Xanthine Lithiasis, Nephrocalcinosis, and Renal Failure in a Leukemia Patient Treated with Allopurinol

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An 11-year-old boy who presented in acute renal failure with significant increases of uric acid and phosphorus in his serum was discovered to have acute lymphoblastic leukemia. Five years later, he had a second and similar episode of acute renal failure, which was responsive to hemodialysis. After three months of daily therapy with allopurinol, a third and final episode of renal failure was unresponsive to peritoneal dialysis. Autopsy revealed an obstructive uropathy; focal nephrocalcinosis; and multiple, small, tan calculi in the calyces of both kidneys. Systemic cryptococcosis was also discovered. The stones, characterized by paper chromatography, electrophoresis, x-ray diffraction, and infrared spectroscopy, were 82% xanthine, 15% oxypurinol, and 3% hypoxanthine. We suggest that attention to the effects of accelerated tumor-cell lysis may protect renal function in patients with a large and drug-sensitive tumor cell load. Similarly, early detection of the fungal complications of leukemic therapy is an essential component of the treatment program.

Additional Keyphrases: cancer - chemotherapy - yeast infection

Rarely, one sees urinary tract calculi consisting of the purine base xanthine. Hereditary xanthinuria due to deficiency of xanthine oxidase (EC 1.1.3.22) has been reported in 45 patients, one-third of whom have had xanthine stones (1). However, some reports of xanthine calculi are difficult to evaluate, because the methodology for the identification of xanthine was not stated or not clearly described (2−8). Xanthine crystalluria and xanthine stones have not been reported in patients treated with allopurinol for primary gout. However, xanthine lithiasis has been reported in patients treated with allopurinol for lymphosarcoma (9) or for Lesch−Nyhan syndrome (10−12).

Here we summarize studies of a patient with acute lymphoblastic leukemia who had an unusual clinical presentation and clinical course. Postmortem examination revealed multiple small xanthine stones in the calyces of both kidneys.

Case Report

At initial presentation, this 11-year-old white boy had a 10-day history of vomiting, abdominal pain, fatigue, sore throat, and epistaxis. Chemical tests at admission revealed acute renal failure. Hematological studies showed a hemoglobin concentration of only 67 g/L, and a leukocyte count of 22.4 × 10⁹/L, with 8% neutrophils, 9% band forms, 77% lymphocytes, 5% monocytes, and 1% eosinophils. The platelet count was 20 × 10⁹/L. Results of bone-marrow examination were consistent with acute lymphoblastic leukemia, but also were suggestive of a tendency toward spontaneous remission. Renal function was normalized by intravenous hydration with isotonic saline and glucose and enemas with "Kayexalate" ion-exchange resin, administered to remove excess potassium. Because the calcium concentration concomitantly decreased to 1.8 mmol/L, calcium gluconate was administered. However, the patient remained somewhat hypocalcemic and hyperphosphatemic for three days, during which this administration of calcium was continued. A standard chemotherapeutic regimen was instituted, including 6-mercaptopurine, methotrexate, vincristine, prednisone, cytoxan, and L-asparaginase at various times. Several short remissions were achieved, but for most of his clinical course the patient remained in only partial remission.

Five years after the initial diagnosis, the patient presented again in renal failure. Hemoglobin concentration was 58 g/L; the leukocyte count was 8.9 × 10⁹/L with 81% lymphoblasts, 7% neutrophils, 3% band forms, 7% lymphocytes, and 2% monocytes. The platelet count was 9 × 10⁹/L. Renal function responded favorably to three courses of hemodialysis, and blood products were administered. Treatment with allopurinol, 900 mg per day in three divided doses, was begun. At his final admission, three months later, he was again in renal failure. The hemoglobin concentration was 92 g/L; the leukocyte count was 3.2 × 10⁹/L with 28% neutrophils, 9% band forms, 38% lymphocytes, 2% monocytes, 1% eosinophils, and 22% lymphoblasts. The platelet count was 23 × 10⁹/L. Platelets and erythrocytes were administered and hydralazine was given for hypertension, but the patient did not respond favorably. Peritoneal dialysis failed to check his deteriorating clinical condition. He began to show signs of decerebrate posturing and died on the seventh day. A postmortem examination was performed.

Methods and Materials

In routine analyses the Kodak Ektachem 400 was used. Standard purine compounds were purchased from Sigma Chemical Co., St. Louis, MO. Stones from the patient were dissolved in 0.1 mmol/L NH₄OH to give a concentration of 5 g/L, and they and serum samples were directly analyzed by chromatography or electrophoresis. For paper chromatography we used 3MM paper (Whatman Ltd., Maidstone, England), with butanol–acetic acid–water (12/3/5 by vol) as the
solvent system. Paper electrophoresis was also performed on Whatman 3MM paper, in borate buffer (40 mmol/L, pH 8.65), at 75 V/cm for 30 min. After the purines were located by illuminating the sheet with an ultraviolet lamp, we cut out appropriate sections of the paper and eluted the purines by soaking the pieces of paper overnight in 10 mmol/L HCl solution. We identified the various compounds by comparison with co-migrating standards and quantified them by ultraviolet spectrophotometry, using published absorptivity values. Monosodium urate, used for standards, was dissolved in water and its concentration determined by ultraviolet spectrometry. Aliquots of the solution were lyophilized, then mixed with pooled normal serum to give the desired concentrations. X-ray diffraction studies were carried out as described by DeVries (13). For infrared analysis of calculi, we used a Digilab 15c Fourier-transform infrared spectrophotometer (FT-IR), and standard potassium bromide pellet procedures.

Results

Table 1 summarizes the laboratory findings for the patient at each admission to the hospital. At his first admission, prior to diagnosis and treatment, remarkably high values for phosphorus and uric acid were seen, along with increases in serum urea nitrogen and creatinine, hyperkalemia, and hypocalcemia. Laboratory measurements during the second admission, after the diagnosis had been made and the treatment program begun, were very similar, although phosphorus measurements were not carried out. At the time of the third and final hospital admission, three months after the introduction of treatment with allopurinol, values for urea nitrogen, creatinine, and phosphorus (measured on the third day of this admission) were above normal. Uric acid and potassium concentrations were within normal limits, but there was a significant increase in serum xanthine.

Ten to 12 small tan calculi, 2–3 mm in diameter, were removed from the cut surface of the kidneys and lightly blotted with filter paper. The stones tended to crumble easily into a coarse, gravel-like consistency. Paper chromatography of the stones revealed three ultraviolet-absorbing spots, which co-chromatographed with authentic xanthine, oxypurinol, and hypoxanthine. On paper electrophoresis three ultraviolet-absorbing spots also co-chromatographed with authentic xanthine, oxypurinol, and hypoxanthine. The ultraviolet spectra of the eluted spots were identical with those of the authentic compounds. Quantification of the stone composition showed that it contained 82% xanthine, 15% oxypurinol, and 3% hypoxanthine. Uric acid and allopurinol were not detected. Infrared spectroscopy of the stones revealed characteristic absorption bands for xanthine, and the x-ray diffraction pattern was consistent with the presence of xanthine.

The activity of the enzyme hypoxanthine–guanine phosphoribosyltransferase (EC 2.4.2.8) was found not to be deficient in the erythrocytes of blood obtained postmortem from the patient.

Discussion

This patient presented initially in renal failure with hyperphosphatemia, hyperkalemia, hyperuricemia, and hypocalcemia. The diagnosis of acute lymphoblastic leukemia was made during this hospitalization, and the histological appearance of a spontaneous ongoing remission was noted. The laboratory findings on the first admission (Table 1) reflect massive cytolysis of tumor cells—the acute tumor lysis syndrome (14–20). In view of the remarkably high values for serum phosphorus and uric acid, it seems likely that some urate nephropathy and nephrocalcinosis had occurred by this time. During the next five years, the patient had several remissions and partial remissions, but his overall response to antileukemic therapy was deemed unsatisfactory. His second major admission was again because of renal failure, with an almost identical biochemical picture (Table 1). Although serum phosphorus was not measured this time, it is reasonable to assume that he was hyperphosphatemic and that there was now further compromise of renal function. His renal function responded favorably to three courses of hemodialysis and he was discharged with allopurinol, now prescribed to be taken daily. This patient was last admitted three months later, again in renal failure. Serum uric acid was now normal on admission and serum phosphorus was 4.84 mmol/L on the third hospital day (Table 1). Peritoneal dialysis was instituted, but the patient continued to show progressive deterioration with evidence of central nervous system involvement.

The magnitude of the hyperuricemia (Table 1) deserves some comment. A wide variety of techniques have been used for determination of serum uric acid, but, irrespective of methodology, extensive population studies generally have shown values ranging from 208 to 506 μmol/L, with a small proportion of patients having values >416 μmol/L—a concentration thought to represent the maximum solubility of sodium urate in plasma at 37 °C (21). Uric acid concentration comparable to those seen in this patient are only rarely found in the literature (19) and were at first viewed with suspicion. However, we confirmed a uric acid value of 4.4 mmol/L during his second hospitalization, a value obtained with the DuPont aco III. The Kodak Ektachem 400 and DuPont aco III uric acid methods are both enzymically based and are reasonably free from false-positive interference (22). The addition of pooled sera to lyophilized samples of monosodium urate resulted in measured concentrations of uric acid between 3 and 3.36 mmol/L in the Ektachem 400, confirmed by paper chromatography. The serum remained clear and translucent for about 1 h at room temperature, then opalescence and crystallization of monosodium urate could begin to be seen. Therefore, the values observed in this patient probably represent a supersaturated state (23).

There was no deficiency of activity of the enzyme hypoxanthine–guanine phosphoribosyltransferase in this hematologic system.
xanthine–guanine phosphoribosyltransferase in the erythrocytes of blood obtained postmortem. No cause other than accelerated tumor-cell lysis could be reasonably associated with this striking hyperuricemia. In retrospect, it seems likely that hyperuricemia may have been associated with the pain, particularly in the extremities, of which the patient complained before treatment with allopurinol was begun.

Acute and accelerated tumor-cell lysis and its adverse effects, particularly on the kidney, have been well studied and described (14–20). In this patient, allopurinol effectively prevented hyperuricemia, as evidenced by his normal uric acid concentration while on the drug—although the actual value may have been somewhat higher because xanthine interferes negatively in the method (22). However, in allopurinol-treated patients with an accelerated cellular turnover, the xanthine concentration in serum may increase to extremely high values, and the concentration in urine may exceed its solubility limit (24). In this patient, serum xanthine was 3.04 mmol/L (mean normal 24, SD 22 μmol/L) on his third admission and the mean value for xanthine in five blood samples, including a postmortem sample, during this hospitalization was 2.07 (SD 0.84) mmol/L, clearly setting the stage for xanthinuria and the initiation and (or) progression of xanthine lithiasis.

During periods of intensive chemotherapy in patients with a large and sensitive tumor-cell load, subclinical damage may be occurring in the kidney. One should monitor and maintain renal function at these times. Similarly, surveillance for infection is an essential component of the treatment program. Close attention to the potential adverse features of the treatment regimen may prevent morbidity and prolong life in patients with neoplastic disease.

We are indebted to Dr. Haynes Robinson (Department of Pathology and Laboratory Medicine) for his autopsy observations. We thank Dr. Jay Tischfield of the Medical College of Georgia for determining hypoxanthine–guanine phosphoribosyltransferase activity. This study was supported by a grant from the Children's Cancer Fund, Akron Children's Foundation.

References