiologic studies were performed to evaluate the rhythm and conduction abnormalities and to assess the need for permanent pacing. During the succeeding days, however, dyspnea developed and increased and pleural effusions recurred. An echocardiogram revealed normal left ventricular size and function but a dilated right ventricle. Eight days after admission, severe abdominal pain developed. During the next 24 hours, the patient became febrile and exhibited physical signs of an acute abdomen. He subsequently became progressively hypotensive and acidic. A decision not to perform surgery was made in collaboration with the patient and his family, and the patient died several hours later.

**Electrophysiologic Findings**

A quadripolar electrode catheter was passed into the heart through the right femoral vein in order to record intracardiac potentials. Simultaneous surface leads X, Y and Z of the Frank orthogonal lead system were displayed on an oscilloscope and recorded simultaneously at a paper speed of 100 mm/sec.

The atrial recordings showed a slow and erratic atrial rate with marked variation in the atrial depolarization complexes (fig. 2). Similar recordings were obtained from multiple right atrial and coronary sinus sites. Attempted atrial pacing from multiple right atrial sites (and from the coronary sinus) failed to result in atrial capture. All explored atrial sites proved inexorable despite use of 10 mA of current flow and a 2-msec pulse duration. No atrial mechanical contractions were visible during fluoroscopy.

Atrioventricular dissociation due to an accelerated junctional pacemaker with only a rare atrial depolarization occurring late in the ventricular diastolic cycle resulted in capture (fig. 3). The HV interval was prolonged (70 msec) and the ventricular complex was broad, with a right bundle branch block contour. Ventricular capture was achieved with a current threshold of 2 mA.

**Pathologic Findings**

The major pathologic abnormalities were found in the heart, lungs, and gastrointestinal tract. There were bilateral serosanguineous pleural effusions, 300 ml on the right and 1200 ml on the left. Fibrinous pleuritis was present bilaterally and there was intraparenchymal hemorrhage extending to the pleural surface in the left lung. Microscopically, there was calcium oxalate deposition within the pulmonary veins, often to the point of complete occlusion with resulting venous rupture.

The mucosa of the entire alimentary tract was hyperemic and friable, with circumscribed hemorrhagic areas. Calcium oxalate crystals were identified in the suberosal and submucosal veins throughout the gastrointestinal tract. There was ulceration, inflammation and coagulation necrosis of the mucosa, which often extended to the serosal surface, in the esophagus, stomach and small and large bowel. Membranous ischemic colitis and areas of infarction were noted in the colon. Extensive bacterial and candidal invasion were present throughout the gastrointestinal tract.

Microscopic oxalosis was present in most organs and tissues. Calcium oxalate deposition was found in the media of all examined medium-sized muscular arteries and throughout the venous system. Parenchym-
mal and interstitial oxalosis were present in the bladder, testes, skeletal muscle, nerves, and bone marrow. The immediate cause of death was thought to be shock secondary to sepsis originating in the gastrointestinal tract.

Cardiac Pathology

Gross Examination

The heart was enlarged and weighed 449 g. Both atria and the left ventricle were hypertrophied and enlarged and the right ventricle was hypertrophied. The endocardium of both atria and both ventricles was focally thickened and whitened.

Microscopic Examination

The sinoatrial and atrioventricular nodes and their approaches and the atrioventricular bundle and bundle branches up to the region of the moderator band were serially sectioned and every tenth section was retained. Consecutive sections were stained with hematoxylin-eosin, Weigert-van Gieson's and Gomori's trichrome stains. The atrial preferential pathways were serially sectioned and every fortieth

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**Figure 2.** Simultaneous recordings of surface leads X, Y and Z of the Frank orthogonal lead system and three close bipolar right atrial electrograms (RA1, RA2 and RA3). This strip shows atrioventricular dissociation due to an accelerated junctional rhythm with an erratic atrial rhythm. The marked variations in the atrial electrograms suggest multifocal atrial activation; retrograde atrial activation cannot be excluded.

**Figure 3.** Simultaneous recordings of surface leads X, Y and Z of the Frank orthogonal lead system and multiple recordings from the region of the tricuspid valve (HBE1,2,3) show a junctional rhythm with the His bundle deflection preceding the surface ventricular complex by 70 msec.
nuclear cells and oxalosis of the adventitia and media of small arteries. The muscle cells, in many instances, were thinned and frayed, with increase of eosinophilia of cytoplasm, marked enlargement of some nuclei and pyknosis of others. Occasional arterioles were thickened and slightly narrowed. Oxalate crystals were occasionally found in the subendocardial areas.

Atrial preferential pathways. A marked infiltration with oxalates was present (fig. 4) and was associated with marked fibrosis of muscles and vascular changes as previously described. Fatty infiltration was marked.

Approaches to the atrioventricular node. There was marked fatty infiltration of the approaches with confluent deposits of oxalate crystals in the inferior and upper approaches to the atrioventricular node. The superior approaches showed marked fibrosis, with a moderate-to-marked infiltration of mononuclear cells in the fat tissue. The media of the ramus septi fibrosi was markedly infiltrated with oxalate crystals (fig. 5).

Findings

Conduction System

Sinoatrial node. The parenchyma showed a slight-to-moderate infiltration of oxalate crystals, with a slight infiltration of mononuclear cells and increase in connective tissue. The media of the nodal artery occasionally showed oxalate crystals with a slight intimal proliferation.

Approaches to the sinoatrial node. Marked oxalosis was present in the myocardium and epicardium. This was associated with a moderate increase in connective tissue, thickening and degeneration of the collagen fibers, fatty infiltration, a slight infiltration of mono-

Figure 4. Atrial preferential pathways showing oxalosis and fibrosis. Weigert-van Gieson's stain; original magnification × 45. Arrows point to some areas of oxalosis.

Figure 5. Ramus septi fibrosi showing oxalosis of media. Weigert-van Gieson's stain; original magnification × 30. Arrow points to an area of oxalosis.
Immediately adjacent to the atrioventricular node, there was marked fatty infiltration (fig. 6) with a moderate mononuclear cell infiltration. The ramus septi fibrosi in this area was thickened and narrowed.

Atrioventricular node. The entire node was markedly infiltrated with oxalate crystals. The large arterioles were considerably thickened.

Atrioventricular bundle, penetrating portion. Marked infiltration with oxalate crystals was present with associated moderate fibrosis.

Atrioventricular bundle, branching portion. A moderate-to-marked infiltration of oxalate was present with moderate fibrosis and slight infiltration of mononuclear cells.

Left bundle branch. There was a moderate infiltration of oxalate crystals, with focal fibrosis (fig. 7), occasional scars, and a slight infiltration of mononuclear cells in the main bundle. In the radiations there was marked fibrosis with oxalate crystals. The peripheral Purkinje cells showed degenerative, necrotic and fibrotic changes.

Right bundle branch. All three parts of the right bundle branch were moderately infiltrated with oxalate crystals. There was moderate fibrosis of the first part, marked fibrosis of the second part (fig. 8) and practically complete replacement of cells and slight fibrosis and fatty infiltration of the third part.

The Remainder of the Myocardium

Left ventricle and atrium. The left ventricle showed degenerative changes of muscle cells as described earlier, present mostly in the inner half of the anterior wall but also present throughout the posterior wall. The large coronary arteries in the epicardium showed marked oxalosis of the media. Some of the nerves

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**Figure 6.** Atrioventricular node and its approaches showing fatty infiltration of the approaches and oxalosis of the atrioventricular node. Weigert-van Gieson's stain; original magnification ×45. Arrow points to an area of oxalosis.
manifestations with particular emphasis on the electrophysiology and the conduction system pathology because this case represents a unique opportunity to correlate these findings.

Findings in the Present Case

Postmortem examination showed widespread deposition of calcium oxalate crystals surrounded by extensive fibrosis. Involvement of the heart, lungs and gastrointestinal tract played a role in the terminal stage of the illness. Undoubtedly, the extensive oxalate deposition noted on the postmortem examination was in part related to the extended survival afforded by dialysis. Despite the extensive myocardial

were infiltrated with mononuclear cells. The left atrium was not as severely involved.

Right ventricle and atrium. The involvement with oxalosis and secondary changes was much less in the right ventricle than in the left ventricle. The media of the right coronary artery showed marked oxalate infiltration. The right atrium was markedly affected by oxalosis.

Ventricular septum. The summit and middle portion of the ventricular septum was heavily infiltrated by oxalate (fig. 9), resulting in myocardial degenerative and necrotic changes as described earlier with fibrosis. Arteriosclerosis of the summit of the ventricular septum and pars membranacea was present.

Discussion

Although primary oxalosis is rare, it has received considerable attention in the medical literature. The metabolic defect or the diverse clinical and pathologic features of this syndrome have been reviewed extensively.₁⁻⁹, ₁₇ We will concentrate upon the cardiac

FIGURE 7. Main left bundle branch showing oxalosis and fibroelastosis. Weigert-van Gieson's stain; original magnification × 45. Arrow points to an area of oxalosis.

FIGURE 8. Second part of the right bundle branch showing oxalosis and fibrosis. Weigert-van Gieson's stain; original magnification × 45. Arrows point to right bundle branch.
fibrosis found on microscopic examination, the patient had no clinical evidence of myocardial dysfunction and an echocardiogram shortly before death showed normal left ventricular size and function. In contrast, the electrocardiographic and electrophysiologic findings were striking. Although occasional P waves with ventricular capture were noted during the initial days of the final hospital admission, during most of this period no atrial activity was present on surface ECGs or during continuous monitoring. Of note was the absence of hyperkalemia or acidosis at the time of electrophysiologic study.

The electrophysiologic studies showed evidence of diffuse involvement of the cardiac conduction system, which was confirmed pathologically. A slow, erratic atrial pacemaker was present and the changes in atrial activation sequence suggested multiple pacemaker sites. Although unlikely, we cannot exclude the possibility of retrograde ventriculooatrial conduction. Our findings could not be characterized as either atrial quiescence (complete absence of atrial depolarization) or atrial standstill (sinus mechanism without atrial mechanical response), but are likely related to the extensive oxalate infiltration of the approaches to the sinoatrial node, the atrial myocardium and atrial preferential pathways and the secondary degenerative and fibrotic changes.

In addition, atrioventricular dissociation with an accelerated junctional rhythm was present and only occasional late atrial depolarizations resulted in ventricular capture. These captured beats were associated with a prolonged PR interval and had an identical contour to that of the junctional complexes (fig. 1). Atrioventricular dissociation may have been related, in part, to atrioventricular block because atrial deflections occurring as late as 500 msec after ventricular activation failed to capture the ventricle and because of the histologic findings of virtual complete replacement of the atrioventricular node by oxalate crystals. Infranodal disease was also reflected in the markedly prolonged HQ interval and right bundle branch block pattern. This correlated well with the marked involvement of both the common bundle and both bundle branches (particularly the right).

This case is unique in several aspects. It is the first clinical-electrophysiologic and anatomic correlation of cardiac oxalosis. In addition, although tachyarhythmias and atrioventricular block have been described previously in patients with oxalosis, to our knowledge no previous case of clinical sinoatrial disease or atrial inexcitability has been reported.

Previous Reports of Cardiac Involvement in Oxalosis

Other reports have described cardiac involvement detected during postmortem examination in patients
with primary oxalosis.\textsuperscript{4-12} As in the present case, crystal deposition, associated with areas of inflammation and fibrosis, has been found in the myocardium, in the interstitium and in the walls of the arteries and veins. There appears to be a predilection for the cardiac conduction system. Although in most cases involvement of the heart was an incidental finding, it led to tachyarrhythmias, conduction disturbances and heart failure in others. Complete atrioventricular block has been noted previously in several patients with primary oxalosis.\textsuperscript{4-8,10-12} In two of these, extensive histologic studies of the conduction system were performed and revealed severe damage\textsuperscript{10,11} to both the right and left bundle branches. No previous reports of electrophysiologic studies are available.

Implications

This case illustrates the severe cardiac involvement that may develop in primary oxalosis. The predominant clinical manifestation of this process is conductive system disease, which may occur at any level. In our case, there was excellent subsequent correlation between the electrophysiologic and histologic findings.

Recently, calcium oxalate deposition and metastatic calcification in the heart have been noted in patients with chronic renal insufficiency who did not suffer from this specific entity.\textsuperscript{18-21} The clinical and pathologic findings in these patients were similar to those in our patient. With more patients being maintained on dialysis, this type of cardiac involvement will become more common. The clinical and electrophysiologic features of our patient are similar to those in patients with other infiltrative diseases of the heart and processes that produce diffuse cardiac fibrosis, so our findings may be of relevance to these entities as well. Therapeutically, there appears to be little to offer these patients, because the visceral oxalosis progresses despite intensive dialysis. In our patient and in a previous report,\textsuperscript{4} renal transplantation failed because of calcification of the grafted kidney. Although ventricular pacing may prevent death from complete atrioventricular block, it is unlikely to prolong life significantly in oxalosis patients once visceral involvement has reached this stage.

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