Generalized Oxalosis with Retinal Involvement
Following Methoxyflurane Anesthesia

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Methoxyflurane (MOF) is well recognized as a cause of renal oxalosis. Calcium oxalate crystals are formed in the kidneys of patients given this agent, with subsequent development of nonoliguric renal failure. Deposition of calcium oxalate crystals in organs other than the kidneys following MOF has not been described. This report documents the occurrence of generalized oxalosis in a patient who developed acute irreversible renal failure after MOF anesthesia. Yellowish-white punctate lesions were observed and photographed in the fundi oculi and at postmortem examination. These were found to be calcium oxalate crystals in a layer of the retina: the retinal pigment epithelium. The nature of the eye changes was documented by histopathology, histochemical analyses, and crystallographic studies, including examination of the optical properties of the crystals and their x-ray diffraction pattern. The occurrence of clinically observed crystals in the eye may be an important and useful sign in generalized oxalosis, in this case apparently associated with MOF anesthesia.

REPORT OF A CASE

In October 1967, the patient, a 61-year-old man, was evaluated at Yale-New Haven Hospital with a three-month history of arthritis and mild bilateral episcleritis. It was noted at this time that the patient's mother had had adult-onset diabetes mellitus and his father had died of a cerebrovascular accident. There was no personal or family history of nephrolithiasis, renal or eye disease. Extensive evaluation revealed mild hypertension, normal urine, and a serum creatinine of 1.5 mg/100 ml. A diagnosis of seronegative rheumatoid arthritis was made and the patient was treated with systemic and ocular corticosteroids, following which the episcleritis resolved. The hypertension was controlled with reserpine and hydrochlorothiazide.

In February 1968, the patient had a routine eye examination and the findings were recorded as entirely normal, bilaterally.

The patient was admitted to Yale-New Haven Hospital in December 1968, at which time he underwent a hemorrhoidectomy under caudal lidocaine anesthesia. Routine eye examination at this time revealed no ocular abnormality. Laboratory data obtained during this hospitalization included a urinalysis showing 3+ protein and a serum creatinine of 2.6 mg/100 ml. The impaired renal function was attributed to the patient's hypertension.

In January 1969, the patient was admitted to the Yale-New Haven Hospital with the signs and symptoms of obstructive jaundice. The retinas were described as normal on the admission examination record. Weight on admission was 140 pounds. The results of laboratory studies at this time included 2+ proteinuria, serum creatinine of 3.5 mg/100 ml, bilirubin 2.4 mg/100 ml, serum amylase 2,400 units/100 ml, and serum glutamic-oxaloacetic transaminase 178 units/100 ml. An intravenous pyelogram revealed poor function bilaterally and a filling defect in the left kidney consistent with a renal infarct. Preoperatively the patient had received phenobarbital and pentobarbital for sedation. The pentobarbital was continued postoperatively (table 1).

The patient underwent an exploratory laparotomy 4½ hours in duration. Premedication included atropine, 0.6 mg, meperidine hydrochloride, 50 mg, and diazepam, 15 mg. Induction of anesthesia and intubation of the trachea were performed using thiopental, 200 mg, suxamethonium, 60 mg, cyclopropane, and oxygen. Anesthesia was then maintained with methoxyflurane, nitrous oxide, and 20% per cent oxygen, administered through a noncalibrated Ohio No. 8 vaporizer for a total of three hours and 35 minutes. d-Tubocurarine, 27 mg, was also administered. Forty minutes before the end of the procedure MOF was discontinued. An antrectomy, vagotomy, and gastroenterostomy were performed for correction of an intermittently obstructing duodenal diverticulum. Although there were no episodes of hypotension or cardiac arrhythmias, acute, irreversible nonoliguric renal failure rapidly ensued. Dialysis was initiated and a percutaneous renal biopsy performed on the thirty-eighth postoperative day showed extensive renal oxalate deposition in the tubules and interstitium.
severe interstitial scarring, tubule dilatation and atrophy, arteriosclerosis, and arteriolosclerosis (fig. 1). The pathologic diagnosis was acute renal failure associated with massive oxalate crystal deposition. The patient was maintained on in-hospital hemodialysis for the subsequent 3½ years. During this interim, however, no ophthalmologic examination seemed indicated or was performed.

In May 1972, the patient was admitted with a three-day history of fever and chills. The admitting physical examination by a medical intern revealed "scattered hard exudates" in both fundi. No hemorrhages were detected, and ophthalmologic consultation was not requested. The patient was discharged four days later with a diagnosis of a presumed systemic viral infection superimposed on his chronic renal failure.

The patient's general medical condition further deteriorated, and in September 1972, during an admission for hemodialysis, he was seen as part of a program in which the eyes of terminal patients are examined and clinical and pathologic correlations are made when possible.¹

Examination of the ocular fundi revealed numerous yellowish-white punctate lesions dif-

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* Oral dosage per 24 hours.

Fig. 1. Photomicrograph of kidney biopsy specimen, showing abundant birefringent calcium oxalate crystals (hematoxylin and eosin, partially polarized light, ×35, reduced from ×40).
fusely scattered throughout the posterior poles and midperipheries of both eyes. The appearance of the optic discs, maculae and vessels was normal, and no lesions were seen in the periphery. Fundus photography documenting the punctate lesions was performed (fig. 2A). The patient died several weeks later.

**Pathology of the Eyes**

On gross examination, the eyes were essentially normal with the exception of the retinas. Under the dissecting microscope, examination of the retinal pigment epithelium following removal of the neurosensory retina showed extensive crystalline deposits. Using a 25-gauge needle, one of these deposits was removed and examined microscopically between crossed polarized filters. The crystalline deposits manifested marked birefringence.

Microscopic examination of sections of the retinal pigment epithelium stained with hematoxylin and eosin revealed multiple birefringent crystalline deposits of both eyes, extending to the midperipheries (fig. 2B).

Slides of the other organs from the general necropsy were then obtained and examined by light microscopy using crossed polarized filters. Identical crystals were found in the pericardium, the bronchial epithelium, the colloid substance of the thyroid gland, the epididymal ductules, and throughout the renal parenchyma (fig. 3). Kidney tissue preserved in formalin was noted to contain grossly visible whitish crystalline deposits which were insoluble in water. These renal crystals and crystals from the retinal pigment epithelium were examined by x-ray diffraction and optical studies and were identified as calcium oxalate-monohydrate (whewellite).2

After identification of the crystals in the kidney and retinal pigment epithelium as calcium oxalate, attention was directed to the other tissues in order to confirm their crystalline content. X-ray diffraction and optical studies of the crystals obtained from the other tissues were not possible because the concentrations of crystals in these tissues were insufficient. However, positive identification of calcium oxalate in the original kidney biopsy, and in autopsy slides of the thyroid, bronchus, and heart, was made by utilization of the histochemical “bubble” test of Johnson.3

**Discussion**

Oxalic acid (HOOC-COOH), a common organic acid formed as a metabolic product, can combine with the calcium ion to yield the insoluble salt, calcium oxalate. An estimated two-thirds of all kidney stones contain some calcium oxalate, while 40 per cent are composed entirely of this compound.4 Diffuse deposition of calcium oxalate in various tissues of the body in a pathologic condition called “oxalosis.” Four varieties of oxalosis have been recognized: 1) diffuse oxalosis, in which calcium oxalate crystals are present in many organs; 2) renal oxalosis, in which the deposition is confined to the kidney; 3) incidental oxalosis, in which occasional calcium oxalate crystals are found in patients who do not have recognized disorders of oxalate metabolism; 4) ocular oxalosis, in which the crystals are found only in the eye.

Diffuse oxalosis has previously been described to occur in only two disorders, primary hyperoxaluria and ethylene glycol poisoning. Primary hyperoxaluria is an extremely rare inborn error of metabolism. Two enzymatic types, glycolic aciduria and glyceric aciduria, resulting from deficiencies of glyoxylate carboligase and D-glyceric dehydrogenase,6 respectively, have been delineated. In these disorders the excessive synthesis and excretion of oxalate leads to nephrolithiasis and nephrocalcinosis, terminating in uremia. Ethylene glycol poisoning7,8 results from ingestion of the commercial antifreeze preparation used in automobile radiators, accidentally or by those seeking an ethanol substitute. Ethylene glycol is catabolized to oxalate. In neither condition has ocular deposition of the crystals been proven. Reference has been made to retinal lesions in patients with diffuse oxalosis, but these have

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Fig. 2A (above), fundus, L.E. showing numerous yellowish-white punctate lesions in the posterior pole. B (below), Microscopic appearance, showing birefringent crystalline deposits in the retinal pigment epithelial cell layer (hematoxylin and eosin, partially polarized light, ×92, reduced from ×100).
not been substantiated with adequate description, retinal drawings, photographs, or histopathology.9–11

Deposition of oxalate confined to the kidney, i.e., renal oxalosis, has been found in conjunction with a variety of renal diseases,4–12 with oxalate intoxication from either the chemical13 or from foodstuffs, as in rhubarb gluttony,14 in ascorbic acid ingestion, following diethylene glycol poisoning, in experimental conditions such as glyoxylate15 or glycolate16 administration, in pyridoxine17 or thiamine18 deficiency, and in a host of systemic diseases, including cirrhosis of the liver, Klinefelter’s syndrome, hyperparathyroidism, sarcoidosis, intestinal disease, and the malabsorption syndrome.19–21 Most recently, renal oxalosis has been reported in instances of infections caused by organisms of the group Aspergillus niger. Oxalic acid production by the fungus caused local tissue injury with oxalate deposition, as well as causing azotemia and decreased renal function by acute oxalosis.22 Renal oxalosis has also been reported to occur following methoxyflurane anesthesia.23

Extrarenal calcium oxalate crystals are occasionally seen as incidental postmortem findings in the thyroid gland, walls of blood vessels, and the myocardium,24 presumably as a result of tissue injury.

A review of the literature disclosed that ocular calcium oxalate deposition previously has been found only intraretinally in the eyes of patients with long-standing retinal detachment,25 and in the lenses of patients with morgagnian cataracts26 and phakolytic glaucoma.27–29 In none of these cases was calcium oxalate in the retinal pigment epithelium noted.

In the present case, a patient with renal insufficiency possibly related to mild persistent hypertension was subjected to prolonged anesthesia with MOF. Preoperatively the patient had received both phenobarbital and pentobarbital (table 1). Barbiturates have been shown to stimulate hepatic microsomes,30 which causes accelerated biotransformation of MOF in experimental animals.31 This resulted in superimposed acute renal failure, and the demonstration of oxalate crystals in the renal biopsy obtained 38 days postoperatively is consistent with MOF-induced renal toxicity. Surprisingly, generalized oxalosis was found at necropsy.

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FIG. 3. Photomicrographs of autopsy specimens showing extensive crystalline deposition. A (above), heart. B (below), bronchus. (Hematoxylin and eosin partially polarized light, ×35, reduced from ×40.)
Intratracheal Cuffs and Aeromedical Evacuation

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Intratracheal cuffs may not perform satisfactorily during aeromedical flights, because cuff pressure against the trachea (cuff tracheal pressure or CTP) varies with aircraft cabin pressure. Thus, cuff tracheal pressure may become excessive either during ascent to 8,000 feet (565 torr), a pressure to which both commercial and military aircraft are commonly depressurized, or during loss of cabin pressure, such as may take place at higher altitudes. Correction to the proper cuff pressure at 8,000 feet may also result in insufficient seal pressure following return to ground-level pressure. Since over- and underinflation1-3 have been implicated in both tracheal damage and aspiration, we evaluated a number of commercially

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The animals involved in this study were maintained and used in accordance with the Animal Welfare Act of 1970 and the "Guide for the Care and Use of Laboratory Animals," prepared by the National Academy of Sciences-National Research Council.