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An atypical presentation of isolated bilateral orbital myeloid sarcoma: A case report

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Abstract
A 10-year-old boy was referred to our hospital, for a one-week history of a rapidly progressing left eye proptosis, preceded by right eye conjunctival lesion that appeared a few weeks prior the onset of proptosis, and was unsuccessfully managed as conjunctivitis. Upon presentation, imaging showed enlargement of the left superior rectus muscle without invasion of adjacent structures, associated with bilateral level II cervical lymphadenopathies. A diagnosis of rhabdomyosarcoma with lymphatic metastasis was suspected. Nevertheless, an incisional biopsy of the right conjunctival lesion enabled establishing the diagnosis of orbital myeloid sarcoma with monocytic differentiation. Upon diagnosis, chemotherapy was initiated with subsequent regression of the lesions. However, due to the unfavorable socioeconomic status of the patient, the management process was not completed in a timely manner, leading to permanent unilateral visual loss due to optic nerve compression by the rapidly expanding mass.

Keywords: Orbital myeloid sarcoma, chloroma, proptosis

Introduction
Myeloid sarcomas are solid tumors formed by leukemia cells, frequently occurring as a synchronous or metachronous extramedullary manifestation of acute myeloid leukemia (AML). [1, 2]. Although rare in adults, myeloid sarcomas are relatively common in the pediatric population, representing 12-40% of the extramedullary leukemia cases, in which orbital involvement is common [1–6]. Myeloid sarcomas, also called granulocytic sarcomas, were first described in 1850's and termed chloromas, owing to the greenish tint produced by the presence of myeloperoxidase. Other appellations that were proposed, which are concomitantly used in the literature, include extramedullary myeloid cell tumor or myeloblastoma [7, 8].
Orbital myeloid sarcoma (OMS) ranks the second most common site of myeloid sarcoma in children, which are more frequently found in M2, M4, and M5 subtypes of AML. The clinical symptomatology is not specific; however, proptosis is common due to the expansive nature of the tumor, with a relatively frequent involvement of the retina or anterior segment. Such a variable and non-specific presentation, along with the absence of diagnosis of an underlying AML, poses a challenge in reaching the diagnosis, as it can mimic the presentation of other serious conditions such as: rhabdomyosarcoma, Ewing's sarcoma, and metastatic neuroblastoma [9–11].
In the present paper, we report the case of a 10-year-old boy with bilateral OMS, with a challenging presentation that resulted in definitive unilateral blindness due to optic nerve compression.

Case report
Patient referral
A 10-year-old boy was referred to our hospital for diagnostic and therapeutic management of a left intra-orbital mass suspected to be a rhabdomyosarcoma, associated with a right conjunctival lesion. Two weeks before presenting to our hospital, the patient presented at the referring center, for left eye subacute proptosis with diplopia for 1 week, that was preceded by two-month history of right temporal conjunctival lesion.

A magnetic resonance imaging (MRI) was then performed and found a left intraconal mass of 4.7*3*2 cm size, sparing the optic nerve and osseous structures. The patient was referred to our structure, a tertiary care teaching hospital, for multidisciplinary management.

First visit findings

On the first day at our department, the patient was complaining of a mild periorbital pain in the left eye that was associated with diplopia. The patient was known to be medically free, with no significant past ocular. Also, he denied having any systemic symptoms, such as neurological, cardiac, respiratory, gastroenterological, urinary, or constitutional symptoms. Family history was non-significant for malignancies, ocular diseases, nor medical conditions. Further reconstruction of the recent history revealed that a right conjunctival lesion developed more than 2 months ago, and was treated as conjunctivitis, with no subsequent resolution. Ophthalmological examination of the right eye was positive for a raised pinkish lesion resembling a salmon patch, which was located in the temporal conjunctiva. The left eye showed axial proptosis with inferior dystopia and limitation of all extraocular muscles' motility, which was particularly severe in supraduction and infraduction, and moderate in abduction and adduction (Figure 1). The rest of the anterior segment examination was normal in both eyes. Optic nerve function tests including pupil pupil reflexes and color vision were within normal limits in both eyes, however, a mild reduction in vision was found as visual acuity was 20/30 and 20/40 in the right and left eye, respectively. Intraocular pressure (IOP) was 16mmHg and 18mmHg, in the right and the left eye, respectively. The dilated fundus exam showed no abnormalities in both eyes. The patient was conscious, alert and vitally stable. Examination of cranial nerves was unremarkable. Lymph nodes examination revealed a small palpable submandibular lymph node in the left side. The rest of the systemic examination was unremarkable.

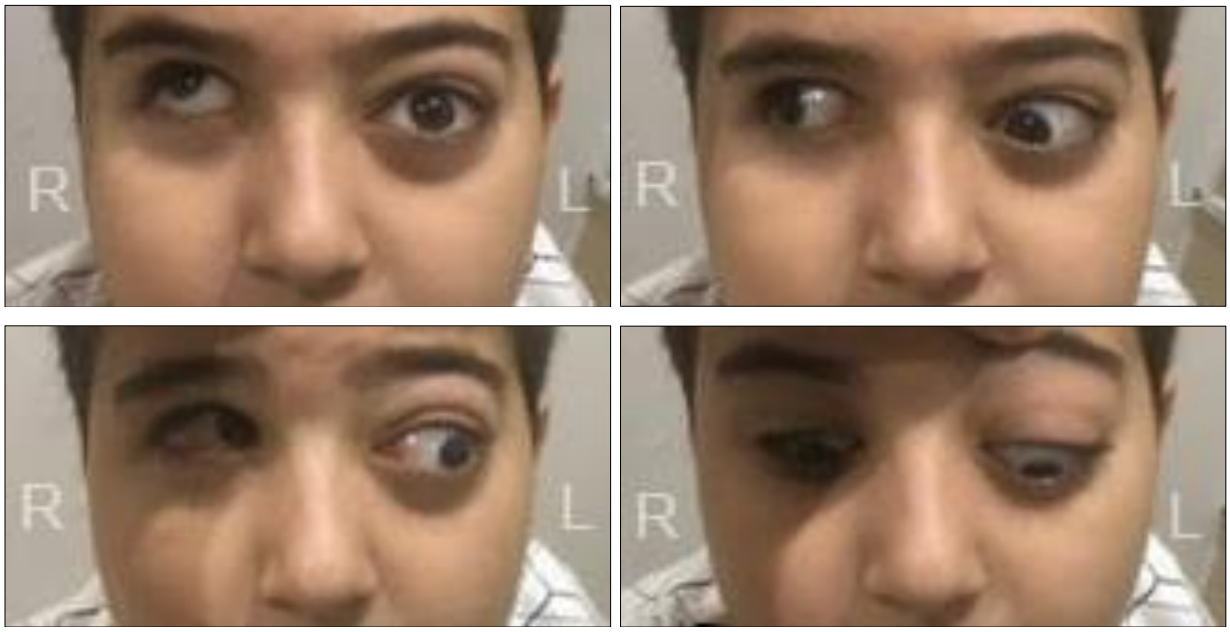
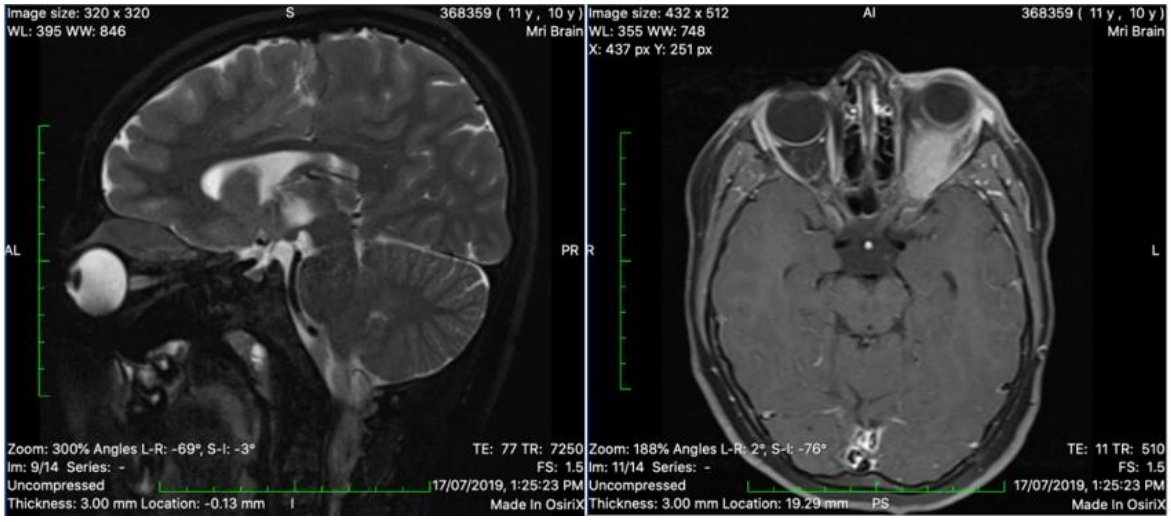


Fig 1: Axial proptosis of the left eye with inferior dystopia, limitation of the extraocular motility, with severe limitation of the upgaze

The MRI images (Figure 2) from the referring center was reviewed at presentation and it concluded an enlargement of the left superior rectus muscle without invasion of adjacent structures. The patient was admitted in the general pediatric ward for further investigations and multidisciplinary management.



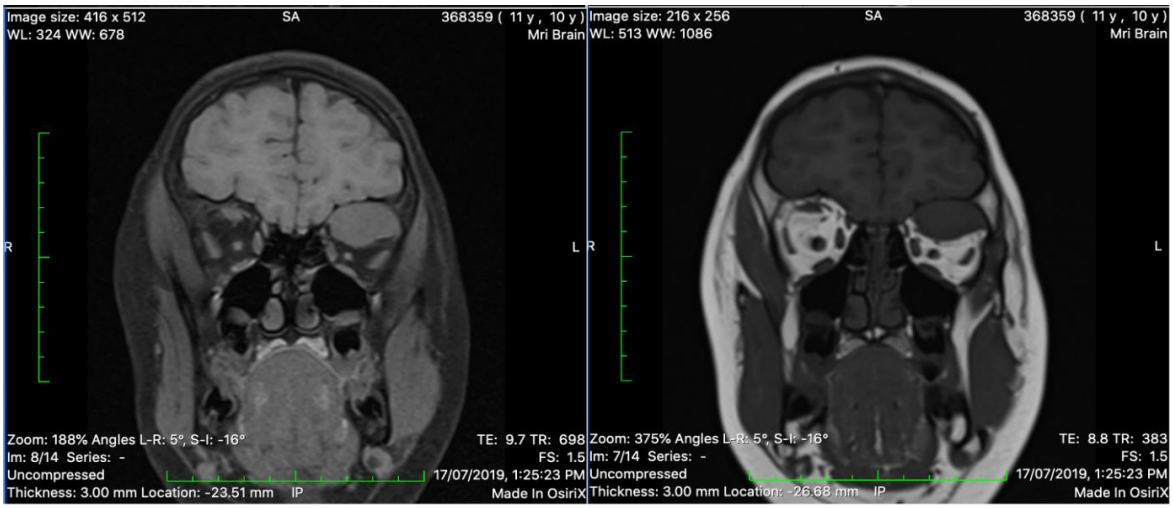


Fig 2: Magnetic reasoning imaging of the brain and orbit showing a massive enlarement of the left superior rectus muscle without adjacent structure invasion, sparing the optic nerve and osseous structures and repulsing the orbit.

During hospitalization

The patient underwent investigations including laboratory workup, blood films, brain and orbit computed tomography scan (CT) and a pan scan to rule out other systemic lesions. Blood workups were carried out and came out unremarkable (Box 1), and imaging showed left superior rectus muscle mass sparing the optic nerve and bilateral, level II cervical lymphadenopathies suggestive for lymphatic metastasis, however, brain, spine, thoracic and abdominal images were unremarkable. Given the age of the patient, the suspected diagnosis was rhabdomyosarcoma with lymphatic metastasis, thus, bone marrow aspiration was decided, in addition to an incisional conjunctival biopsy of the lesion in the right eye.

Table 1: Results of blood workup

Parameter	Result	Parameter	Result
WBC	7.88	AST	14
Lymphocytes		ALT	39
Hemoglobin	12.5	GGT	23
Platelets	278	Total Bilirubin	5
PTT	25.5	Uric acid	220
PT	11.3	CRP	
INR	1	HIV serology	Negative
Sodium	136	CMV serology	
Potassium	3.6	EBV serology	Negative
Chlore	102	Parvoviruses serology	Negative
Urea	6.8	Bone profile	
Creatinine	47 mg/	Ca	2.3
Calcium	2.30	Mg	0.83
Phosphate	1.58		
TP	73%		

An incisional biopsy of the right conjunctival lesion was carried out and the preliminary pathology report showed small-blue-round-cell tumor (SBRCT). The pediatric oncologist was consulted and prescribed intravenous methylprednisolone 1 mg/kg twice a day, waiting for the final pathology report. By the 7th day of hospitalization, the patient became irritable, complaining of vision loss and ocular pain in the left eye. Ophthalmological examination showed progression in proptosis and conjunctival chemosis in the left eye, with evidence of mild exposure keratopathy, due to lagophthalmos. Patient clinical presentation was suggestive of optic nerve compression and mass progression; thus, an urgent CT scan was performed showing significant increase in the size of the mass with optic nerve compression and more pronounced proptosis. In view of the optic nerve compression and in absence of the final pathology results, probabilistic chemotherapy was initiated immediately. The surgical option of debulking was discussed; however, after consulting two experienced oculoplastic and orbital surgeons, it was decided not to undertake the surgery since the tumor was believed to be chemo-sensitive and thus expected to shrink in size without surgical intervention. On the 13th day of hospitalization, the patient showed regression of the ocular pain along with gradual improvement in proptosis, as the patient was able to close his eyes completely. The patient was discharged with scheduled weekly visits to Ophthalmology outpatient clinic, awaiting the final pathology report.

Pathology findings

Grossly one fragment of firm tissue measuring 0.4*0.3 cm was obtained. Microscopically there was a diffuse monotonous proliferation of medium sized to large cells, with ovoid vesicular nuclei, large centrally located nucleoli and dispersed chromatin. The cytoplasm was scant to moderate. The mitotic count was high (Figure 3). Immunohistochemically, the cells were positive for LCA, CD4, lysozyme, CD68 and CD33, while negative for CD3,

CD20, CD24 and NPO. Bone marrow aspiration biopsy and cerebrospinal fluid analysis were carried out and showed no evidence of blasts.

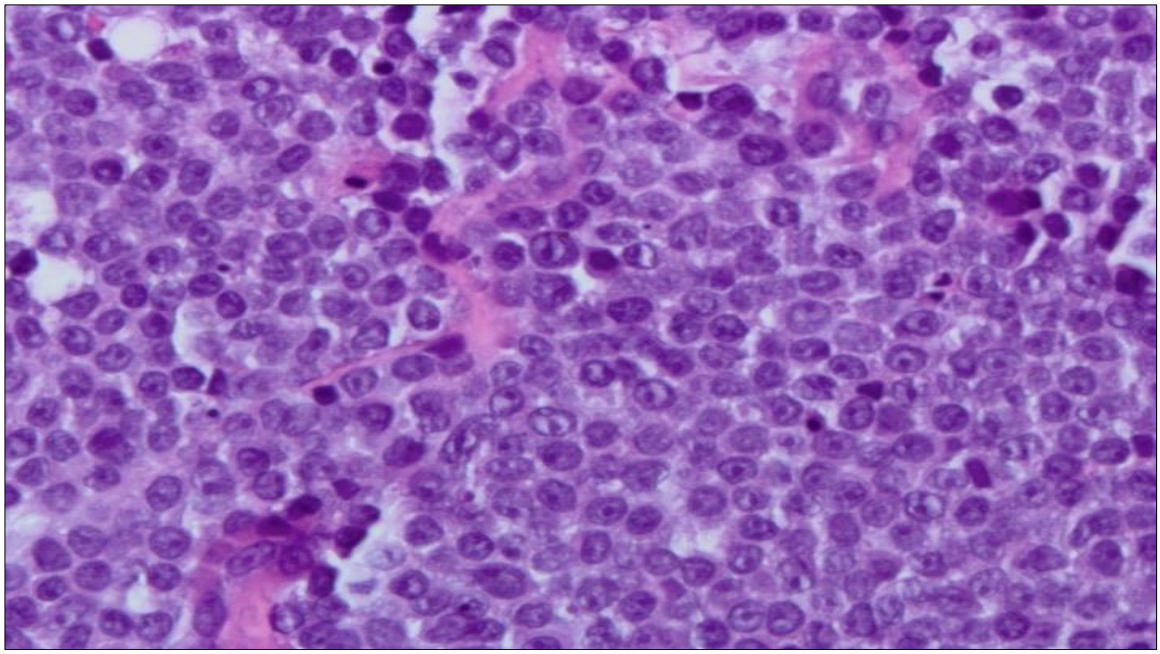


Fig 3: Hematoxylin and Eosin-stained section shows a monotonous proliferation of small round blue cells.

Based on the biopsy findings, the diagnosis of bilateral orbital myeloid sarcoma with monocytic differentiation was established. The patient was contacted regarding hospital admission to start adapted chemotherapy protocol. However, there was difficulty for the parents acquiring an appropriate health insurance, due to their socioeconomic status. After two weeks of social assistance intervention, a charitable association has approved to cover the treatment expenses. The patient was admitted, and chemotherapy protocol was initiated including: Cytarabine, Etoposide and Danorubicin. After the end of the first cycle, the patient was discharged, and readmission was scheduled for the second cycle.

Outcome

Brain and orbit MRI was repeated two months after the start date of chemotherapy protocol and showed a sizeable residual tumor infiltrating the superior rectus muscle and the optic nerve. Ophthalmological evaluation showed visual acuity of 6/6 and no light perception (NLP) in the right and left eye, respectively. Extraocular muscle motility test was unremarkable for both eyes. Anterior segment examination was positive for mild exposure keratitis in the left eye. Dilated fundus exam was unremarkable in the right eye; however, a left flat pale optic disc was appreciated in the left eye. No signs of retinal infiltration were found in either eye. The patient was regularly following up, showing no clinical, radiological or laboratory evidence of recurrence or evolution of the tumor. Also, there was no evidence of concurrent AML. The vision remained impaired in the left eye, with visual acuity of NLP, as it is expected due to the compressive nature of the disease leading to subsequent optic nerve atrophy.

Discussion

The present case posed two major challenges that resulted in delayed diagnosis and management, which has probably impacted the outcome. The first challenge was the isolated presentation of OMS, with no positive or evocative sign for AML in all investigations, including: hematological workup, cerebrospinal fluid analysis and imaging. Imaging was helpful to appraise the extent of the tumor lesion and its invasiveness, which has limited the differentials without addressing the definitive diagnosis. Hence, the initially suspected diagnosis was rhabdomyosarcoma with lymphatic metastasis, given the picture of a rapidly progressive proptosis in a pediatric patient with imaging suggestive for a unilateral malignant, non-infiltrating orbital tumor associated with cervical adenopathy suggesting metastasis. Rhabdomyosarcoma represents the most frequent primary and life-threatening malignant orbital tumor in children, accounting for 10% to 32% of all soft-tissue sarcomas of the head and neck. [12–14] Despite the suspicion of rhabdomyosarcoma, the diagnosis of OMS was still considered, leading to the incisional biopsy of the contralateral conjunctival lesion, assuming a bilateral location. It is to note that the right conjunctival lesion preceded the onset of the left eye proptosis by 3 to 4 weeks and was misdiagnosed and treated as conjunctivitis. The pathological analysis confirmed the diagnosis of isolated bilateral OMS, in absence of any sign of AML, neither during hospitalization nor over the long term follow up period. Bilateral orbital involvement is estimated to be frequent in myeloid sarcoma, although it is rarely described in the literature, probably due to the second eye being often underdiagnosed. Such features make the diagnosis of OMS even more challenging with further differential considerations [15, 16]. Furthermore, isolated, or de novo, forms of OMS are rare, and are defined as the absence of leukemia or myelodysplastic syndrome in the patient history, with absence of bone marrow involvement [2, 8, 17]. In the case of our patient, it is worth noting that the pathology-based diagnosis concerned only the right conjunctival lesion, as the left retro-orbital tumor was not accessible to biopsy and invasive surgery was not encouraged at that stage. Hence, the definitive diagnosis was confirmed by the therapeutic response of the left eye lesion to the specific

protocol, leading to significant decrease of the tumor size and clinical improvement. The second challenge impeding the management of the patient was the financial incapacity of the family to bear the treatment expenses. This resulted in further delay in the initiation of the appropriate CT regimen, which adversely reflected in further tumor progression.

By reconstructing the chronology of the present case, the natural history of the tumor probably started as a unilateral conjunctival salmon patch-like lesion, which was misdiagnosed as a conjunctivitis; whereas the contralateral retro-orbital lesion was subclinical or develop later to this stage. Rapidly, the retro-orbital lesion progressed and dominated the clinical picture, misleadingly presenting as a unilateral space-occupying tumor with signs of lymphatic metastasis, while excluding a myelodysplastic syndrome given the negative specific investigations.

Teachings that should be stressed from this atypical case include: 1) the importance of further exploring treatment-resistant conjunctivitis; 2) the consideration of isolated OMS in the differential diagnosis of unilateral retroorbital tumors; and 3) the heterogenous presentation of bilateral OMS, as the present case had a non-progressive conjunctival lesion with a rapidly expansive contralateral lesion.

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