Ophthalmic Histiocytic Lesions: A Baseline Demographic and Clinicopathological Study of 28 Cases From 2 Eye Centers

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Research Article

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Abstract

Purpose: Ophthalmic histiocytic lesions comprise a heterogeneous rare group of disorders that are characterized by an abnormal proliferation of histiocytes and may affect all age groups of both genders. This rare group of diseases in the ophthalmic practice has not been previously studied in this area of the world and only individual cases reports were reported.

Methods: This retrospective study has been approved on an expedited basis by the Human Ethics Committee/Institutional Review Board (HEC/IRB) at King Khaled Eye Specialist Hospital (KKESH) with a collaborative agreement between KKESH and King Abdulaziz University Hospital (KAUH) in Riyadh, Saudi Arabia aiming to collect all biopsied ocular and periocular histiocytic lesions from both centers from January 1993 to December 2018. The histopathological diagnosis was confirmed, and cases were re-classified by review of all histopathological slides. The corresponding demographic and clinical data were analyzed. Relevant literature review was also carried on for comparison of our collected analyzed data to published data and to draw our own conclusions.

Results: A total of 34 ocular/periocular histiocytic lesions of 28 patients who were mostly Saudis (92.9%) were included. Male to female ratio was 4:3. The median age at presentation was 6.4 years (range: 2.8-35). Twenty-two patients had unilateral involvement and 6 patients had bilateral lesions. In Langerhans cell histiocytosis (LCH)=L group, the most common presenting findings were eyelid swelling (75%), periocular tenderness (37.5%), proptosis/globe displacement (37.5%) eyelid erythema (25%), and orbital pain (12.5%). In Rosai Dorfman disease (RDD)=C group, proptosis/globe displacement occurred in all patients, followed by decreased vision (80%). Patients with C group diseases had variable clinical features owing to the different locations of the histiocytic lesions with the majority involving the eyelids (66.7%). Diagnosis was accurately reached clinically in 38.8%, 33.7%, and 46.7% among patients in the L group, C group, and R group respectively. Overall, the clinical diagnosis was in concordance with the histopathologic diagnosis in 14 only out of 34 lesions (41.2%).

Conclusions: We concluded that C group was the commonest histiocytic lesion encountered in about two-thirds of the lesions with particular prevalence of Juvenile xanthogranuloma (JXG). The histiocytic disease is more likely to be overlooked clinically especially in this group owing to its rarity and is diagnosed mainly with the help of histopathological and immunohistochemical studies. The median age of presentation was higher for R group patients, while there was tendency for JXG to present at a later age compared to the published reports. Intraocular involvement was extremely rare. All L group cases were strictly unilateral disease, while RDD (C group) was most commonly bilateral. Future research on the genetic aspects, management, and prognosis are necessary.

Introduction

Histiocytic disorders are a rare group of diseases that are characterized by an abnormal proliferation of histiocytes. Their clinical presentation ranges from mild localized form to disseminated and, sometimes,

fatal forms. Histiocytic disorders can affect both children and adults of both genders. [1, 2] The first proposed classification of histiocytic disorders was published in 1987 which included three classes: Langerhans Cell Histiocytosis (LCH), Histiocytoses of Mononuclear Phagocytes other than Langerhans cells, and Hemophagocytic Lymphohistiocytosis. [3] In 1997, an updated classification based on the biologic behavior and histopathology was laid out, which included dendritic cell-related, macrophage-related, and malignant disorders. [4] Recent findings regarding the cellular origins, molecular pathology, and clinical presentations of histiocytic disorders have been recognized. Thus, a new classification was published in 2016 based on histology, phenotype, molecular alterations, clinical and imaging characteristics. This revised classification system consisted of five groups of diseases **(Table 1)**. [5] The purpose of this study is to review and describe the different clinical presentations, histopathological and immunohistochemical features of 34 ocular and periocular histiocytic lesions in 28 patients with an extensive updated review of the relevant literature.

Method

This retrospective study has been approved on an expedited basis by the Human Ethics Committee/Institutional Review Board (HEC/IRB) at King Khaled Eye Specialist Hospital (KKESH) with a collaborative agreement between KKESH and King Abdulaziz University Hospital (KAUH) in Riyadh, Saudi Arabia. The histopathology records in both hospitals were manually and electronically searched for all patients with a diagnosis of ocular and/or periocular histiocytic disorder from January 1993 to December 2018 and included 28 patients with biopsy-proven histiocytic disorders.

From the medical records, we extracted the demographic data such as patient age at presentation, gender, as well as information on symptoms and their duration, imaging findings, systemic treatment, and follow-up. The recorded findings on eye examination included visual acuity, laterality, extraocular motility, orbital findings, anterior and posterior segment manifestations. Findings of computed tomography (CT) and magnetic resonance imaging (MRI) scans were documented. Histopathological findings along with immunohistochemical staining -whenever performed- were reviewed to confirm the tissue diagnosis by 2 pathologists. Data were analysed using SPSS® version 22.0 (IBM Inc., Chicago, Illinois, USA). Descriptive analysis was primarily done, where categorical variables were presented in the form of frequencies and percentages. The treatment modalities and outcomes of management were beyond the scope of this study and were not included.

Results

A total of 34 ocular/periocular histiocytic lesions of 28 patients were included in the study. Patient demographics in the three histiocytic groups are depicted in **Table 2.** Overall, 16 patients were males and 12 were females. The median age at presentation was 6.4 years (2.8-35). Among the groups, the median age of presentation was significantly higher for R group patients (26.7 years) compared to C group (6.1 years) and L group (3.8 years) patients. Twenty-two patients had unilateral involvement and 6 patients had bilateral lesions. The main symptoms included eyelid/eye swelling (58.8%) and decreased vision

(17.6%). Proptosis/globe displacement was seen in 32.4% of eyes. The overall median duration of symptoms was 12 weeks (3.0-141.8).

Orbital involvement, defined as primary or secondary involvement (extension or inflammation), was found in 47.1% of all orbits, from which bone erosions were observed in 68.7%. Relevant systemic involvement, defined as a related systemic disease or multifocal distant lesions in a single system or multiple system involvements including extension, was documented in 9 out of 28 patients. These included asthma, intracranial or paranasal sinuses extension, facial/brain tumors, trunk lesions, and bone marrow involvement. All patients, except 2 brothers with Rosai-Dorfman disease, denied any family history of similar presentation.

C group diseases were the most common among the histiocytic disorders at 61.8% of the eyes followed by L group (23.5%), and R group (14.7%) diseases. All patients in the L group had unilateral involvements. Bilateral involvement was seen in 4 out of 17 cases (23.5%) in the C group and 2 out of 3 cases (66.6%) in the R group **(Table 3)**. The orbit was the primary site of involvement in all L and R group cases while only 14.3% of eyes in the C group had orbital disease. In L group diseases (LCH), the most common presenting findings were eyelid swelling (75%), periocular tenderness (37.5%), proptosis/globe displacement (37.5%) eyelid erythema (25%), and orbital pain (12.5%) **(Figure 1)**. In patients with R group disease (RDD), proptosis/globe displacement (100%) and decreased vision (80%) were the most frequent clinical findings **(Figure 2)**. No patient in the latter group complained of pain or periocular tenderness. On the other hand, patients with C group diseases had variable clinical features owing the different localizations of the histiocytic lesions with eyelid (66.7%), ocular surface (28.6%), orbital (14.3%), and intraocular (9.5%) involvements. The presenting clinical features included eyelid swelling (28.6%), ocular surface lesion (28.6%), eye redness (19%), decreased vision (9.5%), hyphema (4.7%), orbital pain (4.7%) **(Figure 3)**. The median duration of symptoms ranged from 3.5 weeks in the L group to 312 weeks in the R group with the C group patients being at 24 weeks.

All L group and R group patients had an associated orbital involvement with bone erosions/destruction occurring in 75% and 100% of L and R group patients, respectively **(Figure 4)**. Among C group patients, as mentioned earlier, 3 out of 21 orbits (14.3%) were involved with no detectable bony erosions. Relevant systemic involvement was documented in 37.5%, 17.6%, and 100% of patients in the L group, C group, and R group, respectively.

The correlation between clinical and histopathologic diagnoses was analyzed **(Table 4)**. The clinical diagnosis was matching the histopathologic diagnosis in 2 out of 8 patients in the L group with a sensitivity of 25%, a specificity of 53.8%, and a positive predictive value (PPV) of 14.3%. In the C group, the clinical diagnoses correlated with histopathologic diagnosis in 10 out of 21 eyes yielding a sensitivity of 57.6%, a specificity of 69.2%, and a PPV of 71.4%. The sensitivity of diagnosing a case of ophthalmic Rosai-Dorfman disease is 40% with a specificity of 58.6% and a PPV of 14.3%. The accuracy of clinically diagnosing a patient in the L group, C group, and R group was 38.8%, 33.7%, and 46.7%, respectively.

Overall, the clinical diagnosis was in concordance with the histopathologic diagnosis in 14 only out of 34 eyes (41.2%).

Discussion

Our understanding of the histiocytic disorders has undergone revolutionary changes in the last few years. Orbital histiocytic lesions comprise a heterogeneous group of disorders that range from eosinophilic granuloma to Langerhans cell sarcoma. The most common lesion among histiocytic orbital lesions is LCH.

LCH, historically, includes three subgroups: Eosinophilic granuloma, Letterer-Siwe disease, and Hand-Schüller-Christian disease. [1] The Working Group of the Histiocyte Society adopted the term Langerhans cell histiocytosis which, encompasses and broadly substitutes the former historical terms used to classify this category of abnormal histiocyte proliferation. [3] Nonetheless, many physicians continue to employ the term eosinophilic granuloma; hence, this terminology is still of both historical and clinical significance. Eosinophilic granuloma is the most common form of LCH seen in clinical practice. It accounts for more than two-thirds of all LCH cases. [6, 7] It can affect the calvarium, vertebrae, ribs, long bones, mandible, and orbit. [8-10] Eosinophilic granuloma of the orbit is typically located in the supero-temporal quadrant of the anterior orbit, unilateral, and unifocal. Infrequently, bilateral orbital involvement is seen where the contralateral side becomes involved months later. [11] Patients with eosinophilic granuloma usually present with progressive proptosis associated with upper eyelid swelling and erythema. The etiopathogenesis is believed to be related to altered immune system versus neoplastic process. This alteration causes abnormal proliferation of pathologic Langerhans cells that typically reside within the orbital plate of the frontal bone. [12] In general, individuals of all ages can be affected by LCH, but the peak is usually in early childhood, between 1 to 4 years of age. [13,14,15] In children younger than 15 years of age, the annual incidence of LCH is approximately 5-9/million compared to 1/million in individuals older than 15 years. [16,17] It is more common in males for whom diagnoses have a later onset compared to females who have an earlier onset and a more aggressive course. [14, 16, 18,19,20] LCH tends to be more common in Caucasians than in other races. [17, 19, 20] In our series of 8 cases of unilateral orbital LCH, the median age of presentation was 3.8 years, which is within the known peak of 4 years. The youngest patient was 1 year old and the oldest was 11.7 years. The disease affected males and females equally. The mean age of presentation was 6.3 years in males and 3.8 years in females thus confirming the reported later onset among males. Seven patients were Saudis, and 1 patient was from Kuwait. Familial LCH have been rarely reported with no known hereditary pattern. [5, 21] All patients in our series had a negative family history, which is expected as mentioned earlier. The bone is the most affected organ by LCH at 80% of cases followed by the skin, pituitary gland, liver, spleen, lungs, and other organs. [61] The incidence of orbital LCH is variable among studies ranging from uncommon to relatively frequent incidence rates reaching 37.5%. [2, 23, 24, 25] Orbital involvement typically presents as a chronic lesion and rarely in an acute disseminated form. [2] The mean duration of symptoms in our patients was 3.5 weeks (1-8), which is less when compared to other series. LCH most commonly features a unifocal, single-system disease. [16, 17, 19] Multisystem LCH is more common in children younger than 3 years of

age, the occurrence of which carries an unfavorable prognosis. [18, 19, 26] There were 2 males and 1 female patients, who presented with relevant systemic associations in the form of bone marrow malignant aspirate, asthma, brain, and sinus extensions. The patients with orbital LCH typically present with unilateral isolated orbital infiltrates. [27, 28, 29] Multifocality or multiple system involvement are rare presentations of this uncommon disease. [12, 20, 27, 30] In the current case series, all patients presented with unilateral and unifocal orbital disease, which is considered typical. If the lesion is located in the anterior orbit, it usually presents clinically as a palpable mass with secondary ptosis and/or erythematous diffuse swelling with or without tenderness. The latter presentation can be mistaken for an infectious process. Proptosis occurs in about half of the cases and is predominantly seen if the posterior orbit is involved. [31, 32]Six out of 8 patients in our series complained of eyelid swelling, 1 complained of eye bulging, and 2 had eyelid redness. On exam, 2 patients were having eyelid erythema and 3 patients had tenderness. Proptosis/globe displacement was present in 3 out of 8 patients (37.5%), this proportion is low when related to other published reports, which might be linked to the earlier presentation of our patients.

The xanthogranuloma family includes several entities. They are defined by the age of presentation, focality (solitary, multiple, or generalized), and the organ involved. [33] Juvenile xanthogranuloma (JXG) is by far the most common non-LCH that typically affects the skin. [13, 14] The eye is the most common extra-cutaneous site of JXG, but the brain, lungs, and spleen in addition to other organs can also be involved. [15, 16] JXG, , is considered to be a benign cutaneous disorder, which is listed under the cutaneous and mucocutaneous histiocytic disorders (C group). [5, 13] In general, lesions appear spontaneously during the first year of life as orange skin nodules in the head and neck region and then resolve spontaneously. [14] JXG can affect the eye (ocular surface or intraocular), the orbit, and can also involve the central nervous system (CNS), lungs, liver, spleen, and other sites. [15, 16] Ocular involvement has been described in approximately 0.3% to 10% of children with cutaneous JXG. [14, 17] Ophthalmic involvement was reported in the eyelid, orbit, iris, retina, choroid, and optic nerve. [34-42] In a series of 53 cases of ophthalmic JXG, the two most commonly affected sites were the iris and eyelid. [35] In another series, the iris was the most common ocular manifestation followed by the conjunctiva. [18] In the present series, the most common ophthalmic sites of JXG were the eyelid (69.2%), followed by the orbit (23.1%) and ocular surface (23.1%), followed by the iris and choroid at 7.7% each. Thus, the distribution of JXG in our series is different from most of the other published reports in which the iris was commonly involved compared to other sites. Forty to 70% of non-congenital JXG occur during infancy. [13] In 2 large case series, the median ages of onset were 5 months 12 months, respectively. [33, 43] In another case series of 30 patients diagnosed with ophthalmic JXG, the median ages of presentations in years were 0.5, 0.25, 2.5, 1.1, 10.3 in patients with eyelid, orbital, conjunctival, iris, and choroidal JXG, respectively. [18] The male to female ratio was 1.4:1. [43] The overall median age of presentation in our cases was 5.9 years, for which our patients had an older age of presentation compared to other reports, owing to the site of involvement commonly encountered in our study. The only patient with iris involvement presented at an age of 2 months, which was significantly lower than the median ages of the other sites of JXG involvement. The eyelid, orbital, and choroidal JXG similarly presented at median ages ranging from 5.9

to 6.1 years while JXG of the conjunctiva and limbus presented at a relatively younger age with a median age of 4 years. The disease affected 5 males (45.5%) and 6 females (54.5%) with no significant difference in the age of presentation.

Adult xanthogranuloma (AXG) is a rare non-LCH lesion that can be single or multiple. AXG has affected 7 eyes of 5 patients in our series, 2 cases of which have been previously reported. [44,45] The median age was 44.3 years (40.9-57.6) that is comparable to previously reported cases. Four patients were males, and one was a female. Two out of 5 patients had bilateral lesions. Three out of 5 patients had eyelid involvement and the remaining 2 cases involved the cornea and/or limbus. In one of the largest case series of adult xanthogranulomatous disease, eyelid skin lesions were noted in 4 out of 8 AXG cases (50%) while the others had only eyelid swelling. [46] Eyelid examination usually reveals elevated, non-tender, yellowish subcutaneous nodules with or without umbilication. [47] We have encountered 3 patients with eyelid AXG. The lesions were involving the eyelid skin and the anterior orbit. Discussion of the corneo-limbal cases is beyond the scope of this paper.

Histopathologically, in JXG numerous histiocytes, eosinophils, and spindle cells with rare Touton giant cells are observed. [18] Classically, JXG lesions express CD68, lysozyme, and Factor XIIIa and fail to express CD1a. Scattered cells may, rarely, show weak staining with S-100 protein. On the other hand, LCH cells show diffuse and intense staining with S-100 protein and CD1a, but not CD68, lysozyme, and Factor XIIIa. [33] CD1a is not expressed in non-LCH diseases and, thus, it is a relatively specific marker for LCH. [48] Moreover, eyelid AXG can be misdiagnosed clinically and histopathologically as xanthelasma. [44] All our cases of JXG and AXG showed the typical histopathological appearance with Touton giant cells as well as the immunohistochemical staining properties **(Figure 5)**. However, one of our patients was initially diagnosed elsewhere as a case of xanthelasma.

Rosai-Dorfman disease (RDD) is a rare histiocytic disorder that was first described by Juan Rosai and Ronald Dorfman in 1969. The pathogenesis of RDD is controversial between supporters of an underlying immunologic reactive process and those for a neoplastic process. [30, 31] A viral infection has also been suggested. [22] Typically, RDD is acquired at a mean age of 20 years, but a delayed presentation has been reported to occur during the eighth decade of life. [20] Clinically, it features a massive, painless lymphadenopathy which is characteristically self-limited. [19] Ophthalmic manifestations occur in 11% of patients with the orbit being the most common site of involvement. [20, 21] RDD can also present as an epibulbar mass, scleritis, uveitis, and serous retinal detachments with choroidal involvement. [21-25] Cases with compressive optic neuropathy and lesions mimicking optic nerve and lacrimal tumors have been reported. [26-29]

In our series, we have defined the clinical features of 5 eyes of 3 patients who presented with isolated extra-nodal orbital RDD and 2 of those patients were brothers. All 3 cases (5 eyes) of ophthalmic RDD, had extra-nodal orbital involvement without lymphadenopathy, which is considered a very rare presentation according to the reviewed literature. The median age of presentation was 26.7 years (26.6-72), but the age of onset is approximately 6 to 8 years less owing to the long duration of symptoms.

Thus, the mean age of onset of the two younger patients were similar to the mean ages in other reports but an onset in the eighth decade is unusual. The disease was bilateral in 2 out of 3 patients. Eye/eyelid swelling, and decreased vision were the presenting complaints in 4 out of 5 eyes with a median duration of 6 years (1-8). Proptosis was observed in all eyes, with a median of 4.5 mm (2-16). Apart from eyelid swelling and proptosis, no other signs of infection or inflammation. Microscopic evaluation typically shows a mixed infiltrate of histiocytes, lymphocytes, and plasma cells. Viable cells are also found within the cytoplasm of large phagocytic histiocytes, a condition termed emperipolesis. In contrast to phagocytosis in which the engulfed cells are destroyed by the lysosomal enzymes, emperipolesis indicates a temporarily phagocytized cells that retain intact normal structure. [49] Emperipolesis is rare outside the setting of RDD and, thus, is a strong indicator for the diagnosis, which was confirmed in all our patients by tissue diagnosis **(Figure 6)**.

There are several reports relating IgG4-RD to histiocytic disorders. Concerning Rosai-Dorfman disease (RDD), it is considered a separate histiocytic entity in the new classification, two studies indicated an overlap with IgG4-RD. [40, 41] However, a study of 32 cases suggested that RDD does not belong to the spectrum of IgG4-RD. [42] We evaluated the IgG4 reactivity in 2 out of 3 patients. There were approximately 30 IgG4+ plasma cells/HPF in one patient, while the other patient showed a non-significant reaction. According to the diagnostic criteria proposed by the Japanese Study Group for IgG4-related ophthalmic disease, the results in our cases were non-confirmatory. [50]

Conclusions

Limitations of this study include the retrospective study design and the small sample size. However, the later limitation is inevitable for studies on such a rare group of diseases. We were still able to confirm that histiocytic disorders are rare even in this part of the world and may have variety of ophthalmic manifestations. We have encountered diseases listed in 3 different groups of histiocytic disorders with approximately two-thirds of the diseases belonging to the C group. The median age of presentation was significantly higher for R group patients, which is in agreement with the known course of diseases in each group. Among the disease entities, there was tendency for the age of presentation to be at a later older age in patients with JXG compared to the published reports. The most common sites of involvement in this series were the orbits followed by the eyelids. Intraocular involvement was extremely rare. All L group cases were strictly unilateral disease, while RDD was most commonly bilateral. The orbit was the primary site of involvement in the L and R groups. On the other hand, patients with C group diseases presented with variable symptoms and signs owing to the different anatomic distributions of lesions. JXG was the most common disease entity in the current study, in which the eyelid was frequently involved. Further studies on the treatment modalities and prognosis in each of the above entities are warranted.

Declarations

Declaration statement:

This study was prepared in accordance with the ethical standards of the human ethics committee at KKESH and expedited approval as a retrospective study from the HEC/IRB of the Research department in accordance with the Helsinki Declaration. A general informed written consent was taken from all cases which includes permission for anonymous use of data for the purpose of publication. The authors have no conflict of interest or financial disclosures in relation to this work. This work did not receive funding from any of the institutions.

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Tables

Table 1. Summary of the entities in the revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. [5]

Group	Entities
L	- Langerhans cell histiocytosis (LCH) - Indeterminate cell histiocytosis - Erdheim-Chester disease (ECD) - Mixed ECD and LCH
C	- Cutaneous non-LCH histiocytoses: Xanthogranuloma family (e.g.JXG), and non-xanthogranuloma family (e.g. necrobiotic xanthogranuloma) - Cutaneous non-LCH histiocytoses with a major systemic component
R	- Familial Rosai-Dorfman disease (RDD) - Classical (nodal) RDD - Extra-nodal RDD - Neoplasia-associated RDD - Immune disease associated RDD - Others: non-C, non-L, non-M, and non-H histiocytoses
M	- Primary malignant histiocytoses - Secondary malignant histiocytoses
H	- Primary Hemophagocytic Lymphohistiocytosis (HLH): Mendelian inherited conditions leading to HLH - Secondary HLH (apparently non-Mendelian HLH) - HLH of unknown/uncertain origin

JXG: Juvenile xanthogranuloma.

Table 2. Demographics of 34 ophthalmic histiocytic lesions in 28 patients.

Variables/Characteristics	L Group (8 eyes) (8 patients)	C Group (21 eyes) (17 patients)	R Group (5 eyes) (3 patients)	Overall (34 eyes) (28 patients)
Age, years				
Median (Q1-Q3)	3.8 (2.1-8)	6.1 (2.1-43.5)	26.7 (26.6-72)	6.4 (2.8-35)
Gender, n (%)				
Male	4 (50)	10 (58.8)	2 (66.6)	16 (57.1)
Female	4 (50)	7 (41.2)	1 (33.3)	12 (42.9)
Nationality, n (%)				
Saudi	7 (87.5)	16 (94.1)	3 (100)	26 (92.9)
Others	1 (12.5)	1 (5.9)	0 (0)	2 (7.1)
Q1, 25th percentile; Q3, 75th percentile				

Table 3. Summary of the clinical features of 34 ophthalmic histiocytic lesions in 28 patients.

Variables/Characteristics	L Group (8 eyes) (8 patients)	C Group (21 eyes) (17 patients)	R Group (5 eyes) (3 patients)	Overall (34 eyes) (28 patients)
Laterality, n (%)				
Unilateral	8 (100)	13 (76.5)	1 (33.3)	22 (78.6)
Bilateral	0 (0)	4 (23.5)	2 (66.6)	6 (21.4)
Clinical features, n (%)				
Eyelid swelling	6 (75)	6 (28.6)	4 (80)	16 (47.1)
Proptosis/globe displacement	3 (37.5)	3 (14.3)	5 (100)	11 (32.4)
Ocular surface lesion	0 (0)	6 (28.6)	0 (0)	6 (17.6)
Decreased vision	0 (0)	2 (9.5)	4 (80)	6 (17.6)
Eyelid erythema	2 (25)	2 (9.5)	0 (0)	4 (11.8)
Tenderness	3 (37.5)	0 (0)	0 (0)	3 (8)
Pain	1 (12.5)	1 (4.7)	0 (0)	2 (5.9)
Hyphema	0 (0)	1 (4.7)	0 (0)	1 (2.9)
Duration of symptoms, weeks				
Median (Q1-Q3)	3.5 (1.2-4.7)	24 (5.5-122.5)	312 (182-416)	12 (3.0-141.8)
Q1, 25^{th} percentile; Q3, 75^{th} percentile				

Table 4. Correlation between the clinical and histopathologic diagnoses in 3 histiocytic groups.

Group	n (%)	TP	FP	TN	FN	Accuracy	Sensitivity	Specificity	PPV	NPV
L Group	8 (23.5)	2	12	14	6	38.8	25.0	53.8	14.3	70.0
C Group	21 (61.8)	10	4	9	11	33.7	47.6	69.2	71.4	45.0
R Group	5 (14.7)	2	12	17	3	46.7	40.0	58.6	14.3	85.0

TP, true positive; FP, false positive; TN, true negative; FN, false negative; PPV, positive predictive value; NPV, negative predictive value.

Figures

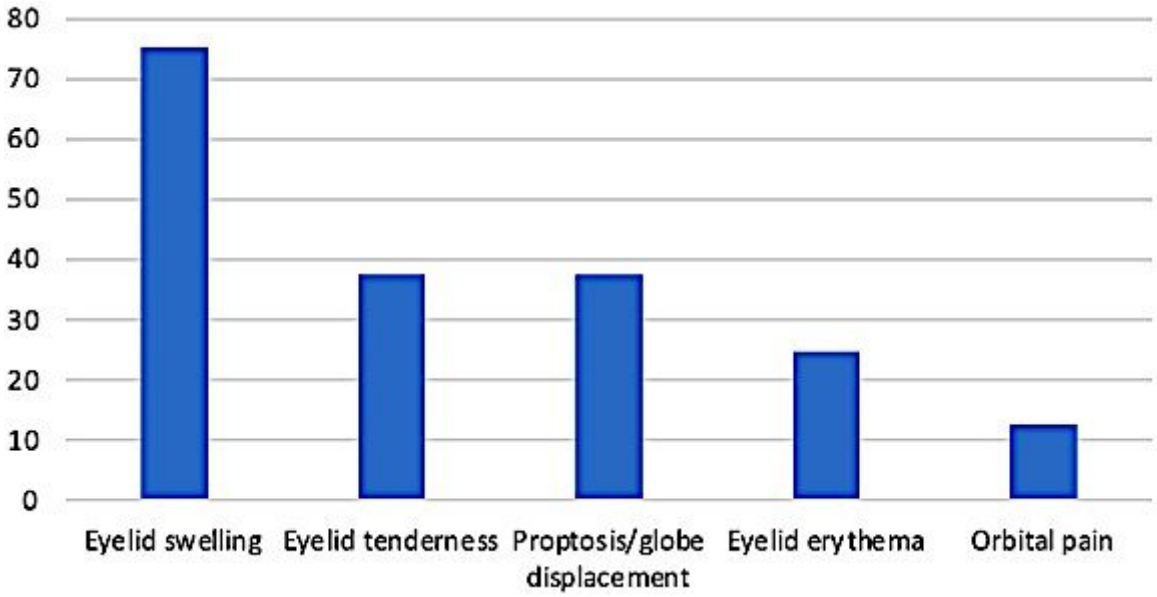

Figure 1

Distribution of symptoms and signs in the L group in order of frequency.

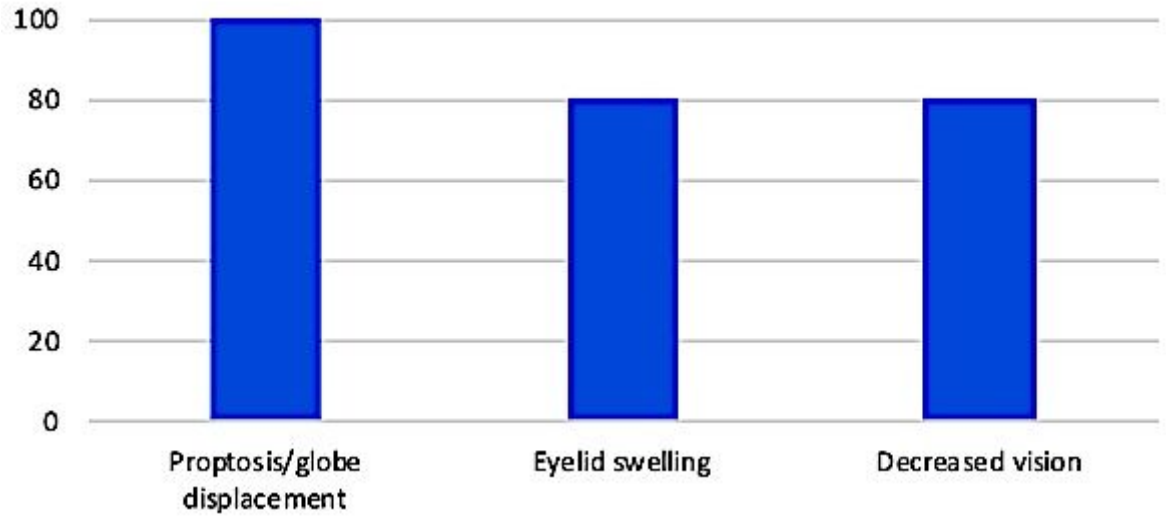

Figure 2

Distribution of symptoms and signs in the L group in order of frequency.

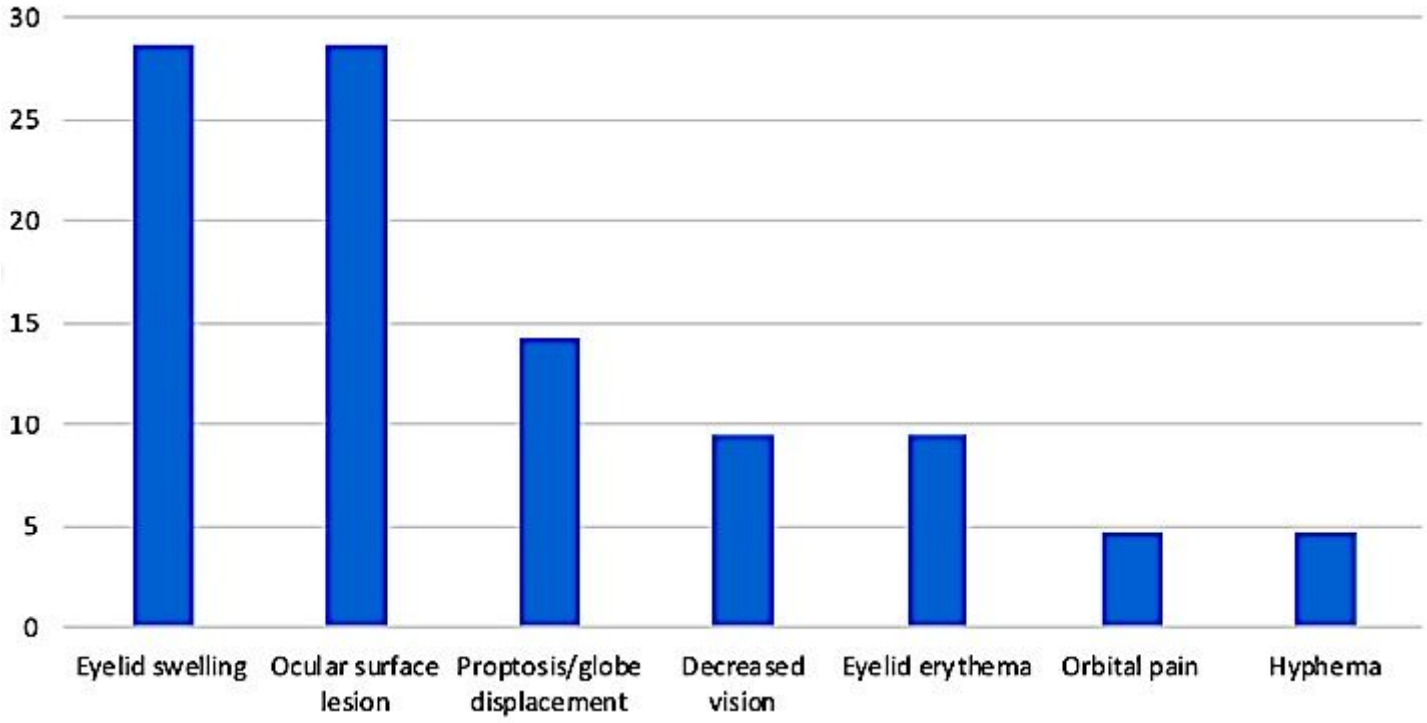

Figure 3

Distribution of symptoms and signs in the R group in order of frequency.

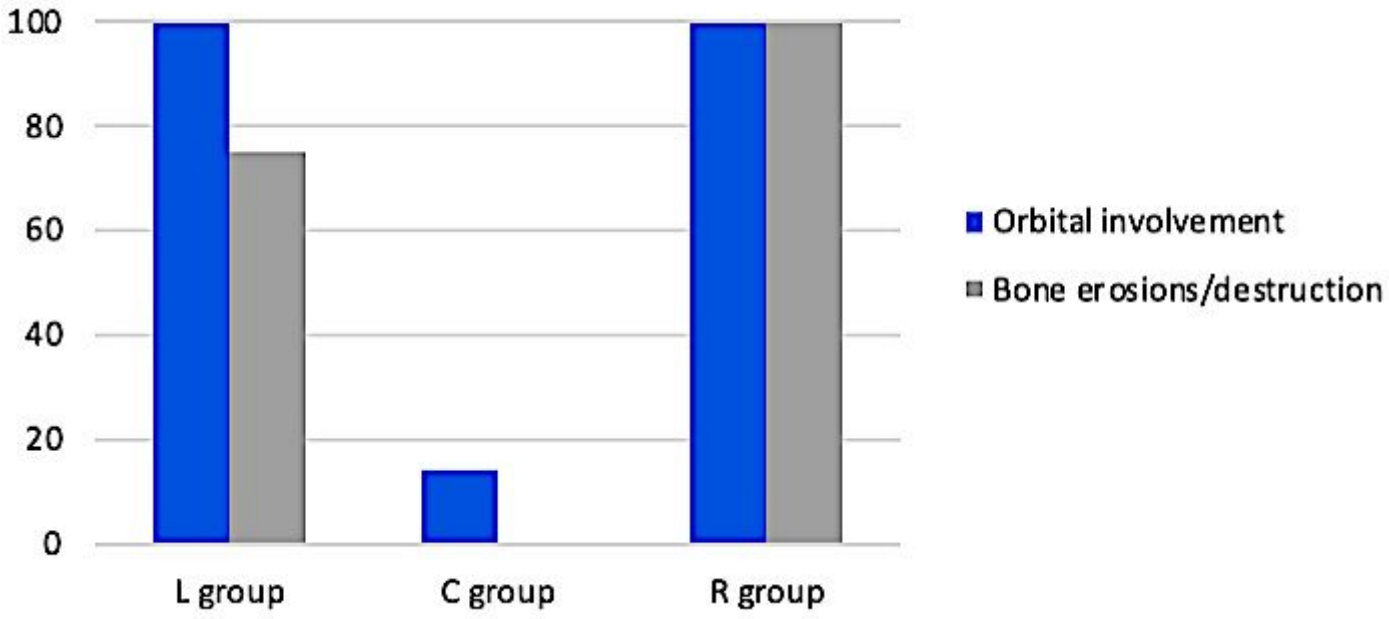

Figure 4

The proportions of orbital involvement and bone erosions in the three histiocytic groups. Orbital involvement indicates either primary or secondary involvement (extension and/or inflammation).

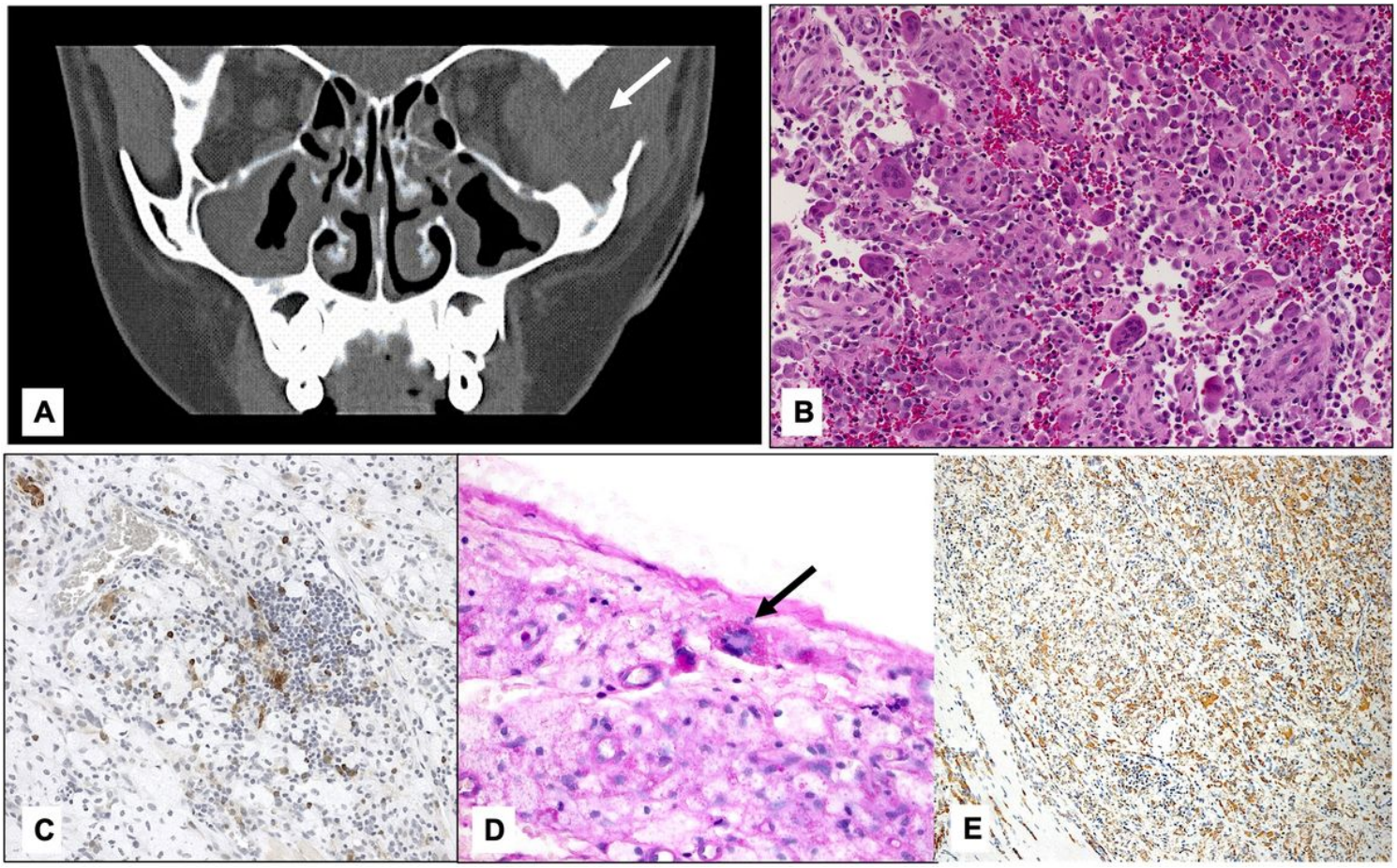

Figure 5

A. Computerized tomography scan of a Langerhans cell histiocytosis (LCH) case showing soft tissue lesion with a cystic component and destruction of left lateral orbital wall (red arrow). B. The histopathological appearance of the tissue histiocytes and giant cells in the same case (Original magnification x 400 Hematoxylin and eosin). C. LCH cells expressing one of the diagnostic immunohistochemical (IHC) markers with positive staining (Original magnification x 400 S-100 stain). D. Histopathology of a case of juvenile xanthogranuloma (JXG) with the typical Touton giant cell marked with black arrow (Original magnification x 400 Hematoxylin and eosin). E. Non-LCH cells in a case of JXG with diffuse positive staining of the cells with proper marker (Original magnification x 100 CD-68 stain).

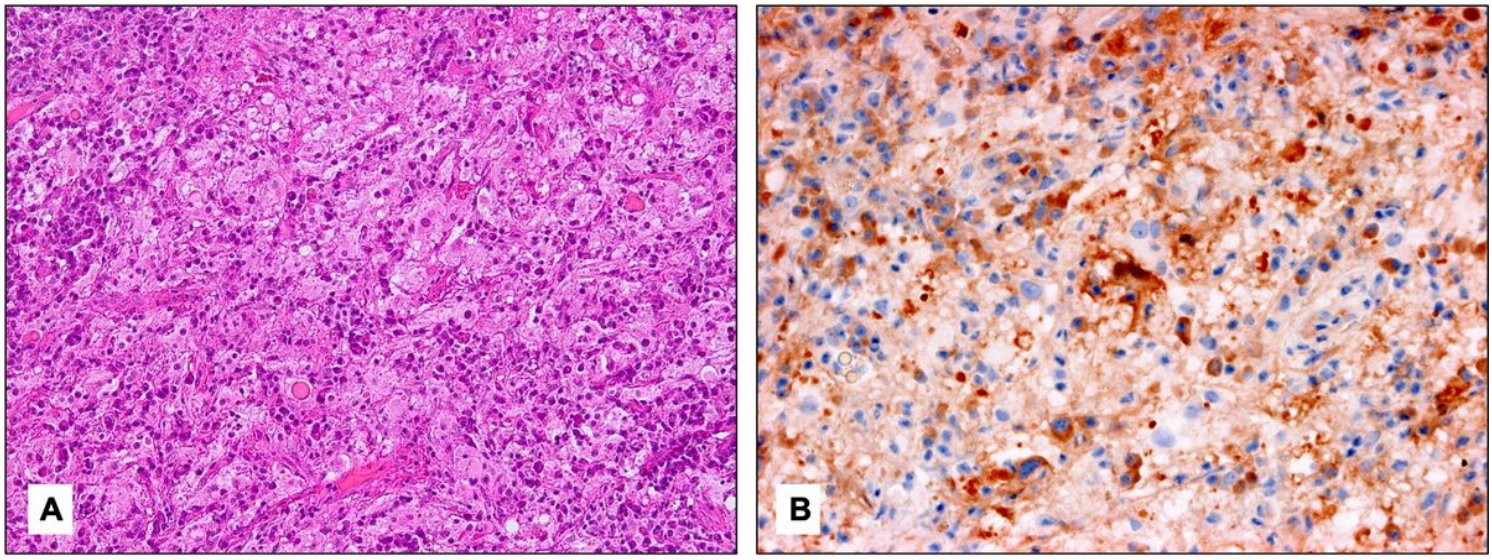

Figure 6

A. Histopathology of a case of Rosai Dorfman disease (RDD) with the mixed infiltrate of histiocytes, lymphocytes, and plasma cells (Original magnification x 200 Hematoxylin and eosin). B. Histopathology of the typical emperipolesis in a case of RDD. Please note the expression of the cells to the specific IHC marker CD1a (Original magnification x 400 CD-1a stain).