Management of Extramedullary Leukemia as a Presentation of Acute Myeloid Leukemia

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Abstract
Extramedullary involvement is considered to be an uncommon presentation of acute myeloid leukemia (AML), although some data suggest it may be present in up to 30% of patients. Extramedullary involvement by AML can present in a variety of clinical manifestations, most notably in the form of myeloid sarcoma, leukemia cutis, and central nervous system involvement. Each presents a unique clinical scenario in terms of symptoms and management. Extramedullary disease in any form presenting without evidence of bone marrow disease is still considered evidence of systemic disease and is usually treated as such. Most commonly, extramedullary disease presents concurrently with bone marrow disease, and although it may require additional local therapy in the form of intrathecal chemotherapy or radiation, the principles of systemic treatment remain unchanged. The prognostic impact of extramedullary disease is unclear. Specifically, whether hematopoietic stem cell transplantation should be considered in first remission irrespective of other prognostic factors has not been established. Patients who undergo transplantation have similar outcomes as patients without extramedullary disease, although they do have a higher rate of extramedullary relapse. More research is needed to define the molecular basis for extramedullary disease, its prognostic impact, and optimal management. (JNCCN 2012;10:1065–1169)

Extramedullary presentation of acute myeloid leukemia (AML) is considered uncommon, although in one series it occurs in up to 30% of patients. Extramedullary involvement usually reflects systemic disease. Very rarely extramedullary disease presents without evidence of overt hematologic disease and if untreated, virtually all of these patients will develop systemic disease. Extramedullary AML can present in a variety of forms. These include myeloid sarcoma (also termed granulocytic sarcoma, chloroma, or myeloblastoma), leukemia cutis (LC), and central nervous system (CNS) disease.

Extramedullary disease at presentation or relapse can pose unique clinical problems. In general, the basic principles of systemic therapy remain the same. The prognostic impact of extramedullary disease is the object of some controversy. Some series suggest a negative effect on prognosis while others do not. Additionally, extramedullary disease has been correlated with specific AML phenotypes and chromosomal abnormalities. This article discusses the 3 main forms of extramedullary AML, namely CNS disease, LC, and myeloid sarcoma.

CNS Leukemia

General Considerations
AML presenting with CNS involvement is rare, particularly when compared with acute lymphoblastic leukemia. Older published data had suggested that in relapsed AML, rates of CNS disease were as high as 10% to 11%. More recent studies estimate the actual occurrence to be less than 5%, and probably in the 2% to 3% range of cases at presentation or relapse. The actual incidence at presentation is not well defined for a variety of reasons. Because CNS involvement is a relatively rare event, lumbar punctures are not routinely performed at diagnosis in the absence of neurologic
symptoms. This practice also stems from the concern that performing a lumbar puncture with circulating blasts may lead to seeding of the CNS space during a traumatic procedure. Furthermore, with the modern AML treatment programs that include high doses of cytarabine, patients actually receive CNS treatment, rendering relapse in that space less common.

Similar to other forms of extramedullary involvement, a relationship exists between CNS involvement and myelomonocytic and monoblastic phenotypes (French-American-British [FAB] subtypes M4 and M5). A recent review of patients at MD Anderson Cancer Center found that in confirmed cases of CNS disease at presentation or relapse, certain cytogenetic abnormalities occur at a higher frequency than other types of AML. Specifically, inv(16), chromosome 11 abnormalities, and complex cytogenetics were more frequently associated with CNS disease. Although a WBC count of 100,000/mcL is generally considered a risk factor for CNS involvement, the mean WBC count associated with CNS involvement in that study was around 36,500/mcL.

Prognosis
The limited data on CNS involvement by AML at presentation makes it hard to determine whether this occurrence constitutes an independent risk factor. Data from pediatric AML series show that in that age group, CNS disease is not associated with a worse survival in general, although these patients do have a higher risk of isolated CNS relapse. On the other hand, the MD Anderson series suggests that CNS disease is associated with worse outcomes. However, in that study, patients with relapsed disease were also included, thus raising the possibility that the inherent negative prognostic impact of relapse may have confounded the analysis.

Management
A lumbar puncture at diagnosis to evaluate the cerebrospinal fluid (CSF) is not routine practice. However, if a patient presents with symptoms suggestive of CNS disease, a lumbar puncture may be warranted. Before the procedure, brain imaging is recommended to ensure that no mass effect nor intracranial hemorrhage is present, particularly in the setting of thrombocytopenia. It is also prudent to reduce the WBC count to a relatively safe level (with hydroxyurea, for instance) to decrease the risk of CNS contamination in case of a traumatic lumbar puncture. Analysis of the CSF should include cytology and flow cytometry. In the rare occurrence of relapsed acute promyelocytic leukemia, CNS evaluation may be warranted at relapse once the coagulopathy has resolved, even in the absence of CNS symptoms.

Although routine CSF sampling at presentation is not performed in all patients, a few high-risk presentations may warrant a lumbar puncture in first remission, including myelomonocytic and monoblastic phenotypes, a WBC count at presentation greater than 100,000/mcL, or a lymphoblastic component in the setting of biphenotypic leukemias. Lactate dehydrogenase has been shown to be statistically higher in patients with AML who have CNS involvement, and may be helpful in selecting patients for a lumbar puncture.

Treatment for CSF disease involves direct intrathecal chemotherapy and systemic chemotherapy with good CNS penetration. For intrathecal chemotherapy, agents generally used are methotrexate and/or cytarabine. Although no standard intrathecal protocol has been established, one approach consists of treating patients twice weekly until clearance of CSF cytology, followed by weekly treatments for 4 to 6 weeks. No single agent is considered superior, and most patients will obtain rapid clearance of their CSF. Additionally, high-dose cytarabine given during either induction or consolidation achieves adequate CNS levels and may obviate the need for additional intrathecal treatments. In patients who present with a CNS chloroma, cranial irradiation should be considered. However, patients should not receive cranial radiation, high-dose cytarabine, or intrathecal chemotherapy concurrently because of the increased risk of neurotoxicity.

Leukemia Cutis
General Considerations
LC represents infiltration of the skin by leukemic cells. It is a relatively rare but well-known clinical finding in AML, and published data estimate its occurrence at 3% of cases. Similar to CNS infiltration, it is more frequent in myelomonocytic and monoblastic phenotypes. It is also important to recognize that not all skin lesions at presentation are LC. A variety of skin reactions can occur in response to infections, medications, and inflammation that may have a similar appearance. Consequently, a skin biopsy is essential.
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Prognosis
Historically, concern was expressed that LC may be a manifestation of more aggressive leukemias. In a large prospective analysis of 381 patients with AML, patients with LC did not differ from those without LC in terms of remission rates. However, a nonstatistically significant trend was seen toward shorter remission when LC was present. An analysis of 202 patients who underwent allogeneic transplant for AML at Memorial Sloan-Kettering Cancer Center showed that the overall risk of relapse posttransplant was not higher in patients who had LC than in those who did not. However, patients with LC had a significantly higher rate of extramedullary relapse. Despite the lack of definitive data to that effect, LC is often considered an indication of more aggressive disease and therefore an indicator of poor prognosis.

Management
Similar to other extramedullary manifestations of leukemia, the presence of LC is considered to be evidence of systemic disease and is treated with standard systemic chemotherapy. Presentation without marrow involvement is exceedingly rare and a negative bone marrow study is presumed to represent a sampling error or bone marrow involvement below the level of detection.

Because of limited data, the prognostic significance of LC is not totally defined. The suggestion of shorter remission in patients with LC has led some investigators to recommend that hematopoietic stem cell transplantation (HSCT) be considered in these patients. However, other factors involved in the decision to consider HSCT (eg, performance status, age, cytogenetic and molecular markers) must be taken into account.

Even without large series to support that point, radiation therapy in patients who obtain a system-
inv(16), 11q23, NPM1, and FLT3 internal tandem duplication mutations. However, in prospective series, t(8;21) and 11q23/MLL abnormalities have been associated with myeloid sarcoma with a higher incidence. The specific molecular mechanisms that lead to tissue localization have not been totally elucidated. For instance, the neural cell adhesion molecule CD56 has been shown to be expressed in a significant number of myeloid sarcoma specimens. However, its role in the pathophysiology of myeloid sarcoma remains to be fully proven.

Prognosis
Some reports suggest that extramedullary AML is associated with a poorer overall prognosis. However, whether presentations with aleukemic myeloid sarcoma truly have a poorer prognosis is still unclear. For instance, Byrd et al suggested that extramedullary disease impacts negatively on the relatively better prognosis associated with the t(8;21). However, in a limited series reported from the MD Anderson Cancer Center, patients with aleukemic myeloid sarcoma who were treated with “AML-type” therapy fared better than patients with leukemic AML matched for age and cytogenetics. Certain cytogenetic aberrations are associated with myeloid sarcoma. Whether, in general, presentation with myeloid sarcoma affects the prognostic impact of these individual abnormalities is unclear.

MLL gene mutations, specifically the classic 11q23 abnormality [excluding the t(9;11)], has a poor overall prognosis when found in AML. MLL gene mutation has been linked to extramedullary involvement, and prognosis remains poor. Again, the data are limited as to whether the extramedullary involvement itself worsens prognosis in this already high-risk group. As for LC, myeloid sarcoma is often considered an indication of more aggressive disease and consequently a worse prognosis.

Management
Myeloid sarcoma most often occurs with concurrent bone marrow involvement, and therefore is usually evidence of systemic disease. Appropriate imaging to identify all potential sites of disease and plan therapy may be warranted. Because myeloid sarcoma generally is associated with systemic disease, the authors believe that, depending on the patient’s age and performance status, initial treatment should be based on standard treatment regimens for induction chemotherapy, with very few exceptions. However, data and trials specific to patients with myeloid sarcoma are limited, and no specific chemotherapy program has been shown to be superior for these patients.

Whether the presence of myeloid sarcoma worsens prognosis has not been clearly shown, although some evidence suggests this. This raises the question of whether patients with myeloid sarcoma should be considered for HSCT in first remission irrespective of other prognostic factors. A retrospective review of European Group for Blood and Marrow Transplantation (EBMT) data analyzed a cohort of 99 patients with myeloid sarcoma who underwent autologeneic stem cell transplant; 30 patients had isolated myeloid sarcoma. Of the cohort, 52% underwent transplant in first remission. Patients had 5-year leukemia-free and overall survivals of 36% and 48%, respectively, suggesting that this treatment option should be considered in appropriate patients. However, no data show that patients with AML who fall into a more favorable prognostic group should undergo HSCT only because of the presence of extramedullary disease. Consequently, the decision to offer HSCT in first remission to these patients should be individualized based on careful consideration of risks and benefits.

The role of radiation therapy in the treatment of myeloid sarcoma is similar to its use in the treatment of LC. It can be considered in an upfront setting if rapid improvement in symptoms is needed, particularly if a vital organ function or structure is compromised or threatened. In general, the lesions are sensitive to relatively low doses of radiation, on the order of 24 Gy in 12 fractions. These doses are not expected to preclude the use of total body irradiation if HSCT is considered. Radiation therapy should also be considered in patients whose extramedullary disease responded to systemic therapy but whose myeloid sarcoma did not show an adequate clinical response, because local recurrence could potentially reseed the bone marrow.

In the EBMT cohort of patients with myeloid sarcoma, 15% had more than 2 sites of extramedullary involvement. Because of the prevalence of multifocal disease, it is reasonable to consider imaging to identify all sites of extramedullary disease before treatment planning. Cases of isolated myeloid sarcoma with no evidence of systemic involvement pose a unique clinical challenge. It is expected that patients who have iso-
lated myeloid sarcoma will eventually have systemic disease. Consequently, these patients are generally approached in a similar fashion to those with overt bone marrow disease at presentation. Radiotherapy should also be considered after chemotherapy for patients with isolated myeloid sarcoma, or if complete resolution of the myeloid sarcoma is not obtained with chemotherapy. Finally, myeloid sarcoma as a presentation of relapse is generally considered to be evidence of systemic relapse and should be treated as such.

Conclusions

Extramedullary disease represents a unique presentation of AML. In general, the treatment principles remain similar to those in situations with overt marrow disease at presentation, with additional therapy targeted at the local site of extramedullary disease. For LC, myeloid sarcoma, and CNS disease, patients should be treated as if systemic disease is present, even if bone marrow studies are negative. Extramedullary disease presenting without systemic disease is rare and most patients will eventually develop systemic disease. The independent prognostic impact of extramedullary AML has not been completely established, but is considered by many as an indication of more aggressive disease. For this reason, in the appropriate patient with LC or myeloid sarcoma, considering HSCT in first remission is justifiable. Intrathecal chemotherapy should be part of the treatment approach for patients with CNS disease. Upfront radiation therapy is an option for all types of extramedullary disease if rapid resolution of symptoms is required or a vital structure is threatened. Isolated recurrence of CNS disease, LC, or myeloid sarcoma should be considered a systemic relapse and treated as such. A clear need exists for further investigation to understand the molecular basis for extramedullary AML and, consequently, its prognostic impact and optimal management.

References


