

Orbital tumor preceded the development of acute myeloid leukemia: A case report and literature review

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ABSTRACT

Acute myeloid leukemia (AML) may rarely involve the orbit as a solid tumor termed granulocytic sarcoma (GS). Orbital GS is a localized tumor consisting of immature myeloid cells. The histological diagnosis is difficult especially in patients with poorly differentiated tumors with no evidence of systemic leukemia. Special stains and immunohistochemistry have a significant role in the diagnosis. This report describes the case of a 14-year-old boy who presented with rapidly progressive unilateral proptosis which was found to be round cell tumor on histopathology. The diagnosis is made by clinical examination, computed tomography (CT), and confirmed by immunohistochemical findings. After 8 months, the patient developed AML with blast cells in the peripheral blood. The patient was treated by a combination of chemotherapeutic drugs. A literature review suggests that leukemia might be the most likely diagnosis in a child with orbital tumor and in many cases GS precedes the systemic manifestations of AML.

Key words: Acute myeloid leukemia, granulocytic sarcoma, histopathology, immunohistochemistry, orbital tumor

INTRODUCTION

Granulocytic sarcoma (GS) refers to a tumor formed by myeloblasts or immature myeloid cells that affects an extramedullary site or soft tissue. The mass, also referred to as an extramedullary myeloid tumor or chloroma, may precede systemic leukemia or present simultaneously with a systemic myeloproliferative disorder or represent a relapse of a disease previously in remission.^[1] It usually involves orbits and subcutaneous tissue, but they may also occur in paranasal sinuses, lymph nodes, bone, the spine, the brain, pleural and peritoneal cavities, the breasts, the thyroid, salivary glands, the small bowel, the lungs, or various pelvic organs, and the skin. Orbital GS has to be differentiated from rhabdomyosarcoma, metastatic neuroblastoma,

African Burkitt's lymphoma, and idiopathic inflammatory pseudotumor. It is more common in the pediatric age group than adults and 60% of patients are younger than 15 years.^[1] This tumor can easily be misdiagnosed as a lymphoma or sarcoma, especially when there is no evidence of hematologic disorders. Immunohistochemical studies are helpful in determining the correct diagnosis.^[2,3] Herein, we report a case of GS of the orbit in a young boy who was subsequently diagnosed as acute leukemia, the clinical onset of which was antedated by the orbital tumor.

CASE REPORT

A 14-year-old previously healthy boy presented to us with 3 weeks history of painful, progressive proptosis, and limited ocular motility in the right eye without any other systemic symptoms. Ophthalmic examination revealed right upper and lower lid edema with marked proptosis and chemosis of the right eye. Cornea showed exposure keratitis. Vision in right eye was drastically reduced and there was downward and lateral displacement of globe. Left eye was normal. Systemic examination, including a complete blood count and chest radiograph, was unremarkable. Computed tomography (CT) scan showed a contrast enhancing large

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mass in the superior aspect of right orbit involving the ethmoid bone [Figure 1]. An excisional biopsy and orbitotomy was performed for diagnosis. Histopathology revealed sheets of round to oval cells with vesicular nuclei and scanty cytoplasm with the presence of mitotic figures suggesting a malignant round cell tumor [Figure 2a]. The differential diagnosis included all the causes of retro-orbital tumors including rhabdomyosarcoma, malignant neuroblastoma, leukemia, lymphoma, and inflammatory pseudotumor. We attempted immunohistochemical examination with antibodies to CD68 and myeloperoxidase (MPO), and both were positive [Figure 2b]. Chromosomal analysis for cytogenetic abnormalities could not be contemplated due to nonavailability of the facility in our institution. From these findings, a diagnosis of GS without evidence of leukemia was made.

Peripheral blood abnormalities were not demonstrated. Bone marrow examination conducted at the same time did not reveal any abnormality, but we planned for systemic chemotherapy with the idea that early therapy might be helpful to prevent the development of acute myeloid leukemia (AML). Unfortunately, because of unwillingness from the part of patient despite proper counseling, the chemotherapy could not be initiated. Local irradiation therapy was performed. Patient showed gradual regression of proptosis. Eight months after initial presentation, the patient developed systemic manifestations of peripheral blood and bone marrow. Peripheral blood smear revealed an elevated white blood cell count of 24,000/ μ L with 20% segmented neutrophils, 37% lymphocytes, 15% monocytes, 10% promyelocytes, and 18% blasts without any anemia or thrombocytopenia [Figure 3]. Serum lactate dehydrogenase (LDH) level was high. Bone marrow biopsy revealed blast cells comprising 22% of myeloid blast cells with myeloid maturation beyond early granulocyte stage. On the basis of these findings, a final diagnosis of M2 AML was made. The patient was transferred to the hematologic department and was treated under the current protocol for newly diagnosed AML. The patient returned home and was lost to further follow-up.

DISCUSSION

GS or chloroma is a tumor composed of immature granulocytes occurring in an extramedullary site. GS was first described in 1811 as a tumor on the retro-orbital site with a green-colored appearance.^[4] The term chloroma "green tumor" is derived from the greenish gross coloration of this lesion, attributable to the myeloperoxidase in the cells of granulocytic lineage.^[5] Rappaport^[6] referred this tumor as GS because not all of the tumors were green.

GS may occur at any age, but a wide age range with a mean onset during middle age is also reported. The incidence of

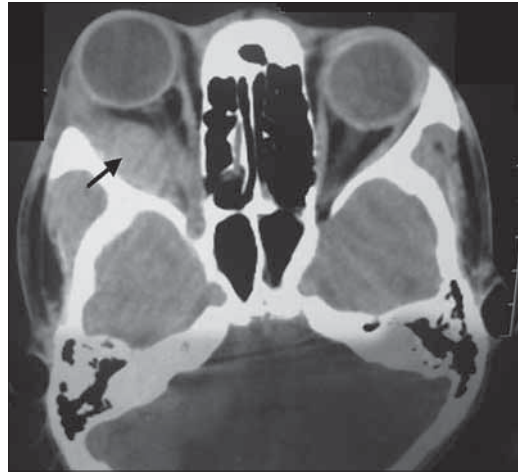


Figure 1: Contrast-enhanced computed tomography of the orbit (axial scan) shows a homogeneous mass with uniform contrast enhancement located in the right superior orbit (black arrow)

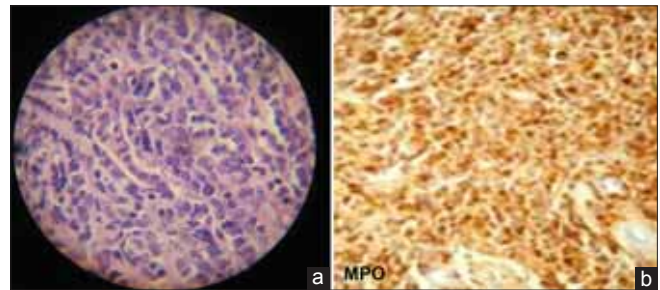


Figure 2: (a) Photomicrograph of the orbital biopsy specimen revealed homogenous infiltrate of round to oval cells with vesicular nuclei and scanty cytoplasm (H and E, $\times 400$). (b) Positive immunohistochemical staining of the tumor cells for myeloperoxidase (anti MPO, $\times 400$)

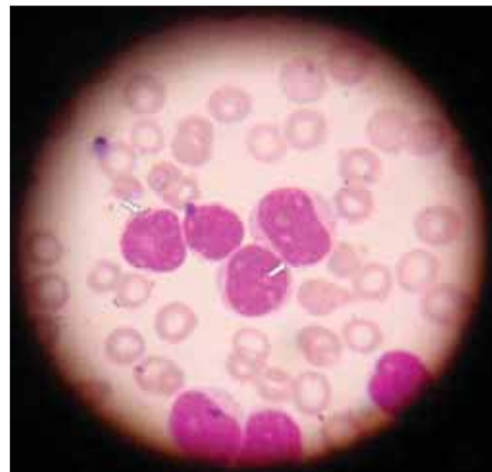


Figure 3: High power ($\times 100$) view of peripheral blood film slide showing myeloblast with the presence of auer rods (white arrows)

myeloid sarcomas in the pediatric age group is up to 30% in some studies of pediatric AML versus 2-5% in adults.^[7] There is no sexual predilection for GS. It is commonly found in the ribs, sternum, pelvis, orbital bone, soft tissues, lymph nodes, skin, and gums. It also involves the spine, small intestine, cervix, and paranasal sinuses.^[1,7] Clinically, GS is

commonly present simultaneously with a new diagnosis of AML or as evidence of disease recurrence, but a significant subset can occur before the presence of systemic leukemia, as a harbinger for AML.^[2,8] Myeloid sarcomas are most common in certain subtypes of AML, in particular M5a (monoblastic), M5b (monocytic), M4 (myelomonocytic), and M2 (myeloblastic with maturation).^[7] The primary GS is rarely encountered and occurs in the absence of any past history of leukemia and often commonly misdiagnosed as lymphoma or sarcoma. One report showed that misdiagnosis occurred in 47% (72 out of 154 cases of primary extramedullary leukemia) of cases, and another study reported an incident rate of 56% (34 cases in 61 biopsies of 50 patients) of misdiagnosis.^[7,9] Thus, immunohistochemical studies must be evaluated for correct diagnosis.

Histologically, GS is composed of immature cells of the neutrophil granulocytic series; the predominant finding being infiltration of immature poorly differentiated cells with round to oval nuclei. The pathological diagnosis of GS is very problematic when myeloid differentiation is minimal in the histological picture. In this situation, differentiation of GS from malignant lymphomas and other small round cell tumors is extremely important.^[3] B and T cell markers (CD45, CD20, UCHL-1, CD3, and CD30) would be helpful to rule out a diagnosis of lymphoma. An immunohistochemical panel with at least myeloperoxidase (MPO), CD68, and CD34 can be used to detect myeloid differentiation. MPO is an important marker and a positive outcome denotes the tumor to be a myeloblastic variant. Anti-lysozyme and chloroacetate esterase are also useful to diagnose GS.^[10] Other monoclonal antibodies to the membrane surface or cytoplasmic antigens such as CD33, CD34, CD99, and HLA-DR can also be useful. In our case, positive results were obtained for antibodies to myeloid cells such as anti-MPO and anti-CD68. Additionally, a positive terminal deoxynucleotidyl transferase (TdT) stain indicates immature or nondifferentiated tumor cells.

There are multiple predisposing factors for the development of primary and secondary GS. Cytogenetic abnormalities like t(8;21), inv(16), FAB subtypes M4 and M5, high white blood cell count, the presence of neural cell adhesion molecule (NCAM) and/or T cell markers (CD 2, CD 4, or CD 7), poor nutrition, and low socioeconomic status are found to be associated with GS development.^[7] The prognosis of GS is not very good. It has a rapid course with high mortality rate, especially when associated with AML. Cases primarily diagnosed as GS with no evidence of leukemia and received systemic chemotherapy are likely to have a lesser probability of developing AML and were shown to be associated with longer survival rates.^[11] Therefore, GS should be treated early in the course of the disease with systemic treatment. Irradiation therapy can

also be used for primary GS. Although radiotherapy is helpful for high radiosensitivity, it has no effect on disease free survival and prognosis.

Orbital GS typically affects children and young adults and must be differentiated from other orbital tumors that typically affect this age group. Of all the orbital lesions, GS accounts for only one of 250 malignant cases with the incidence being slightly higher in Africa and Asia.^[12,13] Orbital involvement by acute myeloid sarcoma is relatively rare among orbital tumors. However, in the setting of bilateral orbital tumors in children, myeloid sarcoma appears to be a highly likely diagnostic possibility. In a study of 86 Indian patients with AML, eight (9.3%) were found to have orbital deposits in one or both eyes.^[14] Majority of the cases present as bilateral proptosis. However, our case showed the rare unilateral presentation. The clinical presentation (site and age) has some association with the molecular lesion. Myeloid sarcomas associated with AML1-ETO (RUNX1-RUNX1T1) translocations [t(8;21) (q22;q22)] are commonly found in the orbital region in children^[15] while those with inv(16) (p13.1q22)/t(16;16) (p13.1;q22) have a high incidence in the gastrointestinal tract or breast in adults.^[2]

To conclude, we clinically experienced a case of GS presenting with an orbital mass, without any evidence of leukemia at presentation. Special stains and immunohistochemistry play an important role in the diagnosis. In many cases proptosis precedes the systemic manifestations of AML and in the absence of systemic features it becomes difficult to diagnose GS. Most cases in patients without a previous diagnosis progress to AML within 1 year and even earlier in the case of an initial orbital disease. Any child with an orbital mass of uncertain origin should undergo prompt evaluation for underlying AML.

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