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Original Article

Histiocytic lesions of the orbit: A study of 9 cases

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Abstract

Purpose: To describe the clinical presentation, treatment, and outcome of patients with histiocytic lesions of the orbit.
Methods: Retrospective study of 9 patients treated and followed up between October 2001 and January 2018.
Results: Eight patients in our series were males and one patient was female. The mean age at presentation was 16.8 years (range, 1 to 42 years). All patients had unilateral disease. The most common presenting complaint was upper eyelid swelling in 8 of 9. All patients underwent preoperative computed tomography (CT) and magnetic resonance imaging (MRI). Eight of 9 patients demonstrated orbital bone erosion with adjacent soft tissue mass. Destruction of the orbital roof and contrast enhancement of dura were detected in 3 cases. All cases underwent orbitotomy and subtotal tumor excision with additional bone curettage (4 cases) and intraorbital steroid (40 mg triamcinolone acetonide) injection (3 cases). Adjuvant systemic chemotherapy consisting of vinblastine and prednisone was administered in 3 cases with dural involvement. External radiotherapy (1000 cGy) was applied in one case because of widespread disease. Histopathologic diagnoses were eosinophilic granuloma (7 cases), necrotic xanthogranuloma (1 case), and Langerhans cell sarcoma (1 case). The mean follow-up period after diagnosis was 19.7 months (range, 1–96 months). There was no systemic or multifocal bone involvement in eosinophilic granuloma cases at initial presentation and follow-up. None of these patients developed diabetes insipidus or neurologic symptoms. The patient with Langerhans cell sarcoma died from systemic disease 1 month after diagnosis of the orbital tumor. The patient with necrotic xanthogranuloma did not develop any malignancy at 9 months follow-up.
Conclusions: Eosinophilic granuloma was the most frequently encountered orbital histiocytic lesion in our series. Eosiophilic granuloma usually responded well to subtotal tumor excision, bone curettage, and intraorbital corticosteroid injections. Systemic chemotherapy was used in cases with full thickness bone destruction and adjacent dural enhancement in an effort to prevent the development of central nervous system disease.

Keywords: Eye, Orbit, Langerhans cell histiocytosis, Necrotic xanthogranuloma, Langerhans cell sarcoma, Eosinophilic granuloma, Intralesional steroids, Chemotherapy, External beam irradiation

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Introduction

Histiocytic disorders are a group of diseases that occur when there is an over-production of white blood cells known as histiocytes that can lead to organ damage and tumor formation. Histiocytic disorders are made up of a wide variety of conditions that can affect both children and adults.[1,2] In 1987, the Histiocyte Society classified these disorders into three groups based on the types of histiocyte cells involved.[3] The first group is called a dendritic cell disorder, and the most common disease in this group is Langerhans cell histiocytosis (LCH). (www.histo.org) Also included in this dendritic cell group are more rare diseases of non-Langerhans cell histiocytosis including juvenile xanthogranuloma (JXG), necrotic xanthogranuloma (NXG), and Erdheim-Chester Disease (ECD). The second group is called a macrophage cell disorder, and includes primarily hemophagocytic lymphohistiocytosis (HLH) and Rosai-Dorfman Disease (RD). The third group is

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called malignant histiocytosis and includes certain kinds of leukemia and malignant tumors such as Langerhans cell sarcoma (LCS). (www.histo.org) In this report, the clinical features and treatment results of 9 orbital histiocytic lesions seen at a tertiary referral center are reported.

Materials and methods

We retrospectively reviewed the clinical and histopathology records of orbital histiocytic lesions managed on the Ocular Oncology Service from October 2001 to January 2018. Histopathologically confirmed cases of orbital histiocytosis were included. Institutional ethics committee approval was obtained and informed consent was available for all cases.

Medical records were analyzed for age at presentation, gender, laterality, symptoms, duration of symptoms, clinical features, radiological features, treatment methods, histopathological diagnosis, and outcome. Computed tomography (CT) and magnetic resonance (MR) images of the orbit were reviewed. All cases underwent anterior orbitotomy to obtain tissue diagnosis. The tumor was debulked with bone curettage and intralesional steroid triamcinolone acetonide (40 mg/ml) injection as necessary. In cases with full thickness destruction of the upper orbital wall and adjacent dural enhancement on MRI, systemic chemotherapy consisting of vinblastine and prednisone was given to prevent central nervous system (CNS) disease. Cases with extensive disease or those in which repeat orbital imaging failed to disclose any resolution were considered for low-dose (1000 cGy) orbital external beam radiotherapy (EBRT). All cases underwent systemic work-up including, complete blood count, chest radiograph, abdominal ultrasound, ultrasonography, and bone scan at initial diagnosis. Repeat systemic evaluation was done by the pediatric or medical oncologist as necessary during follow-up.

Results

A total of 9 patients were included. Patient demographics, clinical features, treatment results, and follow-up are depicted in Table. Eight patients were males and one was female. The mean age at presentation was 19.7 months (range, 1–96 months). All patients had unilateral disease with the right orbit being involved in 6 and left orbit in 3 patients. The presenting complaints included swelling in the upper eyelid (n = 8) (Fig. 1a), proptosis (n = 1), and redness of the upper eyelid (n = 1). The mean duration of symptoms was 6 weeks (median, 3 weeks; range 2–20 weeks). There was no history of trauma, systemic illness, or neurological symptoms in any of the cases. At presentation, inferior globe displacement was seen in 3 cases. A palpable mass lesion was documented in the superior orbit in 2 cases. There was no regional lymphadenopathy. Differential diagnosis included dermoid cyst, rhabdomyosarcoma, metastatic neuroblastoma, and lacrimal gland malignant epithelial neoplasm.

Computed tomography (CT) and/or magnetic resonance imaging (MRI) was done in each case and revealed a superiorly located well defined heterogenous mass with bony erosion involving frontal bone in 6 patients, sphenoid in 1 patient, and frontal and ethmoid in 1 patient (Figs. 1b, c, 2a). Destruction of the orbital roof and adjacent dural enhancement on MRI was seen in 3 patients (Figs. 1b, 1c). The patient with NXG presented with an indurated hard nodule on the upper eyelid and CT showed anterior orbital involvement as well. There was no bone involvement in this patient. The patient with LCS had a diffuse orbital tumor with an epicenter in the inferior orbit and there was also no orbital bone involvement in this patient as well.

All patients underwent anterior orbitotomy via skin approach. An extraperiosteal approach was preferred but this was not possible in many cases with bone destruction. Four cases received bone curettage because of the remaining irregular protruding bone fragments found during orbitotomy. Three cases were given intralesional steroid in the same sitting after debulking the tumor mass. No postoperative complications were noted. Complete resolution of symptoms was seen in all cases except for one case with extensive disease which was treated using external beam radiotherapy (1000 cGy). Three patients having destruction of the orbital roof with enhancement of adjacent dura on MRI were given systemic chemotherapy consisting of vinblastine and prednisone. These 3 patients were followed up for a mean of 20.3 (range 3–54) months. After orbitotomy and tumor biopsy, the patient with NXG underwent systemic evaluation but was negative for paraproteinemia and other hematologic abnormalities. The patient did not accept further treatment and was lost to follow-up after 9 months.

Histopathologic diagnoses were eosinophilic granuloma (7 cases), necrotic xanthogranuloma (1 case) and Langerhans cell sarcoma (1 case). Systemic workup was negative in 8 cases except for the case with Langerhans cell sarcoma. There was no evidence for multifocal involvement in LCH cases (Fig. 2b). The patient with Langerhans cell sarcoma died from systemic disease 1 month after ocular diagnosis and almost 1.5 years after initial diagnosis despite intensive systemic chemotherapy. The mean follow-up period after surgery was 19.7 months (range, 1–96 months) (Figs. 1d, 2c). The final mean visual acuity was 0.007 logMAR (0.00–0.05). All patients or their families were contacted by phone at the time of the writing of this manuscript. Their eye and systemic status were updated and they were asked to send in any pertinent medical documents relating to their condition. The mean follow-up from initial diagnosis to the last phone contact was 103.2 (range: 33–194) months. None of the patients had local recurrence nor developed diabetes insipidus or neurologic symptoms during follow-up.

Gross examination of the excised material showed yellowish-white mass with necrotic appearance in all cases. Histopathologic examination revealed Langerhans cells, eosinophils, and histiocytes with multinucleated giant cells composing a polymorphous granulomatous inflammatory reaction. There were also neutrophils and lymphocytes. The Langerhans cells stained positive with CD1a and S-100 protein immunohistochemically while the histiocytes were CD68 positive. In the case with necrotic xanthogranuloma, histopathological examination showed foamy histiocytes palisading around areas of necrobiotic collagen, fibrosis, Touton giant cells, and lymphocytes. The lipid containing cells did not stain with S-100. The case with Langerhans cell sarcoma exhibited additional cytological markers for malignancy including atypia, nuclear grooving, hyperchromatic nuclei, and prominent nucleoli.

Table. Patient demographics, clinical features, treatment and follow-up in 9 patients with orbital histiocytic tumors.

Case No	Age/ Sex	Laterality	Symptoms	Localization in Orbit	Bone Erosion	Systemic Involvement	Intralesional steroid	Chemotherapy	External Radiotherapy	Follow up[a] (months)	Status
1	1/F	Right	Upper eyelid swelling	Superior	+	–	–	–	–	177	Alive
2	4/M	Right	Upper eyelid swelling	Supero temporal	+	–	–	–	–	33	Alive
3	5/M	Left	Upper eyelid swelling	Superior	+	–	+	+	–	54	Alive
4	9/M	Left	Upper eyelid swelling and redness	Supero temporal	–	–	–	–	–	95	Alive
5	9/M	Left	Upper eyelid swelling	Superior	+	–	–	–	–	145	Alive
6	17/M	Right	Upper eyelids swelling, diplopia	Supero temporal	+	–	+	+	+	117	Alive
7	24/M	Right	Upper eyelid swelling	Superior	+	–	+	+	–	55	Alive
8	41/M	Right	Upper eyelid swelling and redness	Supero nasal	+	+	–	+	–	1	Deceased
9	42/M	Right	Double vision while looking up	Superior	+	–	–	–	–	194	Alive

M: Male, F: Female.
[a] Follow-up as determined by last phone contact.

Discussion

Orbital histiocytic lesions comprise a heterogenous group of disorders ranging from eosinophilic granuloma to Langerhans cell sarcoma. The most frequent lesion among orbital histiocytic lesions is LCH. The term LCH incorporates a group of diseases that includes the acute disseminated form (Letterer-Siwe disease) and the chronic forms including eosinophilic granuloma and Hand-Schüller-Christian disease.[3]

Eosinophilic granuloma is the most frequent form of LCH, accounting for approximately 70% of all LCH cases.[4] The lesion is usually located in the superotemporal quadrant of the orbit. It is usually unilateral and unifocal. Rarely, eosinophilic granuloma can be bilateral and the opposite orbit usually becomes involved months after the diagnosis of the first tumor. Patients often present with progressive upper eyelid swelling and erythema with proptosis and localized tenderness. It is believed that transient immune dysfunction may induce the cytokine-mediated proliferation of pathologic Langerhans cells within the bone marrow of the anterolateral frontal bone, which is the only area of bone that still contains bone marrow. These cells cause osteolysis through elaboration of interleukin-1 and prostaglandin.[5] Hence, bone destruction with soft tissue expansion is seen in almost all cases of eosinophilic granuloma. Hand–Schuller–Christian (HSC) disease represents the multifocal variant of eosinophilic granuloma. The classic triad consisting of bilateral proptosis and diabetes insipidus in addition to multiple punched-out lesions in the cranial bones is rarely seen in HSC disease. The Letterer–Siwe variant is a fulminant systemic disease characterized by hepatosplenomegaly, lymphadenopathy and osseous defects. Orbital involvement rarely occurs in this form.[3] Orbital CT and MRI show a bone destructive orbital mass in eosinophilic granuloma. The lesion may extend into the cranial cavity through destruction of the superior orbital wall as occurred in 3 of our cases.

In the early stages, the lesion appears as an irregular radiolucent area of expanding bone. It usually affects the zygomatic and/or frontal bones. On MRI, the tumor is isointense to hyperintense with respect to muscle on T1-W images and hyperintense on T2-W images and shows marked contrast enhancement.[5] Based on the radiologic appearance, the differential diagnosis of eosinophilic granuloma includes a ruptured dermoid cyst, rhabdomyosarcoma, malignant lacrimal gland tumors, and metastatic neuroblastoma.

Earlier studies postulated that LCH was not a true neoplasm but an atypical proliferation of monoclonal cell population.[6] However, there is an increasing evidence that LCH actually represents myeloid neoplasia with a prominent inflammatory component.[7,8] Badalian-Very et al. studied 61 LCH specimens and demonstrated presence of monoclonal Langerhans cells with oncogenic BRAF V600E mutation in 35 (57%) specimens suggesting that LCH represents a myeloid neoplasia.[8] It is presumed that the lesions in LCH expand by local proliferation of neoplastic Langerhans cells.[9] These new insights have changed the view on LCH and help in partly understanding its pathogenesis; however, the lesion is still mostly benign.[10]

Corticosteroids act in LCH by inhibiting the release of Prostaglandin E2 and Interleukin-1.[5] Harris et al. reported that in a series of 6 cases with unifocal orbital LCH, complete tumor resolution was achieved in 4 cases with subtotal curettage and intralesional steroid injection only.[5] Nonorbital LCH involving bone also responds well to intralesional steroids. Yasko et al. reported a series of 35 cases of nonorbital LCH, and showed that complete response was achieved in 89% cases with one intralesional injection and in 100% cases with two or more injections.[11] In our series, LCH usually responded well to subtotal tumor excision, bone curettage, and intraorbital corticosteroid injections although the individual contribution of each treatment component to the favorable outcome remains unproven. Rare cases of spontaneous resolution of unifocal orbital disease have also been reported.[12] There is an increasing interest towards management of LCH with targeted treatment strategies of MAPK pathway inhibition especially in patients with severe life-threatening LCH.[13]

Orbital involvement with bone destruction and involvement of adjacent dura/CNS by LCH has been postulated as a risk factor for developing LCH-CNS disease, characterized by diabetes insipidus and neurologic symptoms.[10,14,15] As per the guidelines of Histiocyte Society, prophylactic systemic chemotherapy is recommended in cases with multisystem involvement of high-risk organs like liver, spleen,

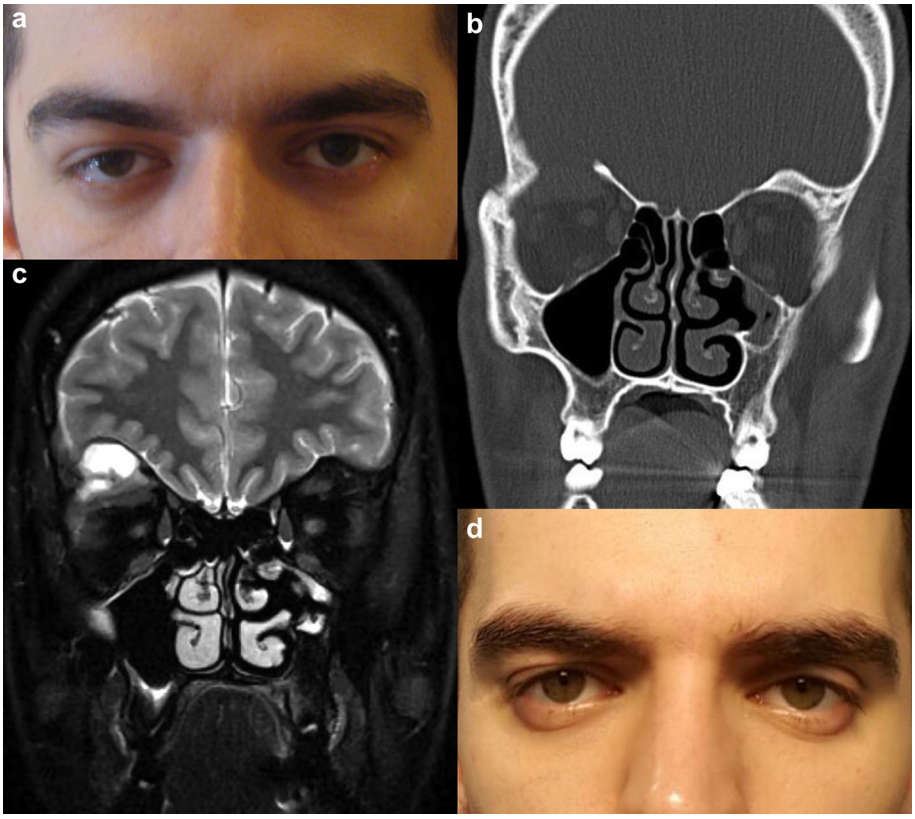

Fig. 1. 24-year-old man with eosinophilic granuloma of the right orbit. (a) Facial photograph shows right upper eyelid edema of 2 months duration. (b) Coronal orbital computed tomography shows an extraconal soft tissue mass measuring 20 × 15 mm in size, compressing the eyeball and destroying the right orbital roof. (c) Coronal magnetic resonance imaging shows upper orbital mass causing destruction of the orbital roof with dural thickening and contrast enhancement. (d) Facial photograph at 3 years follow-up status post orbitotomy, tumor excision, bone curettage, intralesional steroid injection, and systemic chemotherapy (vinblastin + prednisone) shows no residual disease.

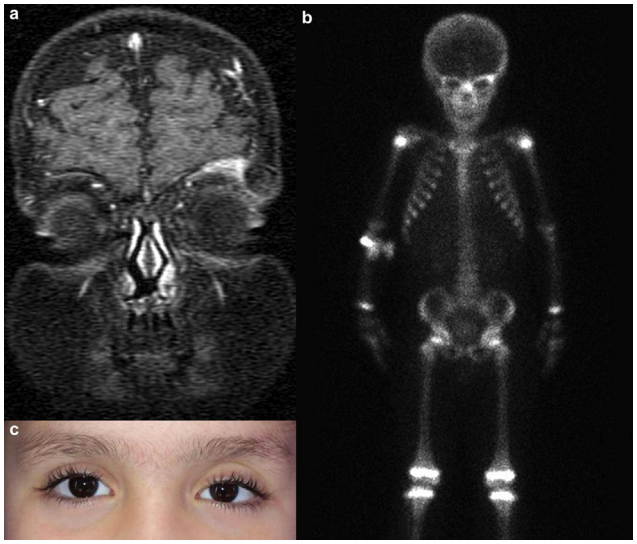

Fig. 2. 5-year-old boy with eosinophilic granuloma of the left orbit. (a) T1 weighted magnetic resonance imaging shows a 16 × 10 mm lesion affecting the upper wall of the left orbit with contrast enhancement after gadolinium injection. (b) Whole body bone scintigraphy shows increased focal osteoblastic activity in the upper lateral aspect of the left orbit. (c) Facial photograph at 3 years follow-up status post orbitotomy, subtotal tumor excision, and systemic chemotherapy shows no residual or recurrent disease.

lungs and skull/orbital bones.[10,14,15] In the LCH III study, all cases that developed diabetes insipidus had orbital involvement with multisystem disease.[10,14,15] In this study, the lesions in the orbital bones with intracranial soft tissue extension were regarded as ''central nervous system (CNS)-risk'' lesions and thus mandated systemic chemotherapy.[10,14,15] However, other reports suggest that unifocal osteolytic lesions that arise in the anterolateral frontal bone with spillover into the intracranial cavity, usually undergo complete resolution after relatively minor local intervention, without the need for systemic chemotherapy.[16,17] In our study, we followed the suggested guidelines and 3 of our patients with bone destruction and adjacent dural involvement underwent systemic chemotherapy consisting of vinblastine and prednisone. As this is not a controlled study, the point as to whether systemic chemotherapy had an effect on preventing the development of LCH-CNS tumor remains uncertain. However, none of these 3 patients developed CNS complications or diabetes insipidus during the mean follow-up period of 20.3 (range, 3–54) months.

Repeated intralesional corticosteroids (triamcinolone acetonide) have also been found to be useful in resolving eyelid/orbital disease in necrotic xanthogranuloma. However, intralesional corticosteroids have no effect on the associated hematologic abnormalities including paraproteinemia and leukopenia and on the subsequent development of lympho-

proliferative disorders and multiple myeloma in these patients.

The treatment options for disseminated disease such as Letterer-Siwe disease and malignant histiocytosis include systemic chemotherapy, bone marrow transplantation, and immunoglobulin therapy.[18,19] Our patient with LCS succumbed to death within 1 month after ocular diagnosis almost 1.5 years after initial diagnosis despite intensive systemic chemotherapy. Due to the rarity of LCS, no standard treatment with good efficacy has been suggested to date especially in cases with orbital involvement.[20] Complete or subtotal tumor resection should be done. Chemotherapeutic regimens, such as a modified ESHAP (etoposide, carboplatin, cytarabine, and methylprednisolone) and MAID (mesna, doxorubicin, ifosfamide, dacarbazine) have been demonstrated to be effective in a proportion of patients.[20] High-dose radiotherapy is also used alongside chemotherapy in the management of LCS.[20]

In summary, eosinophilic granuloma was the most frequently encountered orbital histiocytic lesion in our series. Eosinophilic granuloma usually responded well to subtotal tumor excision, bone curettage, and intraorbital corticosteroid injections. Systemic chemotherapy was used in cases of LCH with bone destruction and adjacent dural enhancement in an effort to prevent the potential development of CNS disease.

Conflict of interest

The authors declared that there is no conflict of interest.

References

1. Lichenstein L. Histiocytosis X; integration of eosinophilic granuloma of bone, Letterer-Siwe disease and Schüller-Christian disease as related manifestations of a single nosologic entity. *AMA Arch Pathol* 1953;**56**:84–102.
2. Moore AT, Pritchard J, Taylor DSI. Histiocytosis X: an ophthalmological review. *Br J Ophthalmol* 1985;**69**:7–14.
3. Writing Group of the Histiocyte Society. Histiocytosis syndromes in children. *Lancet* 1987;**1**(8526):208–9.
4. Harris GJ. Langerhans cell histiocytosis of the orbit: a need for interdisciplinary dialogue. *Am J Ophthalmol* 2006;**141**:374–8.
5. Woo KI, Harris KJ. Eosinophilic granuloma of the orbit: understanding the paradox of aggressive destruction responsive to minimal intervention. *Trans Am Ophthalmol Soc* 2003;**19**:429–39.
6. Yu RC, Chu C, Buluwela L, Chu AC. Clonal proliferation of Langerhans cells in Langerhans cell histiocytosis. *Lancet* 1994;**343**:767–8.
7. Collin M, Bigley V, McClain KL, Allen CE. Cell(s) of origin of Langerhans cell histiocytosis. *Hematol Oncol Clin North Am* 2015;**29**:825–38.
8. Badalian-Very G, Vergilio JA, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. *Blood* 2010;**116**:1919–23.
9. Badalian-Very G, Vergilio JA, Fleming M, Rollins BJ. Pathogenesis of Langerhans cell histiocytosis. *Annu Rev Pathol* 2013;**8**:1–20.
10. Esmaili N, Harris GJ. Langerhans cell histiocytosis of the orbit: spectrum of disease and risk of central nervous system sequelae in unifocal cases. *Ophthal Plast Reconstr Surg* 2016;**32**:28–34.
11. Yasko AW, Fanning CV, Ayala AG, Carrasco Ch, Murray JA. Percutaneous techniques fort he diagnosis and treatment of localized Langerhans-cell histiocytosis (Langerhans cell histiocytosis of bone). *J Bone and Joint Surg* 1998;**80**:219–28.
12. Glover AT, Grove Jr AS. Eosinophilic granuloma of the orbit with spontaneous healing. *Ophthalmology* 1987;**94**:1008–12.
13. Hutter C, Minkov M. Insights into the pathogenesis of Langerhans cell histiocytosis: the development of targeted therapies. *Immunotargets Ther* 2016;**5**:81–91.
14. Mittheisz E, Seidl R, Prayer D, et al. Central nervous system-related permanent consequences in patients with Langerhans cell histiocytosis. *Pediatr Blood Cancer* 2007;**48**:50–6.
15. Laurencikas E, Gavhed D, Stalemark H, et al. Incidence and pattern of radiological central nervous system Langerhans cell histiocytosis in children: a population based study. *Pediatr Blood Cancer* 2011;**56**:250–7.
16. Herwig MC, Wojno T, Zhang Q, Grossniklaus HE. Langerhans cell histiocytosis of the orbit: five clinicopathologic cases and review of the literature. *Surv Ophthalmol* 2013;**58**:330–40.
17. Harris GJ, Woo KI. Is unifocal Langerhans-cell histiocytosis of the orbit a ''CNS-Risk'' lesion? *Pediatr Blood Cancer* 2004;**43**:298–9.
18. Gavhed D, Laurencikas E, Akefeldt SO, et al. Fifteen years of treatment with intravenous immunoglobulin in central nervous system Langerhans cell histiocytosis. *Acta Paediatr* 2011;**100**:36–9.
19. Minkov M. Multisystem Langerhans cell histiocytosis in children: current treatment and future directions. *Paediatr Drugs* 2011;**13**:75–86.
20. Zhang Y, Qu Z, Fang F. Langerhans cell sarcoma originating from left knee subcutaneous tissue: a case report and literature review. *Oncol Lett* 2016;**12**:3687–94.