Isolated Central Nervous System Granulocytic Sarcoma and Meningeal Myeloid Leukemia: Successful Treatment Without Radiotherapy

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Granulocytic sarcoma is an extramedullary manifestation of acute myeloid leukemia, which very rarely precedes bone marrow involvement by leukemic cells. The lesion generally occurs either during the course of AML or after a remission has been achieved; however, GS may also occur in the absence of bone marrow involvement and may represent the sole manifestation of the disease. Chloromas can occur almost anywhere. A few cases of isolated meningeal chloroma without bone marrow involvement have been reported [1].

There are scant data regarding the optimal treatment for GS. Primary GS may present a diagnostic and treatment dilemma, especially in pediatric patients. Patients with GS are at a high risk of developing subsequent systemic disease, and thus the majority of authors recommend early systemic antileukemic chemotherapy. However, the precise type of therapy is not well established. The role of radiotherapy and bone marrow transplantation is also not currently defined.

AML = acute myeloid leukemia
GS = granulocytic sarcoma

We describe an unusual case of an isolated meningeal GS in a child, who had a durable response to systemic and augmented central nervous system-directed therapy without irradiation.

PATIENT DESCRIPTION

A 5 year old girl presented with a history of headache. Neither trauma nor infection was reported. Apart from bilateral papilledema, the physical exam revealed no abnormalities. The peripheral blood smear and chemistry profile were normal. Computed tomography of the head was normal. Lumbar puncture was not diagnostic. The headache and papilledema, however, persisted. Magnetic resonance imaging of the head exhibited diffuse leptomeningeal enhancement, which was thought to be secondary to the lumbar puncture. After 10 days a second lumbar puncture was performed and revealed elevated opening pressure (above 40 cm H_2O) and absence of cells. Pseudotumor cerebri was suspected and treatment with acetazolamide was administered, with minimal effect. Six weeks later the headache and papilledema worsened. A third lumbar puncture revealed 2400 white blood cells/ml in the cerebrospinal fluid. Papanicolaou staining showed atypical mononuclear blast cells. Immunocytochemistry was positive for myeloperoxidase and CD68 and negative for additional markers, findings consistent with an extramedullary myeloid tumor. A cytogenetic study demonstrated the presence of a t(9;11) translocation with split mixed-lineage leukemia gene.

Bone marrow aspirate and biopsy did not demonstrate malignant cells and showed normal immunophenotyping and cytogenetic studies. An osteoplastic craniotomy with MRI-navigated meningeal biopsy was performed. Blast morphology was consistent with myelomonocytes positive for CD68 and negative for Tdt, confirming the diagnosis of GS.

The patient was treated with antileukemic chemotherapy according to the AML-Berlin-Frankfurt-Munster treatment protocol with augmentation of intrathecal treatment. Induction therapy consisted of systemic cytarabine (100 mg/m^2 per day for 8 days), daunorubicin (30 mg/m^2 for 3 days) and etoposide (150 mg/m^2 per day for 3 days) with five doses of triple intrathecal treatment (methotrexate 12 mg, cytarabine 70 mg and hydrocortisone 35 mg). CSF remission was achieved. Two further courses of cytarabine (6 g/m^2 per day for 3 days) and mitoxanthrone (10 mg/m^2 for 2 days) with two doses of triple intrathecal treatment were given as consolidation therapy. The patient received an additional course of cytarabine (6 g/m^2 per day for 3 days). Finally, after the completion of systemic chemotherapy, 12 monthly doses of triple intrathecal treatment were administered. In total, 21 intrathecal treatments were given during the first year of therapy. At present, 60 months after diagnosis and 40

CSF = cerebrospinal fluid

months after the end of treatment, the patient is in complete remission.

COMMENT

More than 90% of patients with extramedullary leukemia reported in the literature have evidence of bone marrow disease at the time of diagnosis or develop it within 1 year. The most common sites of involvement are skin and orbit; isolated CNS leukemia at diagnosis is extremely rare [2]. Our patient did not have systemic involvement at diagnosis and, 60 months after presentation, still does not demonstrate evidence of disease.

The diagnosis of extramedullary leukemia is often very difficult. A high index of clinical suspicion is required for cases without a history of preceding hematological malignancy. One retrospective case series revealed that none of 14 isolated granulocytic sarcomas had a correct primary diagnosis at the time of presentation [3]. Therefore, in cases with difficult and unusual clinical and pathological presentations, additional cytogenetic studies can be useful to establish the diagnosis of EML. In approximately 15% of cases of AML, rearrangements of the 11q23 region are described. The majority of cytogenetic changes result from translocation between the *MLL* gene in 11q23 and different partner genes. In 30–50% of the cases t(9;11) was described. The t(9;11) translocation was seen primarily in FAB M5 AML, a type of leukemia with a high predisposition to extramedullary involvement. In the present case, detection of t(9;11) in malignant cells in CSF substantially contributed to establishing the diagnosis.

Due to the rarity of isolated GS there is no consensus about the treatment of this disorder. In adults, GS is associated with a poor prognosis, a low rate of complete remission and low overall survival. Neither surgery nor radiation therapy appear to improve outcome. In the majority of studies early antileukemic chemotherapy is recommended, without agreement about the type and intensity of chemotherapy. A few studies of primary EML in children have been conducted. Among 1832 patients entered in the Children's Cancer Group chemotherapy trials with AML, 199 patients had EML; in 13 of them bone marrow analysis revealed less than 5% leukemic blasts at presentation. The 5 year estimated event-free survival for this small patient group was significantly better than for the other EML patients and patients without EML [2]. The favorable outcome in older children and infants with AML whose leukemic cells contain the t(9;11) may be attributed to the use of epipodophyllotoxins, agents known to be effective against M5 leukemia [4,5]. Making decisions about the use of radiotherapy, especially for children who attain a complete remission, is not easy. A retrospective case review from the Children's Cancer Group, including all children treated for AML from 1983 to 1995, suggested that routine irradiation of GS can be safely omitted. There was no difference in outcomes between those given radiotherapy and those who were not [4]. Another study from St. Jude Children's Research Hospital examined the outcomes of children presenting with CNS involvement at the time of diagnosis of AML. In this study there was no significant difference in event-free survivial between patients with or without CNS leukemia, a finding that supports the idea that craniospinal irradiation can be omitted in these patients [5].

In accordance with the above mentioned studies, we successfully treated our patient using intensive anti leukemic chemotherapy with CNS-oriented intensification, without craniospinal irradiation or stem cell transplantation. It should be emphasized that the treatment was well tolerated without clinical signs or symptoms of CNS consequences for 5 years after completing treatment.

This case illustrates the importance of combining different diagnostic modalities in the setting of challenging clinical presentations. Although primary meningeal GS may be a harbinger of a poor outcome in adults, pediatric patients with this disease may have a favorable outcome when treated with standard multi-agent AML chemotherapy with CNS-oriented intensification without the addition of craniospinal irradiation.

EML = extramedullary leukemia

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"God is usually on the side of the big squadrons against the small"

Comte Roger de Bussy-Rabutin (1618-1693), French memoir writer