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REVIEW ARTICLE

Orbital lymphomas in autoimmune diseases

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Summary

Primary orbital lymphomas (OL) represent a rare sub-category of non-Hodgkin's lymphomas, but they represent a significant proportion of ocular adnexal lymphomas. The majority of these lymphomas are of the NHL B - cell type. Concerning their exact histopathological discrimination, OLs are characterized as extra-nodal marginal zone B-cell lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, and also follicular lymphoma. Based on the malignancy's aggressiveness, diffuse large B-cell lymphoma and mantle cell lymphoma are high-grade lymphomas, whereas extra-nodal marginal zone B-cell lymphoma and follicular lymphoma are recognized as low-grade. Interestingly, there are limited data regarding the relation between OLs and other diseases. In the current review we focused on the association between OL and autoimmune diseases, such as Sjögren's syndrome, Hashimoto's thyroiditis, and also myasthenia gravis.

Key words: *orbit, lymphoma, autoimmune diseases*

Introduction

Ocular lymphomas are mainly located in the lacrimal gland (50%), in the conjunctiva, in the eye lids, or rarely in the orbit. They can appear either as a primary disease, or rarely as a secondary disease, within the framework of the non-Hodgin lymphoma (NHL). Primary orbital lymphomas (OL) represent a rare sub-category of non-Hodgkin's lymphomas. In contrast, they constitute a significant proportion of ocular adnexal lymphomas as the most common malignancy representing approximately 50-60% of them [1]. The majority of these lymphomas are of the NHL B - cell type. Concerning their exact histopathological discrimination, OLs are characterized as extra-nodal marginal zone B-cell lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, and also follicular lymphoma. Based on the malignancy's aggressiveness, diffuse large B-cell lymphoma and mantle cell lymphoma are high-grade lymphomas, whereas extra-nodal marginal zone B-cell lymphoma and follicular lymphoma are recognized as low-grade. Interestingly, there are limited data regarding the relation between OLs and other diseases [2,3]. In the current review we focused on the association between OL and autoimmune diseases, such as Sjögren's syndrome, Hashimoto's thyroiditis, and also myasthenia gravis.

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Primary OL vs idiopathic orbital inflammatory pseudotumor

Among orbital mass lesions, primary OLs and also idiopathic orbital inflammatory pseudotumors (IOIP) constitute a significant proportion as the prominent lymphoproliferative disorders in this anatomic location. The first represent neoplastic lesions, whereas the last are categorized as non-neoplastic, non-infective inflammatory lesions. Pathologically discriminating these two entities is of utmost importance for handling optimally the corresponding patients. Clinically, OL may appear as a fattening - salmon protrusion of the conjuctiva, with symptoms reflecting infiltration and other pressure phenomena (diplopia, proptosis of the orbital globe, blepharoptosis) [4,5]. It is very important to stress the fact that this can be manifested as proptosis of the orbital globe of slow development. The diagnosis is based on an ocular CT scan, certainly on the tumor biopsy, on the examination for the existence of a systemic disease with the help of a thorax and abdomen and neck CT scan, on serum immunoelectrophoresis, and even on bone marrow paracentesis. Referring to the treatment, besides the surgical extraction of the tumor, localized disease radiotherapy or immunotherapy is provided, whereas in the case of systemic disease, chemotherapy is the preferable treatment strategy. The majority of the patients are diagnosed at early disease stages, demonstrating a good prognosis, since only 25% of the patients show extraorbital disease. The 5-year survival for early stage tumours is about 85%. In contrast, cases with extraorbital disease demonstrate poor prognosis up to 20% [6]. Additionally, presence of other characteristics including dacryoadenitis and diffuse inflammation that are mainly detected in IOIPs could easily lead to a confusion regarding the final accurate diagnosis. As mentioned before, OL is a target for radiation therapy and/or combined chemotherapy, whereas IOIPs demonstrate high response rates to steroid-based regimens combined or not with immune-suppressive therapeutic agents [7,8]. Referring to diagnostic tools in order to discriminate the two lesions, fine needle aspiration provides a high level of diagnostic accuracy, but tissue analysis (biopsy) leads to final and exact histopathological categorization [9].

OL in autoimmune diseases

Clinicopathological studies have shown a conjunction between OL rise and progression and specific autoimmune diseases, such as Sjögren's syndrome, Hashimoto's thyroiditis, even myasthenia gravis. Referring to the orbital localization of the lymphoma in the Sjögren's syndrome, it appears usually at a low stage, with large life expectancy [10]. Concerning clinical features, Sjogren's syndrome is characterized by progressive destruction of the salivary and lacrimal glands causing mucosal and conjunctival dryness. The OL localization in some cases is bilateral, and its rise usually appears in the upper part of the orbit [11,12]. The majority of these lymphomas are of the NHL B-cell type, and the most common subtype is the marginal zone B - cell lymphoma, to which the MALT lymphoma also belongs. They usually appear to women, in late ages (60^{th}-80^{th} decade), except the case of immunocompromized individuals, where they may appear in young age. It is very important to note that, independent of the involvement of Sjögren's syndrome or not, the clinical and immunopathologic characteristics, the prognosis, and the treatment of the lymphoma remain the same [13,14]. The association between the Sjögren's syndrome and the systemic lymphoma is already known, and more specifically, the lymphoid hyperplasia, benign or malignant, is considered to be the utmost important complication of the aforementioned syndrome [15]. Concerning Hashimoto's thyroiditis, there are very limited data and cases that presented also OLs [16,17]. In one of the studies, these entities were combined with Sjögren's syndrome in an old female patient. She demonstrated a very rare co-existence of two autoimmune diseases with her clinical image to include periorbital puffiness and a combination of dry eyes and mouth. Additionally, ocular lesion was constituted by bilateral exophthalmos, impaired eyeball movement, periorbital oedema and also chemosis. Finally, it is well established that another severe autoimmune disease, myasthenia gravis, is correlated to thymoma, but its reported relation with OL is limited and under investigation [18,19]. This rare co-existence is clinically characterized by solid orbital masses combined with diplopia and ptosis. The final biopsy diagnosis is based on a specific immune-profile that demonstrates lymphocytes positive for markers including CD20 and cyclin-D1, leading to a mantle cell lymphoma definition in an analyzed case [20].

In conclusion, primary OL -although rare non-Hodgkin's lymphomas- represent a significant proportion of ocular adnexal lymphomas and the most common malignancy implicated orbit. Co-existence with autoimmune diseases including Sjögren's syndrome, Hashimoto's thyroiditis, and myasthenia gravis is very rare, but very interesting regarding its pathology analysis and diagnosis and also therapeutic strategies that should be applied in the corresponding patients.

Conflict of interests

The authors declare no conflict of interests.

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