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REVIEW

Extramedullary acute myelogenous leukemia

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ABSTRACT

Extramedullary leukemia (EM AML), also known as myeloid sarcoma, is a rare manifestation of acute myelogenous leukemia and often accompanies bone marrow involvement. EM AML is diagnosed based on H&E stains with ancillary studies including flow cytometry and cytogenetics. Isolated EM AML is often misdiagnosed as large cell lymphoma or other lymphoproliferative disorder. The clinical presentation is often dictated by the mass effect and the location of the tumor. The optimal treatment remains unclear. High-dose chemotherapy, radiation, surgical resection, and allogeneic stem cell transplantation are all modalities that can be incorporated into the therapy of EM AML. Cytarabine-based remission induction regimens have been the most commonly used in the upfront setting. There are limited data about the optimal consolidation. Transplantation is ideally offered for high risk disease or in the relapsed setting. In this manuscript, we will review the recent literature about EM AML, focusing on therapy and proposing a treatment algorithm for managing this rare form of leukemia. Further studies addressing risk stratification, role of molecular and genetic aberrations, and optimal treatment strategies are warranted.

1. Introduction

Extramedullary (EM) manifestations of acute myelogenous leukemia (AML) have been described more than two centuries ago [1]. The first description of EM leukemia dates back to 1811. Due to the green color related to the high expression of myeloperoxidase, King was the first to label this rare tumor as "Chloroma" [2]. The relationship between chloroma and AML was not established till 1904, and few decades later, Rappaport used the term granulocytic sarcoma describing tumors of granulocytic origin [3]. The term granulocytic sarcoma is now used to describe tumors related to several myeloid malignancies, including AML, chronic myelogenous leukemia, myelodysplastic syndrome, and other myeloproliferative disorders [4,5]. In the event of skin manifestations, EM AML is usually referred to as Leukemia cutis. Leukemia cutis results from infiltration of different layers of the skin (epidermis, dermis, subcutaneous tissue) by the leukemic myeloid cells resulting in nodular rash that is sometimes also referred to as cutaneous granulocytic sarcoma [6]. EM AML can present upon the initial diagnosis of medullary leukemia [7], or as a manifestation of relapsed disease after chemotherapy or hematopoietic cell transplantation [8]. It is not uncommon for EM AML to present as isolated disease without bone marrow involvement in particular upon disease relapse. EM AML represents a therapeutic dilemma especially in the absence of accompanying bone marrow involvement

In this article, we will review the recent literature and focus on therapeutic options of EM AML, including patients relapsing post-allogeneic hematopoietic cell transplantation (HCT).

2. Pathogenesis of EM AML

AML is a genetically complex and diverse entity in which more than hundred cytogenetic abnormalities and numerous point mutations have been identified. Phenotypically, AML is less diverse, which suggests that many of the observed mutations and rearrangements must target similar transcriptional and signal transduction targets. One or more genetic alterations are needed to develop AML. For example, the introduction of MLL-AF9 fusion oncogne can induce leukemogenesis in murine models [9]. On the other hand, the expression of AML 1/ETO gene rearrangement alone in murine models is not sufficient to induce AML [10]. In most cases, two sets of alterations are needed to develop AML. One group of genetic alterations activates the signal transduction pathways and includes alterations in FLT3, RAS, and KIT and more rarely the BCR-ABL and TEL-PDGFBR fusions. [11]. The second group includes transcription factors such as AML-ETO, CBFB-SMMHC, PML-RARA, NUP98-HOXA9, MLL gene rearrangements, and MOZ-TIF2. The second group of genetic alterations is never observed together in the same leukemia. The second group impairs hematopoietic differentiation and allows the leukemic stem cells to have the self-renewal properties but is not sufficient by themselves to cause leukemia. Cooperating alterations

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from each group induce the AML phenotype that is characterized by enhanced proliferation and self-renewal advantage [12].The key events that will allow AML cells to migrate into extramedullary sites are still not fully understood. Homing to specific tissues is usually controlled by adhesion molecules and chemokine receptors. Blast neural adhesion molecule CD56 has always been associated with a higher incidence of EM disease and is frequently seen in patients with t(8;21) [13]. The high expression of the neural cell adhesion molecule on ovarian, breast, testicular, and gut tissues can explain the homing of CD56 + myeloblasts into these sites [14]. The invasion of myeloblasts into the skin is associated with the expression of T-cell antigens by the blast cells. It is hypothesized that the expression of these T-cell antigens result in skin-selective homing [15].

Certain EM sites such as the CNS and reproductive organs are more prone to being involved by AML at time of relapse due to the fact that these sites function as sanctuary sites for leukemic cells by providing a barrier to systemic therapy. EM relapse post-transplantation is not uncommon and is frequently seen in sanctuary sites for the leukemic cells through these inherent barriers [4]. It has also been suggested that the graft versus leukemia effect may not be as potent in certain extramedullary sites as evident against the bone marrow due to a lower infiltration of tumor specific lymphocytes into these sites [8].

3. Incidence and clinical presentation

The incidence of EM leukemia varies among different reports and it is generally considered to be underestimated as surveillance for EM AML is not a part of the routine workup for newly diagnosed AML. EM AML has been reported in 2–9% of newly diagnosed patients [16,17]. Isolated EM leukemia is rare and incidence has been limited to case reports. It is often challenging to diagnose EM leukemia in the absence of bone marrow involvement with a rate of misdiagnosis reaching 75% in some studies [18]. The most frequent misdiagnosis is large cell lymphoma. Later studies have reported a lower incidence of misdiagnosis in the range of 24–47% with lymphoproliferative disorders being the most common misdiagnosis [19,20]. The PET-AML study prospectively evaluated the prevalence of EM disease among 94 AML patients (newly diagnosed $n = 85$, relapsed $n = 9$). Total body FDG/PET-CT at the time of diagnosis of AML detected EM AML in 17% of the patients [21]. EM leukemia can develop at relapse with or without marrow involvement. The incidence of EM relapse post-allogeneic HCT has been reported in 5% to 12% accounting for 7–46% of total relapses post-HCT [8,22].

EM relapses have been reported to be higher among transplant recipients than patients treated with chemotherapy [23]. Several factors have been reported to be associated with EM AML at presentation versus at disease relapse. Some common chromosomal abnormalities such as t(8;21), inv (16), 11q23, t(9;11), t(8;17), t(8;16), trisomies of chromosomes 4, 8, 11, and deletions of chromosomes 5q, 16q, and 20q have been associated with EM presentation [24–26] Factors reported in various studies to increase the risk of EM disease post-relapse and in particular the relapse post-transplantation include younger age, EM disease prior to transplantation, unfavorable cytogenetics, and M4/M5 FAB subtypes [22].

The spectrum of clinical presentations is variable and highly depends on the location or the organ involved with leukemia. The most common reported locations involve soft tissues, bones, central nervous system, and lymph nodes [25,27]. There are multiple reports of atypical sites of EM involvement such as gall bladder [28], eyes, gonads, and GI system among other sites [29]. The involved sites have been linked to overall prognosis in a recent database analysis through the Surveillance, Epidemiology, and End Results (SEER) database [29].

Leukemia cutis is seen in 3% of patients with AML and is usually associated with M4/M5 French–American–British (FAB) subtypes in 50% of the cases [30]. Leukemia cutis usually presents as diffuse and papulonodular rash that is more common on the lower extremities than the upper extremities and trunk [27]. Leukemia cutis can develop at the same time, following or even preceding the onset of systemic leukemia. The term leukemia cutis is used when patients present with isolated leukemia cutis and is usually diffuse and papulonodular in nature [12]. In most cases, leukemia cutis presents as single or multiple papules or nodules and is diagnosed after systemic leukemia has been identified. The skin involvement tends to have a predilection to areas of prior inflammation or infection [31].

Central nervous system (CNS) involvement is seen in up to 5% of patients with AML. Intracranially, myeloid sarcomas are often continuous with the meninges or the ependyma. Nevertheless, on some occasions, EM involvement of the CNS can invade the brain parenchyma and present as intra-axial mass [32]. In a recent review of reported CNS myeloid sarcoma cases, 21 patients were identified with 24 intracranial myeloid sarcoma mostly presenting as single brain lesion. Six of these 21 patients had concomitant lesions outside the brain [33]. CNS involvement with AML is more common with younger age, high WBC count, FAB M4 morphology, and presence of certain chromosomal abnormalities such as 11q23, inversion 16, trisomy 8, t(9;11), and hyperdiploidism [34–36].

4. Diagnostic workup

Fine needle aspiration is usually inadequate to confirm diagnosis of EM AML, and a tissue biopsy is warranted [25,37]. The H&E morphologic staining will vary according to the degree of differentiation of the leukemic cells. Typically, the biopsy will reveal diffuse infiltration by myeloblasts that are large cells with large nuclei and abundant cytoplasm. Further studies on the biopsy to confirm the diagnosis include immunohistochemical stains, flow cytometry, fluorescence in situ hybridization, and molecular analysis. The feasibility of performing all these diagnostic tests is usually more cumbersome when applied to cells obtained from tissue compared to bone marrow and peripheral blood samples. Immunohistochemical stains such as MPO and lysozyme are typically applied to differentiate myeloid cells, and additional myeloid markers can be added for diagnosis confirmation [5,38]. In addition to immunhistochemical staining, flow cytometry can identify myeloblasts by their characteristic pattern of surface antigen expression. The majority of myeloblasts express CD34, CD117, HLA-DR, CD13, and CD33. The pattern of surface antigen expression can differ among the different AML subtypes [39]. Further workup includes a bone marrow biopsy and aspiration to assess for medullary involvement and is usually sent for the same studies as outlined above. Once diagnosis of EM AML and bone marrow assessment are achieved, the next step in the diagnostic workup includes imaging to assess the extent of tissue involvement. Typically, the best modality of imaging depends on the sites suspected of harboring EM leukemia as magnetic resonance imaging is more sensitive to assess for central nervous system leukemia whereas computed tomography is best suited for soft tissue assessment. FDG-PET CT can be performed to localize and assess for multiple site involvement with leukemia [40,41]. FDG-PET is used for planning of radiation therapy and monitoring the treatment response. We usually perform CT scans with or without FDG-PET to assess for tissue and multiorgan involvement.

5. Prognosis of EM leukemia

EM AML presenting with concurrent medullary involvement carries an overall poor prognosis with a 5-year survival rate ranging between 20% and 30% [29,42]. The presence of EM involvement is associated with worse survival even among AML patients with the good prognostic genetic marker t(8;21) [43]. Patients with isolated EM AML possibly have a better event-free and overall survival when compared to patients with medullary leukemia after cytarabine-based therapy [44]. The superior outcomes with isolated EM when compared to medullary or combined leukemia have also been reported in the relapse setting post-allogeneic HCT [8]. In a recent SEER database analysis, the outcomes of 345 isolated EM AML patients were compared to AML patients without EM involvement. The 3-year survival rate for isolated EM AML 31.9%