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Case Report

Granulocytic Sarcoma, Still a Diagnostic and Therapeutic Challenge

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Abstract

Myeloid sarcoma is a rare myeloid entity that consists of a blastic infiltration of any organ tissue, irrespective of medullary infiltration. We herein report the case of a 75-year-old man with ORL invasion, who had concomitant acute myeloid leukemia and leukemia cutis. He was first in complete remission after chemotherapy, but relapsed with an isolated myeloid sarcoma of the cervical and para-renal region. First relapse was treated by radiotherapy with a favorable response. Second relapse was isolated to the Central Nervous System (CNS) and treated with Azacitidine, Venetoclax and intrathecal chemotherapy, without response. We here bring light on the various presentations of this rare disease for which no standardized protocol has yet arised. Such work seems seeded to help early diagnostic and improve overall outcome.

Keywords: Granulocytic sarcoma; Myeloid sarcoma; Acute myeloid leukemia; Blast; Venetoclax; Azacitidine

Introduction

Myeloid sarcoma (MS), also known as chloroma or granulocytic sarcoma, is an extramedullary blast cell proliferation from one or more myeloid germ line, which disrupt the normal architecture of infiltrated tissues [1].

MS can be a tissue-based manifestation of acute myeloid leukemia (AML), or less commonly myelodysplastic syndrom (MDS), myeloproliferative neoplasm (MPN) or MDS/MPN [2].

It can also occur de novo without any evidence of peripheral blood or bone marrow involvement. The most common locations include the soft tissue, bone, periosteum, and lymph nodes. CNS involvement is rare and distinct from meningeal leukemia [3].

Early diagnosis of isolated MS is extremely difficult and 46–75% of MS cases are initially misdiagnosed, most commonly as a malignant lymphoma or even as non-hematopoietic tumors [4].

Diagnosis of isolated MS mainly depends on pathology and immunohistochemistry (IHC). Laboratory tests, such as flow cytometry (FC), cytogenetics, fluorescence in situ hybridization and molecular analysis have been widely used for the diagnosis of MS in recent years.

Isolated MS can occur at any age of population from pediatric to elderly patients. The period between initial diagnosis of isolated MS and development of AML varies from 0.5 to 24 months (median 3–9 mo). Prognosis of MS is generally poor especially when associated with AML relapse [5].

We report here the case of a patient initially treated for AML with concomitant MS, who relapsed twice with isolated MS.

Case Presentation

A 75-year-old man was initially diagnosed in our department in March 2022 with AML concomitant with leukemia cutis and otorhinolaryngeal sphere myeloid sarcoma. Bone marrow infiltration was 6% blastic with no cytogenetic abnormality nor targetable mutation. RNA sequencing on skin biopsy found a KRAS G12C mutation, compatible with the diagnosis of MS.

The patient underwent an induction chemotherapy consisting of Idarubicin and Cytarabine (3+7 regimen) followed by three cycles of consolidation with intermediate dose Cytarabine (1.5g/m^2). He achieved complete metabolic response assessed by pet scan and the bone marrow examination confirmed morphologic complete remission with multiparameter flow cytometry undetectable measurable residual disease. The maintenance treatment with Onureg (oral form of Azacitidine) was initiated in September 2022.

In June 2023, the patient presented a mass infiltrating the left pyelo-ureteral junction and a cervical mass. Next generation sequencing sequencing performed on the para-renal mass biopsy showed presence of bi-allelic alteration of GATA 2 mutation, compatible with the diagnosis of MS relapse. The bone marrow samples found no blastic infiltration.

Then, patient received radiotherapy, which ended in August 2023 and induced a very good partial metabolic response confirmed by PET scan.

In November 2023, he was readmitted for low back pain radiating to the posterior face of the lower limbs, associated with fecal and urinary incontinence, with no other neurological symptoms.

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On review of his laboratory results, hemoglobin level was 11.8 g/dL, platelet count was 337 G/L and white blood cell count was 8.0 G/L with a normal count of neutrophils of 6.17 G/L. He had normal renal and liver function tests, but a hyponatremia at 122 mmol/L.

An urgent spinal MRI was performed, showing a stenosis of the cervical intracanal lesion posterior to C4, and a degenerative narrowing of the lumbar canal at L2 and L3 with no bone or intracanal lesion detected. Brain MRI was normal.

We then completed with a lumbar puncture. Examinations of the cerebrospinal fluid (CSF) comprising morphology and immunophenotyping tests showed a massive infiltration over 95% of myeloblasts with a granular differentiation profile: CD34-, CD38+/-, CD123+/-, CD13+/-, CD33++, CD117+, HLADR-, CD36-, CD7-, CD19-, CD56-.

A bone marrow sample showed a normal hematopoiesis without blast infiltration. In conclusion, it was an isolated meningeal relapse of the MS.

The salvage therapy consisted of the association of Azacitidine (75 mg per square meter of body-surface area subcutaneously during 7 days), Venetoclax (target dose, 400 mg per day) and intrathecal chemotherapy (40 mg of Cytarabine, 15mg of Methotrexate and 40mg of Hydrocortisone hemisuccinate).

Unfortunately, 15 days after the beginning of the Azacitidine-Venetoclax cycle, there was no improvement of the clinical symptoms, and the CSF remained blastic after 4 intrathecal chemotherapies. The decision was made to switch to exclusive palliative care.

Discussion

Extramedullary manifestation of acute myeloid leukemia was first described in 1811 by Burns [6] and then named "chloroma" by King due to its green color caused by the presence of myeloperoxidase (MPO) [7]. Five decades later, the relationship of MS to acute leukemia was identified [8]. Lately, in 1965, the word "myeloblastoma" was coined, encompassing a more appropriate histologic description of the lesion [9]. Concurrently, the terms "granulocytic sarcoma" [10,11] and "myeloid sarcoma" (MS) were proposed [12].

MS appears to be the most appropriate term for this entity, and is still adopted by the latest version of the World Health Organization (WHO) in the classification of myeloid neoplasms. MS represents a unique tissue-based manifestation of AML or transformed MDS, MDS/MPN, or MPN, but can also occur in an isolated form with an essentially normal bone marrow [2]. In this case, it is usually followed by the development of metachronous AML [3].

MS shows male dominance with a male to female ratio of 1.2–1.8:1 [13,14]. The disease could occur at any age, but it's incidence in children is up to 30% as compared to 2-5% in adult patients [15].

MS can present anywhere in the body, with different clinical presentations depending on the site of onset. The most common locations include the soft tissue, bone, periosteum, lymph nodes, gastro-intestinal tract and breast, but it can also affect kidneys, lungs and the CNS [3,16].

In a study from Denmark only 0.4% of patients had CNS involvement [3], and yet only seven patients had primary CNS MS [17]. Leukemic cells can infiltrate into brain parenchyma after the disruption of the blood-brain barrier [18].

In the case of our patient, MS first invaded the otorhinolaryngeal sphere and the skin (more commonly called leukemia cutis) at first presentation, and then relapsed in the cervical and para-renal regions. The second relapse was meningeal, but the brain parenchyma wasn't infiltrated, since brain MRI was normal.

In the absence of a clinical history of leukemia, the diagnosis of MS can be difficult. It is often misdiagnosed with non-Hodgkin lymphoma in up to 46% of patients [15]. This occurs most often with poorly differentiated MS, in which the morphology may resemble large-cell non-Hodgkin lymphoma when the cells are MPO-negative and weakly stained and positive for lymphoid lineage antigens such as CD19, cCD79a and CD7 [17].

Also included in the differential diagnosis: lymphoblastic leukemia, melanoma, Ewing sarcoma, blastic plasmacytoid dendritic cell neoplasm, and extra-medullary hematopoiesis following administration of growth factors such as granulocyte colony-stimulating factor (G-CSF) that can produce pseudotumoral masses [19,20].

Therefore, the diagnosis of MS should be confirmed with histological examination, immunohistochemistry and immunophenotyping with markers including CD34, MPO, CD117, and CD33 [21], but also, fluorescence in situ hybridization, and molecular analysis. In addition, a bone marrow sample should be done to establish the potential diagnosis of concomitant AML [3].

In our case, CSF cytology ultimately led to a definite diagnosis of meningeal MS with positivity of myeloid antigens such as CD33 and CD117.

The t (8;21) translocation is the most commonly reported cytogenetic abnormality associated with EM involvement, both at presentation and at relapse [3]. Other cytogenetic abnormalities have been found in MS patients such as the inv (16) translocation and mutations in the RAS pathway, DNMT3A, NPM1, IDH2, JAK2, KRAS, PTPN11, TET2, BCOR, and RAD21 [22]. However, Pileri et al. [23] found a normal karyotype in 13 cases (46.4%) and Kaygusuz et al. [24] reported no cytogenetic abnormalities in 6 cases (54.5%).

Our patient had normal karyotype at diagnosis with KRAS G12C mutation detected in skin biopsy at first presentation, and bi-allelic alteration of GATA II in the para-renal mass biopsy at first relapse.

There are no consensus guidelines for the treatment of MS due to its rarity, and the latest version of European Leukemia Net (ELN) offers no specific recommendations [25]. However, the National Comprehensive Cancer Network (NCCN) recommends systemic chemotherapy as the treatment of choice, even for isolated MS, since it has been shown to decrease progression to AML and increase overall survival [20,26].

Standard induction chemotherapy with anthracycline (Daunorubicin or Idarubicin) and Cytarabine, followed by intermediate-dose or high-dose Cytarabine, is the preferred chemotherapy regimen at first diagnosis [3, 19]. However,

Tsimberidou et al. [27] analyzed 21 cases of non-leukemic MS from the Anderson Cancer Center, and the results suggested that chemotherapy combined with radiotherapy resulted in better survival than chemotherapy alone.

Usually, radiotherapy is considered in patients with isolated MS, inadequate response to chemotherapy, recurrence after allogenic HSCT, and in circumstances that require rapid symptom relief because of vital structure compression. It has shown durable local control at the targeted site [26,28].

Allogenic HSCT is considered for MS associated with systemic disease in remission after first induction chemotherapy, but should be performed based on individual comorbidities, including the risk of graft-versus-host disease [29].

Our patient had initially MS associated with AML and was therefore treated with systemic chemotherapy. However no Allogenic HSCT have been performed due to his age and comorbidities. The choice of radiotherapy was made for the first relapse, since it was an isolated MS of the cervical and para-renal region, without medullary infiltration.

As for the second relapse, which was meningeal, we opted for the association of Venetoclax and Azacitidine combined with intrathecal chemotherapy. Hypomethylating agents as azacitidine were reported to induce clinical remission in MS, but this medication was used in less than 20 cases including treatment-naive and relapse/refractory MS [30,31]. As for Venetoclax, an anti-BCL2 agent, some cases have highlighted its efficacy in the context of MS [32,33], and its diffusion through the cerebro-spinal membrane is advantageous for treating CNS involvement [34].

Some studies suggested that isolated MS involving the pelvis/genitourinary organs, eyes/gonads, and gastro-intestinal mucosa had better outcome than disease localization in primary soft tissues, lymphatic/hematopoietic organs, or CNS [35]. However, the prognosis in patients with both isolated and synchronous MS is controversial and depends not only on tumour site, but also on timing of presentation, genetics, and treatment strategies, with a reported 5-years survival rate of approximately 24% [36,37]. The most common causes of death are relapse and infection [37]. In our case the patient died of progression of his disease.

Conclusion

Myeloid sarcoma is a rare entity among myeloid neoplasms, probably underestimated. It can manifest in various organs at first presentation and relapse, within the same patient, as described in this case (Skin, oropharyngeal area, cervical, para-renal and meningeal localizations). There is no standard treatment yet and the prognosis remains poor, but with further knowledge of molecular pathways and pathogenesis of the disease, we may have novel treatment options in the future, which can change outcome of this disease.

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