Angiolymphoid Hyperplasia with Eosinophilia of the Orbit and Adnexa

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Key Words

Angiolymphoid hyperplasia with eosinophilia · Kimura disease · Epithelioid hemangioma · Orbit · Dacryoadenitis · Proptosis

Abstract

Purpose: Angiolymphoid hyperplasia with eosinophilia (ALHE) is a rare disorder presenting with solitary or multiple nodules in the dermis or subcutaneous tissues. ALHE shares clinical as well as histopathological characteristics with Kimura disease (KD), but they have been considered to be two distinct entities based on their histological features. Orbital and adnexal involvement in ALHE is rare. The published literature is limited to few case reports featuring single cases. **Methods:** We report a series of 5 cases of ALHE presenting with diverse clinical features seen at a tertiary referral care centre in India. We also review the published literature with a special emphasis on the treatment modalities for orbital and adnexal ALHE. **Results:** Three patients of this series presented with orbital involvement, while the remaining 2 had involvement of the eyelid. Three patients underwent incisional and/or excisional biopsy, whereas 2 were managed conservatively. There were no recurrences seen on follow-up. **Conclusions:** ALHE can rarely involve the orbit and adnexa. There is no consensus on the best modality of manage-

ment of this rare entity. ALHE and KD have often been considered variations of the same disease, but it is important to differentiate between the two entities for optimal patient management.

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Introduction

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a benign disorder which typically presents as subcutaneous nodules in the head and neck region and is more often seen in females. The clinical features of ALHE and Kimura disease (KD) are often indistinguishable. However, several reports have shown that, despite clinical similarities, ALHE and KD can be differentiated on histopathological examination based on their vascular endothelial cell morphology [1–6]. ALHE appears to be a benign neoplastic disorder of the vascular endothelium with a secondary inflammatory response, while the features of KD are more consistent with an allergic or autoimmune process with male predominance, peripheral eosinophilia, nephrotic syndrome, and/or lymphadenopathy [1, 4, 5]. Orbital and ocular adnexal involvement in ALHE is relatively rare compared to its occurrence in other locations.

Subjects and Methods

We report 5 cases of ALHE presenting with diverse clinical features as well as their management. The study adhered to the principles outlined in the Declaration of Helsinki. All the subjects gave their informed consent and the study protocol was approved by the Institutional Review Board.

Case 1

A 50-year-old woman presented with a history of protrusion of her left eye for the previous year. She had been treated with multiple courses of oral steroids elsewhere, with no apparent improvement. Visual acuity and pupillary examinations were unremarkable in both eyes. Hertel exophthalmometry showed 9 mm of axial proptosis of the left eye. Slit-lamp examination of the left eye showed conjunctival hyperaemia and punctate epithelial erosions of the inferior cornea.

Computed tomography (CT) scanning showed moderate thickening of the left inferior, medial, and lateral rectus muscles. A homogeneous ill-defined intra- and extraconal soft-tissue lesion was seen between the inferior and lateral recti extending from the mid-orbital level to the orbital apex. The patient underwent incisional biopsy with debulking of the lesion. Histology of the specimen showed multiple collections of plump epithelioid endothelial cells lining the blood vessel, which is characteristic of ALHE (fig. 1). Chronic inflammatory infiltrates including eosinophils, lymphocytes, and plasma cells as well as fibrocollagenous and adipose tissue with myxoid components in the stroma were also seen.

Postoperative CT scans showed residual soft tissue between the inferior and medial rectus muscles and inferior orbit at the apex. Since the lesion was refractory to steroids but otherwise asymptomatic, no other intervention was advised. At 6 months of follow-up, the patient had residual proptosis of 1 mm in the left eye.

Case 2

An 8-year-old female child presented with proptosis of the left eye and binocular diplopia for the previous 3 months. She had been treated with oral steroids for 1 month elsewhere. However, she was still symptomatic despite some improvement. There was a recurrence of proptosis following cessation of the therapy.

On examination, an ill-defined, firm, non-tender mass was felt in the superolateral quadrant of the left orbit. The visual acuity was 20/20 and 20/40 in the right and the left eye, respectively, with trace relative afferent pupillary defect in the left eye. There was resistance to retropulsion and inferomedial dystopia. Hertel exophthalmometry showed 8 mm of proptosis of the left eye with limitation of elevation.

Magnetic resonance imaging (MRI) showed an ill-defined extraconal lesion displacing the superior rectus and levator muscle complex, extending from the superior periocular region to the orbital apex (fig. 2a). An incisional biopsy was done, which showed typical features of ALHE (fig. 2b). Subsequently, the patient underwent surgical debulking of the orbital mass. Postoperatively, her visual acuity improved to 20/20 in the left eye with gradual resolution of proptosis. However, proptosis recurred on tapering of the steroids, even though the patient maintained normal vision. MRI was repeated at the 3-month follow-up, which revealed incomplete resolution of the lesion. An intralesional triamcinolone acetonide injection was given under general anaesthesia. The patient was lost to follow-up.

Fig. 1. Photomicrograph showing epithelioid endothelial cells (asterisk) in a blood vessel, surrounded by lymphocytes and eosinophils. HE. $\times 40$.

Case 3

A 53-year-old man presented with a history of fullness of the left upper eyelid for the last 3 months which had increased over the previous month. On examination, there was a palpable, firm swelling in the left superolateral quadrant of the orbit which was non-tender and non-pulsatile. This was causing mechanical ptosis due to the effect of the mass (fig. 3a). A cover test showed left hypotropia with restricted elevation. Hertel exophthalmometry showed 1 mm of proptosis of the left eye. The rest of the ocular examination was within normal limits.

A CT scan showed soft-tissue oedema involving the left upper eyelid and diffuse enlargement of the left lacrimal gland involving both orbital and palpebral lobes, which was suggestive of dacryoadenitis (fig. 3b). The patient was started on oral antibiotics, non-steroidal anti-inflammatory agents, and topical lubricants. At the subsequent follow-up after 1 week and 4 weeks, there was no appreciable change in the size of the lesion. Hence, an incisional biopsy of the lesion was done. Histological examination showed multiple lymphoid aggregates with germinal centres. The intervening tissue showed numerous eosinophils around blood vessels and plump endothelial cells in the vessel walls, which was suggestive of ALHE (fig. 3c). The erythrocyte sedimentation rate was also raised. The patient was prescribed oral steroids. At the follow-up after 4 weeks, the eyelid swelling and ptosis had resolved with no discernible lesion.

Case 4

A 55-year-old woman presented with complaints of fullness of the right upper eyelid for the previous 6 months associated with redness of the right eye. She reported a history of a similar swelling in the left upper eyelid 9 months previously for which she had undergone biopsy elsewhere. Review of the old CT scan showed a diffuse soft-tissue lesion in the left upper eyelid. At the time of presentation, she was taking 5 mg of methotrexate twice a week.

On examination, there was fullness of the right upper eyelid with mechanical ptosis, while the left upper eyelid appeared nor-

Fig. 2. a T2-weighted axial and T1-weighted coronal MR images showing an ill-defined extraconal lesion (arrow) extending from the superior periocular region to the orbital apex (asterisk). **b** Photomicrograph showing blood vessel and lymphoid follicles. HE. $\times 40$.

Fig. 3. a Clinical photograph of the patient (case 3) showing fullness of the left upper eyelid with mechanical ptosis. **b** Contrast-enhanced axial CT scan showing diffuse enlargement of the left lacrimal gland (arrow). **c** Photomicrograph showing proliferation of blood vessels with infiltration of lymphocytes and eosinophils. HE. $\times 20$.

Fig. 4. Photomicrograph showing multiple lobular infiltrations of inflammatory cells with central proliferation of vessels. HE. $\times 10$.

mal. The best-corrected visual acuity was 20/20 in both eyes. Anterior segment and fundus evaluations were within normal limits. She was advised to undergo CT scanning, which showed complete resolution of the lesion on the left side and a similar soft-tissue lesion in the right upper eyelid in the preseptal area. Review of the biopsy specimen from the left eyelid lesion revealed typical features of ALHE (fig. 4). Since the left eye lesion had responded to methotrexate, she was advised to continue the same treatment and to return for re-examination, but she was lost to follow-up.

Case 5

A 36-year-old woman presented with a history of a mass lesion in her right upper eyelid over the previous 12 years. However, she had noticed a rapid increase in size during the past 6 months. A diagnosis of a right upper eyelid capillary haemangioma had been made by her primary physician, and she had received 3 injections of intralesional triamcinolone acetate in the previous 5 months without any noticeable improvement.

On examination, a soft, pendular, non-tender mass lesion was seen on the medial right upper eyelid, resulting in mechanical ptosis. The lesion was fixed to the overlying skin, with dilated vessels over the surface and a local rise of temperature. Pulsation was felt over the base of the lesion (fig. 5a). The remainder of the ocular examination was within normal limits. A haemogram showed eosinophilia and leucocytosis. A CT scan of the orbit showed a lobulated preseptal soft-tissue lesion involving the right upper eyelid and the medial canthal region extending up to the nasal bridge (fig. 5b). A postcontrast study showed non-homogeneous intense enhancement on delayed scans, which was suggestive of an arteriovenous malformation. A Doppler study showed a predominantly arterial flow within the lesion. The anterior part of the lesion did not show any flow, which was reminiscent of thrombosis. A cerebral angiogram was done, which was suggestive of a large arteriovenous malformation. The opinion of an interventional radiologist was sought regarding embolization of the feeder vessel. Embolization was not performed, since the supply was mainly from the ophthalmic artery. The patient underwent excision of the

lesion via a superior eyelid crease approach. A superior eyelid crease incision was made, the feeder vessel was identified and ligated, and the excision was carried out with radiofrequency cautery. Histopathology of the lesion showed vascular malformation with an intense, dense collection of eosinophils with lymphoid aggregates and scattered lymphocytes suggestive of ALHE (fig. 5c, d). The postoperative period was uneventful. At the 3-month follow-up, MRI was repeated, revealing a small residual mass that was subsequently excised with no further recurrence.

Discussion

Historical Perspective

ALHE was first described by Wells and Whimster [7] in 1969. They suggested that subcutaneous ALHE is identical or closely related to KD. Although histologic differences between the two entities had previously been noted, the authors felt those variations represented changes occurring over time, with ALHE representing an earlier and KD a later stage in the disease process. Rosai et al. [5] proposed the term 'histiocytoid haemangioma' and drew attention to the presence of proliferation of a distinct type of cell descriptively identified as 'histiocytoid endothelial cell' in ALHE. Weiss and Enzinger [8] coined the term 'epithelioid haemangioma' to describe an unusual, benign lesion of endothelial cell proliferation. Googe et al. [1] described ALHE and KD as two distinctive entities based on pathogenesis. They felt that ALHE is a primary neoplastic disorder of the vascular endothelium with a secondary inflammatory response and KD is an allergic or autoimmune process.

KD differs from ALHE in several clinical and histopathological characteristics, namely, male predominance, striking lymphadenopathy, the higher incidence of peripheral blood eosinophilia, and the lack of a distinctive endothelial cell as a marker [9, 10].

Pathogenesis

The pathogenesis of ALHE remains unclear. Various theories that have been proposed range from ALHE as a neoplasm developing from endothelial cells [5, 11–14] to ALHE representing a reactive process secondary to artery or vein damage [15–17]. This is supported by the histological evidence of vascular damage, such as fragmentation of elastic lamina, fibrointimal proliferation, and disruption of the vascular wall [10, 16]. Arteriovenous shunts as a possible cause of ALHE have also been proposed [18]. Fernandez et al. [19] postulated that renin, through angiotensin II, may stimulate the proliferation of vessels and, therefore, may be involved in the pathogenesis of ALHE.

Fig. 5. **a** Pedunculated mass lesion of the right upper eyelid. **b** Axial contrast CT scan showing the preseptal lesion extending up to the nasal bridge. **c, d** Photomicrographs showing blood vessels lined by epithelioid endothelial cells and surrounded by lymphocytes, plasma cells, and eosinophils. HE. **c** $\times 10$. **d** $\times 40$.

Pathological Features

ALHE usually involves the dermis or subcutaneous tissue. Histopathologically, ALHE lesions are characterized by atypical vascular proliferation associated with variable chronic inflammatory cell infiltrate of the lymphocytes, eosinophils, and scattered lymphoid follicles. Eosinophils may predominate to the total exclusion of other inflammatory cell types. Lymphoid follicles may or may not be present in ALHE. When present, they are rare to few in number and are usually associated with older or deeper lesions that also have a more intense inflammatory infiltrate than the more superficial lesions. The characteristic finding in ALHE is the presence of peculiar, plump, vacuolated endothelial cells of epithelioid or histiocytoid appearance lining the vascular lumina which may extend to vascular spaces, which led to the term 'epithelioid haemangioma'. These endothelial cells have a vesicular nucleus, one or more nucleoli, abundant cytoplasm, and an oval, round, or cuboidal shape resembling histiocytes or epithelial cells. Proliferating arteries, veins, and capillaries and uncanalized aggregates of endothelial cells are

present in ALHE. The presence of endothelial cell clusters around larger vessels is thought to be a distinctive feature of ALHE [1, 4–6, 8, 18].

Immunohistochemistry

Immunohistochemistry usually shows a majority of T lymphocytes with occasional B cells forming lymphoid follicles [20]. The endothelial cells show reactivity for the endothelial markers CD34, CD31, UEA-1 (*Ulex europaeus* agglutinin 1), and factor VIII [6]. Histochemically, endothelial cells of ALHE are positive for non-specific esterase, acid phosphatase, succinic dehydrogenase, cytochrome oxidase, and NADPH diaphorase and negative for alkaline phosphatase [21].

Differential Diagnosis

Apart from KD, other differential diagnoses of ALHE include Kaposi sarcoma, angiosarcoma, angiomatous lymphoid hamartoma, epithelioid hemangioendothelioma, bacillary angiomatosis, pyogenic granuloma, and parasitic infections [9, 12, 15]. The clinical features of or-

Table 1. ALHE of the orbit and adnexa: a summary

Case No.	Age, years/sex	Duration	Site	Laterality	Presentation	Imaging	Management	Follow-up
1	50/F	1 year	Orbit	OS	Axial proptosis	Homogenous ill-defined intra- and extraconal soft-tissue lesion between the inferior and lateral recti extending from the mid-orbit level to the orbital apex	Surgical debulking (non-responsive to steroids)	6 months; proptosis reduced, imaging shows residual soft-tissue lesion, asymptomatic
2	8/F	3 months	Orbit	OS	Eccentric proptosis and diplopia	Extraconal lesion displacing the superior rectus	Excisional biopsy and debulking, intralesional steroids, oral steroids	Lost to follow-up
3	53/M	3 months	Lacrimal gland	OS	Fullness in left upper eyelid; mechanical ptosis	Soft-tissue edema involving the left upper eyelid, and diffuse enlargement of the lacrimal gland	Oral steroids	4 weeks; symptoms resolved
4	55/F	6 months	Eyelid	OU (sequential involvement)	Fullness of right upper eyelid; mechanical ptosis	Diffuse soft-tissue swelling	Methotrexate	Lost to follow-up
5	36/F	6 months	Eyelid	OD	Mass lesion in upper eyelid; mechanical ptosis	Vascular preseptal mass lesion	Complete excision (multiple sittings)	1 year; no recurrence

bital ALHE closely resemble those of idiopathic orbital inflammatory disease (IOID). IOID can also present with pain, proptosis, thickened extraocular muscles, lacrimal gland swelling, and ptosis. The diagnosis depends on distinguishing clinical and histopathological differences between each of these lesions. The presence of vascular hyperplasia with plump endothelial cells that protrude into the lumen is the most distinctive feature in establishing the diagnosis of ALHE, whereas the cellular infiltrate in a classic case of IOID will consist mainly of mature lymphocytes, with plasma cells, macrophages, histiocytes, eosinophils, and, occasionally, neutrophils [1, 22]. Clinically, a diagnosis of IgG4-related sclerosing disease should also be considered, especially when evaluating refractory cases of non-specific IOID. IgG4-related disease is a fibroinflammatory condition characterized by dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and, often, elevated serum IgG4 concentrations [23].

Clinical Manifestations

ALHE is a rare condition characterized by single or multiple light pink to red brown papules or nodules. It usually involves the dermis and subcutaneous tissue. Papules and plaques are usually located in the dermis,

while nodules occur in the subcutaneous layer. ALHE shows a distinct predilection for the head and neck region, especially the preauricular area. These lesions are usually asymptomatic. ALHE is more common in women, and its onset occurs typically in the 3rd or 4th decade [9].

The natural course of ALHE varies from an indolent and self-limiting condition with spontaneous resolution within months to a prolonged disorder persisting for several years. Malignant changes have not been reported [4].

Orbital and adnexal involvement in ALHE is rare and has been reported infrequently. The true incidence of orbital and periocular ALHE is difficult to gauge because of the overlapping of features with KD and the fact that the earlier literature described the two as an analogous entity. In fact, Buggage et al. [9] reviewed the clinicopathological information provided for 33 cases of assumed ALHE involving either the orbit or the ocular adnexa and came up with a revised diagnosis of KD in 19 cases and of ALHE in only 3 cases. The remaining 11 cases were considered indeterminate, as the authors were unable to differentiate between KD and ALHE with certainty.

In the periocular region, ALHE may involve the lacrimal glands, intra- and extraconal orbital spaces, medial

and lateral canthal regions, conjunctiva, and eyelids [15, 24–29]. Recently, Alder et al. [30] reported bilateral involvement of the orbit in ALHE.

Our case series demonstrates the diverse modes of presentation of ALHE, requiring a customized approach to the management of this condition in each case. Cases 1 and 2 presented with proptosis as well as poorly circumscribed lesions involving the orbit and the extraocular muscles. In case 1, the patient was refractory to oral steroids but was successfully managed by surgical debulking. Case 2, the youngest patient in our series, initially responded to oral steroids, but recurrence was seen on cessation of the therapy. Intralesional injections of triamcinolone acetonide were tried, but unfortunately she was lost to follow-up. Case 2 clearly demonstrates a tendency for recurrence frequently seen in diffuse ALHE. Management should be tailored to the individual patient and may require a multipronged approach wherever indicated.

Case 3 presented chronic dacryoadenitis-like features. A biopsy was done when the lesion failed to respond to conservative management. Histopathological examination revealed features of ALHE, and, subsequently, a complete surgical excision of the lesion was performed without any recurrence.

Case 4 had sequential eyelid involvement. The patient was on oral methotrexate for biopsy-proven ALHE of the left upper eyelid. Though the initial lesion regressed, she developed a similar involvement of the fellow eye while still on treatment.

Case 5 presented with a pulsatile mass in the eyelid extending into the anterior orbit. Angiography showed the ophthalmic artery to be the feeder vessel. The final outcome was satisfactory, with no recurrence after surgical excision (table 1).

ALHE has infrequently been reported to arise from local blood vessels. Cornelius et al. [31] reported a case of ALHE that presented as a postauricular, pulsatile, progressively enlarging mass. Angiography revealed a postauricular aneurysm originating from the posterior auricular branch of the external carotid artery. The patient was treated by surgical excision of the lesion.

A few cases of ALHE have been histopathologically misreported as angiosarcoma and malignant angioendothelioma because of the exuberant vascular proliferation. These patients had undergone aggressive surgical resection before the correct diagnosis of ALHE was made [32].

To the best of our knowledge, this is the first report of ALHE of the eyelid presenting as an arteriovenous malformation.

Treatment

The primary treatment of ALHE is surgical excision; however, a recurrence rate of 33% has been reported following surgery. The cause of recurrence is the lack of well-defined surgical margins. Circumscribed lesions with clear margins have a low recurrence rate following complete surgical excision [9, 10, 12, 24]. A review of the case reports on lacrimal gland involvement in ALHE shows that excision often leads to a good outcome and appears to be the favoured approach of management among the authors of these studies [24–26].

Treatment with oral and intralesional steroids in case of diffuse involvement, with or without surgical debulking of the lesion, has been reported, even though the recurrence rate is high with this approach [15]. Treatment with cryotherapy and chemotherapy has also been described [9–12]. Cytotoxic drugs such as cyclophosphamide and methotrexate are useful in diffuse lesions, particularly in cases where there is either a resistance to steroids or there are intolerable adverse effects. Baker et al. [33] reported favourable outcomes following subcutaneous methotrexate (20 mg/week) over a period of 2.5 years in a patient with orbital ALHE who had earlier responded poorly to oral steroids. However, it is important to remember that patients on methotrexate require close monitoring of their renal and liver function as well as blood counts to detect adverse effects. Irradiation, oral isotretinoin, and topical imiquimod have been tried with variable results on ALHE [34, 35].

In conclusion, ALHE should be considered as a differential diagnosis in patients presenting with mass lesions in the orbit and adnexa, especially in those who do not respond to conventional therapy. The mode of presentation of ALHE can vary and may mimic several other entities, as has become clearly evident in this series. Histological proliferation of plump histiocytoid endothelial cells is the corner stone of diagnosis. Recognition of these lesions will permit an appropriate and customized approach to the management of these patients. The drawback of this study is the short follow-up of the patients.

Statement of Ethics

The study adhered to the tenets of the Declaration of Helsinki, and institutional review board approval was obtained.

Disclosure Statement

The authors declare no conflict of interest.

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