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A 78-Year-Old Man with Acute Myeloid Leukemia (AML) and Acute Renal Failure

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 78
Final Diagnosis: Acute myeloid leukemia (AML)
Symptoms: Dyspnea • fatigue
Medication: Idarubicin followed by cytarabine
Clinical Procedure: Chemotherapy
Specialty: Hematology

Objective: Unusual clinical course

Background: Renal failure is a common presentation of acute myelomonocytic and monocytic leukemia. It is usually the result of a combined glomerular and tubular dysfunction and is associated with a poor prognosis. No guidelines exist for treatment.

Case Report: We herein describe the case of a 78-year-old Caucasian man who presented with acute myeloid leukemia M5, leukostasis with a white count of 340 000/ml, and acute renal failure with a creatinine of 7.7/dL. The patient was initially treated with leukapheresis and 3 days of idarubicin in the setting of continuous renal replacement therapy that resulted in rapid reversal of his renal failure. He then received 7 days of continuous infusion cytarabine and went into a complete remission.

Conclusions: Renal failure may complicate the presentation of AML but can be reversible with treatment. Dose adjustment of the chemotherapy is not needed and the treatment can be greatly facilitated with the use of continuous renal replacement therapy, as indicated in our case report. In addition, we emphasize that organ dysfunction, even in elderly patients, is not necessarily a contraindication to aggressive treatment if it is felt to be disease-related and reversible.

MeSH Keywords: Acute Kidney Injury • Cytarabine • Hemofiltration • Idarubicin • Leukemia, Myeloid, Acute • Leukostasis

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Background

Leukostasis, acute renal failure, and extramedullary tissue infiltration are more likely to be present at diagnosis in patients with acute myelomonocytic and monocytic leukemias (M4 and M5) than in other subtypes of AML [1–3] and have been associated with poor prognosis and death within the first week of presentation [2]. The combination of acute renal failure, proteinuria, hypokalemia, and hypophosphatemia specifically appears to be characteristic for patients with AML M4 and M5 because it is not found in other subtypes and is the result of a combined glomerular and tubular dysfunction.

Although this is a relatively common presentation, there is no good data to guide initial treatment decisions in patients with AML and acute renal failure. In our review of the literature we identified 1 case report describing reversibility of renal failure and tubule dysfunction with chemotherapy treatment in a patient with AML M5 who presented with leukostasis and did not require renal replacement therapy [4]. In another case of a pediatric patient presenting with AML M4 and renal failure, radiation therapy to the kidneys was attempted and apparently failed, and then dose-reduced chemotherapy in the setting of hemodialysis reversed the renal failure and induced remission of the leukemia [5].

We report a case of a patient presenting with AML M5, leukostasis, acute renal failure, and hypophosphatemia. To our knowledge this is the first case describing complete reversibility of the renal failure and tubule dysfunction after treatment of the underlying leukemia with full-dose chemotherapy and in the setting of continuous renal replacement therapy.

Case Report

A 78-year-old Caucasian man with atrial fibrillation, hypertension, and dyslipidemia presented to our service with 2 days of oliguria after a week of fevers, dyspnea, fatigue, and sore throat. Initial laboratory evaluation revealed abnormal blood counts: 340×10^9/l white blood cells (98% blasts), 59×10^9/l platelets, and a 26.9% hematocrit. Serum chemistries were significant for the following values (in mg/dL unless otherwise noted, abnormal values are in bold): sodium 140, potassium 4.0, chloride 101, bicarbonate 24, blood urea nitrogen 49, creatinine 7.7, uric acid 16.2, calcium 11.6 (11.9 corrected), phosphate 0.9, magnesium 2.4, and lactate dehydrogenase 1329 IU/L. His urinalysis showed many cellular casts consisting of white cells that had the appearance of blasts.

Chest x-ray showed bilateral infiltrates suggesting leukemic infiltration or infection. A bilateral renal ultrasound showed normal-sized kidneys and no hydronephrosis.

A bone marrow biopsy was performed, showing that 99% of the aspirate cellularity consisted of large cells with large nuclei, with irregular nuclear containing an open chromatin, prominent nucleoli, moderate nuclear/cytoplasmic ratio; basophilic cytoplasm and occasional cytoplasm vacuoles, consistent with blasts. The marrow was packed, with overall cellularity approaching 100%. There was an interstitial infiltrate of immature cells consistent with blasts occurring in sheets occupying 99% of marrow cellularity. Cell marker analysis demonstrated that the majority of the cells isolated from the peripheral blood/bone marrow expressed immature antigens CD34, HLA-DR, myeloid associated antigens CD117, CD13 (dim), CD15 (variable), CD11c, CD64 (subset), and CD71, whereas lymphoid-associated antigen CD7 and were negative for CD10 (cALLa), B-cell antigens, other T-cell antigens CD2, CD3, CD5, CD4, CD8, as well as CD33, CD14, CD41, CD56, and Glycophorin A. Overall picture was consistent with AML, FAB subtype M5 without chromosomal abnormalities. FLT3 and NMP1 mutations were negative.

The gravity of his diagnosis was conveyed to the patient and palliative care was offered. The patient, highly functional and still productive in the community, opted for aggressive treatment and was admitted to the intensive care unit. He was started on aggressive intravenous hydration (initially 250 ml/hr and then 125 ml/hr of D5W with 150 mEq/L of sodium bicarbonate), antibiotics (cefepime), and hydroxyurea at 1000 mg twice a day. He received rasburicase and underwent 3 sessions of leukapheresis. Continuous venovenous hemofiltration with dialysis (CVVHD) was initiated. He was then started on induction therapy with idarubicin at 9 mg/m2 on day 1 and 12 mg/m2 on days 2 and 3. By day 4, his white cell count had returned to normal levels, his creatinine had improved to 1.3 mg/dL and uric acid to 5.9 mg/dL, and CVVHD was discontinued. On Day 5 he was started on 7 days of cytarabine at 100 mg/m2/day as a continuous infusion. His day 14 bone marrow was ablated, his peripheral counts recovered by day 28, and his day 28 marrow showed normal hematopiesis without an excess of blasts. His hospital course was complicated by enterococcal bacteremia, candidemia, pulmonary aspergillosis, and a gastrointestinal bleed, but he recovered and was discharged to home on day 44.

He then underwent consolidation chemotherapy with 6 cycles of low-dose idarubicin and cytarabine. He relapsed 14 months after the time of first remission. He was subsequently reinduced with clofarabine and cytarabine and went into a second remission. He underwent further consolidation with clofarabine and cytarabine but relapsed 6 months later. He was retreated with decitabine but developed a viral gastrointestinal infection that resulted in acute tubular necrosis requiring hemodialysis. Thereafter, he chose palliative care and died 22.5 months after his original presentation.

Discussion

Renal dysfunction and failure is a common presenting sign in patients with acute myelocytic and monocytic leukemia. The etiology of renal failure in patients with AML M4 and M5 is multifactorial and the result is a combined glomerular and tubular dysfunction, which is a unique manifestation compared to the other types of leukemia [6,7]. Older studies suggested that eventually all patients with M4 and M5 develop proteinuria and about 50% of them develop "azotemia" [6]. A main cause for glomerular dysfunction is direct infiltration of the kidneys by blasts. Enlarged kidneys are a sign of leukemic infiltration but patients may also have microscopic infiltration as indicated by autopsy series in which leukemic infiltration of the kidneys was found in almost all patients with M4 and M5 [8,9].

In addition, patients with AML M4 and M5 have a high serum and urine level of lysozyme, thought to originate from the blast cells [10]. Lysozyme directly damages tubule cells, leading to proximal tubular acidosis similar to Fanconi's syndrome and patients present with proteinuria and with hypokalemia and hypophosphatemia despite sometimes having a very high cellular turnover and/or renal failure. ("lysozyme kidney") [6,7,11]. In addition patients with myelocytic and monocytic leukemia may have hypergammaglobulinemia (in contrast to the hypogammaglobulinemia seen in the other subtypes of AML), which has also been implicated as a contributing factor to tubular dysfunction [6].

Spontaneous tumor lysis has in rare cases been described in patients with acute leukemia [12,13] and can also lead to acute renal failure at presentation, but the characteristic electrolyte abnormalities (hypokalemia and hypophosphatemia) associated with the "lysozyme kidney" can help distinguish between the 2 syndromes. Another mechanism that can explain renal failure at presentation is leukemic thrombi in the renal vasculature, but this seems to be rare [14].

In our patient, the cause of renal failure was most likely multifactorial. He had renal infiltration, as evidenced by the presence of leukemic blast casts, but also had tubular dysfunction with hypokalemia and hypophosphatemia. We did not pursue a kidney biopsy because it would be a significant risk and unlikely to alter management. Instead we used rasburicase to control his uric acid level and initiated CVVHD. Continuous venovenous hemofiltration (CVVH) has been used successfully in patients with Burkitt's lymphoma and acute lymphoblastic leukemia both to prevent and treat tumor lysis syndrome and to allow for the safe administration of chemotherapy in the setting of renal insufficiency [15–17]. In theory the slow, continuous removal of metabolites achieved by CVVH should be physiologically superior and better tolerated compared to the intermittent forms of dialysis [18]. If the hemofiltration provided by CVVH is not sufficient to remove the metabolites, then continuous dialysis can easily be started in the form of CVVH with dialysis (CVVHD).

We decided to treat his underlying leukemia with idarubicin first (slightly dose-reduced only on day 1) because it is hepatically cleared and can be safely administered. The dose adjustment for continuous infusion cytarabine in patients with renal failure has not been established but there is a concern for accumulation of its toxic metabolite Ara-U [19,20]. In addition, cytarabine is a dialyzable small molecule (243.22 kilodaltons – KD) that can be easily removed by CVVH, sharply limiting its efficacy [21]. Idarubicin, on the other hand, is a large (533.96 KD), non-dialyzable molecule [22]. Lysozyme is also a small molecule (15 KD) and it is likely that CVVH contributed to the rapid reversal of our patient's renal failure by quickly lowering his lysozyme levels. In addition, a sharp decline in the number of lysozyme-producing leukemic cells was achieved with leukapheresis, hydroxyurea, and idarubicin. The end result was a rapid reversal of his renal failure and tubular dysfunction, indicating that the damage induced by leukemic infiltration and lysozyme can be temporary. The return of his renal function to normal allowed us to safely administer the cytarabine after the completion of idarubicin. Administering cytarabine out of sequence did not appear to negatively affect the day 14 or 28 marrow results or overall outcome.

Conclusions

Renal failure due to combined glomerular and tubular dysfunction may complicate the presentation of acute myelocytic and monocytic leukemia but can be rapidly reversible with treatment. Dose adjustment of the chemotherapy is not needed and the treatment can be greatly facilitated with the use of continuous renal replacement therapy, as indicated in our case report. Because anthracyclines are not renally cleared, they can be administered first, and cytarabine administration can begin after the reversal of kidney dysfunction and discontinuation of continuous renal replacement therapy. We emphasize that organ dysfunction, even in elderly patients, is not necessarily a contraindication to aggressive treatment if it is felt to be disease-related and reversible.

Statement

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The authors have no conflicts of interest to declare.

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