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RESEARCH ARTICLE

BILATERAL CONJUNCTIVAL LYMPHOMA OF THE MALT TYPE : ABOUT A CASE

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Abstract

Conjunctivallocalization of MALT lymphomais rare but remains the mostfrequentoculo-annexaltumor, either in itsprimary or secondaryform. Although the clinicalpresentationis not specific, it must besystematicallyevoked in front of anyconjunctival mass of salmoncolor. The therapeutic management ismultidisciplinary with severalmodalities. The prognosisisgenerally good.We report the case of a 62-year-old woman with bilateralprimaryconjunctival MALT lymphomawhowasinitiallyadmitted for bilateralexophthalmos of progressive onset, presenting as a painlesssalmon-pink mass in the conjunctiva of botheyes. The diagnosiswasestablished by morphological and immunohistochemicalanalysis. Treatmentwasbased on systemicmultidrugtherapy.

Introduction:-

MALT (Mucosal Associated Lymphoid Tissue) lymphoma belongs to the group of non-Hodgkin's type B lymphoma, associated to the marginal zone. Counting for approximately 8% of extra-digestive **[1]** the conjunctival involvement for this type of lymphoma remains the most frequent of the primary tumors of the orbit (25% of ocular localizations) **[2]**. Its pathophysiology is still poorly understood. It usually appears as a painless pink-salmon infiltration, which can often be localized. The diagnosis is only based on histological analysis based biopsy samples. The prognosis remains generally favorable, with treatment based primarily on a multidisciplinary approach after an exhaustive assessment of its extension. Long term monitoring is usually necessary for the detection of tumor recurrence. We report a new case of conjunctival lymphoma.

Observation:-

A 62-year-old female patient, without any notable pathological history, consulted for a non-painful exophthalmos interesting both eyes, and evolving for 1 year without any visual acuity decrease or other associated ophthalmological or extra-ophthalmological signs.

The examination of the right eye showed a visual acuity of 10/10, a non-axial, non-pulsatile, painless exophthalmos with no inflammatory signs on the skin **[figure 1-A],** and a pinkish-salmon conjunctival infiltration in the temporal area extending from the external conjunctival sac to the limbus, responsible for a slight limitation of the outward gaze **[figure 1-B].** Anterior segment examination found a clear cornea, a quiet anterior chamber, direct and consensual photomotor reflex were conserved. After dilation, we noticed an opalescent lens, and a normal ocular tone. The fundus examination showed a normal excavation papilla with a flat retina, and a good macular reflection.

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In the left eye, the visual acuity was preserved (10/10ths), and we noticed the less marqued non-axial, non-pulsatile and painless exophthalmos without any inflammatory signs on the skin **[figure 1-A].** First examination also showed a pink-salmon conjunctival lesion at the level of the external fornix, 7 mm away from the limbus, also responsible for a slight limitation of the gaze outside **[figure 1-C].** The examination of the anterior segment was unremarkable. The direct and consensual photomotor reflex was present. Ocular tone was normal, the lens opalescence and the fundus were without abnormalities. General examination found no systemic signs, including no fever, weight loss or altered general state. No lymph nodes or splenomegaly were clinically found.

A cerebral-orbital CT scan was later performed and showed a well-limited, isodense, external conjunctivo-palpebral tissue lesion process of the right orbit, measuring 27x9x23mm, in contact with the external rectus muscle and the eyeball, pushing it to the left and causing a grade 1 exophthalmos. The mass showed no infiltration of the extra-conical intra-orbital fat, bone lysis, or optic nerve involvement. On the left side, another lesion was located in the external conjunctival sac, presenting the same density, measuring 6x23mm without any infiltration of the oculomotor muscles or the optic nerve **[Figure 2].**

After a surgical biopsy of the two lesions was performed, the histological and immunohistochemical analysis were in favor of a non-Hodgkin's type B lymphoma of the marginal zone (MALT type), showing a dense lymphocytic infiltrate of small and medium cells of B phenotype (CD20+, CD5-, CD23-, CD10-, cyclinD1-, KI67 + to 20%), associated with some rare T cells (CD3+).

An extension workup was performed, including a C-TAP scan which did not reveal any secondary tumor location. There were no biological or cytological (myelogram) evidence of a hematological involvement. No signs of a liver or renal impairment. Conversion enzyme assay was normal, and there no sign of any gastro-duodenal location based on fibroscopy and biopsy fragment analysis.

The patient is later transferred to the hematology unit, and labeled as IPI 1 (international prognostic index), WHO 0, and treated with six courses of chemotherapy based on the RCHOP regimen (Rituximab-Cyclophosphamide-Doxorubicin-Vincristine-Prednisone) after implanting a subcutaneous port. The therapeutic response was good, reaching 91.5%, and marked by a significant regression of the right side process (from 17x5mm to 27x9mm), and complete disappearance of the mass on the left side after the fourth course of chemotherapy **[Figure 3,4].**

Discussion:-

Oculo-annexal lymphomas represent 2% of all extraganglionic lymphomas. Conjunctival lymphomas count for 25% of all such lymphomas **[1]**. B-cell non-Hodgkin's lymphoma is the most frequent form (98%), with four histological subtypes amoung which the extranodal marginal zone lymphoma (also called MALT lymphoma) **[2,3].**

The pathophysiology of MALT lymphoma is unclear and several hypotheses have been described. Extranodal marginal zone lymphoma (EMZL) often affects the stomach, but can affect any other organ, including the ocular region. According to several authors, it rarely results from the native organized MALT, which is located in the conjunctival sac **[12].** Usually, EMZL originates from acquired MALT following chronic inflammation triggered by persistent infections or autoimmune diseases **[12,13]** (such as dysthyroid orbitopathy, Hashimoto's thyroiditis, Sjögren's syndrome) and even in sites that do not contain epithelial structures **[4].** In general, EMZLs at different extranodal sites share some common morphologic, phenotypic, and molecular features, but the type of infectious agent differs depending on the primary site of involvement.

In gastric EMZL, H. pylori is the causative agent in almost all cases **[5],** while an association between EMZL of the ocular region and C. Psittaci was suggested in an Italian study in patients with oculo-annexal lymphoma **[7].** This association was largely criticized by several studies, pointing at that the disparity of geographical and environmental conditions **[6],** and also the variable response to antibiotic therapy. In our patient, no C. Psittaci was biologically identified, and no autoimmune pathology was found.

These lymphomas are usually primary, whereas in 10-30% of cases they are secondary tumors in patients with disseminated lymphoma **[9, 11].** Systemic lymphoma is more commonly found in patients with conjunctival sac or medial bulbar conjunctiva involvement, and in those with bilateral tumors **[11].**

Ocular adnexal lymphoma particularly affects women in their 70s and is most often located in the bulbar conjunctiva and particularly the fornices. The presentation is often unilateral; however bilateral involvement is quite common (20 to 38%) **[9].** In conjunctival locations, lymphoma often appears as a fleshy, painless salmon-pink mass with a smooth surface or sometimes as a multinodular lesion or follicular conjunctivitis **[9].**

The average consulting time is 6 to 8 months for this disease, due to a lack of clinical expression **[1,2,3].** Sometimes, symptoms might be more blatant; presenting as a red or watery eye, an exophthalmos or even a painless mass that evolves gradually **[1,9].** In our case, the patient consulted after one year for a progressively evolving exophthalmos.

Benign reactive lymphoid hyperplasia, other benign malignant tumors of the ocular surface, ocular inflammation due to scleritis, episcleritis as well as chronic follicular conjunctivitis must be ruled out **[10, 9].**

Clinical differentiation between these entities and lymphoid malignant lesions is impossible; therefore, a histopathological and immunohistochemical study is necessary to establish the positive diagnosis based on tumor biopsy **[14].**

The monomorphic B nature of the tumor infiltrate as well as the presence of lymphoepithelial lesions with a low Ki-67 index support the diagnosis of MALT lymphoma **[14].**

Molecular biology clonality assays, such as Southern blot hybridization and polymerase chain reaction (PCR), are needed to distinguish between different subgroups of oculo-annexal lymphoma **[15].**

Targeted use of fluorescence in situ hybridization (FISH) in cytospin preparations may be useful to confirm specific subclasses of NHL by showing t(11;18), t(11;14), t(3;14) translocations and may also provide valuable prognostic information **[13,14].**

An extension workup is performed to rule out a systemic localization and includes a CT scan or orbital MRI, a complete hematological workup (CBC, lymphocyte phenotyping in blood, an ESP, and a medullogram), and a CTAP scan or even a body scan.

Prognostic criteria for these oculo-annexal lymphoma are the age of the patient, the anatomical location of the tumor, the stage of the disease (at the moment of diagnosis), the level of LDH (serum lactate dehydrogenase), the subtype of the lymphoma according to the W.H.O. classification of hematopoietic and lymphoid tissues tumors, and the growth rate of the tumor cells **[12, 16].** The management of conjunctival lymphoma must involve a multidisciplinary approach, particularly with the hemato-oncology and radiotherapy team **[17].**

Due to their indolent nature, conjunctival lymphomas have several treatment options compared to other oculo-annexal lymphomas, including external radiation therapy, brachytherapy, cryotherapy, intralesional interferon injections, systemic rituximab **[17].**

Chemotherapy gives good results but its toxicity limits its use. It is still indicated in cases where radiotherapy is refused or contraindicated.

External radiotherapy with a dose ranging from 25 to 36 Gy in 10 to 15 fractions of 1.5 - 1.8 Gy, delivered over 3 or 4 weeks, gives good results for the control of this disease especially in forms localized to the orbit, and minimizes the risk of recurrence with a survival rate of 97% at 5 years and 93% at 10 years **[18].**

The indication for intrinsec injections of interferon alpha-2b, which is a glycoprotein produced by leukocytes and has an anti-tumor effect, is rather limited to low-grade lymphomas because of the risk of evolution towards a systemic lymphoma after regression of the conjunctival lesion **[19].**

The use of rituximab injections, which is a chimeric monoclonal antibody that targets the CD20 antigen, has been shown to be effective in several isolated cases of conjunctival MALT lymphoma. The adjunction of autologous serum may also increase the bioavailability of effectors within the tumor tissue, and thus enhancing the activity of rituximab**[20, 21].**

Alternatively, some studies have demonstrated spontaneous regression of low-grade conjunctival lymphoma **[22].**

Our patient had refused external radiotherapy and was therefore treated with systemic multidrug therapy.

Conjunctival lymphoma generally has a good prognosis, with a 5-year progression-free survival of 66% and a 5-year overall survival rate of 76% **[16].** The recurrence rate according to a recent study is 38%, over a mean duration of 2 years, so regular monitoring every 3 months during the first year and then every 6 to 12 months in the long term is recommended **[9].**

In our patient, the therapeuticresponse to chemotherapywas good bothclinically and CT, and a quarterly follow-up ismaintaineduntilcompleteremission.

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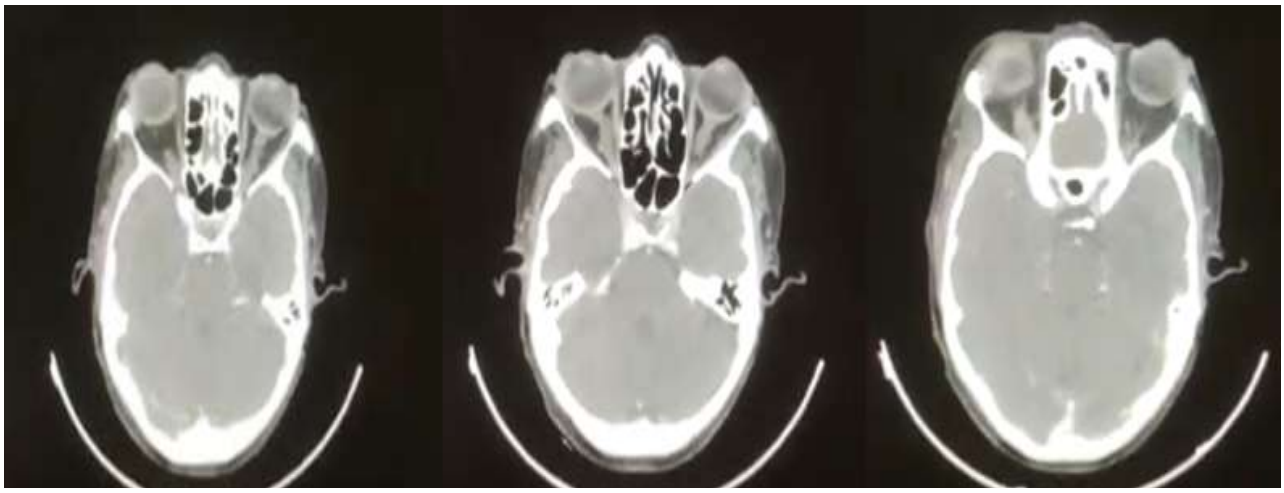

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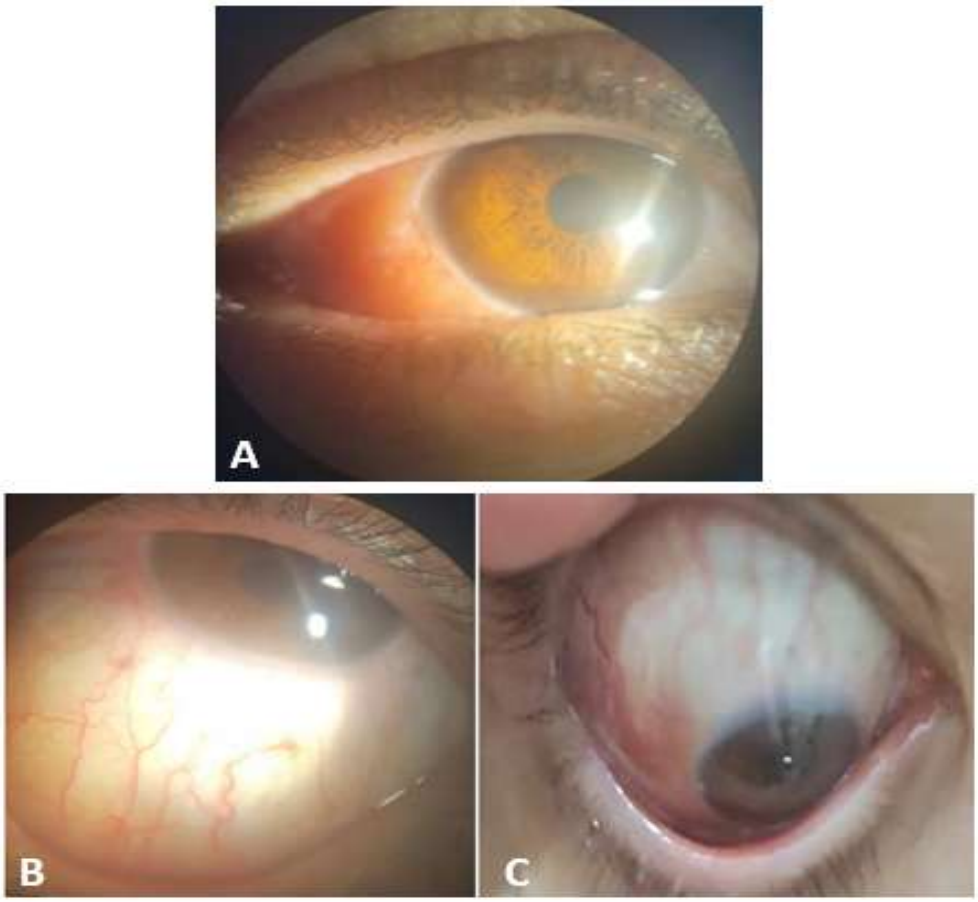

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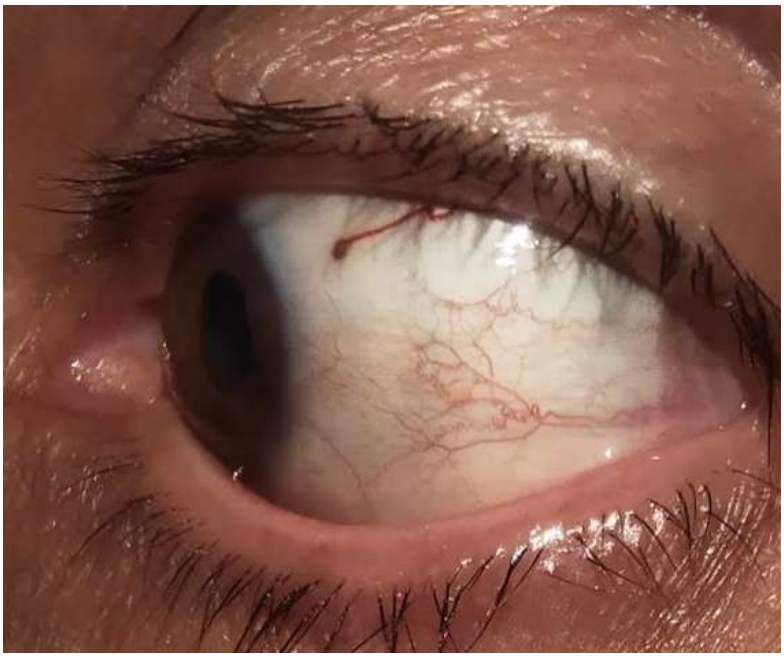

Figure 4:- Photo-colour of the lefteyeshowingcompleteregression of the conjunctivaltumour.

Conclusion:-

Conjunctival lymphoma is the second most common ocular adnexal tumor, and marginal zone B-cell lymphoma (MALT-type lymphoma) is the most frequently identified subtype on biopsy and immunohistochemical studies. Some forms of MALT lymphomas may be related to chronic inflammatory or autoimmune diseases.

Although the mainstay of treatment for localized disease is external radiation therapy, other treatment modalities have been shown to be effective in various case reports and series. Systemic treatment with chemotherapeutic agents is reserved for patients with disseminated or recurrent disease.

Because approximately 20% of patients with adnexal lymphoma eventually progress to disseminated disease, follow-up is essential and should be continued indefinitely.

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