American Journal of Ophthalmology Case Reports 19 (2020) 100806

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Orbital myeloid sarcoma (chloroma): Report of 2 cases and literature review

Mohammad A. AlSemari [a,*], Marianna Perrotta [b], Camilla Russo [b], Hind M. Alkatan [c,d], A. Maktabi [a], S. Elkhamary [a], Rosa Maria Di Crescenzo [f], Massimo Mascolo [f], Andrea Elefante [b], Luca Rombetto [e], Raffaella Capasso [g], Diego Strianese [a,h]

[a] King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia
[b] Department of Advanced Biomedical Sciences, University "Federico II", Naples, Italy
[c] Department of Ophthalmology, College of Medicine, King Saud University, Riyadh, Saudi Arabia
[d] Department of Pathology, College of Medicine, King Saud University, Riyadh, Saudi Arabia
[e] Department of Neurosciences, Reproductive and Odontostomatological Sciences, University "Federico II", Naples, Italy
[f] Department of Advanced Biomedical Sciences - Pathology Unit, University "Federico II", Naples, Italy
[g] Department of Medicine and Health Sciences "Vincenzo Tiberio", Università degli Studi del Molise, Campobasso, Italy
[h] Institute of Ophthalmology, School of Medicine and Surgery, University of Naples Federico II, Naples, Italy

ARTICLE INFO

Keywords:
Myeloid sarcoma
Acute myeloid leukemia
Orbital pathology
Pediatric tumor
Magnetic resonance imaging

ABSTRACT

Purpose: Myeloid sarcoma (MS) of the orbit is an uncommon condition in occurring in children, generally coupled to myeloproliferative neoplasms.

Observations: We describe two rare cases of orbital MS in young boys with aggressive local symptoms but without evidence of acute myeloid leukemia (AML), both patients underwent orbitotomy for gross-tumor resection and biopsy. At follow up, there was no evidence of recurrence nor evolution of the myeloproliferative neoplasms clinically and by radiological and laboratory work-up. We also provide a detailed description of the magnetic resonance imaging presentation, with an extensive pathological analysis correlation.

Conclusions and importance: A comprehensive revision of the literature on isolated orbital MS was carried out with particular emphasis on clues for differential diagnosis and treatment options, stressing the need to consider MS even in the absence of sign and symptoms of an underlying myeloproliferative disorders.

1. Introduction

Myeloid sarcoma (MS) is an extra-medullary solid tumor caused by an abnormal proliferation of primitive immature precursors of the granulocytic series of white blood cells.[1] First described in 1811, MS is also called "chloroma" because of its green color secondary to the presence of intracellular myeloperoxidase.[2,3] Subsequently, because of its macroscopic appearance variability, the tumor was renamed granulocytic sarcoma in 1966.[4]

MS is a rare disease, often related to other underlying unrecognized myeloproliferative conditions. Indeed, MS occurs in 2.5–9.1% of patients with acute myeloid leukemia (AML).[5] Less frequently it occurs as a harbinger of AML in non-leukemic patients, or in association with myelodysplastic disorders or chronic myeloid leukemia (CML) with impending blast crisis.[1,2] In pediatric population, orbit is one of the most common sites of occurrence.[1]

The correct diagnostic assessment of orbital MS is challenging due to its uncommon presentation and to the high number of possible mimickers, by both clinical and radiological examination. Nevertheless, a prompt diagnosis is important especially in patients with a non-leukemic presentation, because AML-type chemotherapy and or allogeneic hematopoitic cell transplantation improves overall free survival.[6]

Herein we report two rare cases of orbital MS in a 2 young male patients without evidence of AML, detailing their magnetic resonance imaging (MRI) features and highlighting possible pitfalls and useful clues in neuroradiological differential diagnosis. A comprehensive literature review of all included reports were available from PubMed, PMC and MEDLINE database of references and abstracts.

Only pediatric-onset MS were included in the literature revision. Orbit involvement was considered positive when solid tissue was

* Corresponding author.
E-mail address: Dr.Mas-89@hotmail.com (M.A. AlSemari).

https://doi.org/10.1016/j.ajoc.2020.100806
Received 5 May 2020; Accepted 28 June 2020
Available online 11 July 2020
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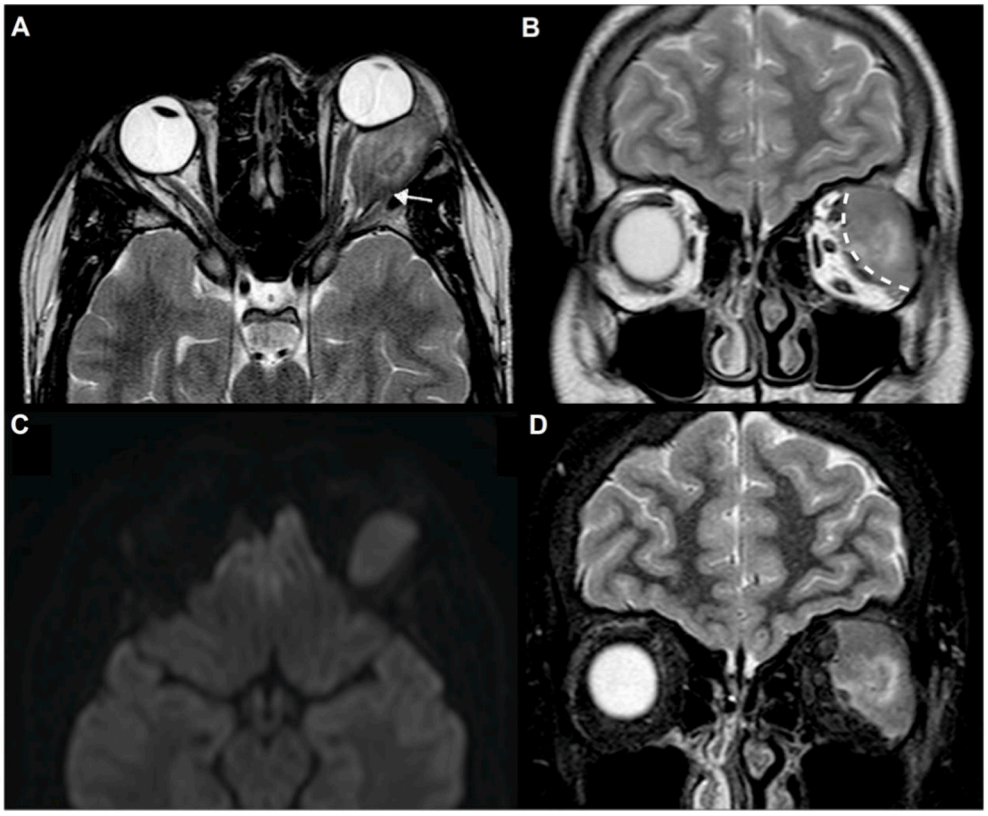

Fig. 1. Axial (a) and coronal (b–d) T2w images showing expansive extra-conal orbital lesion arising along the external border of superior and lateral rectus muscles and superior oblique muscle. The lesion presents mild hyperintensity with inhomogeneous core, and slightly restricted water diffusion on DWI (c) indicating hypercellularity. Extra-ocular muscles and optic nerve are displaced (*white dotted line*); marked left eye proptosis is also present. The lesion does not spear lacrimal gland that seems to be infiltrated (*not shown*); bony erosion and invasion of the lateral wall of the orbit are clearly visible (*white arrow*).

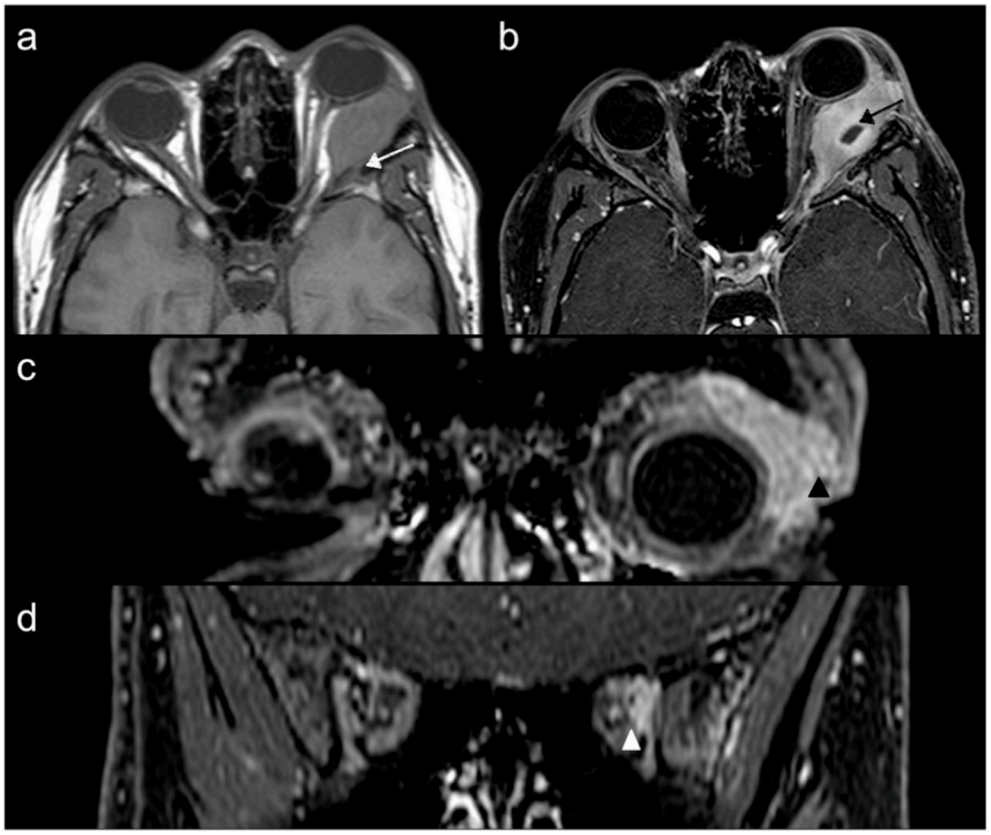

Fig. 2. Axial pre (a) and post-contrast (b) T1w showing lesion vivid enhancement and inner un-enhancing necrotic area (*black arrow*); the great wing of the sphenoid seems to be infiltrated (*white arrow*). Multi-planar reconstruction on coronal plane shows lesion extent from the lacrimal fossa of the frontal bone (c) (*black arrowhead*) to the orbital apex (d) (*white arrowhead*).

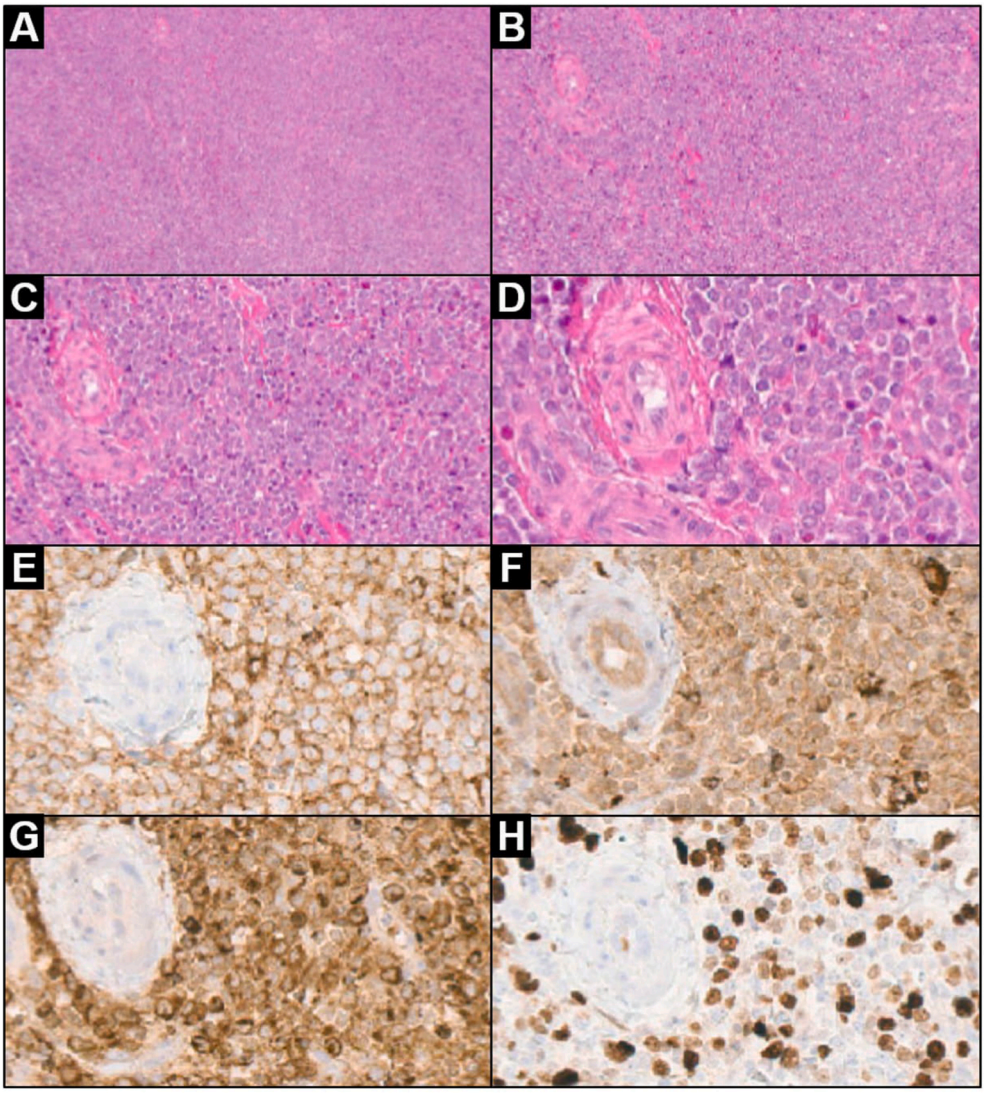

Fig. 3. Low and high magnification lesion histology after surgery: (a) low magnification showing a dense, diffuse infiltrate (H&E 4×); (b) the tumor consists of a cohesive proliferation of small/medium-sized cells (H&E 10×); (c) a discrete number of eosinophils are admixed with tumor cells (H&E 20×); (d) neoplastic cells show large oval nuclei, prominent nucleoli and poor cytoplasm (H&E 40×). Lesion immunophenotype: (e–g) neoplastic cells diffusely expressed CD45RO/LCA (anti-CD45RO/LCA, 40×), CD68 (anti-CD68, 40×) and myeloperoxidase (anti-MPO, 40×); (h) Ki-67 proliferative index is positive in about 50% of neoplastic cells (anti-Ki-67, 40×).
Legend: H&E = hematoxylin and eosin stain.

documented at CT/MRI examination within the orbital pyramid, independently of possible site of origin; association with AML or other myeloproliferative diseases (MDs) was considered positive both when myeloproliferative neoplasm preceded, co-occurred with or followed the diagnosis of MS. Publications in other languages than English and previous literature reviews have not been considered in this analysis.

2. Case 1

A caucasian 14-year-old boy came to the Orbital Pathology Department with one-month history of left eye upper and lower eyelid swelling, refractory to corticosteroid therapy. His previous ocular, personal and family history was negative. At physical examination eyelid edema, conjunctive hyperemia and inferior displacement of the left eye were detected, with exotropic deviation of about 2mm at Hirschberg test. Upright clinical exophthalmometry revealed a severe protrusion (33mm) of the left eyeball. At infrared oculography voluntary eye movements were unilaterally restricted in all directions, excepted for adduction that was preserved. Visual acuity on Early Treatment Diabetic Retinopathy Study chart rows and fundus examination were normal.

Ultrasonography revealed a well-circumscribed mass characterized by heterogeneous mild echogenicity, with moderate intra-lesional vascularity at doppler US, located in the upper and lateral quadrant of the orbit. MRI examination confirmed the presence of a supero-lateral extra-conal orbital mass (maximum diameters 38 × 20 × 37mm, approximate volume 10 cm^3) between the superior and lateral rectus muscles occupying in the lacrimal fossa (Fig. 1a and b). The lesion was isointense on T2w and slightly hyperintense on T2w images compared to muscle tissue, with restricted water diffusion on diffusion weighted imaging (DWI) indicating hypercellularity (Fig. 1c and d). Lacrimal gland was not clearly dissociable from the mass, and focal bony erosion and invasion of the lateral wall of the orbit were also noted (Fig. 2a, *white arrow*). After gadolinium injection the lesion presented with in homogeneous and vivid contrast enhancement with a small inner necrotic core (Fig. 2b–d, *black arrow*). Dynamic contrast-enhanced (DCE) MRI perfusion demonstrated fast contrast media wash-in and wash-out, highly suggestive for malignancy. The mass caused displacement without infiltration of adjacent muscles, as well as minimal dislocation of the optic nerve. A locally infiltrating solid tumor, possibly sarcomatous, was then hypothesized. The patient underwent left lateral orbitotomy for biopsy, and possibly lesion maximal resection. A whitish fish-flesh tumor with some internal hemorrhage compressing the adjacent structures was found, and a gross total tumor resection was carried out.

Pathological examination revealed a cohesive proliferation of small to medium-sized cells with large oval and often indented nuclei, prominent nucleoli and scant cytoplasm (myeloblast-like), mixed with a discrete number of eosinophils (Fig. 3a–d). Neoplastic cells expressed

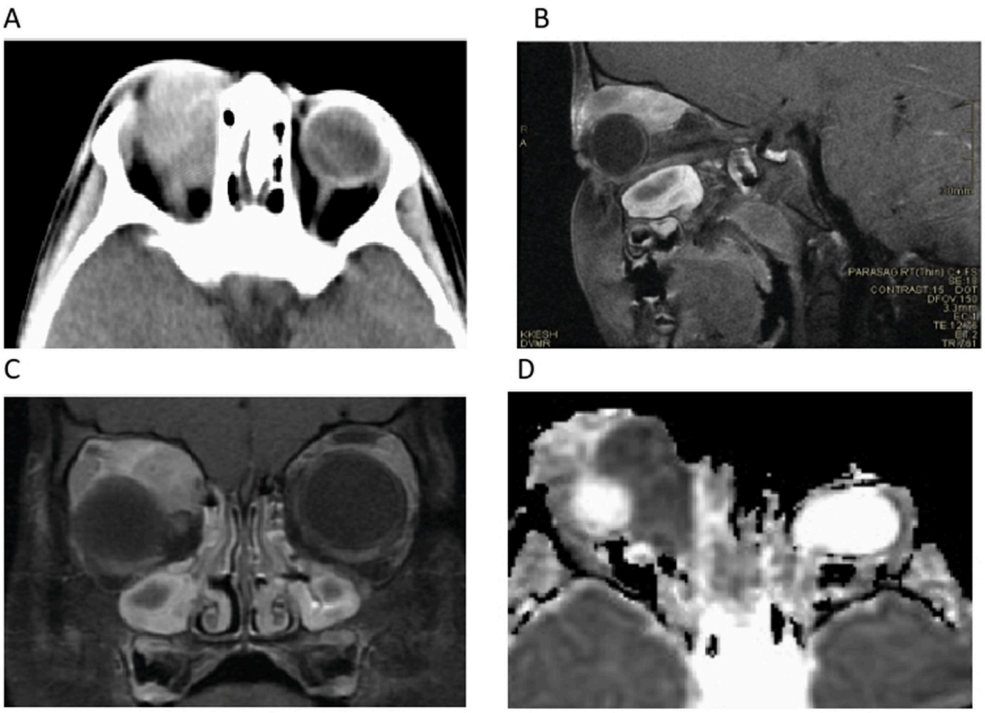

Fig. 4. Axial CT scan orbit (a) and sagittal T1 fat suppressed post contrast (b,c) and axial DWI (D) images showing solid lobulated extra-conal orbital lesion arising superiorly along the orbital roof and nasal infiltrating the recti muscles and superior oblique muscle. The lesion presents marked restricted water diffusion on DWI (c) indicating high degree of cellularity. The lesion abutting the lacrimal gland with no definite line of separation.

leucocyte common antigen (LCA/CD45RO), CD68 and myeloperoxidase (MPO); there was also a focal reactivity for CD34. Ki-67 staining was 50% (Fig. 3e–h). Final diagnosis was consistent with MS. Due to the common association with AML, blood sampling was collected to document the presence of altered white blood cell count; final results did not showed peripheral blood abnormalities. Bone marrow aspirate was negative for tumor infiltration.

After surgery followed by 1 month of induction chemotherapy according to European Leukemia Network recommendations for AML treatment, proptosis resolved and MRI demonstrated no evidence of residual and/or recurrent local disease. The patient is under clinical, laboratory and radiological follow-up with no sign of recurrence after one year from surgery.

3. Case 2

4 year old boy presented to Emergency room at King Khaled Eye Specialist Hospital with a growing mass in right upper lid over the last

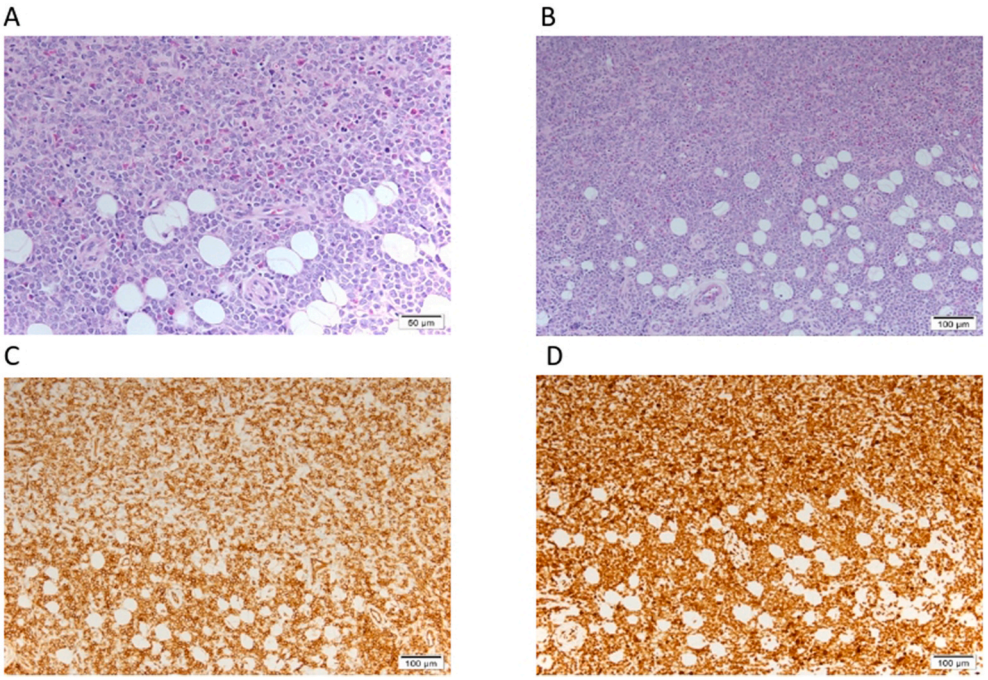

Fig. 5. Low and high magnification lesion histology after surgery: (a) high magnification showing a highly vascular soft tissue of poorly differentiated malignant cells infiltrating the adipose tissue with eosinophils (H&E 400×); (b) low magnification showing a dense, diffuse infiltrate (H&E 100×); (c) CD34 expression in neoplastic cells (CD34, ×100) (d) neoplastic cells diffusely expressed CD45RO/LCA (anti-CD45RO/LCA, 100×).
Legend: H&E = hematoxylin and eosin stain.

one month. He is medically free and his previous ocular, personal and family history was negative. On examination visual acuity in the right eye was 20/50 and left eye was 20/30. Extraocular muscle movement was full in both eyes. Pupil round, regular and reactive with no relative afferent pupillary defect on both sides. Examination grossly of the right eye showed well circumscribed upper and medial mass about 3 × 2 cm in size with smooth surface. It was hard in consistency but non-tender or mobile. The globe was displaced inferiorly with exotropia. The overlying skin was normal with no discoloration. Slit lamp examination showed normal anterior segment and fundus examination was unremarkable in both eyes.

MRI examination confirmed the presence of an extraocular solid mass involving the superior aspect of the right orbit with intermediate signal intensity on T1-weighted and T2-weighted image which was seen infiltrating and extending through the pre-septal into the post-septal part. It was a well-defined mass and measured approximately 3.5 × 2.4 cm in diameter with subsequent minimal displacement of the related part of the right globe. The mass lesion had marked restricted pattern on diffusion weighted image(ADC value equal to $0.475 \times 10^{(-3)}\,mm^{(2)}/sec$) (Fig. 4a–d). The mass was seen separated from the medial rectus muscle and abutting the superior rectus muscle and displacing the superior oblique with evidence of mild degree of prominent vascularities. There was no evidence of bony infiltration and no evidence of intraspinous nor intracranial extension. Rhabdomyosarcoma was clinically suspected. The patient underwent incisional biopsy which showed a yellow-grey mass.

Pathological examination revealed a highly vascular soft tissue of poorly differentiated malignant cells infiltrating the adipose tissue with few eosinophils suggestive of malignant orbital tumor in the right eye, The tumor cells expressed the following immunohistochemical markers: CD45, 34, 43, 117, Lysozyme, CD68 (KP1) and Myeloperoxidase indicating myeloid lineage but did not show expression of CD20 and CD3 (Fig. 5a–d).

Final diagnosis was consistent with MS and because of common association with AML, blood sampling was collected to document the presence of altered white blood cell count; final results was unremarkable except for below normal neutrophils. The patient referred to King Faisal Specialist Hospital and Research center and started systemic chemotherapy with a complete remission at 6 months follow up. At present, the patient is under clinical, laboratory and radiological follow-up with no sign of recurrence at four years from surgery.

4. Discussion

MS is a rare condition occurring in 2.5–9.1% patients with AML; it is characterized by the presence of one or more tumor masses in extramedullary sites such as bone, subcutaneous tissues, orbit, lymph nodes, gastro-intestinal tract and central nervous system[7] In pediatric population skin and orbit constituted the most common sites of invasion.[8] Scattered isolated cases of pediatric orbital MS have been described, frequently associated to a high misdiagnosis rate. Isolated orbital MS frequently exhibits clinical features mimicking inflammatory process or lymphoproliferative disease.[9–14] The most frequent manifestation is the unilateral exophthalmos; other possible signs include ptosis, painful lacrimal gland swelling, conjunctival mass, retinal hemorrhages, diffuse iris or uveal alterations.[8] We are presenting two cases with isolated orbital MS that were associated with dystopia.

Table 1
Summary of main findings described in current scientific literature on pediatric myeloid sarcoma (MS) with orbital involvement.

	n		%
Total Orbital MS Reports	243		100
No MDs	25		10.3
MDs	218		89.7
	AML	215	88.4
	CML	1	0.41
	Other	2	0.82
Risk factors	Absent	216	88.8
	Trauma	2	0.82
	Surgery	0	0
	Other	0	0

Legend: MS = Myeloid Sarcoma; MD = Myeloproliferative Disease; AML = Acute Myeloid Leukemia; CML = Chronic Myeloid Leukemia.

In patients whose anamnesis is positive for hematologic malignancies, the diagnosis of MS is relatively easy to evoke, while diagnosis of primary MS with no AML can be challenging[15] and imaging assessment become then crucial. In these cases, differential diagnosis with orbital infections and inflammations can be performed with the use of diffusion weighted and contrast-enhanced imaging techniques.[16–20] Other more challenging mimickers to be considered include vascular lesion, lymphoma (especially African Burkitt), metastatic neuroblastoma and rhabdomyosarcoma. Dynamic contrast-enhanced Computed Tomography (CT) or MRI can be very helpful in demonstrating the vascular nature of these lesions because of their progressive enhancement, starting from a small and generally central portion and then filling up the entire mass; eventually this enhancement pattern is typically associated to benign findings.[21] Orbital lymphoid tumors are rare in children, with the only exception of Burkitt lymphoma; in this setting, lymphoid tissue commonly shows lower apparent diffusion coefficient values compared to other neoplastic lesions.[21] Neuroblastoma metastases are not rare in pediatric population, but they are generally associated with important focal bony destruction and invasion of adjacent structures.[16] Rhabdomyosarcoma imaging features might be not clearly distinguishable from MS. Few clues may help the radiologist in correct assessment, such as a marked involvement of muscles that is not frequently observed in MS.[22]

It has been reported that orbital MS on CT appears as a well-defined mass, isodense or hyperdense to brain tissue, with homogeneous enhancement after contrast media injection. However, in some cases it can exhibit heterogeneous enhancing with non-enhancing areas corresponding to the inner necrotic areas, which is considered by some as a sign of rapid growth.[23] On MRI images, the orbital lesion appears isointense or slightly hypointense to the brain both on T1w and T2w images. With gadolinium contrast enhancement, it can present with a more or less homogeneous enhancement depending on the presence of necrotic areas within the mass. Associated bone marrow involvement and low signal intensity on T2w imaging may be helpful in differentiating these tumors from other lesions.[20,24] MRI has been proved to provide useful and more comprehensive information for lesion characterization compared to CT scan, avoiding any exposure to ionizing radiation.[19,20,25] In the first case the MRI showed mild hyperintensity on T2w images, with inhomogeneous core and slightly restricted water diffusion due to hypercellularity; vivid enhancement and inner un-enhancing necrotic area after contrast administration along with adjacent bone infiltration helped in differential diagnosis of malignancy (Figs. 1–2). While in the second case the solid mass lesion showed intermediate signal intensity on T1-weighted and T2-weighted image which was seen infiltrating and extending through the pre-septal into the post-septal part. Diffusion weighted image (DWI) demonstrating high signal at the site of the mass indicating restricted diffusion, likely reflecting increased cellularity (Fig. 4). Differential considerations include lymphoma, rhabdomyosarcoma or other malignant mass with high dense cellularity.[26]

However, despite the guidance given by an accurate neuroradiological examination, biopsy remains the only method for a final diagnostic assessment particularly in patients who develop granulocytic sarcoma in absence of a diagnosis of leukemia. In this study, immunohistochemical staining for myeloid markers, such as CD45RO/LCA (anti-CD45RO/LCA) CD68 (anti-CD68, and myeloperoxidase (anti-MPO) allowed the diagnosis. Cell surface markers including CD4, CD30, CD34, TdT, and glycophorin A are also useful for diagnosis of MS.[27] Among the

Table 2
Articles included in the literature review on Pediatric myeloid sarcoma (MS) with orbital involvement until 2019.

Author(s)	Year of Publication	Type of Study	N	Location	Key Findings	Unilateral/ Bilateral	Risk Factor	AML/ Other MDs	Type of Treatment	Prognosis
Lim et al.	2018 (Turkey)	Case report	1	Extra-conal	Multifocal involvement	Unilateral	NTR	AML	CT	Median remission 30 m
Cheng et al.	2018 (China)	Case report	1	Intra-conal	NTR	Unilateral	Trauma	Absent	CT + RT	Disease-free at 24 m follow up
Wang et al.	2018 (USA)	Case report	1	Sphenoid wing	Multifocal skeletal involvement	Unilateral	NTR	Absent	CT	NA
Gupta et al.	2017 (India)	Case report	1	Retro-conal	NTR	Unilateral	NTR	AML	CT	Relapse at 12 m follow up
Siraj et al.	2017 (India)	Case series	1	Extra-conal	NTR	Unilateral	NTR	AML	CT + RT	Disease-free at 18 m follow up
Qian et al.	2016 (USA)	Case report	1	Extra-conal	NTR	Unilateral	NTR	Absent	CT	NA
Mohanlal et al.	2016 (South Africa)	Case report	1	Extra-conal, peri-orbital	Glycophorin A positive	Unilateral	NTR	PEL	CT	NA
Huanh et al.	2015 (Taiwan)	Case report	1	Extra-ocular muscles	NTR	Bilateral	NTR	AML	CT	Disease-free at 12 m follow up
Karmegaraj et al.	2014 (India)	Case report	1	Peri-orbital	Flu-like onset	Bilateral	NTR	AML	CT	Disease-free at follow up
Aggarwal et al.	2014 (India)	Original article	23	Either intra- or extra-conal	NA	Unilateral	NA	23 AML	CT	Median remission 36 m
Thakur et al.	2013 (India)	Case report	2	NA; NA	NTR	Unilateral; Unilateral	NTR	2 AML	NA; NA	NA; NA
Dinand et al.	2013 (India)	Case report	1	Extra-conal, intra-conal	NTR	Unilateral	NTR	Absent	CT	Disease-free at 6 m follow up
Chaudhry et al.	2012 (Saudi Arabia)	Case report	1	Extra-conal	NTR	Unilateral	NTR	AML	CT	Disease-free at 10 m follow up
Johnston et al.	2012 (USA)	Original article	23	NA	15/23 CNS involvement	NA	NA	19 AML; 4 Absent	CT + RT	Remission at 12 m follow up
Isik et al.	2011 (Turkey)	Case report	2	Retroconal; Intra-conal,	NTR	Unilateral	NTR	2 Absent	CT; CT	Both disease-free at follow up
Baldwin et al.	2010 (USA)	Case report	1	Extra-conal	NTR	Unilateral	NTR	AML	CT + RT	Disease-free at 20 m follow up
Alkatan et al.	2008 (Saudi Arabia)	Case report	1	Extra-conal	NTR	Unilateral	NTR	Absent	NA	NA
Hmidi et al.	2007 (Tunisia)	Case report	1	Extra-conal	NTR	Unilateral	NTR	AML	CT	Disease-free at 24 m follow up
Janic et al.	2007 (Serbia)	Case report	1	NA	Kidney involvement	Bilateral	NTR	Absent	CT	NA
Choo et al.	2006 (USA)	Case report	1	Extra-conal	NTR	Unilateral	NTR	AML	NA	NA
Bhat et al.	2005 (India)	Case report	1	Extra-conal	NTR	Unilateral	Trauma	Absent	S + CT + RT	Relapse 3 m after treatment
Porto et al.	2004 (Germany)	Case series	3	Extra-conal; Extra- and intra-conal; Extra-conal	Previous neuroblastoma; NTR; NTR	Unilateral; Unilateral; Unilateral	NTR; NTR; NTR	3 AML	CT; CT; CT	Deceased few months from diagnosis; Remission; NA
Söker et al.	2003 (turkey)	Case report	1	Extra-conal	NTR	Bilateral	NTR	AML	NA	NA
Shields et al.	2003 (USA)	Case report	1	Extra-conal	NTR	Bilateral	NTR	AML	CT	Disease-free at 3 m follow up
Steinwexler et al.	2002 (USA)	Case report	1	Extra-conal	NTR	Unilateral	NTR	AML	CT	Disease-free at 1 m follow up
Bönig et al.	2002 (Germany)	Case report	1	Extra- and retro-conal	NTR	Unilateral	NTR	AML	CT + RT	Disease-free at 20 m follow up
Fisgin et al.	2002 (Turkey)	Case report	1	Extra- and intra-conal	PVB19 infection	Bilateral	NTR	AML	CT	Remission at follow up
Hung et al.	2002 (Taiwan)	Case report	1	Extra- and intra-conal	NTR	Bilateral	NTR	AML	CT	Disease-free at 19 m follow up
Bisschop et al.	2001 (NL)	Original article	35	NA	NA	NA	NA	35 AML	CT	NA
Uyesugi et al.	2000 (USA)	Case report	1	Extra- and intra-conal	NTR	Bilateral	NTR	AML	CT + RT	Deceased 1 m from diagnosis
Lakhkar et al.	2000 (India)	Case report	1	Extra-conal	NTR	Bilateral	NTR	NA	CT	Remission at follow up
Felice et al.	1999 (Argentina)	Original article	5	Either intra- or extra-conal	NA	NA	NA	5 AML	1 S + CT; 1 RT + CT; 3 CT	7 Remission at follow up; 1 Deceased within 1y from diagnosis
Puri et al.	1999 (UK)	Case report	1	Extra-ocular muscles	NTR	Unilateral	NTR	AML	CT	NA
Schwyzer et al.	1999 (South Africa)	Original article	9	All extra-conal and peri-orbital	NA		NA	9 AML	CT	

(*continued on next page*)

Table 2 (*continued*)

Author(s)	Year of Publication	Type of Study	N	Location	Key Findings	Unilateral/ Bilateral	Risk Factor	AML/ Other MDs	Type of Treatment	Prognosis
						Either unilateral or bilateral				8 Remission at follow up; 1 No Remission
Luckit et al.	1998 (UK)	Case report	1	Retro-conal	NTR	Unilateral	NTR	AML	CT	Disease-free at 42 m follow up
Tanigawa et al.	1998 (Japan)	Case report	1	Extra-conal	NTR	Unilateral	NTR	AML	CT	Remission at follow up
Stockl et al.	1997 (Canada)	Original article	7	NA	NTR	Unilateral	NTR	7 AML	CT	Remission at follow up
Girardot et al.	1996 (Morocco)	Case report	1	Extra-conal	NTR	Unilateral	NTR	AML	CT + RT	Disease-free at 36 m follow up
Hiçsönmez et al.	1996 (Turkey)	Case report	1	NA	NTR	Unilateral	NTR	AML	CT	Disease-free at 36 m follow up
Bulas et al.	1995 (USA)	Case report	1	Extra-conal	NTR	Bilateral	NTR	AML	CT	No remission al follow up
Pui et al.	1994 (USA)	Original article	31	NA	NA	NA	NA	30 AML; 1 CML	18 CT; 9 CT + RT; 3 S + CT; 1 S + RT + CT	16 Deceased 2.5–143.9 m from diagnosis; 15 Disease-free
Cavdar et al.	1993 (Turkey)	Case report	1	Intra-conal	NTR	Bilateral	NTR	AML	CT	Deceased 7 m from diagnosis
Cavdar et al.	1993 (Turkey)	Original article	10	Either intra- or extra-conal	NA	Either unilateral or bilateral	NA	10 AML	CT	NA
Kalmanti et al.	1991 (Greece)	Case report	2	Retroconal; Extra-conal	NTR	Unilateral; Unilateral	NTR	2 AML	CT; CT	Disease-free at 8y follow up; Deceased 2y from diagnosis
Banna et al.	1991 (Saudi Arabia)	Case series	4	Either intra- or extra-conal	NTR	2 Unilateral; 2 Bilateral	NTR	4 AML	CT + RT	NA
Cavdar et al.	1989 (Turkey)	Original article	33	Either intra- or extra-conal	NA	17 Bilateral; 16 Unilateral	NA	21 AML; 12 Absent	CT	All deceased within 20 m from diagnosis
Davis et al.	1985 (USA)	Case report	1	Extra-ocular muscles	CNS involvement	Unilateral	NTR	AML	CT	Remission at follow up
Rajantie et al.	1984 (Finland)	Case report	1	Extra-conal	NTR	Unilateral	NTR	AML	S + CT	Deceased 11 m from diagnosis
Cavdar et al.	1978 (Turkey)	Original article	20	NA	NA	11 Unilateral; 9 Bilateral	NA	20 AML	CT	Median remission 9 m

Legend: N = Number of patients; AML = Acute Myelocytic Leukemia; MDs = Myelodysplastic Disease; NTR = Nothing To Report; CT = Chemotherapy; RT = Radiotherapy; S = Surgery NA = Not Available; PEL = Pure Erythroid Leukemia; CNS = Central Nervous System.

various markers, MPO, lysozyme, and CD68 are the most sensitive and essential markers for myeloid differentiation in addition to molecular genetic.[22,28]

Alkatan and Chaudhry,[29] documented that FISH using the DNA probe for t(8; 21) was positive in only 2% of the cells, which was significant for the diagnosis and expected prognosis since the finding of such translocation is expected to be associated with higher chance for the development of systemic leukemia.

When comparing our observation to current literature reports, out of the 243 cases reported from 1978 to present time (Table 1), around 10% patients ($n = 25$) presented with an isolated lesion with no evidence of AML. Indeed, the majority ($n = 218$) were preceded, accompanied or followed by the evidence of generalized hematopoietic malignancies. Interestingly, two isolated cases had history of orbital trauma preceding the onset,[21] proposed to be a possible trigger event for the onset of this type of malignancy; however, further evidences need to be collected to verify this hypothesis. A more detailed description of literature review in term of location of orbital mass, key finding, laterality, risk factor, association with acute myelocytic leukemia and myelodysplastic disease, type of treatment and prognosis on pediatric myeloid sarcoma is provided in (Table 2).

Since orbital MS has been generally thought to be an antecedent disease entity able to evolve into AML, treatment strategies have been mainly focused on inducing a remission to prevent evolution to AML: isolated MS left untreated, commonly evolves into AML within 1 year.[23] Regarding therapeutic options, due to tumor rarity, no universal consensus on the best treatment planning has yet been reached and no unified protocol has been identified. Out of 6 patients with isolated orbital MS who initially received high-dose methylprednisolone treatment, followed by the Acute Myeloid Leukemia-Berlin Frankfurt Munster 2004 treatment protocol, 2 (33.3%) later developed AML; on the other hand, out of 12 patients with isolated MS who received only external beam radiotherapy, 11 (91.7%) developed AML during the follow-up period.[30]

Lee et al. reported that 22.2% of patients with isolated MS who had undergone only local treatment (such as surgery and/or local radiotherapy) did not progress to AML, particularly with a complete remission durations of 1.8 months whose treatment was surgery alone and 83.9 months for those who received radiotherapy; at the same time these Authors also reported that, in contrast, 44.4% of patients who received systemic chemotherapy treatment had evolved to AML within a median time of 13.4 months.[5] Tsimberidou et al. reported a review of 20 cases of non-leukemic MS in which the combined treatment with chemotherapy and radiotherapy resulted in better survival than chemotherapy alone.[31] Therefore local treatment, such as surgery or radiotherapy, might play an important role in controlling primary disease and relieving symptoms, without significant toxicity and additional risk of evolution into AML.[32,33] Nevertheless, although the number of isolated orbital lesions is very limited and the treatment results reported in literature are still confusing, it seems that combining systemic and local treatment for patients with isolated orbital MS might be a more promising therapeutic strategy to achieve complete remission compared with any other

treatment alone. In this light, after gross surgical resection the first patient received systemic chemotherapy with complete remission at one-year follow-up and the second patient received a systemic chemotherapy with complete remission at 6 months follow-up and disease free at four years follow up.

5. Conclusion

MS generally occurs in patients with AML, but it can also occasionally precede myeloproliferative disorders within a matter of months in patients with no evidence of hematological disease at the time of bone marrow aspiration and biopsy at the initial diagnosis (isolated, primary or non-leukemic MS). Particularly in these patients, a prompt diagnosis of MS is essential to the most effective clinical management, because conventional AML-type chemotherapy and or allogeneic hematopoitic cell transplantation improves overall free survival. In this light it is important to recognize the few radiological features that can guide the radiologist in differentiating orbital MS from other pediatric orbital masses. Eventually the use of multi-planar and multi-parametric MRI, with particular reference to diffusion weighted and contrast-enhanced sequences, may be crucial to the purpose.

Patient consent

The patient(s)/patient's legal guardian consented to publication of the case in writing/orally.

Funding

No funding or grant support.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Declaration of competing interest

The following authors have no financial disclosures (MP, MA, CR, HA, AM, SE, RM, MM, AE, LR, RC, DS).

Acknowledgements

The author thanks King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia, for financial support.

References

1. Guermazi A, Feger C, Rousselot P, et al. Granulocytic sarcoma (chloroma): imaging findings in adults and children. *AJR*. 2002;178(February):319–325.
2. Lee B, Fatterpekar GM, Kim W, Som PM. Granulocytic sarcoma of the temporal bone. *AJNR*. 2002;23(October):1497–1499.
3. Maka E, Lukáts O, Tóth J, Fekete S. Orbital tumour as initial manifestation of acute myeloid Leukemia : granulocytic sarcoma: case report. *Pathol Oncol Res*. 2008;14:209–211. https://doi.org/10.1007/s12253-008-9028-x.
4. Thakur B, Varma K, Misra V, Chauhan S. Granulocytic sarcoma presenting as an orbital mass: report of two cases. *J Clin Diagn Res*. 2013;7(8):1704–1705. https://doi.org/10.7860/JCDR/2013/5582.3260.
5. Lee JY, Chung H, Cho H, et al. Clinical characteristics and treatment outcomes of isolated myeloid sarcoma without bone marrow involvement: a single-institution experience. *Blood Res*. 2017;52(3):184–192.
6. Bitan M, He W, Zhang M, et al. Transplantation for children with acute myeloid leukemia: a comparison of outcomes with reduced intensity and myeloablative regimens. *Blood*. 2014;123(10):1615–1620.
7. Pileri SA, Ascani S, Cox MC, et al. Myeloid sarcoma: clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients. *Leukemia*. 2007;21:340–350. https://doi.org/10.1038/sj.leu.2404491.
8. Samborska M, Derwich K, Skalska-Sadowska J, Kurzawa P, Wachowiak J. Myeloid sarcoma in children – diagnostic and therapeutic difficulties. *Contemp Oncol*. 2016;20(6):444–448. https://doi.org/10.5114/wo.2016.65602.
9. Cavazza S, Bocciolini C, Laudadio P, Tassinari G, Dall'Olio D. Two anomalous localizations of mucocele: clinical presentation and retrospective review. *Acta Otorhinolaryngol Ital*. 2007;27:208–211.
10. Kiratli H, Sekeroglu MA, Tezel GG. Orbital heterotopic glial tissue presenting as exotropia. *Orbit*. 2008;27:165–168. https://doi.org/10.1080/01676830701523889.
11. Strianese D, Elefante A, Matarazzo F, Panico A, Ferrara M, Tranfa F. Orbital lymphoma mimicking lacrimal gland pleomorphic adenoma. *Case Rep Ophtalmol*. 2013;4:109–113. https://doi.org/10.1159/000354963.
12. Chirapapaisan N, Chuenkongkaew W, Pornpanich K, Vangveeravong S. Orbital pseudotumor: clinical features and outcomes. *Asian Pac J Allergy Immunol*. 2007;25(4):215–218.
13. Strianese D, Piscopo R, Elefante A, et al. Unilateral proptosis in thyroid eye disease with subsequent contralateral involvement: retrospective follow-up study. *BMC Ophthalmol*. 2013;13(21).
14. Ugga L, Stilo S, Napolitano P, et al. Orbitofrontal cholesterol granuloma: case report and review of the literature. *Quant Imaging Med Surg*. 2017;7(3):373–377. https://doi.org/10.21037/qims.2017.04.04.
15. Yilmaz AF, Saydam G, Sahin F, Baran Y. Granulocytic sarcoma: a systematic review. *Am J Blood Res*. 2013;3(4):265–270.
16. Ahmed S, Goel S, Khandwala M, Agrawal A, Chang B, Simmons I. Neuroblastoma with orbital metastasis: ophthalmic presentation and role of ophthalmologists. *Eye*. 2006;20:466–470. https://doi.org/10.1038/sj.eye.6701912.
17. Jakobiec FA. Granulocytic sarcoma. *AJNR*. 1991;12(March/April):263–264.
18. Noh BW, Park S, Chun J, Kim JH, Kim HJ, Lim MK. Granulocytic sarcoma in the head and neck: CT and MR imaging findings. *Clin Exp Otorhinolaryngol*. 2009;2(2):66–71. https://doi.org/10.3342/ceo.2009.2.2.66.
19. Tortora F, Prudente M, Cirillo M, et al. Diagnostic accuracy of short-time inversion recovery sequence in Graves' ophthalmopathy before and after prednisone treatment. *Neuroradiology*. 2014;56(5):353–361. https://doi.org/10.1007/s00234-014-1332-4.
20. Purohit BS, Vargas MI, Ailianou A, et al. Orbital tumours and tumour-like lesions: exploring the armamentarium of multiparametric imaging. *Insights Imaging*. 2015. https://doi.org/10.1007/s13244-015-0443-8.
21. Chung EM, Smirniotopoulos JG, Specht CS, Schroeder JW, Cube R. From the archives of the AFIP pediatric orbit tumors and tumorlike lesions: nonosseous lesions of the extraocular orbit. *Radiographics*. 2007;27(6):1777–1800.
22. Alexiev BA, Wang W, Ning Y, et al. Myeloid sarcomas: a histologic, immunohistochemical, and cytogenetic study. *Diagn Pathol*. 2007;42(2):1–8. https://doi.org/10.1186/1746-1596-2-42.
23. Yamauchi K, Yasuda M. Comparison in treatments of nonleukemic granulocytic sarcoma. Report of two cases and a review of 72 cases in the literature. *Cancer*. 2002;94(6):1739–1746. https://doi.org/10.1002/cncr.10399.
24. Hakyemez B, Yildirim N, Taskapilioglu O, et al. Intracranial myeloid sarcoma: conventional and advanced MRI findings. *Br J Radiol*. 2007;80(June):109–112. https://doi.org/10.1259/bjr/16630393.
25. Comerci M, Elefante A, Strianese D, et al. Semiautomatic regional segmentation to measure orbital fat volumes in thyroid-associated ophthalmopathy. A validation study. *Neuroradiol J*. 2013;26(4):373–379. https://doi.org/10.1177/197140091302600402.
26. Razek AA, Elkhamary S, Mousa A. Differentiation between benign and malignant orbital tumors at 3-T diffusion MR-imaging. *Neuroradiology*. 2011;53:517–522.
27. Campidelli C, Agostinelli C, Stitson R, Pileri SA. Myeloid sarcoma. Extramedullary manifestation of myeloid disorders. *Am J Clin Pathol*. 2009;132:426–437. https://doi.org/10.1309/AJCP1ZA7HYZKAZHS.
28. Janečková V, Semerád L, Ježíšková I, et al. Molecular genetic testing for acute myeloid leukemia. *Klin Onkol*. 2016;29(6):411–418.
29. Alkatan H, Chaudhry I. Myeloid sarcoma of the orbit. *Ann S Med*. 2008;28(6):461–465.
30. Aggarwal E, Mulay K, Honavar SG. Orbital extra-medullary granulocytic sarcoma: clinicopathologic correlation with immunohistochemical features. *Surv Ophthalmol*. 2014;59(2):232–235. https://doi.org/10.1016/j.survophthal.2013.06.004.
31. Tsimberidou A, Kantarjian HM, Estey E, et al. Outcome in patients with nonleukemic granulocytic sarcoma treated with chemotherapy with or without radiotherapy. *Leukemia*. 2003;17:1100–1103. https://doi.org/10.1038/sj.leu.2402958.
32. Antic D, Elezovic I, Milic N, et al. Is there a "'gold'" standard treatment for patients with isolated myeloid sarcoma? *Biomed Pharmacother*. 2013;67(1):72–77. https://doi.org/10.1016/j.biopha.2012.10.014.
33. Bakst R, Wolden S, Yahalom J. Radiation therapy for chloroma (granulocytic sarcoma). *Int J Radiat Oncol Biol Phys*. 2012;82(5):1816–1822. https://doi.org/10.1016/j.ijrobp.2011.02.057.