Case Study

De Novo Splenic Myeloid Sarcoma Masquerading as Mesenteric Artery Occlusion Associated Acute Abdomen

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Abstract: We present a case of a 41-year-old male who was admitted to an outside hospital for abdominal pain with increasing severity and reported past medical history of seizures and pancreatitis. Abdominal CT imaging revealed acute mesenteric ischemia and a splenic infarction. Concurrently, the patient's white blood cell count showed minimal leukocytosis with relative monocytosis. Patient underwent a laparotomy that resulted in a mesenteric embolectomy and splenectomy. Reviewing the histological sections of the spleen, accessory spleen and mesenteric emboli clot sections along with additional studies performed at our institution confirmed the diagnosis of an isolated de-novo myeloid sarcoma with monocytic differentiation. Staging of the disease included trephine bone marrow biopsy and ancillary testing on the bone marrow aspirate (*i.e.* cytogenetics and FISH studies). These studies were negative for bone marrow involvement by acute myeloid leukemia. Follow up positron emission tomography/computed tomography highlighted no new sites of involvement. To the best of our knowledge, this is the second reported case in the literature of an isolated splenic myeloid sarcoma without bone marrow involvement and no history of receiving any treatment. This is the first reported case in the medical literature of this disease entity clinically presenting as mesenteric artery occlusion.

Keywords: Spleen, Myeloid Sarcoma

Introduction

Myeloid sarcoma (MS), first described in 1811 by Burns, is a rare neoplastic tumor mass of immature myeloid cells involving an extramedullary site [1, 2]. Extramedullary sites commonly include subperiosteal bone (e.g. skull, paranasal sinuses, sternum, ribs, vertebrae and pelvis); skin and lymph nodes. Moreover, involving the pancreas, heart, brain, mouth, breast, gastrointestinal system, prostate, urinary bladder, spleen and gynecological tract have been described in the literature [3–10].

This entity was further delineated through myeloperoxidase, which gave the neoplasm a greenish color after air exposure, colloquially coined chloroma [3]. Not until 1966, Rappaport proposed the term granulocytic sarcoma [3]; however, further studies revealed that myeloid leukemias are derived from granulocytes, monocytes, erythroids, and megakaryocytes. In 2002, the diagnostic term myeloid sarcoma was accepted by the World Health Organization (WHO) [1].

Routinely MS are diagnosed in patients with

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known acute myeloid leukemia, myeloproliferative (MPN) or myelodsyplastic (MDS) neoplasms, recurrence of previously treated primary or secondary leukemia and de novo [4]. The WHO recognizes three major variants: 1) blastic variant; 2) immature variant with myeloid progenitors; and 3) differentiated variant with more mature granulocytes [1]. MS tumor cells lack specific B and T-lymphocytic markers and express myeloid and/or monocytic markers, such as CD13, CD33, myeloperoxidase (MPO), CD14 or CD64. In addition, these tumor cells express CD68, CD34, CD163, lysozyme, and CD43 [10]. Rare cases of megakaryoblastic (CD61-positive/CD42b-positive) and erythroblastic (CD71-positive) have been reported [10]. In diagnosing MS, the immunophenotype is vital for lineage delineation and differential diagnoses at any anatomical location. In this paper we report an isolated splenic myeloid sarcoma with an unusual clinical presentation without bone marrow involvement by a myeloid neoplasm or known history of chemotherapeutic intervention.

Case Report

Our patient is a 41-year-old Caucasian male with a significant past medical history of seizure disorder and pancreatitis. He initially presented to an outside hospital for abdominal pain and elevated liver function tests. Computed tomographic (CT) imaging of the abdomen initially suggested an ileus; however, with abdominal pain worsening a repeated abdominal CT revealed a questionable filling defect of the superior mesenteric artery and wall thickening of the small bowel and cecal fold. Radiologic impression of the spleen, included multiple wedge-shaped areas of decreased attenuation, that was concerning for infarction. Concurrent laboratory tests revealed mild leukocytosis (13.7 K/mcL) with relative monocytosis, elevated liver function tests (alkaline phosphatase 190 IU/L), normal hemoglobin (15 g/dL) and normal platelet count (430 K/mcL). Other than mild elevation of alkaline phosphatase, the remaining biochemical testing panel was within normal limits. At the same outside institution a transthoracic echocardiogram was performed to rule out infective endocarditis. The echocardiogram showed a slightly mobile solid area adjacent to the superior aspect of the aortic wall; however, infective endocarditis was essentially ruled out after additional studies. Given the patient's worsening abdominal pain and probable mesenteric ischemia an exploratory laparotomy was the next course in the patient's management. Ultimately, the patient underwent a splenectomy, small bowel segmental resection and embolectomy of the superior mesenteric artery. At the outside institution the specimen was received in formalin and paraffin-embedded. Hematoxylin & eosin (H&E) stained slides of the spleen revealed an expanded red pulp involved by an atypical myelomonocytic infiltrate with surrounding areas of hemorrhage, necrosis and infarction [Figure 1A]. The atypical cells were intermediate-sized with ovoid to irregular shaped vesicular nuclei, dispersed chromatin and a subset displaying prominent nucleoli [Figure 1B and 1C]. Angiolymphatic invasion of the CD34-positive infiltrate is readily appreciated in the splenic vessels [Figure 1D]. The white pulp was comprised primarily of lymphocytes with mature cytological features. Histologic sections of the mesenteric embolic clot section showed areas of thrombus formation and necrotic tissue with dispersed tumor cells. The cytomorphologic features of the tumor cells seen in the mesenteric embolic clot section were similar to those found in the splenic tissue. The small bowel sections showed no tumor cells, but classic ischemic-type mucosal injury that extended to the designated surgical margins. The atypical cells by immunohistochemistry were immunoreactive against antibodies for CD43 (bright), lysozyme, CD14 (subset), CD163, CD68, CD34 (subset), CD117 (subset), CD45 (variably dim to negative) and were negative for CD3, CD20, EMA, MART-1, pan-cytokeratin and S-100 [Figure 2A-I], consistent with a myelomonocytic immunophenotype. The mesenteric embolic clot sections revealed the atypical myelomonocytic popula-

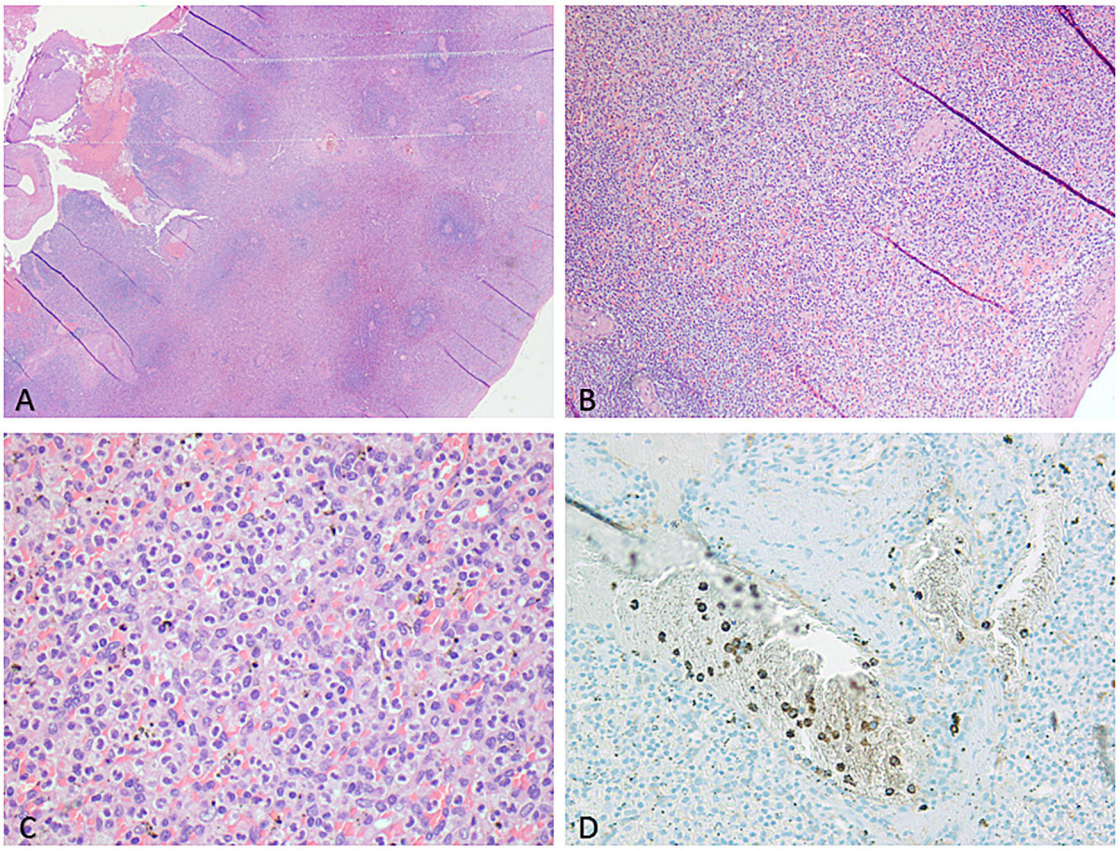

Figure 1: (**A**) Sections of the spleen reveal an expanded red pulp, hemorrhage and unremarkable white pulp, H&E x40. (**B**, **C**) Within the expanded red pulp of the spleen the atypical myelomonocytic infiltrate display medium to large-sized cells with ovoid nuclei, prominent nucleoli and dispersed chromatin, H&E x100, H&E x400, respectively. (**D**) CD34-positive atypical infiltrate involving a splenic vessel, x400.

tion admixed with neutrophils, red blood cells, and fibrin [Figure 3A and 3B]. Additional immunostains, lysozyme and CD68, were positive in the atypical cells seen in the mesenteric clot section [Figure 3C and 3D]. Molecular studies, such as next-generation sequencing (NGS), and cytogenetic studies, including karyotyping and FISH, were not performed on the spleen or mesenteric embolic clot section.

After the surgery the patient was transferred to our institution and underwent staging work up protocol. The staging work up included PET imaging, trephine bone marrow biopsy, bone marrow aspirate and ancillary studies (i.e. flow cytometry, fluorescence in-situ (FISH), and cytogenetics), which were performed on the bone marrow aspirate sample. The trephine bone marrow biopsy and aspirate with concurrent flow cytometric analysis were negative for involvement by myelodysplasia or acute myeloid leukemia or increased abnormal myeloblasts and monoblasts. Cytogenetic studies revealed a normal male karyotype (46,XY[20]) with no evidence of an acquired clonal abnormality. The acute myeloid leukemia FISH panel analysis revealed no evidence of a t(8;21), inv(16) or aberrations associated with chromosomes 5, 7 or 13. Additionally, a myeloid mutation panel of the peripheral blood revealed no variants of known or unknown significance in myeloid malignancies. The PET imaging highlighted a 2.2 cm

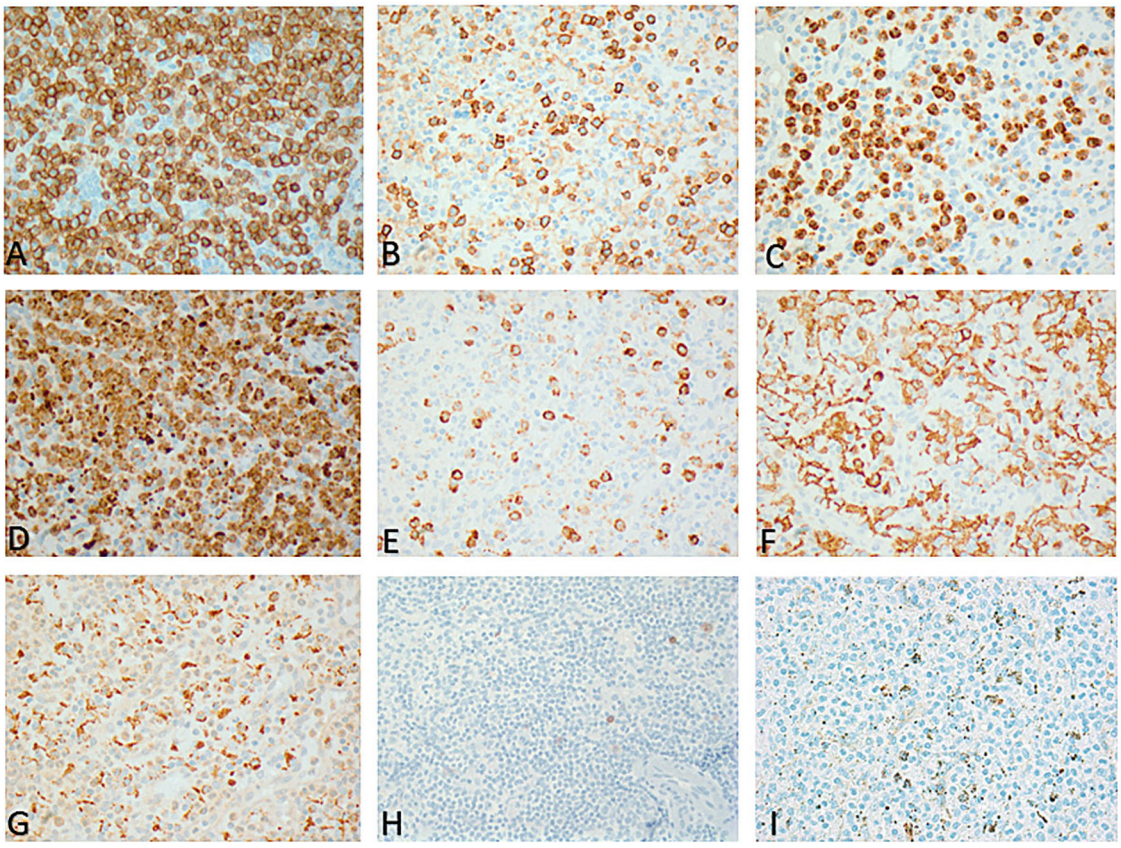

Figure 2: (**A-I**): Immunohistochemical stains performed on the spleen demonstrate the atypical cells are immunoreactive against antibodies for CD43, Lysozyme, CD14 (subset of cells), CD163, CD68, CD34 (focal) and CD117 (focal) (seen in **A, D, E, F, G, H** and **I** respectively, x400). CD45 (**B**) is variably dim to negative, contrasting the CD43 staining (x400). Myeloperoxidase (**C**) highlights a small subset of the atypical cells, along with a neutrophilic portion of the atypical infiltrate (strong) x400.

hypermetabolic area in the postsurgical site that was likely due to reparative/inflammatory changes. Four months later, a repeat PET scan showed similar hypermetabolic activity in this post-surgical site, which was concluded to be remnants of splenic tissue. A repeat bone marrow biopsy and aspirate approximately nine months after initial presentation were negative for involvement by a myeloid neoplasm and demonstrated normal trilineage hematopoiesis and morphology. Currently, the patient is in good health with mild fatigue and shows persistent normal blood counts without signs of pancytopenia. This patient has not been given chemotherapy for his MS or has been diagnosed with acute myeloid leukemia or a myeloid neoplasm at an outside institution.

Discussion

According to our knowledge, this is the first reported case of *de novo*/isolated splenic myeloid sarcoma masquerading as mesenteric artery occlusion associated with acute abdomen and the second reported case of an isolated splenic myeloid sarcoma without bone marrow or peripheral blood involvement.

Myeloid sarcoma is a very rare diagnosis and is often a challenge for the clinician and hematopathol-

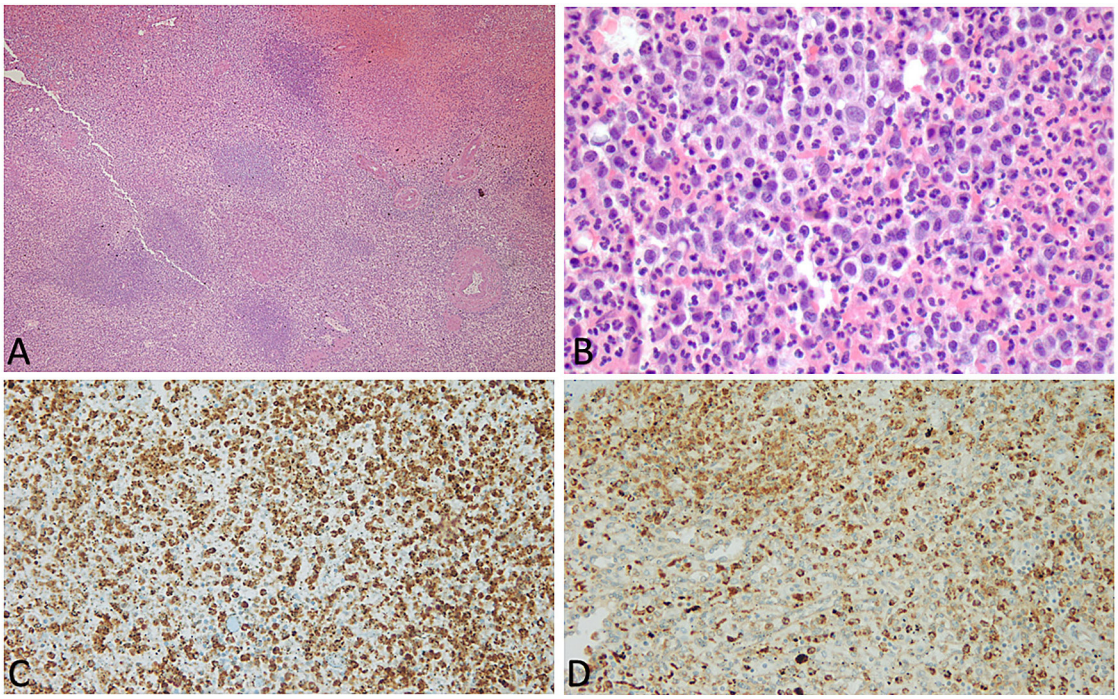

Figure 3: (**A**) Mesenteric embolic clot section show areas of hemorrhage, necrosis and infiltrating groups of atypical cells (H&E, x40). (**B**) The atypical myelomonocytic population is admixed among neutrophils, red blood cells and fibrin (H&E, x400). Immunohistochemical stains performed on the clot section demonstrate the atypical infiltrate in the embolus clot section express lysozyme (**C**) and CD68 (**D**), x200.

ogist. MS routinely presents with vague symptoms and can occur at multiple anatomical locations. The pathogenesis of MS regarding extramedullary infiltration is still currently under investigation. Therefore, our case imposed a diagnostic challenge due to age, site and the clinical presentation. Myeloid sarcoma can be solitary and/or show multifocal involvement. Without concomitant acute myeloid leukemia, the diagnosis of myeloid sarcoma becomes more challenging and difficult to ascertain. According to Pileri *et al*. in a large series of ninety-two MS patients demonstrated 35% of cases occurred concomitantly with acute myeloid leukemia (AML), 38% of cases had a previous AML history and 27% of cases presented as isolated MS [11]. Also, a recent study from our institution revealed 39% of MS patients presented primarily as a manifestation of relapsed acute myeloid leukemia [12].

MS has a relative poor prognosis, where approximately 87% of patients diagnosed with myeloid sarcoma subsequently develop acute myeloid leukemia (range 1 to 49 months) [13]. Furthermore, trephine bone marrow biopsy and aspirate are paramount to rule out concurrent bone marrow involvement, which our patient has had three bone marrow studies since this diagnosis. Concurrent cytogenetic, FISH, and myeloid mutation panel (by next-generation sequencing) analysis were performed because chromosomal abnormalities or aberrations have a high incidence, but were all normal in our patient. Moreover, positron emission/computed tomography is a useful diagnostic tool in determining the location of MS; however, the follow up PET scans done on our patient were both negative with an exception of mild enlargement of two abdominal lymph nodes. Excisional biopsy of these lymph nodes revealed reactive lymphoid hyperplasia without involvement by a myeloid neoplasm.

Common hematolymphoid pitfalls that can mimic MS include B -or T cell lymphoproliferative disorders and metastatic lesions; therefore, immunohistochemistry is vital for definitive diagnosis. From our experience, when tumor cells express CD43, a T-lymphocyte marker, without co-expression of CD3, we must rule out a myeloid neoplasm before considering a neoplasm of T-lymphocyte origin, as was seen in this case. An immunohistochemical panel should include at least the following markers CD3, CD20, CD43, lysozyme, MPO and CD68 or CD163 to adequately identify the majority of MS cases in formalin-fixed paraffin-embedded (FFPE) tissue sections. Correlation with ancillary studies (cytogenetics and FISH) and radiologic imaging are vital for further elucidating the behavior and biology of MS.

The most frequent chromosome abnormality associated with myeloid sarcoma is t(8;21)(q22;q22) [1]. Additional chromosomal abnormalities include inv(16), trisomy 8, 5q-, and monosomy 7. Pileri *et al*. found that monosomy 7 and trisomy 8 are common; however, rare genetic abnormalities including increased WT-1 gene expression, NPM1 gene mutation, FLT3-ITD mutation, as well as the occurrence of fusion genes including AML-ETO, SET/CAN, MLL-AF10 and MLL/AF9 have been reported [11, 13, 14]. Therefore, the role of cytogenetics has become increasingly important. A recent study by Kawamoto *et al*. revealed that out of 131 MS cases, there was no significant difference in overall survival between de novo MS and AML with concurrent MS [15]. However, underlying MDS/MPN was a prognostic factor in MS progression, further elucidating the significance of cytogenetic testing necessary for this hematopoietic neoplasm.

The significance of correctly diagnosing MS and underlying myeloid neoplasms are not only important to the pathologist, but to the clinical team for appropriate chemotherapeutic intervention. Therapy is routinely delayed due to the high incidence of misdiagnosis. The current therapy recommendation is with conventional AML-type chemotherapy, which has been shown to be more effective than radiation or surgical resection alone [16]. In regards to hematopoietic stem cell transplantation (HSCT), there was no significant difference in overall survival compared to chemotherapy. However, in patients, younger than 40, who received combined therapy (HSCT and chemotherapy) demonstrated longer event-free survival [17]. Therefore, a more systematic approach to treatment based on staging workup findings is recommended for isolated myeloid sarcoma. Our staging workup ultimately lead to the patient not receiving any chemotherapeutic interventions.

New areas of research include exploring the FLT3 protein (a known mutation in AML with poor prognosis [1]), CXCR4 and CD56 [15]. FLT3 protein, known to activate the JAK-STAT pathway in the Golgi and CXCR4 expression in the Golgi are suggestive of possible causes of treatment resistance patients. Moreover, CD56 expression has been associated with both extramedullary leukemia and multidrug resistance [18] and a prognostic factor in AML [19]; however, Kawamoto *et al*. showed that CD56 had no significant difference in prognosis [15]. They did summate, which was previously seen, that CXCR4 might be more functionally involved the biology and progression of MS and/or AML [15, 20]. Presently, this report expands our understanding of de novo MS clinical presentation creativity and our knowledge of the tactical approach a pathologist performs to accurately diagnose MS.

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