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

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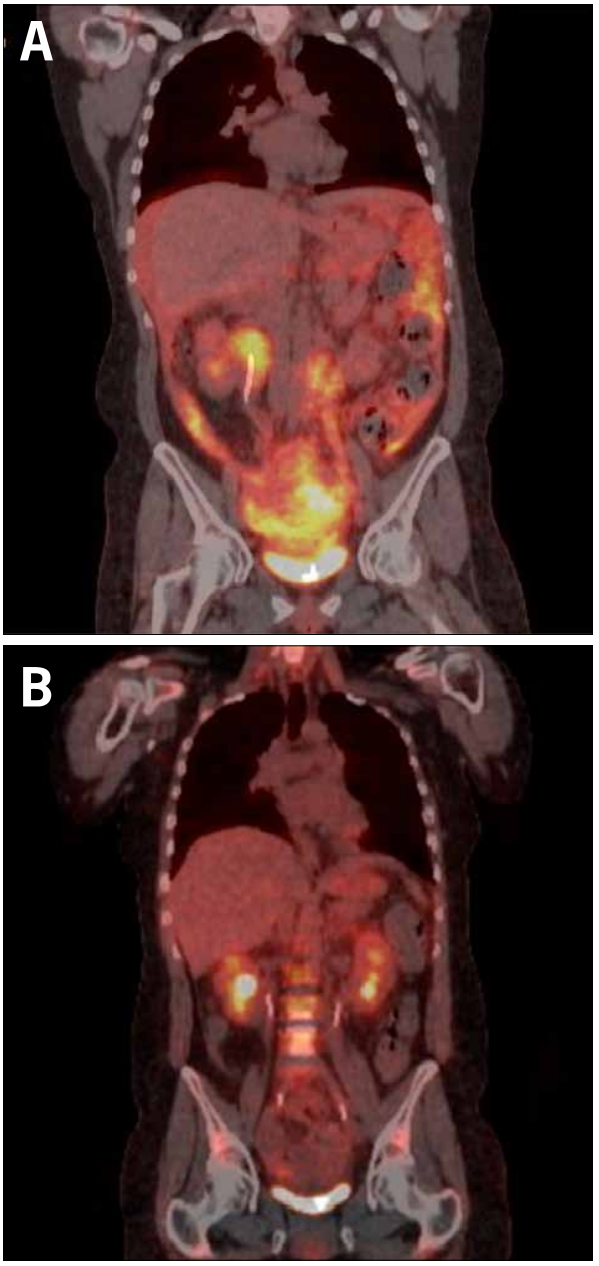

Figure 1. Positron emission tomography (PET) scan image at presentation (A) and after induction chemotherapy (B). A) Coronal view of the PET scan image at presentation illustrating the hypermetabolic soft tissue stranding and thickening of the mesentery, peritoneum, and urinary bladder. B) The PET scan was repeated on day 21 after induction chemotherapy and revealed a significant decrease in the areas of hypermetabolic activity, especially in the mesentery and above the urinary bladder.

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.[1] 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.[2] In 1904, the link between leukemia and chloroma was first identified.[3] Since 30% of these tumors can be of other colors (eg, white and gray), they were renamed *granulocytic sarcoma* by Rappaport,[4] 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.[5] 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,[6] only 44% of 61 cases of myeloid sarcoma had the correct initial diagnosis, further empha-

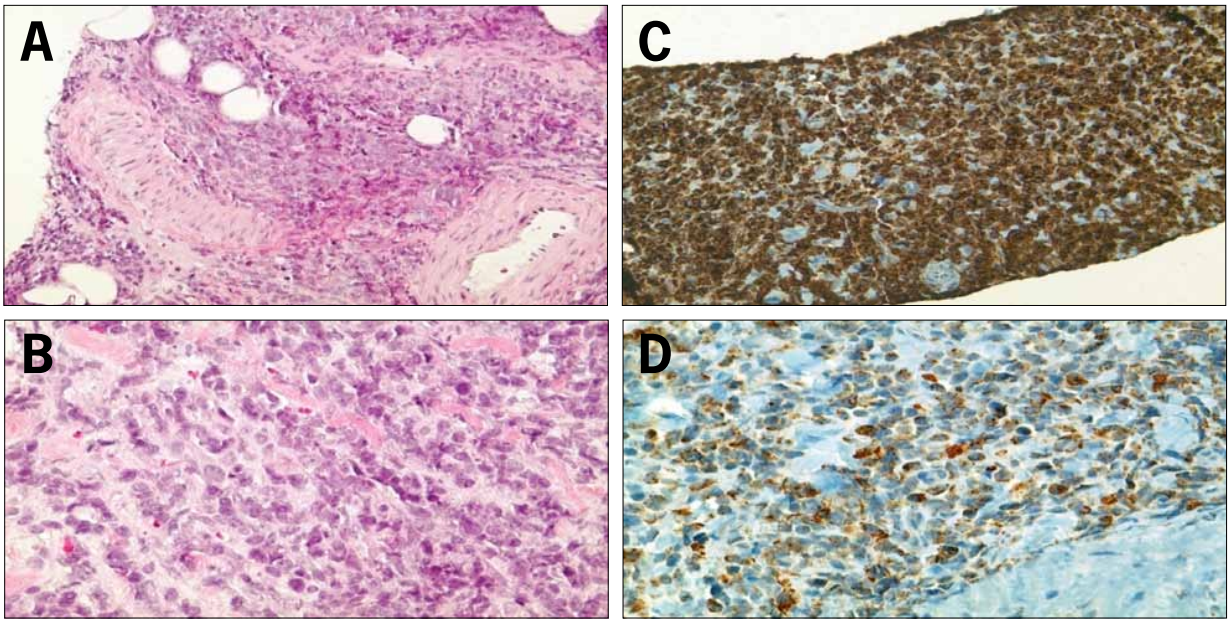

Figure 2. Posterior cul-de-sac biopsy specimen. A) Hematoxylin and eosin (H&E) stain; approximately 200 × magnification. Sheets of medium to large–sized cells with fine nuclear chromatin. Few eosinophils are present, and there is no evidence of differentiation. B) H&E stain; approximately 400 × magnification. Medium to large cells with very fine ("blastic"-appearing) nuclear chromatin; many have small nucleoli. C) Immunohistochemical stain for myeloperoxidase; approximately 200 × magnification. Very strongly positive myeloperoxidase stain, indicating myeloid lineage. D) Immunohistochemical stain for CD68; approximately 400 × magnification. Many of the immature-appearing cells show positive staining for CD68. CD68 is generally considered a monocyte/macrophage marker; however, the specific CD68 clone (antibody) we use also stains immature granulocytes. This positive reaction helps confirm myeloid lineage. It suggests, but is not specific for, monocytic lineage.

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[5] 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.[7,8] 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.[5]

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.[9-12] 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.[5] 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.

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

Case	Age/ Sex	Location	Diagnosis	Cytogenetics	Treatment	Status	Time From Diagnosis to Last Follow-Up
Liu et al[8]	NR	Bladder	AML	NR	NR	NR	NR
Chaitin et al[23]	29/F	Bladder trigone	MS	NR	Doxorubicin, vincristine, cytarabine, prednisone	Complete remission	13 months
Cartwright et al[24]	16/M	Left urethra	AML and MS	NR	External radiation	Death	2 months
Bekassyet al[25]	17/M	Bladder	AML	NR	Surgery, chemotherapy	Alive	75 months
Aki et al[26]	36/M	Bladder	Misdiagnosed as TCC then MS	NR	MVAC followed by cytarabine plus doxorubicin	Death	16 days into treatment
Kerr et al[27]	80/M	Bladder	RAEB relapsing as MS	NR	Local radiation	Recurrence	NR
Hasegeli Uner et al[28]	57/F	Urinary bladder cell	MS	NR	Ara-C plus idarubicin and radiation	Complete remission	1 month
Al-Quran et al[29]	47/M	Bladder trigone and right epididymis	Poorly differentiated, neoplasm, MS	Bone marrow 47XY, inv(16), +22; bladder inv(16) by FISH	Ara-C plus idarubicin	Complete remission	32 months
Kong et al[30]	NR	Urinary bladder	MS	NR	NR	NR	NR
Geok Chin et al[31]	70/F	Urinary bladder and abdominal wall	AML and MS	Bone marrow AML	NR	NR	NR
Present case	39/F	Bladder mesentery	MS	Bone marrow 46XX, inv(16)	Ara-C plus idarubicin, Ara-C, and consolidation	Complete remission	8 months

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.

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

for symptom relief.[7] Prognosis, however, is not improved with radiation therapy.[16] 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%.[17]

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%.[18] The authors of this study did not find any difference in outcomes with isolated myeloid sarcoma versus leukemia-associated myeloid sarcoma.[19] 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.[5] 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.[20]

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-MYHII* gene fusion has been associated with good prognosis in patients with AML, generally demonstrating a 5-year overall survival rate of 58%[21]; 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.[22]

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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SJ wrote the manuscript and was assisted by HAA. TD, WK, and JH reviewed the article, and MC wrote and edited the manuscript. We appreciate the assistance of Dr. Amber Borden, who reviewed the manuscript.

References

1. Burns A. *Observations On the Surgical Anatomy of the Head and Neck*. Edinburgh: Thomas Royce & Co; 1811:364-366.
2. King C. A case of chloroma with orbital involvement locally benefited by x-ray therapy. *Trans Am Ophthalmol Soc*. 1934;32:340-353.
3. Dock G, Warthin AS. A new case of chloroma with leukemia. *Trans Assoc Am Phys*. 1904;19:64-115.
4. Rappaport H. Tumors of the hematopoietic system. In: *Atlas of Tumor Pathology*. Washington DC: Armed Forces Institute of Pathology; 1966:241-243.
5. Pileri SA, Ascani S, Cox MC, et al. Myeloid sarcoma: clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients. *Leukemia*. 2007;21:340-350.
6. Neiman RS, Barcos M, Berard C, et al. Granulocytic sarcoma: a clinicopathologic study of 61 biopsied cases. *Cancer*. 1981;48:1426-1437.
7. Bakst RL, Tallman MS, Douer D, Yahalom J. How I treat extramedullary acute myeloid leukemia. *Blood*. 2011;118:3785-3793.
8. Liu PI, Ishimaru T, McGregor DH, Okada H, Steer A. Autopsy study of granulocytic sarcoma (chloroma) in patients with myelogenous leukemia, Hiroshima-Nagasaki 1949-1969. *Cancer*. 1973;31:948-955.
9. Gohring G, Erlacher M, van Buiren M, Juttner E, Niemeyer CM, Schlegelberger B. Mesenteric chloroma with t(16;16) followed by acute myelomonocytic leukemia with clonal evolution. *Cancer Genet Cytogenet*. 2007;179:162-164.
10. Fujieda A, Nishii K, Tamaru T, et al. Granulocytic sarcoma of mesentery in acute myeloid leukemia with CBFB/MYH11 fusion gene but not inv(16) chromosome: case report and review of literature. *Leuk Res*. 2006;30:1053-1057.
11. Billio A, Pianezze G, Amato B, Fabris P. "Isolated" peritoneal granulocytic sarcoma with molecular and chromosomal bone marrow involvement. *Haematologica*. 2002;87:EIM01.
12. Zhang XH, Zhang R, Li Y. Granulocytic sarcoma of abdomen in acute myeloid leukemia patient with inv(16) and t(6;17) abnormal chromosome: case report and review of literature. *Leuk Res*. 2010;34:958-961.
13. Byrd JC, Edenfield WJ, Shields DJ, Dawson NA. Extramedullary myeloid cell tumors in acute nonlymphocytic leukemia: a clinical review. *J Clin Oncol*. 1995;13:1800-1816.
14. Tallman MS, Hakimian D, Shaw JM, Lissner GS, Russell EJ, Variakojis D. Granulocytic sarcoma is associated with the 8;21 translocation in acute myeloid leukemia. *J Clin Oncol*. 1993;11:690-697.
15. Xavier SG, Fagundes EM, Hassan R, et al. Granulocytic sarcoma of the small intestine with CBFbeta/MYH11 fusion gene: report of an aleukaemic case and review of the literature. *Leuk Res*. 2003;27:1063-1066.
16. Lan TY, Lin DT, Tien HF, Yang RS, Chen CY, Wu K. Prognostic factors of treatment outcomes in patients with granulocytic sarcoma. *Acta Haematol*. 2009;122:238-246.
17. Tsimberidou AM, Kantarjian HM, Estey E, et al. Outcome in patients with nonleukemic granulocytic sarcoma treated with chemotherapy with or without radiotherapy. *Leukemia*. 2003;17:1100-1103.
18. Chevallier P, Mohty M, Lioure B, et al. Allogeneic hematopoietic stem-cell transplantation for myeloid sarcoma: a retrospective study from the SFGM-TC. *J Clin Oncol*. 2008;26:4940-4943.
19. Chevallier P, Labopin M, Cornelissen J, Socie G, Rocha V, Mohty M. Allogeneic hematopoietic stem cell transplantation for isolated and leukemic myeloid sarcoma in adults: a report from the Acute Leukemia Working Party of the European group for Blood and Marrow Transplantation. *Haematologica*. 2011;96:1391-1394.
20. Dusenbery KE, Howells WB, Arthur DC, et al. Extramedullary leukemia in children with newly diagnosed acute myeloid leukemia: a report from the Children's Cancer Group. *J Pediatr Hematol Oncol*. 2003;25:760-768.
21. Delaunay J, Vey N, Leblanc T, et al. Prognosis of inv(16)/t(16;16) acute myeloid leukemia (AML): a survey of 110 cases from the French AML Intergroup. *Blood*. 2003;102:462-469.
22. Tsimberidou AM, Kantarjian HM, Wen S, et al. Myeloid sarcoma is associated with superior event-free survival and overall survival compared with acute myeloid leukemia. *Cancer*. 2008;113:1370-1378.

23. Chaitin BA, Manning JT, Ordonez NG. Hematologic neoplasms with initial manifestations in lower urinary tract. *Urology*. 1984;23:35-42.
24. Cartwright PC, Faye-Petersen O, Bybee B, Snow BW. Leukemic relapse presenting with ureteral obstruction caused by granulocytic sarcoma. *J Urol*. 1991;146:1354-1355.
25. Bekassy AN, Hermans J, Gorin NC, Gratwohl A. Granulocytic sarcoma after allogeneic bone marrow transplantation: a retrospective European multicenter survey. Acute and Chronic Leukemia Working Parties of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 1996;17:801-808.
26. Aki H, Baslar Z, Uygun N, Ozguroglu M, Tuzuner N. Primary granulocytic sarcoma of the urinary bladder: case report and review of the literature. *Urology*. 2002;60:345.
27. Kerr P, Evely R, Pawade J. Bladder chloroma complicating refractory anaemia with excess of blasts. *Br J Haematol*. 2002;118:688.
28. Hasegeli Uner A, Altundag K, Saglam A, Tekuzman G. Granulocytic sarcoma of the urinary bladder. *Am J Hematol*. 2004;75:262-263.
29. Al-Quran SZ, Olivares A, Lin P, Stephens TW, Medeiros LJ, Abruzzo LV. Myeloid sarcoma of the urinary bladder and epididymis as a primary manifestation of acute myeloid leukemia with inv(16). *Arch Pathol Lab Med*. 2006;130:862-866.
30. Kong CH, Singam P, Hong GE, et al. Clinicopathological features of bladder tumours in a single institution in Malaysia. *Asian Pac J Cancer Prev*. 2010;11:149-152.
31. Geok Chin T, Masir N, Noor Hussin H, Mohd Sidik S, Boon Cheok L, Yean T. Myeloid sarcoma of the urinary bladder with cutaneous tumour seeding after percutaneous suprapubic catheterization. *Malays J Pathol*. 2011;33:47-51.

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.[1] 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 CBFβ-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, CD99, and CD117 are the most common IHC markers used to establish and confirm a neoplasm of myeloid origin.[2,3] 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.[4] 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

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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.[5,6] A predisposition to extramedullary disease within the abdomen with inv(16) AML has additionally been suggested.[7,8] 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 extramedullary disease.[7,9-13] 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.[13-17] 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 AML development is in the range of 5–12 months.[18-22] While both radiation therapy and/or surgery may be indicated in the clinical scenario where rapid symptom relief is needed or in the setting of vital organ compromise, systemic AML chemotherapy is needed for curative intent. Whether to proceed with hematopoietic stem cell transplant (HSCT) in remission is less clear, and should ideally be an individualized decision, taking into consideration the patient's age, performance status, comorbidities, and cytogenetic and molecular leukemia characteristics.[13,23]

References

1. John S, Ali Ahmad H, Dunn T, Kern W, Holter J, Cherry M. Unusual presentation of bladder myeloid sarcoma causing acute renal failure: case report and review of the literature. *Clin Adv Hematol Oncol*. 2013;11:388-392.
2. Pileri SA, Ascani S, Cox MC, et al. Myeloid sarcoma: clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients. *Leukemia*. 2007;21:340-350.
3. Campidelli C, Agostinelli C, Stitson R, et al. Myeloid sarcoma: extramedullary manifestation of myeloid disorders. *Am J Clin Pathol*. 2009;132:426-437.
4. Salto-Tellez M, Shelat SG, Benoit B, et al. Multiplex RT-PCR for the detection of leukemia-associated translocations: validation and application to routine molecular diagnostic practice. *J Mol Diagn*. 2003;5:231-236.
5. Le Beau MM, Larson RA, Bitter MA, et al. Association of an inversion of chromosome 16 with abnormal marrow eosinophils in acute myelomonocytic leukemia. A unique cytogenetic-clinicopathological association. *N Engl J Med*. 1983;309:630-636.
6. Delaunay J, Vey N, Leblanc T, et al. Prognosis of inv(16)/t(16;16) acute myeloid leukemia (AML): a survey of 110 cases from the French AML Intergroup. *Blood*. 2003;102:462-469.
7. Zhang XH, Zhang R, Li Y. Granulocytic sarcoma of abdomen in acute myeloid leukemia patient with inv(16) and t(6;17) abnormal chromosome: case report and review of literature. *Leuk Res*. 2010;34:958-961.
8. Garcia MG, Deavers MT, Knoblock RJ, et al. Myeloid sarcoma involving the gynecologic tract: a report of 11 cases and review of the literature. *Am J Clin Pathol*. 2006;125:783-790.
9. Xavier SG, Fagundes EM, Hassan R, et al. Granulocytic sarcoma of the small intestine with CBFbeta/MYH11 fusion gene: report of an aleukaemic case and review of the literature. *Leuk Res*. 2003;27:1063-1066.
10. Schwyzer R, Sherman GG, Cohn RJ, et al. Granulocytic sarcoma in children with acute myeloblastic leukemia and t(8;21). *Med Pediatr Oncol*. 1998;31:144-149.
11. Vega-Ruiz A, Faderl S, Estrov Z, et al. Incidence of extramedullary disease in patients with acute promyelocytic leukemia: a single-institution experience. *Int J Hematol*. 2009;89:489-496.
12. Specchia G, Lo Coco F, Vignetti M, et al. Extramedullary involvement at relapse in acute promyelocytic leukemia patients treated or not with all-trans retinoic acid: a report by the Gruppo Italiano Malattie Ematologiche dell'Adulto. *J Clin Oncol*. 2001;19:4023-4028.
13. Slomowitz SJ, Shami PJ. Management of extramedullary leukemia as a presentation of acute myeloid leukemia. *J Natl Compr Canc Netw*. 2012;10:1165-1169.
14. Byrd JC, Weiss RB, Arthur DC, et al. Extramedullary leukemia adversely affects hematologic complete remission rate and overall survival in patients with t(8;21)(q22;q22): results from Cancer and Leukemia Group B 8461. *J Clin Oncol*. 1997;15:466-475.
15. Tsimberidou AM, Kantarjian HM, Wen S, et al. Myeloid sarcoma is associated with superior event-free survival and overall survival compared with acute myeloid leukemia. *Cancer*. 2008;113:1370-1378.
16. Chang H, Brandwein J, Yi QL, et al. Extramedullary infiltrates of AML are associated with CD56 expression, 11q23 abnormalities and inferior clinical outcome. *Leuk Res*. 2004;28:1007-1011.
17. Ruiz-Arguelles GJ, Morales-Toquero A, Manzano C, et al. t(8;21) (q22;q22) acute myelogenous leukemia in Mexico: a single institution experience. *Hematology*. 2006;11:235-238.
18. Meis JM, Butler JJ, Osborne BM, et al. Granulocytic sarcoma in nonleukemic patients. *Cancer*. 1986;58:2697-2709.
19. Neiman RS, Barcos M, Berard C, et al. Granulocytic sarcoma: a clinicopathologic study of 61 biopsied cases. *Cancer*. 1981;48:1426-1437.
20. Tsimberidou AM, Kantarjian HM, Estey E, et al. Outcome in patients with nonleukemic granulocytic sarcoma treated with chemotherapy with or without radiotherapy. *Leukemia*. 2003;17:1100-1103.
21. Yamauchi K, Yasuda M. Comparison in treatments of nonleukemic granulocytic sarcoma: report of two cases and a review of 72 cases in the literature. *Cancer*. 2002;94:1739-1746.
22. Antic D, Elezovic I, Milic N, et al. Is there a "gold" standard treatment for patients with isolated myeloid sarcoma? *Biomed Pharmacother*. 2013;67:72-77.
23. Bakst RL, Tallman MS, Douer D, et al. How I treat extramedullary acute myeloid leukemia. *Blood*. 2011;118:3785-3793.