

CASE REPORT



## Transformation of CMML to AML presenting with acute kidney injury

Rebecca DeBoer<sup>a</sup>, Ian Garrahy<sup>a</sup>, Andrew Rettew <sup>a</sup> and Robert Libera<sup>b</sup>

<sup>a</sup>Department of Medicine, Reading Hospital, Reading, PA, USA; <sup>b</sup>Doctor of Osteopathic Medicine Program, Philadelphia College of Osteopathic Medicine, Philadelphia, PA, USA

### ABSTRACT

Characterized by bone marrow dysplasia and peripheral blood monocytosis, chronic myelomonocytic leukemia (CMML) is one of the most aggressive chronic leukemias and has a propensity for progression to acute myeloid leukemia (AML). Patients with newly diagnosed AML generally present with symptoms related to complications of pancytopenia but can also present with renal insufficiency. We present a 79-year-old male with a past medical history of CMML and chronic kidney disease stage 3 (baseline creatinine 1.8 mg/dL) who presented with one day of inability to urinate and 20-lb unintentional weight loss, fatigue, and bone pain over 3 months. Laboratory evaluation revealed leukocytosis of  $88.5 \times 10^3/\mu\text{L}$  (normal  $4.8\text{--}10.8 \times 10^3/\mu\text{L}$ ) with 24.0% monocytes on differential, creatinine 2.94 mg/dL (baseline creatinine 1.7–1.9 mg/dL), uric acid 19.8 mg/dL, potassium 4.0 mmol/L, phosphorus 4.0 mg/dL, calcium 9.2 mg/dL, and albumin 3.2 g/dL. Urinalysis was significant for protein 200 mg/dL, 20/LPF granular casts, and 7/LPF hyaline casts. Bone marrow biopsy revealed 20–30% blasts with monocytic features of differentiation consistent with acute myeloid leukemia. Computed tomography (CT) of the abdomen and pelvis appreciated splenomegaly with retroperitoneal, and pelvic lymphadenopathy. Kidney failure can complicate the presentation of AML but can be rapidly reversible with treatment. In patients with CMML who have progressive renal insufficiency and hyperuricemia, there should be a high index of suspicion for progression to AML.

### ARTICLE HISTORY

Received 6 April 2020  
Accepted 22 May 2020

### KEYWORDS

Acute myeloid leukemia; chronic myelomonocytic leukemia; acute kidney injury; hyperuricemia; lysozymuria

## 1. Introduction

CMML, a myeloid neoplasm with features of myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN), is characterized by dysplasia in one or more hematopoietic cell lineages, abnormal production and accumulation of monocytic cells, and an elevated risk of transforming into secondary acute myeloid leukemia (AML) [1].

Prognosis is extremely variable in CMML. The rate of leukemic transformation to AML has an approximate incidence of 15%–20% over five years [2]. In most prognostic studies, the percentage of blasts in peripheral blood and bone marrow appear to be the most important factors in determining survival [3]. The prognostic grading system proposed by the World Health Organization (WHO) splits CMML into CMML-0, CMML-1, and CMML-2 based on the blast cell count (see Figure 4) [4].

Patients with AML generally present with symptoms related to complications of pancytopenia, including weakness and easy fatigability, infections, and/or hemorrhagic findings such as gingival bleeding and menorrhagia [5]. More rarely, acute myeloid leukemia can present with acute kidney injury (AKI). There are different mechanisms that can contribute to AKI in this setting, which include hypoperfusion, acute tubular necrosis, kidney infiltration by leukemia, intrarenal leukostasis, tumor lysis syndrome,

hyperuricemia, lysozymuria, and obstruction (see Figure 5) [6]. A case report of spontaneous tumor lysis syndrome secondary to the transformation of CMML to AML highlights the importance of recognizing sTLS as a cause of renal failure and electrolyte disturbance before cancer treatment begins [7]. Although our case does not meet the criteria for laboratory or clinical tumor lysis syndrome based on Cairo-Bishop criteria, ours is the only other reported case of severe hyperuricemia and AKI in the setting of CMML transformation to AML. It is important that internists consider transformation to AML in patients with CMML presenting with AKI and hyperuricemia.

## 2. Case description

A 79-year-old male with a past medical history of CMML diagnosed 4 years prior, anemia related to CMML and CKD receiving erythropoiesis-stimulating agent, hypertension, and chronic kidney disease stage 3 (baseline creatinine 1.8 mg/dL) presented with one day of decreased urination and an unintentional 20 pound weight loss and fatigue over the preceding three months.

The patient's blood pressure was 141/84 mmHg, pulse 104 beats per minute, respiratory rate 16 respirations per minute, SpO<sub>2</sub> 96%, and temperature of 36.6°C. The physical exam did not reveal any abdominal tenderness to palpation but did reveal

splenomegaly. There was no palpable cervical, supraclavicular, axillary, or inguinal lymphadenopathy.

Laboratory evaluation was significant for profound leukocytosis,  $88.5 \times 10^3$  cells per  $\text{mm}^3$ , with 24.0% monocytes compared to his baseline WBC  $4.5\text{--}7 \times 10^3$  cells per  $\text{mm}^3$  over the preceding 4 years. Additional laboratory abnormalities were significant for uric acid 19.8 mg/dL and creatinine 2.94 mg/dL as well as potassium 4 mmol/L, phosphorus 4 mg/dL, calcium 9.2 mg/dL, and albumin 3.2 g/dL. Urinalysis was significant for protein 200 mg/dL, 20/LPF granular casts, and 7/LPF hyaline casts. A renal ultrasound measured the left kidney as 10.2 cm long, with at least two cysts the largest at 3.5 cm, and without hydronephrosis. The right kidney measured as 10.5 cm long, with one cyst at 2 cm, and also without hydronephrosis. The CT of the chest, abdomen, and pelvis identified splenomegaly with a splenic diameter of 14.6 cm. No renal calculi were appreciated. Also visualized were several borderline subcentimeter retroperitoneal and pelvic lymph nodes.

Peripheral blood smear was performed and revealed a myeloid predominance with left shift and a small blast population (0.6%) as well as monocytic phenotypic aberrance (see Figure 1). Subsequently, a bone marrow biopsy was performed which identified 20–25% of CD 34+ blasts and morphologic features consistent with AML with monocytic differentiation (see Figures 2 and 3). Flow cytometry showed prominent monocytes which demonstrated loss of expression of HLA-DR and CD14 as well as coexpression of CD56. Next generation sequencing (NGS) revealed a pathogenic mutation in the NPM1 gene.

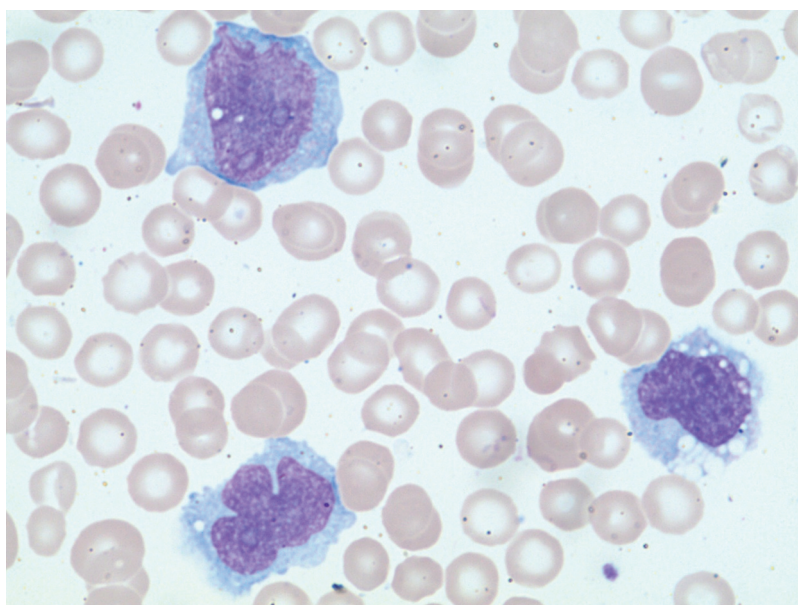
With presenting hyperuricemia and acute on chronic kidney injury, he received one dose of rasburicase 3 mg IV given concern for early TLS with

concomitant initiation of daily allopurinol. He commenced cytoreduction with hydroxyurea 1000 mg twice daily and after 48 hours, his white blood cell count and uric acid down-trended to  $48.5 \times 10^3$  cells per  $\text{mm}^3$  and 5.5 mg/dL respectively. Creatinine also trended down to 1.98 mg/dL.

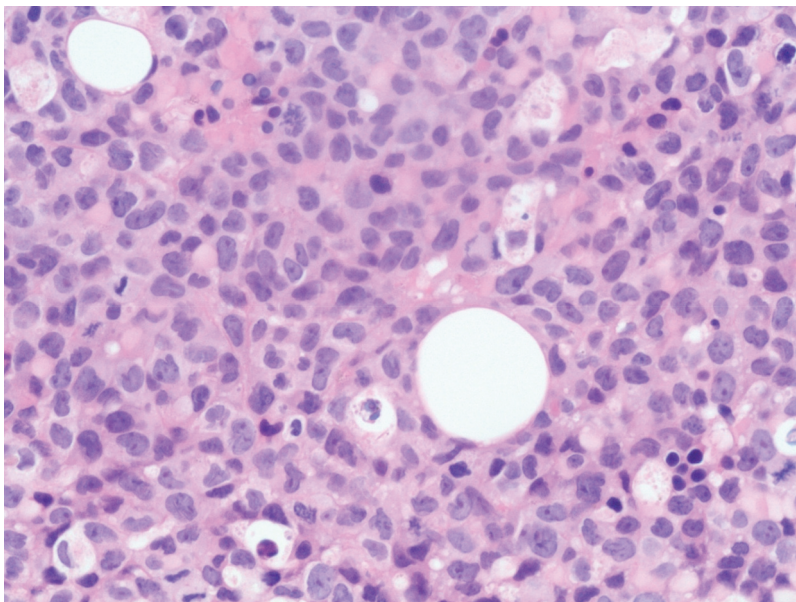
Due to the patient's performance status and age, hematology offered reduced-intensity therapy consisting of azacitidine with or without venetoclax or best supportive care rather than intensive induction chemotherapy. Ultimately, the patient elected for home hospice services and passed away 10 days later.

### 3. Discussion

Renal dysfunction is a common presentation in patients with AML. It is usually the result of combined glomerular and tubular dysfunction and is associated with a poor prognosis. There are many different causes for renal injury, most common of which are pre-renal or post-renal. Once these more common causes are ruled out, the focus can shift to intra-renal pathology. Pre-renal etiology was excluded, as our patient continued to have adequate blood pressure with mean arterial pressure greater than 65 mmHg in addition to continuous oral intake and adequate hydration. Post-renal etiology was also excluded, as there was an absence of hydronephrosis, renal calculi, or other pathology suggestive of obstruction on both renal ultrasound and CT of chest, abdomen, and pelvis. Then intra-renal causes must be considered. Three major causes of intra-renal AKI include leukemic infiltration, hyperuricemia, and lysozymuria.



**Figure 1.** Note the immature and atypical monocytic elements. Sections of this peripheral blood smear reveal myeloid predominance with left shift and small blast population as well as monocytic phenotypic aberrance. (x 100).

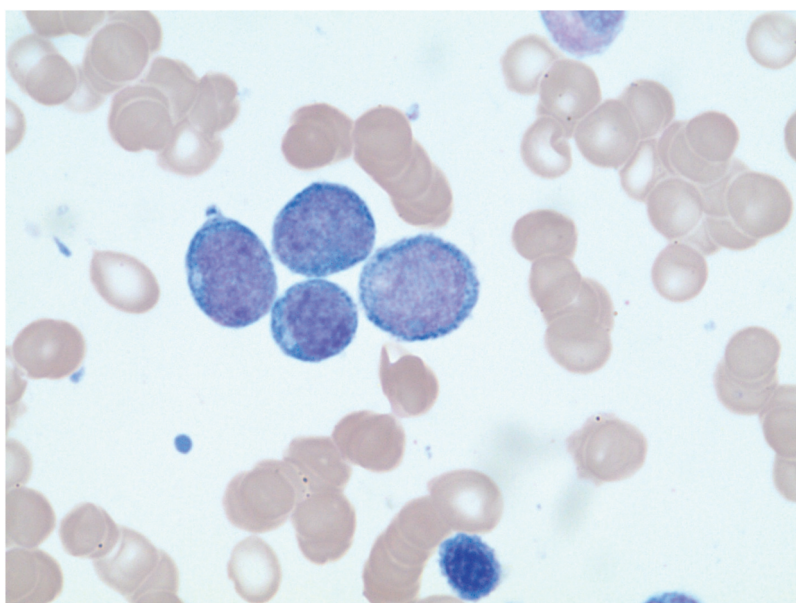


**Figure 2.** Note the immature mononuclear cells with folded nuclear contours, suggestive of monocytic differentiation. Sections of this bone marrow core biopsy reveal an acute myelogenous leukemia with monocytic features of differentiation. Approximately 20 to 25% of the cellularity is composed of blasts, monoblasts, and promonocytes. The bone marrow cellularity is nearly 100%. Large portions of marrow are replaced by immature monocytic cells. (x 40).

One cause for glomerular dysfunction is direct infiltration of the kidneys by blasts which can cause enlarged kidneys as a sign of leukemic infiltration [8] which most commonly occurs in AML with monocytic differentiation, like our patient. This particular AML subtype predisposes patients to granulocytic sarcomas, or chloromas, which are both terms used to describe an extramedullary tumor occurring in soft tissue or bone with the presence of atypical myeloid or monocytic blast cells [9]. The presence of renal leukemic involvement is extremely rare about 1%, although there are a few reported cases of renal

failure secondary to diffuse bilateral infiltration [10]. In our case, there was no reported nephromegaly on CT imaging.

A second mechanism is an increase in lysozyme production, which is postulated to be from high concentrations of circulating monocytes and granulocytes. Normally, lysozyme is reabsorbed in the proximal convoluted tubule. However, increased concentration of lysozyme can be a direct tubular toxin leading to damage of the proximal tubule cells. This is similar to the tubular disorder in adult Fanconi syndrome [11]. An absolute monocytosis of  $1 \times 10^9/L$  or



**Figure 3.** Note the cluster of blasts with blue gray cytoplasm. Sections of the bone marrow aspirate reveal an acute myelogenous leukemia with monocytic features of differentiation. (x 100).



Subtype	Blast %
CMML-0	<2 % blasts in PB and < 5% blasts in BM
CMML-1	2-4% blasts in PB and/or 5-9% blasts in BM
CMML-2	5-19% blasts in PB, 10-19% in BM, and/or when any Auer rods are present

Figure 4. 3 blast-based groupings of CMML dependent on the percentage of blasts.

Causes of AKI	N (%) or median [IQR]
Hypoperfusion	
Tumor lysis syndrome	
Acute tubular necrosis	
Nephrotoxic agents	
Hemophagocytic lymphohistiocytosis	
Kidney infiltration by malignancy	
Urinary tract obstruction	
Pyelonephritis	
Hemolytic-uremic syndrome	
More than one cause of AKI	

Figure 5. Etiologies of AKI in the setting of AML.

greater that persists for more than 3 months is needed to meet the diagnosis of CMML. Our patient had a persistent absolute monocytosis of  $21.1 \times 10^9/L$ . With such a significant absolute monocytosis, we postulate that lysozymuria was a contributing etiology to the AKI in our patient. As the gold standard test is a kidney biopsy, it was decided not to pursue this as the patient was frail and comfort-directed after the diagnosis of AML. There was no known cause for the patient's underlying chronic kidney disease (CKD) stage 3 with no history of diabetes mellitus or hypertension. Lysozymuria may actually have been the etiology for his CKD given significant monocytosis which preceded his CKD by 2 years.

Another postulated mechanism of kidney injury in our patient is hyperuricemia. In states of increased purine breakdown, such as leukemia, the insoluble uric acid load accumulates in the kidneys leading to intrarenal precipitation. Most commonly, cell lysis and the increase in purine byproducts occur with chemotherapy and radiation. However, spontaneous TLS is not an uncommon event in AML, but appears much less described as a presenting feature of CMML transforming to AML with only 1 case in the literature [7]. The Cairo-Bishop definition of tumor lysis syndrome consists of laboratory evidence for tumor lysis plus at least one clinical complication, which include creatinine  $1.5 \times$  ULN, cardiac arrhythmia, or seizure. Laboratory tumor lysis syndrome requires two or more laboratory changes within three days before or seven days after cytotoxic therapy. These laboratory changes from baseline include 25% increase of uric acid, 25% increase in potassium, 25% increase in phosphorus, and 25% decrease in calcium. As our patient only met one of the laboratory criteria in conjunction with the AKI, he did not meet strict criteria for clinical tumor lysis syndrome.

Even in the absence of tumor lysis syndrome, hyperuricemia can cause acute urate nephropathy with serum uric acid levels greater than 15 mg/dL [12,13]. It is postulated that uric acid may lead to renal insufficiency through two mechanisms. The first being obstruction of tubule lumens and the second being hindrance of renal venous blood flow [14]. Our patient had uric acid of 19.8 mg/dL supporting the possibility of uric acid nephropathy contributing to his renal pathology.

The etiology of his AKI was likely multifactorial. We postulate that lysozymuria and hyperuricemia both played a role in his progressive renal decline. Further supporting hyperuricemia and lysozymuria as causes of our patient's AKI was his dramatic improvement in kidney function with treatment of his hyperuricemia and leukocytosis. Two days later after a single dose of rasburicase and being started on hydroxyurea 1000 mg twice daily, creatinine decreased to 1.98 mg/dL from 2.94 mg/dL while uric acid and white blood cells decreased to 5.5 mg/dL and  $48.5 \times 10^3$  cells per  $mm^3$  respectively. Rasburicase is safe and highly effective for the prophylaxis or treatment of hyperuricemia in patients with leukemia or lymphoma [15]. As lysozymuria is hypothesized to be from the high concentration of circulating monocytes, the cytoreductive therapy with hydroxyurea would be expected to reduce lysozymuria and hence improve renal function.

An important indicator of transformation from CMML to AML can be AKI. CMML has a poor prognosis, and risk of transformation to AML is directly proportional to age and blast count. For 2 years prior to admission, our patient had 0% blast count in his peripheral blood consistent with CMML-0 subtype, which has a 31-month median survival

time [16]. There should be a high index of suspicion for transformation to AML in any patient with CMML who presents with AKI particularly after excluding pre- and post-renal causes. Furthermore, once pre- and post-renal causes are ruled out, then intra-renal causes such as lysozymuria and hyperuricemia, even in the absence of clinical tumor lysis syndrome, should be considered as precipitating factors for AKI.

## Acknowledgments

The authors would like to thank Dr. Sharon Swierczynski, Department of Pathology, Reading Hospital, Tower Health System, for providing the peripheral blood smear, bone marrow biopsy, and aspirate photos for the manuscript.

## Disclosure statement

No potential conflict of interest was reported by the authors.

## ORCID

Andrew Rettew  <http://orcid.org/0000-0003-4358-8230>

## References

- [1] Patnaik MM, Parikh SA, Hanson CA, et al. Chronic myelomonocytic leukaemia: a concise clinical and pathophysiological review. *Br J Haematol.* 2014 May;165(3):273–286.
- [2] Germing U, Gattermann N, Minning H, et al. Problems in the classification of CMML-dysplastic versus proliferative type. *Leuk Res.* 1998;22(10):871–878.
- [3] Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Bennett J Blood.* 1997 Mar 15;89(6):2079–2088.
- [4] Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016;127(20):2391–2405.
- [5] Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. *Cancer.* 2005 Aug 15;104(4):788–793. PubMed PMID: 15973668.
- [6] Canet E, Zafrani L, Lambert J, et al. Acute kidney injury in patients with newly diagnosed high-grade hematological malignancies: impact on remission and survival. *Plos One.* 2013;8:e55870.
- [7] Langridge A, Musgrave K, Upadhye Y. Spontaneous tumour lysis syndrome secondary to the transformation of chronic myelomonocytic leukaemia into acute myeloid leukaemia. *BMJ Case Rep.* 2016 Mar 9;2016. DOI:10.1136/bcr-2015-213095. PubMed PMID: 26961554; PubMed Central PMCID: PMC4785427.
- [8] Schwarze EW. Pathoanatomical features of the kidney in myelomonocytic and chronic lymphocytic leukemia. *Virchows Arch A Pathol Anat Histol.* 1975;368(3):243–251.
- [9] Patigaroo A, Banday S, Rashid W, et al. Isolated granulocytic sarcoma of head and neck region without any marrow involvement. *Internet J Otorhinolaryngol.* 2010;13(2).
- [10] Randolph VL, Hall W, Bramson W. Renal failure due to lymphomatous infiltration of the kidneys. *Cancer.* 1983;52:1120–1121.
- [11] Pruzanski W, Platts ME. Serum and urinary proteins, lysozyme (muramidase), and renal dysfunction in mono- and myelomonocytic leukemia. *J Clin Invest.* 1970;49(9):1694–1708.
- [12] Ries F, Sculier JP, Bron D. Spontaneous hyperuricemic acute renal failure. *Bull Soc Sci Med Grand Duché Luxemb.* 1987;124(1):57–60.
- [13] Feinstein EI, Quion-Verde H, Kaptein EM, et al. Severe hyperuricemia in patients with volume depletion. *Am J Nephrol.* 1984;4(2):77–80.
- [14] Perazella MA, Eisen RN, Frederick WG, et al. Renal failure and severe hypokalemia associated with acute myelomonocytic leukemia. *Am J Kidney Dis.* 1993;22(3):462–467.
- [15] Pui CH, Mahmoud HH, Wiley JM, et al. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients With leukemia or lymphoma. *J Clin Oncol.* 2001;19(3):697–704.
- [16] Schuler E, Schroeder M, Neukirchen J, et al. Refined medullary blast and white blood cell count based classification of chronic myelomonocytic leukemias. *Leuk Res.* 2014 Dec;38(12):1413–1419. Epub 2014 Sep 17. PubMed PMID: 25444076.