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Review Article

A practical approach to diagnose soft tissue myeloid sarcoma preceding or coinciding with acute myeloid leukemia

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ABSTRACT

Myeloid sarcoma involving soft tissue is rare and may present a pathologic diagnostic challenge, particularly when it precedes or coincides with hematological malignancies. Furthermore, it may mimic non-Hodgkin lymphoma, poorly differentiated carcinoma, melanoma, or round blue cell tumors, which is a potential diagnostic pitfall. In addition to a retrospective review of myeloid sarcoma (MS) cases seen at our institution, we describe differential diagnoses, diagnostic pitfalls, and practical approaches to diagnosing soft tissue MS preceding or coinciding with acute myeloid leukemia. Our institutional retrospective review (1999-2011) of MSs identified 12 cases of MS in which there was no known blood or bone marrow involvement at diagnosis. A panel of immunohistochemical stains and/or flow cytometry was reviewed; marker selection was subject to the pathologist's discretion. These tumors were consistently positive for CD117 (9/9), CD43 (7/7), myeloperoxidase (8/10), CD68 (4/5), and CD34 (5/9) by flow cytometry and/or immunohistochemistry. We also described a referral case, which had classic MS morphology and a myelomonocytic immunophenotype including positivity for CD45, lysozyme, and CD117 with supporting molecular information. Based on our institution's experience and review of the literature, we recommend that when the index of suspicion for MS is high, an immunohistochemical stain and/or flow cytometry panel should include CD43, lysozyme, CD117, CD68, CD33, Human Leukocyte Antigen DR (HLA-DR), and myeloperoxidase, in addition to thorough review of the patient's history, cytogenetic studies, and proper discussion with the clinician.

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1. Introduction

Myeloid sarcoma (MS) is an uncommon, extramedullary proliferation of immature myeloid cells that may be a diagnostic challenge if it precedes acute myeloid leukemia (AML). One facet of this challenge is illustrated, historically, by the variety of names MS has held, including granulocytic sarcoma, chloroma, extramedullary myeloid tumor, and myeloblastoma.

Myeloid sarcoma may arise in a background of AML, myelodysplastic syndrome, myeloproliferative neoplasms, and mixed myelodysplastic-myeloproliferative neoplasms [1]. However, it is when MS presents de novo months or even years before the evolution of AML that creates the diagnostic dilemma [1,2]. It has been reported that as many as 27% of MS cases present de novo and that the mean interval between discovery of isolated MS and bone marrow involvement is 10 months [1,3]. The diagnosis of de novo MS is equivalent to the diagnosis of AML. Myeloid sarcoma can mimic other entities histologically, clinically, and radiographically [1,2,4]. The most common locations for involvement are the skin, soft tissue, bone, gastrointestinal tract, or lymph nodes [1,2]. Of note, MS with the t(8;21)(q22;q22) is associated with orbital manifestations in children [1,2,5]. Despite these predilections, MS may be found at any site in the body. Grossly, the tumor is often described as having a green hue, which is how it earned the name “chloroma”.

As our understanding of molecular pathology deepens, pathologists may use a more standardized and sophisticated approach to suspected MS. However, these techniques may not be readily available to the general pathologist in community practice. Moreover, the pitfalls surrounding MS preceding AML may ensnare a pathologist who is not in a multidisciplinary setting or is not subspecialized. Although there are many excellent reviews on this subject in the literature, due to the rarity of this entity, we still encounter cases from the community, referred to our comprehensive cancer center, which were initially misdiagnosed. To more readily achieve the correct diagnosis and appropriate management for MS, we provide differential diagnoses, diagnostic pitfalls, and practical approaches for soft

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tissue MS diagnosis when it precedes or coincides with AML based on our experience and a review of the literature. In addition, we provide a prototypical case that was referred to our institution for confirmation.

2. Our experience with MS

2.1. Materials and methods

A retrospective review (1999-2011) of soft tissue tumors, including MS, alternatively termed granulocytic/monocytic sarcoma, chloroma, extramedullary myeloid tumor, and myeloblastoma was conducted using our pathology database following our institutional review board protocol. Patient data were retrieved for those with biopsy-confirmed soft tissue MS either preceding blood or marrow involvement or as a solitary lesion. Surgical specimens were fixed in 10% formaldehyde and embedded in paraffin. The paraffin blocks were then sectioned at 5 μm and stained with hematoxylin and eosin (H&E) per standard laboratory procedure. Immunohistochemical stains were ordered, when appropriate, and performed following the below procedure. All initial diagnoses were made by board-certified hematopathologists and/or anatomical pathologists. Histologic review was performed to confirm the diagnosis for all cases.

Immunohistochemical staining was performed using commercially available antibodies, a steam-induced epitope retrieval process, and a Ventana platform (Tucson, AZ) on formalin-fixed, paraffin-embedded sections following the supplier's protocol with appropriate positive and negative controls. Information on the immunohistochemical antibodies is summarized in Table 1. Flow cytometry was performed by a BD FACSCalibur flow cytometer platform (BD Biosciences, San Jose, CA).

Clinical, radiologic, and pathologic data were compared with literature reviewed.

2.1.1. Cases reviewed at our institution

Cases reviewed at our institution included patients who presented to our institution for initial diagnosis and management as well as patients who had prior diagnoses and were referred for confirmation and/or management. Of the 1200 soft tissue tumors reviewed at our institution, 12 patients (1%) were confirmed to have MS either without blood or marrow involvement at diagnosis (8/12) or as primary presenting lesion with no clinical history of hematopoietic disorder (4/12). There were 6 male patients and 6 female patients, giving a male-to-female ratio of 1:1. The patient's ages ranged from 2 to 67 years, with a mean of 50.8 years. A summary of pertinent clinical and pathologic features is presented in Table 2. The tumor locations included breast (2/12), mediastinum (2/12), extremities (2/12), neck (2/12), spine (1/12), gallbladder (1/12), appendix (1/12), and abdominal wall (1/12).

Of 12 patients, 3 (25%) had classic morphological clues of MS on H&E, including effacement of tissue architecture by neutrophilic or promyelocytic myeloblasts with scant cytoplasm, round-oval nuclei, fine chromatin, and small nucleoli. The remaining 9 cases resembled other neoplasms with differential diagnoses including lymphoma, poorly differentiated carcinoma, melanoma, neuroendocrine carcinoma, Ewing sarcoma, neuroblastoma, and Langerhans cell histiocytosis.

By immunohistochemistry and/or flow cytometry, the tumors were consistently positive for CD117 (9/9), CD68 (4/5), and CD43 (7/7), when these markers were interrogated. Myeloperoxidase (MPO) was strongly positive in 5 of 10 cases and weakly positive in 3 of 10 cases. CD34 was positive in 5 of 9 cases, and CD56 was strongly positive in 1 case. CD99 was positive in 1 of 3 cases. CD45 was weak or dim by immunohistochemistry or flow cytometry, respectively, in 28.6% (2/7) cases, the other 5 cases being positive. This included 1 case in which poorly differentiated carcinoma was in the differential diagnosis due to the tumor's morphological features. Our immunohistochemical and/or flow cytometric findings are summarized in Fig. 1. Cytogenetics and molecular studies were either not performed or were not available in our database for all but 1 case in which the tumor had normal chromosomes and was negative for FLT3 and NPM1 mutations.

2.1.2. Prototypical case

One example case referred to our institution involves an elderly lady with a history of abdominal pain. The patient was an 85-year-old Peruvian native with no significant family history. She was a lifetime nonsmoker. For 2 months, she had been experiencing intermittent, worsening, abdominal pain that necessitated a visit to her community emergency department. The initial computed tomographic scan was suggestive of acute appendicitis. However, an obstructive soft tissue mass was discovered, intraoperatively, in the area of the small bowel. The mass was resected and, grossly, featured an area of stricture and thickening of the small bowel wall. Histologically, there was infiltration by small- to medium-sized cells with scant, lightly basophilic cytoplasm and gray, round to oval, slightly irregular nuclei with open chromatin and an occasional folded nucleus. The initial

Table 1
Summary of immunohistochemical antibodies used and their relevant staining patterns

Antibody	Clone	Dilution	Supplier	Staining pattern	Specificity
CD34	QBEnd/10	RTU	VMS[a]	Membranous	Vascular progenitor cells, endothelial cells, certain leukemic blasts, and certain soft tissue tumors
CD43	L60	RTU	VMS[a]	Membranous, cytoplasmic	T cells, myeloid cells, subset of B cells, T- and B-cell lymphomas
CD45	RP2/18	RTU	VMS[a]	Membranous	T and B lymphocytes, monocytes, macrophages, mast cells, weakly on granulocytes
CD56	1B6	RTU	LB[b]	Membranous	Neurons, astrocytes, Schwann cells, NK cells, subset of activated T lymphocytes
CD68	KP-1	1:50-100	VMS[a]	Cytoplasmic, membranous	Monocyte/macrophage lineage cells
CD99	O13	1:500	CI[c]	Membranous	Ewing sarcoma, some primitive neuroectodermal tumors, and peripheral neuroepitheliomas
CD117	YR145	1:800	CM[d]	Cytoplasmic, membranous	Interstitial cells of Cajal, germ cells, bone marrow stem cells, melanocytes, breast epithelium, and mast cells
MPO	Polyclonal	1:4000	Dako[e]	Cytoplasmic	Myeloid lineage cells
Lysozyme	Polyclonal	RTU	BG[f]	Cytoplasmic	Myeloid and monocyte/macrophage lineage cells
S-100	4C4.9	RTU	VMS[a]	Cytoplasmic	Melanoma, neuronally derived cells, monocyte/macrophage lineage cells, clear cell sarcoma

Abbreviation: *RTU*, ready to use.
[a] Ventana Medical Systems, Tucson, AZ.
[b] Leica Biosystems, Wetzlar, Germany.
[c] Covance, Inc, Princeton, NJ.
[d] Cell Marque Corporation, Rocklin, CA.
[e] Dako, Inc, Carpinteria, CA.
[f] BioGenex, Fremont, CA.

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