



Localized ocular crystal-storing histiocytosis and associated lymphoma - Report of two cases and review of literature

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ABSTRACT

Purpose: To add to the existing yet limited body of knowledge around crystal-storing histiocytosis (CSH) with two case reports of localized ocular CSH and associated mucosa-associated lymphoid tissue (MALT) lymphoma involving the lacrimal and orbital soft tissues without underlying systemic lymphoproliferative disorders and to provide a literature review of all cases of CSH with associated ophthalmic findings reported to date.

Observations: A 62-year-old male presented with a one-year history of right greater than left upper eyelid swelling and epiphora. Ophthalmic exam and computed tomography (CT) head scan revealed bilateral soft tissue masses superior to the globe encasing the supraorbital artery with poor margins from the superior rectus muscle. A biopsy of the lesion showed low grade B-cell lymphoma and associated CSH with lymphoma making up the bulk of the tumor and with CSH comprising a minor component of the overall tumor volume. Further investigations did not show any evidence of systemic lymphoproliferative disorders. He received local irradiation of orbits, which resulted in complete resolution of disease.

An 85-year-old female with no significant past ocular history referred to ophthalmology services for an incidental finding of an enlarged left lacrimal gland on a CT head scan. Ophthalmic exam and subsequent magnetic resonance imaging (MRI) demonstrated an enlarged left lacrimal gland. A biopsy of the lesion showed MALT lymphoma associated with CSH. In this case, CSH comprised the bulk of the clinical mass rather than lymphoma. Following negative systemic investigations, she received a short course of localized radiotherapy with a 50% regression of disease seen on follow-up CT scan.

Conclusion and Importance: These two cases demonstrate a spectrum of morphology associated with CSH. In addition, they show that although localized ocular CSH is rare, CSH should be considered in the differential of an orbital mass and should lead to consideration of further investigation for systemic lymphoproliferative disorders.

1. Introduction

Crystal-storing histiocytosis (CSH) is a rare finding characterized by intra-lysosomal accumulation of crystalline material in the histiocyte cytoplasm.¹ The crystals often consist of immunoglobulins (Ig), in particular kappa light chains, without an association of any specific type of Ig heavy chain.¹ The vast majority of CSH cases are associated with disorders that express monoclonal immunoglobulin including multiple myeloma (MM), lymphoplasmacytic lymphoma, or monoclonal gammopathy of undetermined significance (MGUS).¹⁻³ Most often, CSH is commonly localized to the head and neck, lung and pleura, and bone

marrow, but can also be generalized to involve more than one organ such as the lymph nodes, liver, spleen, and kidney.¹ Although ocular structures have been reported as the most common site of localized CSH, cases of ocular CSH are still rare in the literature.¹ We report two cases of localized ocular CSH with mucosa-associated lymphoid tissue (MALT) lymphoma involving the lacrimal and orbital soft tissues without underlying systemic lymphoproliferative disorder. This report adds to the existing yet limited body of knowledge around CSH and provides a literature review of all cases of CSH with associated ophthalmic findings reported to date.

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2. Findings

2.1. Case 1

A 62-year-old male presented with a one-year history of right greater than left upper eyelid swelling and epiphora. He denied any pain with eye movement, tenderness, or changes in his vision. He reported transient worsening of the swelling in the morning, but his symptoms were otherwise unchanged. Past ocular history was only significant for a recent diagnosis of glaucoma in both eyes. He had coronary artery bypass graft surgery three years prior but has not noticed any recent changes to his health.

On exam, he was found to have a solid, mobile, right upper eyelid lesion without any other pertinent ophthalmic findings. A computed tomography (CT) scan of the orbits showed a $2.5 \times 2.6 \times 1.4$ cm soft tissue mass superior to the right globe extending into the retrobulbar fat and encasing the supraorbital artery with poor margins to the superior rectus and superior oblique muscles (Fig. 1). There was a similar mass superior to the left globe measuring $1.9 \times 2.1 \times 0.7$ cm also encasing the supraorbital artery with poor margins to the superior rectus muscle.

An incisional biopsy was taken. The pathology showed diffuse and monotonous proliferation of small lymphocytes infiltrating orbital fat. Most of the mass was compromised of lymphoma, but there were scattered foci of histiocytes with granular eosinophilic cytoplasm (Fig. 2). At higher power, the eosinophilic cells had refractile cytoplasm with many cells showing linear crystals within the cytoplasm (Fig. 3). Immunohistochemistry showed these cells to be CD68-positive histiocytes. The diagnosis of lymphoma was based on our institution's standard 10 immunostain panel for mature B-cell lymphomas. At our institution, all lymphoma diagnoses are reviewed by an expert lymphoma group. Representative immunostains are illustrated in Fig. 4. This case showed sheets of CD20 positive lymphocytes with kappa light chain restriction, and CD3, CD5, CD10, and cyclin-D1 stains that were negative. CD21 demonstrated underlying disrupted and expanded follicular dendritic meshworks.

Complete blood count (CBC) and differential, renal and liver function, liver enzymes, and electrolytes were unremarkable. Serum protein electrophoresis panel (SPEP) did not demonstrate monoclonal antibodies. Serum free light chain assay and beta-2 microglobulin were within normal limits. Bone marrow biopsy and aspirate were negative for lymphoma. Staging investigations were all negative. The diagnosis of stage IVa bilateral orbital low-grade B-cell lymphoma including CSH was made. It was, therefore, treated with local irradiation of orbits within a two-week period. Repeat CT scan three months post radiation shows complete resolution without any areas of disease. Mild vision deterioration of the left eye was noted but confounded by recent diagnosis of glaucoma.

2.2. Case 2

An 85-year-old female was referred to ophthalmology for an incidental finding of an enlarged left lacrimal gland on a CT head scan performed to rule out head injury after a fall. She was asymptomatic and had not noticed any change in her health. Her past medical history included atrial fibrillation, hypertension, chronic renal failure, and coronary artery disease. She had no significant past ocular history. Her ophthalmic exam demonstrated an enlarged left lacrimal gland but was otherwise unremarkable. Her original CT head scan and subsequent MRI of the orbits (Fig. 5) revealed an enlarged left lacrimal gland measuring $2.0 \times 0.9 \times 2.5$ cm.

An incisional biopsy of the left lacrimal gland revealed dense sheets of CD68-positive histiocytes with granular crystals within the cytoplasm in a background of small mature lymphocytes and plasma cells. In contrast to the first case, at low power, there was a predominance of CSH in proportion to lymphoma (Fig. 2). At high power magnification, rhomboid shaped crystals were seen (Fig. 3). Similar to case one, this case underwent our institution's standard panel for mature B-cell lymphoma, which showed sheets of CD20 positive lymphocytes with kappa light chain restriction, and CD5, CD10, and cyclin-D1 stains that were negative (Fig. 6). The diagnosis of low-grade B-cell lymphoma was given, most consistent with extra-nodal marginal zone lymphoma (MALT lymphoma).

CBC and differential, renal and liver function, liver enzymes, electrolytes, peripheral blood smear, SPEP, and urine protein electrophoresis were all unremarkable. Staging CT scan was also within normal limits. She received a single dose of 400 cGy localized radiotherapy via volumetric modulated arc therapy. A three-month follow-up CT scan post radiotherapy showed about 50% regression of disease.

3. Discussion

Case reports outlining ocular findings associated with CSH and lymphoma are limited (Table 1). There are only a few reports describing CSH within certain ocular structures such as the cornea, conjunctiva, lacrimal gland, and orbital soft tissues, with most patients having an underlying lymphoproliferative or a plasma cell disorder including MM, lymphoplasmacytic lymphoma, MALT lymphoma and MGUS.²⁻¹³ A small proportion of CSH is noted to be related to benign disease that is autoimmune or inflammatory in nature.^{1,3} In the two case reports that we present here, the lesions in the lacrimal gland and orbital soft tissues showed localized ocular CSH with associated lymphoma without any systemic involvement. Interestingly, these two cases show differences not only in the proportional amount of lymphoma and CSH, but the characteristics of crystals seen under high power microscopy (Figs. 2 and 3).

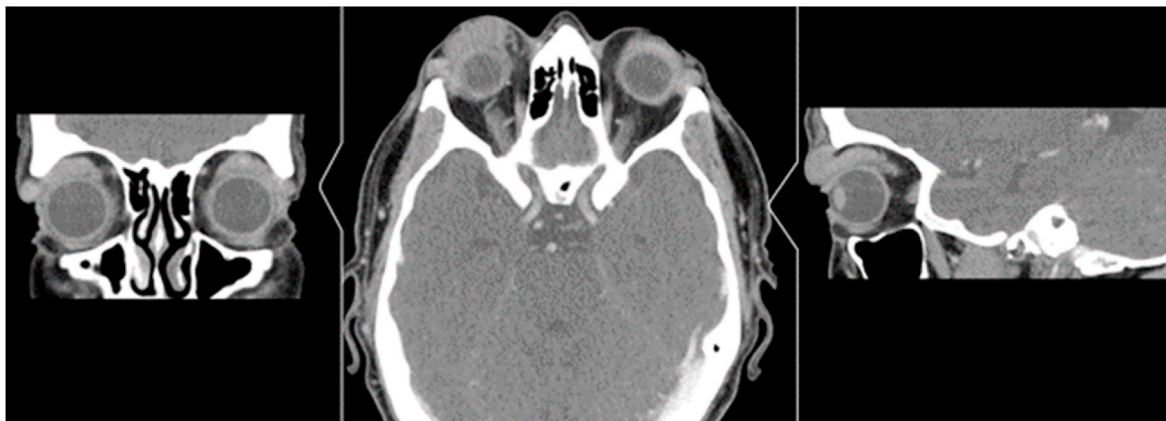


Fig. 1. Case 1 - CT scan of the orbits showing bilateral soft tissue masses superior to the globes.

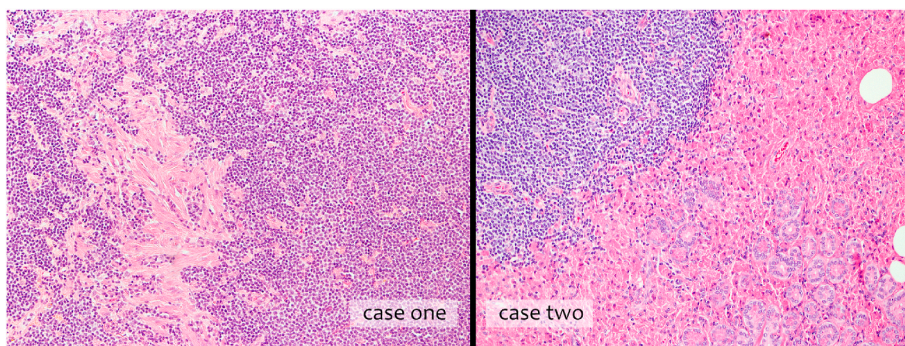


Fig. 2. A comparison of the low power appearance of the two cases: case one predominantly lymphoma and case two predominantly CSH, involving the lacrimal gland.

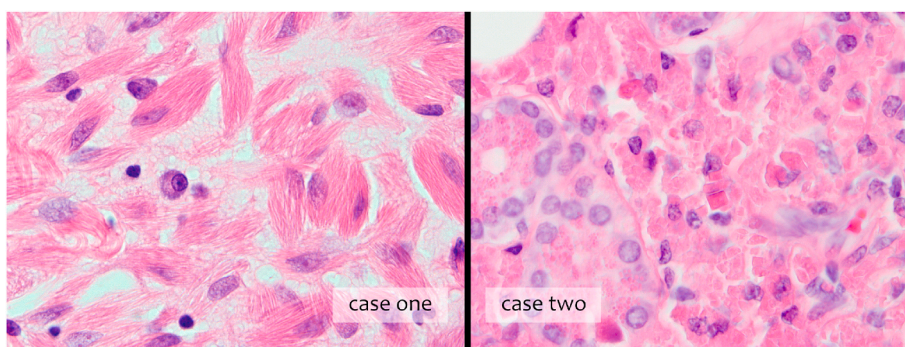


Fig. 3. A comparison of the high power appearance of the two cases: case one with linear crystals and case two with granular or rhomboidal crystals.

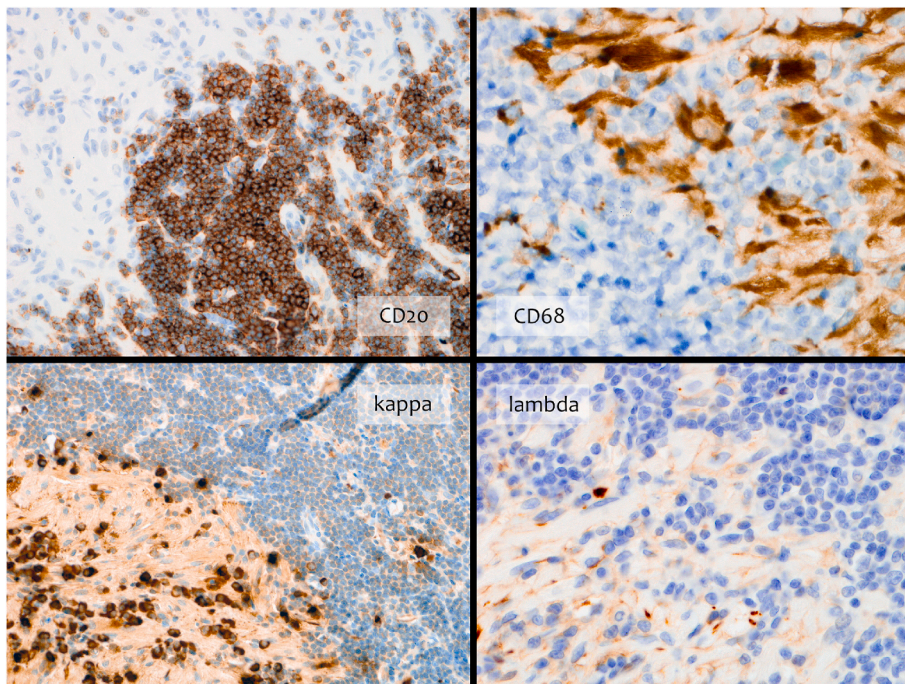


Fig. 4. Immunopanel for case one demonstrating a clonal proliferation of CD20 positive lymphocytes with kappa light chain restriction. Histiocyte population is CD68 positive.

The mechanism by which immunoglobulins contribute to crystal formation is not well understood. It is presumed that the overproduction and conformational alterations in the immunoglobulin chains or impaired enzymatic degradation by histiocytes contribute to the

accumulation of crystals.^{3,11} Most commonly, crystals seen in CSH are associated with kappa light chains, which are associated with hematological disorders such as MM.¹⁻⁴

In previous reports of CSH in ocular structures, authors speculated a

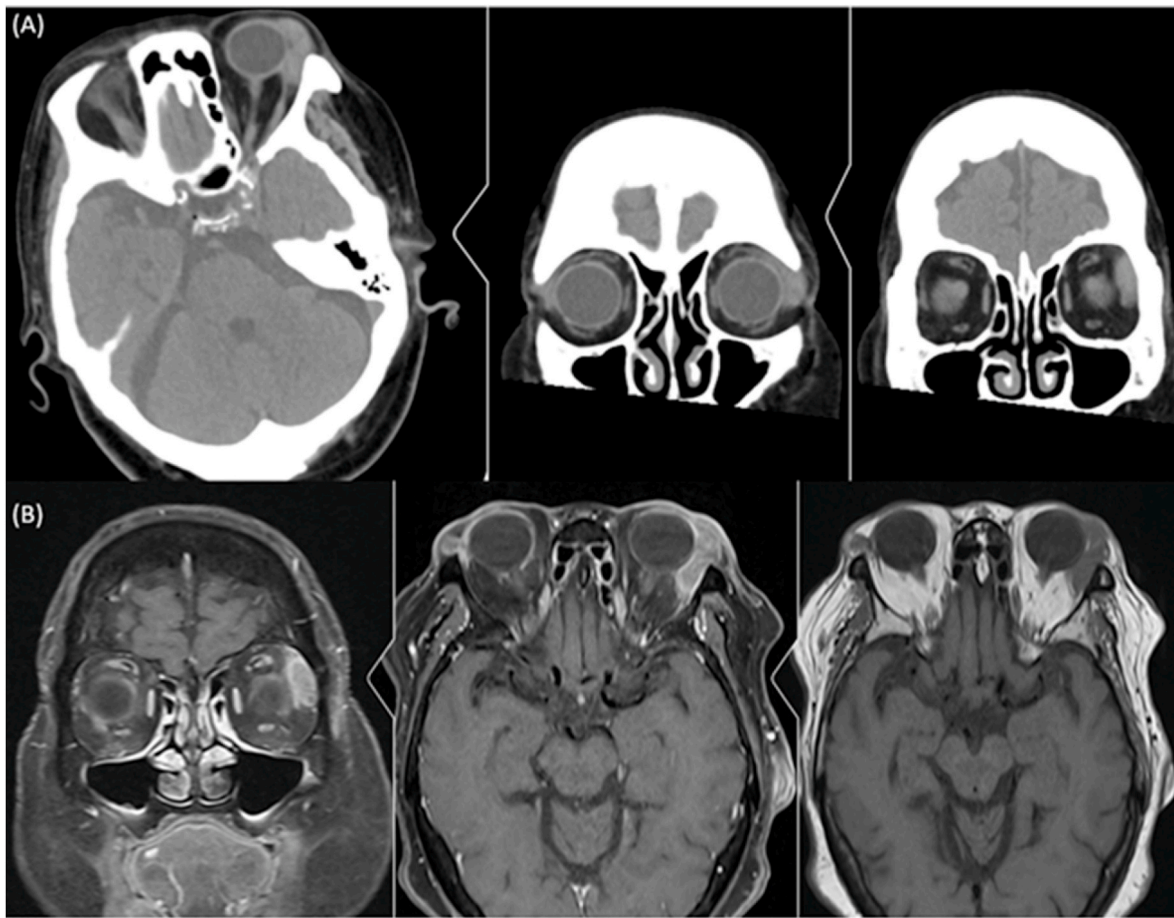


Fig. 5. a) Case 2 - CT scan of the head showing an enlarged left lacrimal gland. b) Case 2 - MRI head showing an enlarged left lacrimal gland.

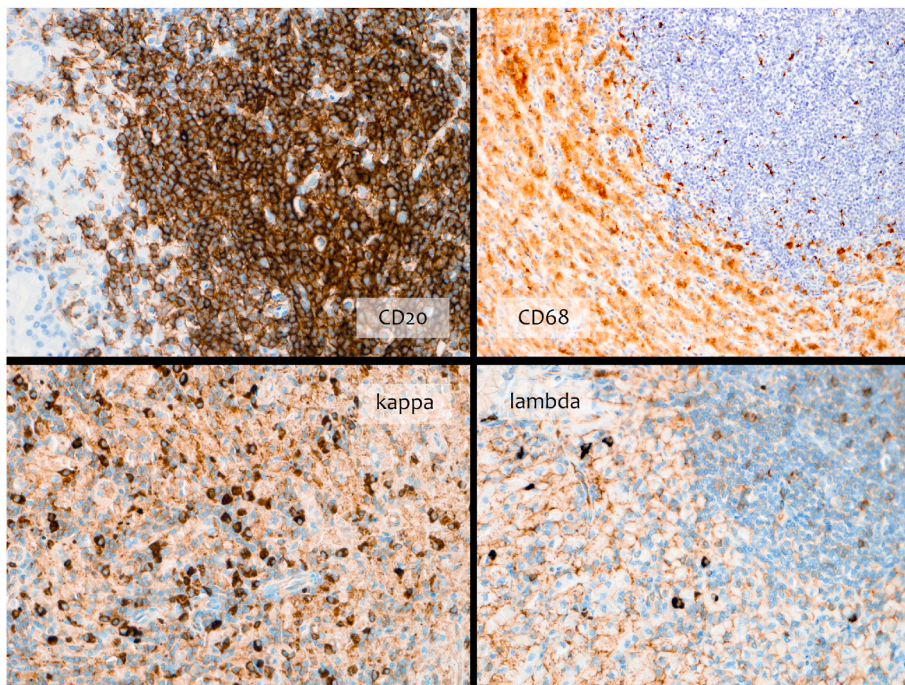


Fig. 6. Immunopanel for case 2 demonstrating a clonal proliferation of CD20 positive lymphocytes with kappa light chain restriction. Histiocyte population is CD68 positive.

Table 1
Literature review of cases with ophthalmic findings associated with CSH.

	Year	Age/ Sex	Underlying Disorder	Organ(s) Involved	Ophthalmic findings	Management
<i>Pinkerton & Robertson</i> ⁵	1969	50/ M	MM	Cornea, conjunctiva	Corneal and conjunctival crystals	Not reported
<i>Rao & Font</i> ⁶	1980	17/F	MGUS	Bilateral Conjunctiva	Exophytic papillary conjunctivitis	Topical and subconjunctival steroids were ineffective. Surgical excision of all 4 eyelids were carried out.
<i>Grossniklaus et al.</i> ⁷	1990	64/F	Paraproteinemia	Cornea, conjunctiva	Conjunctival and corneal crystals	Not reported
<i>Yamamoto et al.</i> ⁸	1991	75/ M	MM	Bilateral cornea Other: Bone Marrow, Kidney	Bilateral corneal crystals worsening over 6 years	Penetrating Keratoplasty for visual rehabilitation
<i>Garcia et al.</i> ⁹	1998	44/ M	Immunocytoxa with systemic multifocal fibrosclerosis	Bilateral orbit Other: mesenteric panniculitis, peritoneal, mediastinal fibrosis	Bilateral proptosis due to sclerosing orbital inflammation	Partial response to steroid
<i>Coupland et al.</i> ³	2002	62/F	EMZL	Unilateral lacrimal gland	Subconjunctival mass with diplopia, eyelid swelling, and proptosis, Recurred 5yrs later as lacrimal gland tumor after treatment with radiation.	Local radiation with resolution of initial mass, recurrence was treated with incisional biopsy
<i>Kusakabe et al.</i> ⁴	2006	81/F	MALT lymphoma	Unilateral lower eyelid	5-month history of a slowly enlarging tumor on her left lower eyelid, Extension to inferior oblique and inferior rectus muscles	Surgical excision and regional radiotherapy, no recurrence 1 yr post.
<i>de Alba Campomanes et al.</i> ¹⁰	2009	66/ M	MGUS	Unilateral orbit, EOM, cornea	3-year history of progressive ptosis, proptosis, external ophthalmoplegia and corneal crystals	Not reported
<i>Radhakrishnan et al.</i> ¹¹	2014	53 M	MALT lymphoma	Unilateral orbit	8-year history of painless, gradually progressive right inferior orbital swelling and proptosis	Local external beam radiation x 3weeks with complete resolution of mass and proptosis
<i>Yu et al.</i> ¹²	2014	32/ M	EMZL	Unilateral conjunctiva	Salmon coloured conjunctival patch lesion	Excisional biopsy
<i>Mittal et al.</i> ¹³	2015	58/ M	EMZL	Unilateral Conjunctiva Other: mediastinal and abdominal lymph nodes	2-year history of a subconjunctival pink 'salmon-coloured' tumor with prominent blood vessels	Complete resolution with chemotherapy (rituximab 375 mg/m2 iv; cyclophosphamide 750 mg/m2 iv; vincristine 1.4 mg/m2 iv; prednisone 40 mg/m2 iv)
<i>Boudhabhay et al.</i> ²	2018	60/ M	MM	Bilateral cornea, retina and optic nerve Other: kidney, bone marrow	2-year history of reduced vision with bilateral corneal crystals, macular and optic nerve edema with crystalline deposits	Reduction of macular and optic nerve edema with chemotherapy (bortezomib, cyclophosphamide, and dexamethasone). Corneal and retinal crystals stable.
<i>Present case 1</i>	2020	62/ M	MALT lymphoma	Bilateral orbit	1-year history of bilateral upper eyelid swelling and epiphora	Localized radiotherapy
<i>Present case 2</i>	2020	86/F	MALT lymphoma	Unilateral lacrimal gland	Incidental finding on CT scan	Localized radiotherapy

MM - multiple myeloma; monoclonal gammopathy of undetermined significance (MGUS), MALT - mucosa-associated lymphoid tissue; EMZL - extranodal marginal zone lymphoma.

potential triggering event associated with the development of CSH.^{3,4} In the case report of MALT lymphoma involving the lacrimal gland, it was suggested that the low dose radiation to treat conjunctival lymphoma contributed to abnormal immunoglobulin production and subsequent crystal formation.¹ Another case report suggested that estrogen depletion in elderly women may have contributed to the reduction of histiocyte enzymatic activity, promoting crystal accumulation.⁴ Although the latter case's hypothesis may explain the pathogenesis of the CSH involving the lacrimal gland incidentally found in one of our cases, it does not explain the previous cases seen in men, including our first case. In addition, the patient described in our first case did not receive any radiotherapy that could have contributed to localized CSH.

CSH is a rare clinical complication of systemic lymphoproliferative disease.^{4,11} However, these two case reports demonstrate extensive crystal deposition in the lacrimal and orbital soft tissues with associated lymphoma, and without systemic lymphoproliferative disease. Thus, for patients presenting with an orbital mass, it is important to consider CSH in the differential and to consider further investigations for any systemic evidence of lymphoproliferative disorders.

Since the reported cases of localized CSH in the orbit are limited, it poses challenges in accurately diagnosing, identifying the most appropriate management, and predicting the prognosis of this disease.

Challenges in correct diagnosis may arise from the dominance of histiocytes masking the underlying neoplastic lymphocytes and plasma cells and/or the deformed appearance of histiocytes as a result of the crystals that may resemble other types of histiocytosis such as histiocytosis X.^{4,15}

In the limited cases of localized ocular CSH and associated lymphoma, treatment varied from surgical excision, local radiotherapy, or a combination of both.^{3,4,11,12} Both patients in our cases received localized radiotherapy with one patient having complete resolution of disease and the other patient having 50% regression of disease on repeat imaging three months following treatment. We speculate that the difference in outcome is related to the predominance of lymphoma that was treated with radiation in the first case, in contrast to the second case where CSH was much more abundant than lymphoma. Although these two patients treated with localized radiotherapy did not suffer from any negative effects of radiation, it is still important to consider potential side effects such as radiation retinopathy, radiation neuropathy and/or significant visual impairment.¹⁴ This begs the question of whether treatment is at all necessary to change the outcomes for this indolent disease.

4. Conclusion

Although localized ocular CSH is rare, CSH should be considered in the differential of an orbital mass. These two cases demonstrate a spectrum of disease alerting physicians to a wider range of clinical and pathological features of ocular CSH (Table 2). If ocular CSH is present, further investigation for underlying local and systemic evidence of lymphoproliferative disorders is warranted. To date, it is challenging to identify the most optimal management of localized CSH given the limited body of knowledge and literature. Ultimately, ongoing follow up and surveillance will be helpful in characterizing the natural progression of CSH and determining the most appropriate and safest management of this rare disease.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patients.

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Authorship

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

Conflicts of interest

No conflict of interest exists.

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Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

IRB approval was obtained (required for studies and series of 3 or more cases).

Written consent to publish potentially identifying information, such as details or the case and photographs, was obtained from the patient(s) or their legal guardian(s).

Table 2

A summary comparing the two cases.

	Case one	Case two
Age/Gender	62 M	85F
Low power histology	Predominantly lymphoma	Predominantly crystal storing histiocytosis
High power histology	Linear crystals	Rhomboidal crystals
Response to radiotherapy	Full resolution	50% regression

Authorship

We confirm that the manuscript has been read and approved by all named authors.

We confirm that the order of authors listed in the manuscript has been approved by all named authors.

Declaration of competing interest

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