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Unusual Presentation of Bladder Myeloid Sarcoma Causing Acute Renal Failure: Case Report and Review of the Literature

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Background
Granulocytic sarcoma, also known as chloroma or myeloid sarcoma, is a pathologic term generally used to describe extramedullary solid tumors composed of myeloblasts. Rarely, it can occur as an isolated finding of acute myeloid leukemia (AML), without bone marrow or blood involvement. Primary involvement of the urinary tract without evidence of leukemia is exceedingly rare. Here, we report a case of granulocytic sarcoma presenting as acute renal failure due to an obstructive bladder mass with mesenteric involvement. Although the bone marrow was not involved morphologically, inversion of chromosome 16 (inv[16][p13q22]) was identified by reverse transcription polymerase chain reaction (RT-PCR) testing. This case illustrates the importance of the prompt use of appropriate immunostaining and molecular testing to unveil the correct diagnosis due to the urgency in treatment initiation. We performed a literature review of this rare clinical presentation to alert physicians about the optimal diagnosis for prompt treatment.

Case Report
A 39-year-old Hispanic woman with no significant medical history presented at the Oklahoma University Medical Center emergency department with a 2-month history of lower quadrant abdominal pain, nausea, vomiting, increased urinary frequency, and acute renal failure, with no urinary or vaginal bleeding. Vital signs were normal on presentation. Her physical exam was remarkable for hypogastric and lower abdominal tenderness, with the remainder of the exam unremarkable. Initial laboratory tests—including complete blood count, comprehensive metabolic panel, and urine analysis—revealed normocytic anemia with hemoglobin of 12.6 mg/dL, renal failure with creatinine of 2.64 mg/dL, and microscopic hematuria. A pregnancy test was negative. Computed tomography (CT) of the abdomen and pelvis showed a 10 cm × 8 cm pelvic mass with severe bilateral hydronephrosis. Transvaginal ultrasound showed an 8.3 cm × 5.6 cm × 7 cm left hypoechoic mass. As the initial presentation was consistent with pelvic malignancy, workup for gynecologic and urologic malignancy was done. Cervical and endometrial biopsies were negative for malignancy, and bladder wash was suspicious for malignant cells. Pap smear, CA125, and carcinoembryonic antigen (CEA) were normal. Evaluation of renal insufficiency included renal ultrasound, which revealed grade 3 bilateral hydronephrosis with a mixed cystic and solid mass lesion within the pelvis. The mass was located on the dome of the urinary bladder and anterior to the uterus, associated with deformation of the bladder. Positron emission tomography (PET) showed peritoneal carcinomatosis, bilateral hydronephrosis, and multiple hypermetabolic, left internal mammary metastases (Figure 1A). Bilateral ureteral stents were placed for management of hydronephrosis. Urinary bladder and soft tissue biopsies from the posterior cul-de-sac performed during cystoscopy revealed granulocytic sarcoma.

Immunohistochemical staining of the bladder biopsy showed that the malignant cells were positive for myeloperoxidase, CD68, CD99, CD34, and CD117 (Figure 2, A–D). Bone marrow biopsy showed mildly hypocellular marrow with trilineage hematopoiesis. Flow cytometry of the bone marrow revealed predominance of maturing granulocytes with 1% blasts, predominately myeloblasts, with no phenotypic abnormalities. Standard cytogenetic
analysis of 20 metaphases on the bone marrow biopsy sample revealed a normal female karyotype (46, XX), but reverse transcriptase-polymerase chain reaction (RT-PCR) for a series of gene rearrangements associated with leukemias and lymphomas performed on the bone marrow sample (mDx HemaVision; DNA Technology A/S, Risskov, Denmark) showed inv(16) involving fusion of the \( MYH11/CBFB \) genes. \( FLT3, NPM1, \) and \( KIT \) mutational analyses were all negative.

Based on the presence of the inv(16) in the bone marrow biopsy and evidence of granulocytic sarcoma in the bladder biopsy, the patient was treated with systemic chemotherapy consisting of a standard regimen with 7 days of continuous cytarabine infusion at 100 mg/m\(^2\)/day and 3 days of idarubicin infusion at 12 mg/m\(^2\)/day (“7 + 3”). Repeat PET/CT with [18F]-fluorodeoxyglucose (FDG) on day 21 after chemotherapy (Figure 1B) showed significant improvement of diffuse peritoneal carcinomatosis and a marked decrease in uptake in the pelvic mass. The patient received consolidation chemotherapy with high-dose cytarabine infusion at 3 g/m\(^2\) twice daily for 3 days per cycle, for 3 cycles. She tolerated the chemotherapy well and had complete remission, as documented by a follow-up PET scan 6 months after chemotherapy initiation, which showed no evidence of disease.

**Discussion**

Myeloid sarcoma was first described by the British physician A. Burns in 1811. The condition was later referred to as *chloroma* because of the greenish tint the cells display under microscopic exam, due to the presence of myeloperoxidase. In 1904, the link between leukemia and chloroma was first identified. Since 30% of these tumors can be of other colors (eg, white and gray), they were renamed *granulocytic sarcoma* by Rappaport, who defined them as invasive and destructive tumor masses that are usually green in appearance and composed of immature cells of the granulocytic series. In the revised 2008 World Health Organization (WHO) classification of myeloid neoplasms and AML, myeloid sarcoma is defined as a separate pathologic entity for an extramedullary proliferation of blasts of myeloid lineage. The term *myeloid sarcoma* has now replaced the previous nomenclature.

There have been many instances in which myeloid sarcoma has been misdiagnosed as non-Hodgkin lymphoma, small round cell tumors (including neuroblastoma, rhabdomyosarcoma, Ewing’s sarcoma, peripheral neuroectodermal tumor, and medulloblastoma), undifferentiated carcinoma or melanoma, malignant histiocytosis, and malignant mastocytosis with atypical mast cells. Of these, non-Hodgkin lymphoma has been the most common misdiagnosis, occurring in approximately 50% of cases. In an autopsy study by Neiman and associates, only 44% of 61 cases of myeloid sarcoma had the correct initial diagnosis, further empha-
sizing the importance of immunohistochemical studies in the diagnosis of this neoplasm.

Myeloid sarcoma can be classified histologically into blastic, immature, and well-differentiated disease, involving the granulocytic, myelomonocytic, or monocytic series. Pileri and colleagues found no association between histologic type and anatomic site of involvement, with the exception that 50% of the monoblastic forms occurred in the skin.

Myeloid sarcoma is considered rare, and is reported in 2–9% of the cases of myeloid neoplasms. It occurs most frequently in acute myeloid leukemia (AML) but may also occur in chronic myeloid leukemia, myelodysplastic syndrome (MDS), and other myeloproliferative syndromes (MPS); in the latter settings, it would indicate acute blastic transformation. In such patients, myeloid sarcoma may occur concomitantly with the disease, precede it, or be the only sign of relapse. Isolated myeloid sarcoma, which is exceedingly rare, is defined by the absence of any history of leukemia, MDS, or MPS, and negative bone marrow biopsy. In one study, it was reported that 25% of cases occur de novo; 32% occurred in patients with myeloid neoplasms like AML, MPD, or MDS simultaneously; and 35% of cases were in patients with previous histories of myeloid neoplasms and were a sign of relapse.

Presenting symptoms of myeloid sarcoma can vary depending on the anatomic site; the most common sites of occurrence are the skin, bone, periosteum, lymph nodes, and soft tissues. However, myeloid sarcoma has been reported in a wide variety of other tissues, including the urinary bladder, pancreas, cervix, breast, CNS, orbit, intestines, mediastinum, epidural region, ovary, and bladder. In our literature search, we identified 4 prior cases of myeloid sarcoma with inv(16) involving the mesentery. We also found 10 reported cases of involvement of the urologic system by myeloid sarcoma. Most of these cases, including all 7 cases involving the bladder, had no documented cytogenetic studies. These cases are illustrated in Table 1.

Pathologic diagnosis is largely dependent on adequate biopsy and immunohistochemical analyses, but can be augmented by molecular testing. CD68/KP1, which is a marker for macrophages, is the most commonly expressed marker and is seen in 100% of cases. Myeloperoxidase is the second most common marker, followed by CD117, CD99, CD34, and TdT. Bone marrow biopsy, cytogenetics, and molecular analysis are currently considered an integral part of the diagnosis of myeloid sarcoma.
Previous studies have shown a relative increase in the incidence of myeloid sarcoma among patients with specific cytogenetic abnormalities, such as t(8;21) or inv(16). Other risk factors include M2, M4, or M5 in the FAB classifications, myeloblast co-expressing T-cell surface markers (CD56, CD2, CD4, CD7), age, and high peripheral white blood cell counts.13

The most common cytogenetic abnormality associated with myeloid sarcoma is t(8;21), which is seen in approximately 7% of cases.14 As seen in our patient, inv(16) is another common cytogenetic abnormality and is most frequently observed in myeloid sarcoma involving the abdomen. Xavier and coworkers speculated that the increased incidence of myeloid sarcoma in patients with inv(16) may be related to the deregulation of core binding factor (CBF) transcription factors involved in cellular adhesion and recognition, but there are no studies demonstrating this process.15

As most cases of untreated myeloid sarcoma eventually proceed to AML, most experts agree that systemic chemotherapy is the treatment of choice. As used in our patient, treatment with standard induction and consolidation chemotherapy with cytarabine and an anthracycline followed by high-dose cytarabine for consolidation is recommended. Radiation therapy can be used in cases of isolated myeloid sarcoma or inadequate response to chemotherapy. Also, radiation has been used in recurrent cases after hematopoietic stem cell transplantation (HSCT) and

### Table 1. Case Studies of Myeloid Sarcoma Involving the Urinary Tract

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/ Sex</th>
<th>Location</th>
<th>Diagnosis</th>
<th>Cytogenetics</th>
<th>Treatment</th>
<th>Status</th>
<th>Time From Diagnosis to Last Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al8</td>
<td>NR</td>
<td>Bladder</td>
<td>AML</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Chaitin et al23</td>
<td>29/F</td>
<td>Bladder trigone</td>
<td>MS</td>
<td>NR</td>
<td>Doxorubicin, vincristine, cytarabine, prednisone</td>
<td>Complete remission</td>
<td>13 months</td>
</tr>
<tr>
<td>Cartwright et al26</td>
<td>16/M</td>
<td>Left urethra</td>
<td>AML and MS</td>
<td>NR</td>
<td>External radiation</td>
<td>Death</td>
<td>2 months</td>
</tr>
<tr>
<td>Bekassyet al25</td>
<td>17/M</td>
<td>Bladder</td>
<td>AML</td>
<td>NR</td>
<td>Surgery, chemotherapy</td>
<td>Alive</td>
<td>75 months</td>
</tr>
<tr>
<td>Aki et al26</td>
<td>36/M</td>
<td>Bladder</td>
<td>Misdiagnosed as TCC then MS</td>
<td>NR</td>
<td>MVAC followed by cytarabine plus doxorubicin</td>
<td>Death</td>
<td>16 days into treatment</td>
</tr>
<tr>
<td>Kerr et al27</td>
<td>80/M</td>
<td>Bladder</td>
<td>RAEB relapsing as MS</td>
<td>NR</td>
<td>Local radiation</td>
<td>Recurrence</td>
<td>NR</td>
</tr>
<tr>
<td>Hasegeli Uner et al28</td>
<td>57/F</td>
<td>Urinary bladder cell</td>
<td>MS</td>
<td>NR</td>
<td>Ara-C plus idarubicin and radiation</td>
<td>Complete remission</td>
<td>1 month</td>
</tr>
<tr>
<td>Al-Quran et al29</td>
<td>47/M</td>
<td>Bladder trigone and right epididymis</td>
<td>Poorly differentiated, neoplasm, MS</td>
<td>Bone marrow 47XY, inv(16), +22; bladder inv(16) by FISH</td>
<td>Ara-C plus idarubicin</td>
<td>Complete remission</td>
<td>32 months</td>
</tr>
<tr>
<td>Kong et al30</td>
<td>NR</td>
<td>Urinary bladder</td>
<td>MS</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Geok Chin et al31</td>
<td>70/F</td>
<td>Urinary bladder and abdominal wall</td>
<td>AML and MS</td>
<td>Bone marrow AML</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Present case</td>
<td>39/F</td>
<td>Bladder mesentery</td>
<td>MS</td>
<td>Bone marrow 46XX, inv(16)</td>
<td>Ara-C plus idarubicin, Ara-C, and consolidation</td>
<td>Complete remission</td>
<td>8 months</td>
</tr>
</tbody>
</table>

AML = acute myeloid leukemia; FISH = fluorescence in situ hybridization; MS = myeloid sarcoma; MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin; NR = not reported; RAEB = refractory anemia with excess blasts; TCC = transitional cell carcinoma.
for symptom relief. Prognosis, however, is not improved with radiation therapy. In a recent study of 20 patients with myeloid sarcoma, the total rate of complete remission (CR) was 65%; 16 of these patients who were treated with chemotherapy alone had a CR rate of 63%; 1 patient was treated with radiation therapy and also obtained a CR, while 3 patients were treated with combination chemotherapy and radiation and had a CR rate of 67%.

Further therapy is often offered in the form of allogeneic HSCT, depending on the prognostic risk profile. In a retrospective multicenter study, allogeneic HSCT showed promising results with a 5-year overall survival of 47% and a leukemia-free survival of 36%. The authors of this study did not find any difference in outcomes with isolated myeloid sarcoma versus leukemia-associated myeloid sarcoma. In a retrospective study conducted by Pileri and associates, overall survival of patients receiving HSCT was 76% at 48 months compared to 0% in patients who did not undergo HSCT. HSCT offered a median survival of 52.5 months compared to 7.1 months with chemotherapy alone, while the median survival with radiation therapy alone was only 1 week. In pediatric patients, isolated myeloid sarcoma is a good prognostic marker, especially in those with extramedullary presentation at non-skin sites, compared to children who have AML or extramedullary myeloid sarcoma involving the skin. The utility of HSCT for patients with isolated myeloid sarcoma demonstrating favorable cytogenetic markers, such as inv(16), is unclear. Inv(16) and the resulting CBFB-MYH11 gene fusion has been associated with good prognosis in patients with AML, generally demonstrating a 5-year overall survival rate of 58%; however, studies evaluating the prognosis of patients with myeloid sarcoma and inv(16) are lacking. In a study comparing the outcomes of patients with myeloid sarcoma and AML treated with “7 + 3” standard therapy, patients with myeloid sarcoma showed better response rates, event-free survival, and overall survival.

Conclusion

Our case emphasizes that, despite its rarity, myeloid sarcoma can be identified appropriately with proper immunohistochemical and molecular testing. Correct diagnosis is essential for selection of appropriate therapy. Bone marrow biopsy, cytogenetic studies, and molecular studies should be routinely performed in all cases. Myeloid sarcoma should be routinely treated with systemic chemotherapy, HSCT may be considered, although myeloid sarcoma has not been shown to be associated with a higher risk in patients with favorable cytogenetic profiles.

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References

### Review

#### Isolated Myeloid Sarcoma of the Genitourinary System

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#### Discussion

John and associates describe the unusual case of an isolated myeloid sarcoma of the genitourinary system, presenting as a large pelvic mass with severe bilateral hydronephrosis and renal failure in a previously healthy 39-year-old woman. While the clinical and radiographic presentation suggested malignancy of primary gynecologic or urologic origin, immunohistochemical (IHC) staining of the bladder biopsy with myeloperoxidase (MPO), CD34, CD68, and CD117 unexpectedly identified a tumor of myeloid origin. The complete blood count at diagnosis was not provided, although normocytic anemia with hemoglobin of 12.6 mg/dL and microscopic hematuria is recorded, without other findings concerning for a primary marrow process. With the IHC results in hand, a bone marrow aspirate and biopsy were then performed. They revealed a mildly hypocellular marrow for age with trilineage hematopoiesis, an unremarkable blast percentage of 1%, and no morphologic evidence of leukemia in the bone marrow. Cytogenetic evaluation revealed a normal female karyotype of 46, XX in 20 metaphases.

Of diagnostic importance, application of a commercially available reverse-transcriptase polymerase chain reaction (RT-PCR) assay for common leukemia and lymphoma translocations identified the CBFB-MYH11 fusion protein, pathognomonic of inversion(16) acute myeloid leukemia (AML). The patient was then treated with systemic chemotherapy in the standard “3 + 7” AML induction therapy fashion with idarubicin 12 mg/m²/day for 3 days and cytarabine 100 mg/m²/day for 7 days. The patient went on to receive high-dose cytarabine consolidation therapy with 3 g/m² twice daily for 3 days for a total of 3 cycles, and she remains in a complete remission, now 6 months from diagnosis.

Several valuable teaching points can be gleaned from this interesting case. First, the appropriate application of IHC testing in the setting of a tumor of unknown primary is central to establish the correct pathologic diagnosis, especially considering that myeloid sarcoma is frequently misdiagnosed. MPO, lysozyme, CD34, CD68, and CD117 are the most common IHC markers used to establish and confirm a neoplasm of myeloid origin. Next, and of crucial importance, is the use of cytogenetic and molecular diagnostic studies to best inform AML risk stratification and treatment decisions. Multiplex RT-PCR assays have been rationally designed to detect the most common leukemia (and/or lymphoma, depending on the specific assay) translocations, ensuring improved diagnostic accuracy as well as cost-effectiveness using clinically validated methodology. Identification of cytogenetic or molecular abnormalities at diagnosis can then also be applied during the course of a patient’s leukemia therapy to monitor for minimal residual disease (MRD) and further tailor therapeutic decisions.

Inv(16) AML has unique clinical and pathologic characteristics, including myelomonocytic differentiation.
with bone marrow eosinophilia (French-American-British [FAB] classification M4eo), younger age at diagnosis, and a propensity for extramedullary leukemic involvement, including central nervous system (CNS) disease, leukemia cutis, and myeloid sarcomas. A predisposition to extramedullary disease within the abdomen with inv(16) AML has additionally been suggested. It is also notable that the 3 fusion transcripts associated with particularly favorable prognosis in AML—namely CBFβ/MYH11 in inv(16), AML1/ETO in t(8;21), and PML/RARα in t(15;17)—have all been associated with an increased rate of myeloid sarcoma and extramedul- lary disease. This implies that particular diligence should be made upon the identification of myeloid sarcoma to evaluate for these translocations with favorable prognostic importance.

The identification of isolated myeloid sarcoma in the absence of bone marrow involvement is a rare presentation, and there are no randomized trial data to inform clinical decision-making. While some reports suggest that myeloid sarcoma confers a poor prognosis, other reports support an equivalent or even favorable prognosis in patients with isolated myeloid sarcoma. Confounding these reports are the variable cytogenetic and molecular features of the identified AML, as well as the therapeutic regimen administered. It is evident that even in the setting of a “normal bone marrow” examination, localized therapy of an isolated myeloid sarcoma using surgical and/or radiation-based therapies is not sufficient, and in the absence of systemic therapy, the median time to frank myeloid sarcoma and extramedullary disease.

References