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Case Presentation

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MALT Lymphoma of the Lacrimal Gland in the Context of Multicentric Castleman Disease: Case Report

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Abstract

Introduction: Castleman Disease (CD) is an infrequent lymphoproliferative disorder. Orbital Castleman Disease is an exceedingly rare manifestation of the broader spectrum of CD. Additionally, recent studies suggest that CD can play a role in the genesis of lymphomas and other inflammatory states in the orbit.

Case report: A 51-year-old, Mexican woman, with multicentric Castleman Disease (MCD), presented with a progressively enlarging right upper eyelid mass over one year. Histopathological findings were consistent MALT lymphoma, on protocol to initiate rituximab immunomodulatory treatment.

Conclusions: Castleman Disease is a risk factor for the development of lymphomas, which can appear in areas such as the orbit. More studies are needed to further explain this relationship. Rituximab is one of the main treatment options for Castleman Disease and for MALT lymphomas, which point to a common pathophysiological pathway.

Keywords: Lacrimal gland lymphoma; MALT lymphoma; Castleman disease; Orbit; Extranodal marginal zone lymphoma; Non-Hodgkin´s lymphoma; Rituximab

Introduction

Castleman Disease (CD) is an infrequent lymphoproliferative disorder with characteristic histopathological changes and lymph node enlargement. Its etiopathogenesis is related to B and T cell impaired functions with overproduction and dysregulation of pro inflammatory cytokines and autoantibodies [1]. It can be presented as a localized form (Unicentric CD, UCD) or a more aggressive and potentially lethal systemic form (Multicentric CD, MCD). UCD usually presents as a single enlarging mass of a lymph node causing symptoms related to local compression. MCD presents inflammation, typically with fever, weight loss, edema, and/or

generalized lymphadenopathy with splenomegaly. Histopathologically, either UCD or MCD divide into three subtypes: plasma-cell, hyaline-vascular (the most frequent), and mixed-cell. The estimated incidence of CD is less than 1 per 100,000, with no predilection between sexes [2]. Treatment options depend on the subtype and severity, ranging from surgical excision in UCD to radiotherapy, corticosteroids, and immunomodulatory therapies in MCD [3-5]. Orbital Castleman Disease is an exceedingly rare manifestation of the broader spectrum of CD. It can appear in the periorbital area, in the extraconal or intraconal spaces or in the lacrimal gland, and it can be characterized by the same clinical and histopathological classifications previously mentioned. Additionally, recent studies suggest that the orbit can also be involved indirectly, by means of a common pathophysiological pathway of chronic inflammation, and autoantibodies dysregulation giving rise to orbital B-cell lymphomas and other similar conditions [6-9].This review aims to provide a summary of all reported cases of indirect orbital involvement in Castleman Disease. Additionally, we report a case of right lacrimal gland MALT lymphoma, in the context of a patient with CD**,** which to our knowledge is the second case reported in the literature [9].

Case Presentation

The patient is a 51-year-old, Mexican woman, who presented with a progressively enlarging upper right eyelid mass over one year, with no other important ophthalmic findings or B-symptoms **(Figure 1 and 2)**.

Figure 1: Right upper eyelid mass.

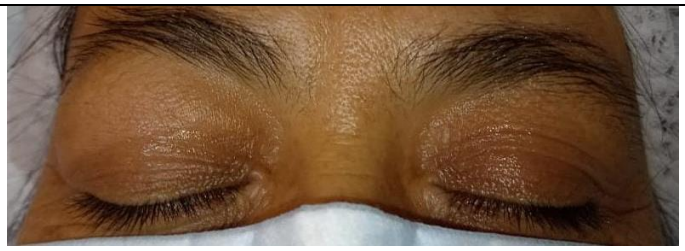

Figure 2: Mass dimensions: 30x20 mm.

Contrasted CT scan revealed a heterogenous lesion in the right lacrimal fossa with characteristics suggestive of lymphoproliferative disorder **(Figure 3 and 4)**.

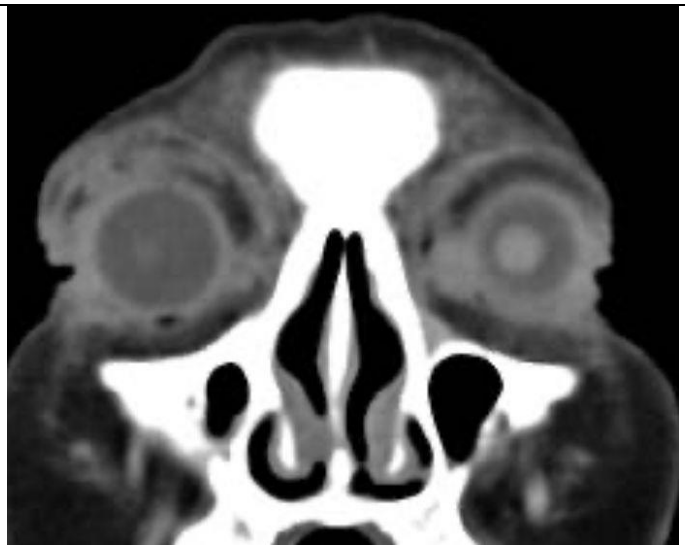

Figure 3: Contrasted CT scan: coronal view.

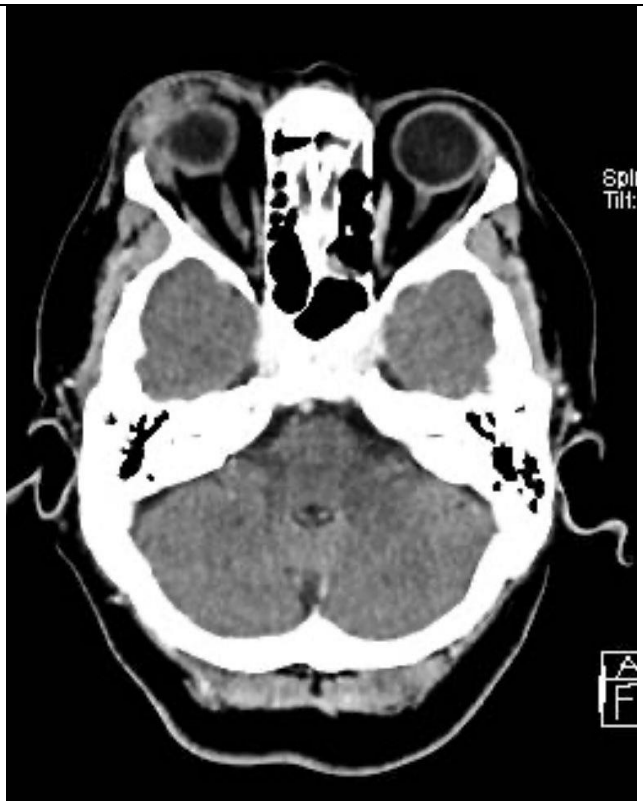

Figure 4: Contrasted CT scan: axial view.

An incisional biopsy was performed, with histopathological findings consistent with extranodal marginal zone B-cell lymphoma of Mucosa-Associated Lymphoid Tissue (MALT) lymphoma, and positive markers for CD20, BCL2, CD43, KI67 and Lambda, and negative for CD10, BCL6 and Kappa **(Figure 5)**.

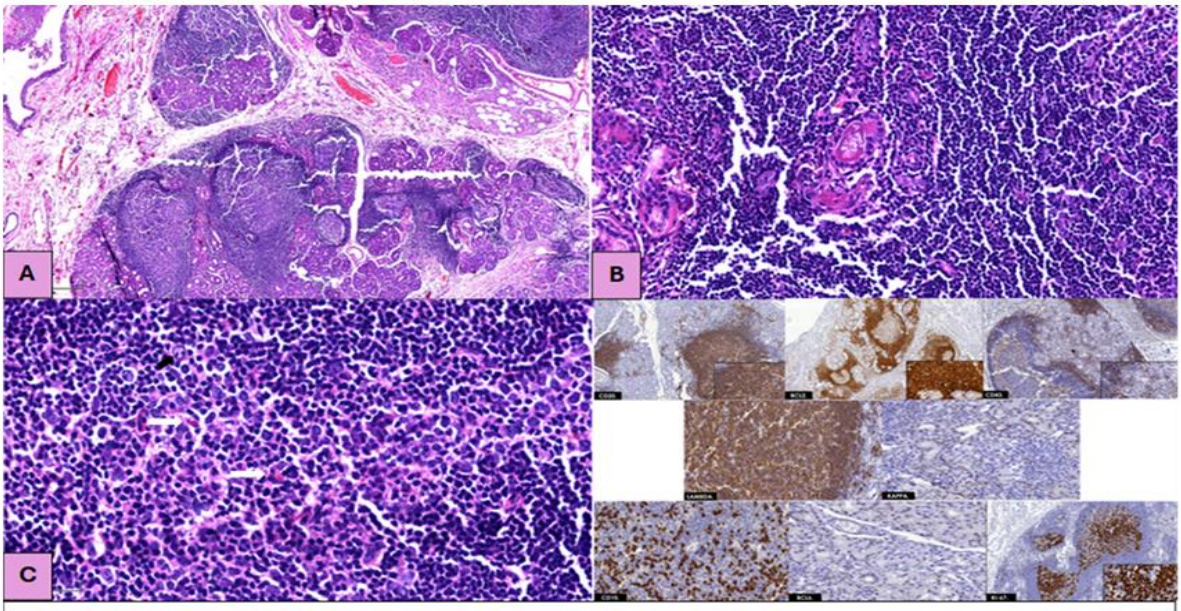

Figure 5.
A. 4×: Minor lacrimal gland with nodular lymphoid infiltrates replacing glandular tissue.
B. 10×: Lymphoepithelial lesions with centrocyte-rich infiltrate distorting gland architecture.
C. 40×: Mixed small centrocyte-like cells, centroblast-like lymphocytes, and plasmocytoid cells with Dutcher (black arrowhead) and Russell (white arrows) bodies.
Immunoprofile: CD20+, BCL2+, CD43+, λ+, κ–, CD10–, BCL6–, KI-67 ~40%.
Dx: Consistent with extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma.

Previous systemic evaluation had confirmed 15 years ago the presence of multicentric Castleman Disease (MCD). Two months after the MALT lymphoma diagnosis, the patient presented a Castleman Disease reactivation, requiring a right axillary lymph node excisional biopsy, resulting positive to the plasma-cell histopathological subtype. Over the years the patient has required multiple excisional surgeries of affected lymph nodes and chronic systemic corticosteroids. During routine screening (on protocol to initiate immunotherapy) the patient resulted positive (QuantiFERON-TB Gold) to latent tuberculosis and was therefore treated with isoniazid and pyridoxine. The oncology/hematology department is currently waiting for clearance from the infectious diseases department to initiate rituximab-based immunotherapy (375mg/m2 weekly, for 4 weeks) to target CD-20 positive B-cell proliferation associated with MCD and MALT lymphoma.

Discussion

To date, and to the best of our knowledge, after conducting a structured search in available databases, only 26 other case reports (5 of which belong to the same study) have documented direct (twenty-three cases) or indirect (three cases) orbital involvement in patients with Castleman Disease [9-30]. Most of these cases report histopathological diagnoses of Orbital Castleman Disease [10-28]. In addition, there may be a correlation with CD and an indirect orbital involvement through lymphomagenesis [9,29]. Inatani et al. described a case of bilateral orbital pseudo tumor as the initial manifestation of MCD, which later transformed into Non-Hodgkin Lymphoma (NHL), treated unsuccessfully with corticosteroids and later with rituximab (29). Matsuo et al. reported the concurrent presence of orbital extranodal marginal zone B-cell MALT lymphoma in a patient with unicentric CD, suggesting the possibility that localized lymphoproliferative activity within reactive hyperplasia could also contribute to the formation of secondary malignancies in distant anatomical places. It was successfully treated with radiotherapy and excisional surgery [9]. These cases underline the lymphoproliferative nature of CD and its potential role as a precursor or cofactor in lymphomagenesis, adding complexity to the diagnosis of a patient with CD and an orbital mass, such as our patient. The other case of indirect orbital involvement is a patient who developed bilateral lacrimal gland swelling (dacryoadenitis) with localized IgG4 elevation in the context of MCD, treated with corticosteroids [30]. In a 2002 retrospective study, 23 cases of CD + NHL (non-Hodgkin Lymphoma) and 27 cases of CD + HL (Hodgkin Lymphoma) were identified, making this association stronger with MCD

(31). Our patient presented right lacrimal involvement and was diagnosed with a subtype of NHL: extranodal marginal zone B-cell MALT lymphoma in the context of multicentric Castleman Disease, furtherly supporting this correlation.

In relation to marginal zone lymphoma (MZL), it is a B-cell lymphoma that can be classified into three subtypes according to their site of origin: extranodal MZL(EMZL), lymph node MZL, and splenic marginal zone MZL. EMZL, also known as MALT lymphoma, usually displays a favorable prognosis. In relevance to our case, it is the most common subtype of primary lymphoma of the ocular adnexa, accounting for 67-80% of cases. This relatively high incidence could mean that our patient presented EMZL from a differing pathophysiological mechanism independent from CD inflammatory mechanisms. However, the pathogenesis of MALT lymphoma has been shown to be associated with chronic antigenic stimulation, which could also mean that Castleman Disease can be considered at least an important risk factor for the development of this kind of lymphoma, given the autoimmune dysregulation it promotes [6-8]. Regarding treatment, we will describe therapeutic options for Castleman Disease and for MALT lymphoma of the lacrimal gland. In the case of CD, the consensus over the past two decades indicates that curative surgery is the gold standard for UCD and monoclonal antibody-based immunotherapy is the standard of care in MCD [4]. In a prospective study of 113 patients with HIV-associated MCD, those who received rituximab as treatment, presented a significantly less incidence of NHL (4.2 per 1000 persons/year) in contrast to those who did not receive rituximab (69.6 per 1000 persons/year) [32]. This emphasizes the role of immunotherapy for CD and the prevention of secondary lymphomas, although not specific to HIV negative cases.

In the case of MALT lymphoma of the lacrimal gland there is no consensus, however the prognosis is good with surgical excision alone, or radiotherapy [6]. Nonetheless, as Di Rocco explains, the choice of treatment for MALT lymphoma must consider various aspects including age, comorbidities, performance status, and life expectancy. The options include chemotherapy, surgery, immunotherapy, radiotherapy, or watch and wait [7]. Matsuo´s case was related to unicentric Castleman Disease, showing a favorable outcome with surgery and radiotherapy. However, in the context of multicentric Castleman Disease reactivation and the concurrent emergence of a MALT lymphoma of the lacrimal gland it is reasonable to conclude that immunotherapy becomes a better option, that could even prevent recurrences, requiring further research to support its generalized use.

Conclusions

The analysis of reported cases of CD with orbital involvement and the relationship between lymphoma and CD reveals five key findings:

- **Histopathological Association:** There appears to be a correlation between CD and B-cell lymphomas.
- **Pathophysiological Mechanism:** Chronic systemic or localized inflammatory states and hyper activation of cytokines and autoantibodies observed in Castleman Disease may contribute to lymphomagenesis and inflammation in extranodal sites, including the orbit and lacrimal glands.
- **Therapeutic Implications:** Surgical resection remains the mainstay for localized disease, while surgery, radiotherapy and **immunotherapy** are effective for MCD and associated lymphomas.
- **Prognostic Considerations:** MCD with direct orbital involvement (Orbital CD) carries a worse prognosis compared to unicentric forms, highlighting the need for early diagnosis and aggressive therapeutic intervention. On the other hand, MALT lymphoma is the most common subtype of primary lymphoma of the ocular adnexa and carries an excellent prognosis. It also is the most common form of indirect CD orbital involvement.
- **Future Directions:** Further research is needed to elucidate molecular pathways linking CD with lymphomagenesis and to optimize therapeutic strategies for orbital involvement. At present, surgical excision, radiotherapy and immunotherapy are the main available therapeutic options.

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