

An Unusual Case of Disseminated Lymphadenopathy

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Introduction

Myeloid sarcoma (MS) is an aggressive tumor of immature myeloid cells that is believed to be a variant of acute myelogenous leukemia (AML). Most cases of MS progress to AML. Involvement of multiple anatomic sites is rare.

Case Report

A 54-year-old Caucasian female was admitted for fevers, night sweats, decreased appetite, weight loss of 20 pounds in 1 month, diffuse rash, and purpuric lesions on her lower extremities. Physical examination revealed a diffuse maculopapular rash on the anterior chest and trunk and a palpable, 1-cm, inguinal lymph node.

Initial laboratory studies revealed hemoglobin of 9.1 g/dL, hematocrit of 28.4%, white blood count of $10.6 \times 10^3/\mu\text{L}$, platelet count of $486,000/\mu\text{L}$, C-reactive protein of 224.3 mg/L, erythrocyte sedimentation rate of 88 mm/hr, and serum lactate dehydrogenase of 257 U/L. Normal results were found in analysis of rapid plasma regain, blood cultures, rheumatoid factor, antinuclear antibody, direct Coombs test, cytoplasmic antineutrophil cytoplasmic antigen (ANCA), perinuclear staining ANCA, atypical perinuclear ANCA, cancer antigen 125, and carbohydrate antigen 19-9. HIV testing was negative.

Computed tomography (CT) with contrast of the chest, abdomen, and pelvis revealed extensive mediastinal, retroperitoneal, periaortic, pelvic, and inguinal lymphadenopathy. An inguinal lymph node biopsy and bone marrow biopsy showed no evidence of lymphoma. The right inguinal lymph node biopsy revealed granulomatous inflammation and caseating necrosis. The

bone marrow biopsy revealed mildly hypercellular bone marrow with trilinear hematopoiesis; no granulomas or tumors were seen. Acid-fast bacillus and silver fungus stains were negative. Iron stain revealed increased iron stores. The patient's rash resolved with prednisone, and she was discharged home.

One month later, the patient was re-admitted for fever, chills, and a 3-day history of leg pain. Physical examination showed a new palpable left supraclavicular lymph node and right lower extremity edema with associated calf tenderness. Doppler ultrasound of the lower extremities revealed a right deep vein thrombosis and prominent bilateral groin lymph nodes, the largest measuring 4×2 cm. A CT angiogram was negative for pulmonary emboli but did show supraclavicular and axillary lymphadenopathy—which had not been evident on the CT angiogram obtained 3 months prior—and worsening of the diffuse thoracic and abdominal lymphadenopathy. Repeat bone marrow biopsy was again negative for malignancy. A second lymph node biopsy was never performed due to unacceptable operative risk. The patient was discharged after receiving therapeutic anticoagulation for the deep vein thrombosis.

One week after being discharged, the patient presented with acute renal failure, progressing to septic shock and multi-organ failure. CT of the abdomen and pelvis showed worsening of the intra- and extra-peritoneal lymphadenopathy with encasement of the retroperitoneal vasculature and severe compression of the intra-abdominal inferior vena cava (Figure 1). The patient died on the fourth day of her hospital course.

Autopsy revealed MS with extensive involvement of the retroperitoneum, mediastinum, and axillary lymph nodes. The skin, spleen, soft tissue, and pleural space were also notably infiltrated by immature myeloid cells. Diagnosis was made by immunohistochemistry with staining, including CD45 (Figure 2). Although the complete immunohistochemistry panel

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Figure 1. This computed tomography scan of the abdomen shows worsening of the lymphadenopathy with mass effect and compression of the intra-abdominal inferior vena cava.

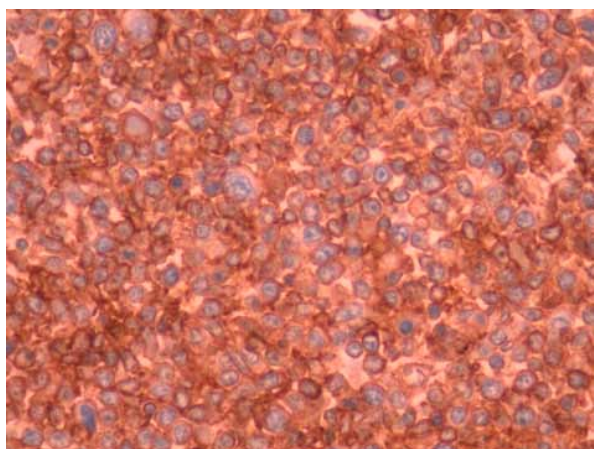


Figure 2. A definitive diagnosis of myeloid sarcoma is by immunohistochemistry. This stain with CD45 of the lymph nodes shows myeloblasts.

was not reported, the autopsy report stated that the diagnosis of MS was supported by postmortem histologic findings and immunostains. The bone marrow was found to be aplastic, with no evidence of acute leukemia. Bilateral pulmonary emboli secondary to hypercoagulability from malignancy was identified as the cause of death.

Discussion

MS is a tumor of myeloblasts or immature myeloid cells occurring in the bone marrow or extramedullary sites. It was first described by Burns¹ in 1811 and was initially called a *chloroma* by King² in 1853, owing to its green appearance due to myeloperoxidase enzymes in the myeloblasts. It can occur in any anatomic site but

commonly involves the bone marrow, lymph nodes, periosteum, soft tissue, and skin. Involvement of multiple anatomic sites—as was seen in this patient—is very rare. Infiltration of skin with neoplastic cells, known as *leukemia cutis*, is a harbinger of poor prognosis and indicates an aggressive course, with death occurring within 6–7.5 months.^{3,4} Our patient died within 6 months of her initial hospitalization.

The clinical presentation can be very variable. It is now believed that this condition is a tissue variant of AML, and its diagnosis is equivalent to a diagnosis of AML. The incidence of this disease in AML is 3–5%. It can manifest *de novo* in healthy patients, who then go on to develop AML months to years later. In very rare cases, including our patient, leukemia does not develop. This disease can occur in known AML in the active phase or as the first manifestation of relapse in previously treated patients. It may also present as a blastic transformation in chronic myelogenous leukemia, chronic myeloproliferative disorder, or myelodysplastic syndrome.

Misdiagnosis as non-Hodgkin lymphoma (NHL) can occur due to histologic similarities of the blasts to large-cell NHL, which is especially true in poorly differentiated MS.⁵ Definitive diagnosis is based on immunohistochemistry, including stains for myeloperoxidase, lysozyme, CD45, CD43, and CD68.⁶ Cytomorphology via fine needle aspiration of palpable masses or bone marrow biopsy can also be used to aid in the diagnosis. Paradoxically, the presence of a normal bone marrow biopsy, as was seen in our patient, generally correlates with a worse outcome.⁵

Given the rarity of this disease, there are limited studies and currently no consensus on the treatment of myeloid sarcoma, whether it is isolated or accompanied by a hematologic malignancy. Treatment is the same as that for AML, even for isolated tumors without hematologic involvement. Currently, it is believed that systemic chemotherapy should be given to all patients. Additionally, surgical removal of the tumor and/or radiation is indicated if the tumor is massive or if there is spinal cord compression. Patients treated with surgery and/or local radiotherapy generally have a shorter survival as compared to those treated with systemic chemotherapy.⁷ Furthermore, aggressive therapy must be initiated for isolated myeloid sarcoma, because even after treatment, patients with MS are still at risk of developing AML. Although steroids are not standard therapy, they have been shown to reduce the size of the lymphadenopathy and the number of blasts in the bone marrow.⁸ Survival appears to be slightly higher in patients who have undergone an autologous or allogeneic bone marrow transplant, although studies are limited.⁵

Conclusion

The true incidence of MS is unknown and likely underestimated, given this entity's difficult diagnosis and lack of distinctive features. A high degree of clinical suspicion, to enable early diagnosis of this aggressive disease and subsequent intensive treatment with chemotherapy, is imperative in this uncommon variant of AML.

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Review

Isolated Myeloid Sarcoma Without Bone Marrow Involvement

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Zhou and colleagues¹ described a case of a 54-year-old woman presenting with disseminated lymphadenopathy that was initially misdiagnosed as a lymphoproliferative disorder and recognized as myeloid sarcoma (MS) only at autopsy. The term *myeloid sarcoma* was first used to describe an extramedullary mass composed of immature granulocytic cells and later used to encompass all forms of leukemic infiltrates. MS is now identified as a wide spectrum of manifestations characterized by the occurrence of 1 or more extramedullary masses with or without bone marrow leukemic involvement. The most commonly involved sites are the bone, skin, and lymph nodes, although other rare localizations have been reported.² Histologic architecture of involved sites by MS is subverted by the growth of myeloblasts, with or without promyelocytic maturation or monoblastic/myelomonocytic morphologic features.³ MS may occur as a de novo disease or concurrently with acute

myeloid leukemia (AML),⁴ myelodysplastic syndromes (MDS),⁵ or myeloproliferative neoplasms.⁶ Sometimes it may anticipate, over a wide range of time, an overt AML, or it may be the first manifestation of a relapsed AML.⁷

Clinico-Biologic Common Features

MS is more common in men than in women, with a male/female sex ratio of 1.2:1. The most commonly reported median age is 56 years. The 2008 World Health Organization classification indicated that cytochemical stains for myeloperoxidase, naphthol AS-D chloroacetate esterase, and nonspecific esterase may be of help to identify and differentiate granulocytic lineage from monoblastic forms.⁸ In regard to immunophenotyping performed in paraffin section, CD68-KP1 was the most commonly expressed marker; other reported markers were myeloperoxidase, CD117, CD99, CD68/PG-M1, lysozyme, CD34, terminal deoxynucleotidyl transferase, CD56, CD61/linker of activated T lymphocyte/von Willebrand antigen, CD30, glycophorin A, and CD4.⁹ Aberrant antigenic expression was observed infrequently, and the combination of those antigens allowed the differential diagnosis between MS and aggressive lymphomas (eg, lymphoblastic lymphoma, Burkitt lymphoma, and diffuse large B-cell lymphoma) or nonhematopoietic neoplasms (eg, neuroblastoma, rhabdomyosarcoma). Genetic/cytogenetic aberrations, including MLL rearrangement or t(8;21), were reported in 55% of the cases. Pileri and associates reported a systematic application of fluorescence in situ hybridization (FISH) analysis at diagnosis in MS and described several common aberrations, including monosomy 7, trisomy 8, inv(16), trisomy 4, monosomy 16, 16q deletion, 5q deletion, 20q deletion, and trisomy 11.³ NPM1 mutations have been described in 16% of MS patients, and

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t(8; 21) was more frequently observed in children. Again, Pileri and associates reported that response to therapy and clinical behavior was not influenced by age, sex, anatomic site, primary or secondary MS to AML, MDS, myeloproliferative neoplasms, or phenotype or cytogenetic findings.³

Large Series of MS Cases Reported in the Literature

Owing to the rarity of the disease, only retrospective analyses and case studies have been described. Based on these reports, it is difficult to determine the best type of initial treatment and maintenance therapy. It emerges from these publications that many patients with MS are misdiagnosed as having aggressive lymphoma. In 2004, we described a series of 12 MS patients, with the goal to analyze presenting features, frequency, and outcome of this subset of leukemic patients.¹⁰ In our institution, 2% of AML patients had MS, and the median age was 45 years. All patients were misdiagnosed as having an aggressive lymphoma, with a median time of 2.9 months from the initial onset of symptoms to the correct diagnosis of MS. Of the 12 patients described, 3 had an isolated MS without marrow involvement, whereas 7 had an MDS condition and 2 showed a concurrent AML condition. Ten patients were treated with intensive AML-like chemotherapy, while 2 patients received only local therapy and subsequently developed AML. Patients treated within 4 months from the initial MS diagnosis achieved complete remission of both MS and marrow involvement, whereas patients treated after this time obtained only complete disappearance of MS without response at the bone-marrow level. Our data, although consisting of a small series of patients, suggested the importance of an accurate and prompt identification of this rare disease, and indicated that, even in patients with isolated MS, the early administration of AML-like intensive chemotherapy followed by bone marrow transplantation might reduce the risk that systemic disease will develop.¹⁰ Tsimberidou and colleagues² reported a retrospective series of 21 non-leukemic MS patients, with an incidence of 1.4% of all AML cases. The median age was 57 years, which was higher compared to that reported in other series of patients; the most common chromosome change was represented by chromosome 8 anomalies. Thirteen patients achieved complete remission with intensive chemotherapy, with a median overall survival of 20 months. The median time to AML development was 5 months, comparable to that of other reported series of patients. As suggested by Imrie and coworkers,¹¹ patients who received intensive AML-like chemotherapy at the time of diagnosis—even if MS was localized without leukemic involvement—had a subsequent low probability to develop systemic disease with prolonged survival. Chromosome abnormalities in MS patients have been associated with poorer prognosis compared to patients

without karyotypic changes.^{9,10} Pileri and associates³ reported a large series of 92 MS cases (25 as isolated MS), which were evaluated at the morphologic and immunohistochemical levels; 50% of cases were classified as blastic type, and CD68/KP1 was the most commonly expressed marker. Among 25 isolated MS cases, 10 patients were initially misdiagnosed with aggressive lymphoma. Chromosomal aberrations were revealed in 54% of patients; the most frequent aberrations were monosomy 7 and trisomy 8, whereas cases with t(8;21) were rare. There were no statistically significant correlations between clinical findings (age, sex, histotype, de novo presentation, clinical course, type of therapy received) and karyotypic changes. Any clinical and biologic findings did not influence the clinical behavior and response to therapy.

Conclusion

Published reports highlight the rarity of MS and demonstrate the wide range of clinical behavior of these leukemic manifestations. Large series of MS patients suggest that most MS cases are initially misdiagnosed as aggressive lymphoma; and—even in cases of isolated non-leukemic MS—optimal therapy is AML-like intensive chemotherapy, which is associated with prolonged overall survival and failure-free survival only when high-dose therapy is followed by transplant procedures. Application of adequate and broad histopathologic and phenotypic characterization is mandatory in patients with peculiar localization at presentation. Novel therapeutic strategies are warranted for this particular subset of patients.

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