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Medicine

OCULAR INVOLVEMENT IN MALIGNANT LYMPHOMA

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ABSTRACT:
THIS PAPERS AIM IS TO REVIEW AND TO SYNTHETIZE THE OCULAR INVOLVEMENT IN LYMPHOMA BECAUSE THE INCIDENCE OF OCULAR LYMPHOPROLIFERATIVE DISEASES, ESPECIALLY OCULAR LYMPHOMA, HAS INCREASED OVER THE LAST 20 YEARS. INSPITE OF THAT, CLASSIFICATION AND PROPER AND DEFINITIVE TREATMENT ARE STILL CHALLENGING FOR MANY DOCTORS. A GOOD COLLABORATION BETWEEN THE OPHTHALMOLOGIST AND THE HEMATOLOGIST IS NECESSARY BECAUSE ORBITAL LYMPHOPROLIFERATIONS HAVE SPECIAL CHARACTERISTICS AND PROGNOSIS. WE ALSO PRESENT 4 CASES OF LYMPHOMA -2 OF PRIMARY ORBITAL LYMPHOMA AND 2 OF NON- HODGKIN LYMPHOMA. WE HAVE CHOSEN CASES OF DIFFERENT SEVERITY AND INVOLVEMENT TO HIGHLIGHT ONES AGAIN THE IMPORTANCE OF DIAGNOSIS AND PROPER THERAPEUTICAL MANAGEMENT.

KEY WORDS: LYMPHOMA, OCULAR INVOLVEMENT, DIAGNOSIS, THERAPY

Lymphomas originate from immune system cells at different stages of differentiation and represent any neoplastic disorder of lymphoid tissue.
There are no lymph nodes in the orbit, so the orbital lesions are considered to be extraganglionar in lymphoma evaluation[5]. The only populations of lymphocytes are found in the conjunctiva and the lacrimal gland - because of this indigenous lymphocyte group the association between

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conjunctival and systemic lesions is very rare. On the other hand, the involvement of the eyelid is associated with a high risk of systemic lymphoma[6].
Over the years different **lymphoma classification systems** have been used[7]:

- Rappaport - used until the 1970s, Lukes& Collins, Kiel
- National Cancer Institute Working Formulation
- Revised European-American Lymphoma Classification (R.E.A.L)
- A unanimously accepted classification was published in 2001: World Health Organization (WHO)

World Health Organization lymphoma classification (2001)[3]:

Precursor cell lymphoma:

- Lymphoblastic lymphoma, T cell, B cell

Peripheral B-cell neoplasms:

- B-chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-prolymphocytic leukemia
- Lymphoplasmacytic lymphoma
- Mantle cell lymphoma
- Follicular lymphoma
- Extranodal marginal zone B-cell lymphoma of MALT (mucosa-associated lymphatic tissue) type
- Nodal marginal zone B-cell lymphoma
- Splenic marginal zone B-cell lymphoma
- Hairy cell leukemia
- Diffuse large B-cell lymphoma
- Burkitt's lymphoma (including Burkitt-like lymphoma)
- Plasmacytoma/plasma cell myeloma

Peripheral T and NK cell neoplasms; T-prolymphocytic leukemia:

- T-cell granular lymphocytic leukemia
- Aggressive NK cell leukemia
- Mycosis fungoides/Sezary syndrome
- Peripheral T-cell lymphoma, not otherwise characterized
- Angioimmunoblastic T-cell lymphoma
- Extranodal NK/T cell lymphoma, nasal and nasal-type
- Enteropathy-type T-cell lymphoma

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- HepatosplenicT-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Anaplastic large cell lymphoma, T/null cell systemic type
- Anaplastic large cell lymphoma, T/null cell cutaneous type

Ocular involvement in malignant lymphoma[8]

- can include orbital, conjunctival, eyelid, uveal, and vitreal localization
- is primary when it arises spontaneously from one of these locations, and secondary when it is associated with metastatic spread from an extraorbital site
- Hodgkin's lymphoma (LH) rarely affects the eye
- Non-Hodgkin's lymphoma (LNH) is the most common type of ocular lymphoma

Orbital lymphoma

- lymphoma represents more than half of all orbital malignancies (55 %)[9]
- 1–10% of NHL cases[10]
- may be unilateral or bilateral
- most frequently found in the seventh decade with a female preponderance[11]

Epidemiology

- LNH risk - 2.08%[12]
- the incidence of ocular lymphoproliferative diseases, especially ocular lymphoma, has increased over the last 20 years

Pathophysiology[13]:

Immunosuppression has long been known as the main factor contributing to the pathophysiology of orbital lymphoma.

However, recent molecular studies show the existence of viral DNA in ocular lymphoma cells, suggesting the role of infectious agents in the pathology of these disease. Other associations, with *Chlamydia psittaci* and *Helicobacter pylori* were found[14].

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Hypotheses explaining the**increased incidence** of ocular LNH[15]:

- High performance imaging techniques
- Enhanced biopsy techniques
- Higher life expectancy
- Immunodeficiency patients
- Increased access to medical care

Clinical presentation[16]

- nonspecific in general
- symptoms may be unilateral or bilateral
- depends on the location of the lymphoma
- infiltration of the globe or optic nerve is rare, so vision is usually unaffected

Conjunctiva - pink or red "salmon patch" of swollen conjunctiva/conjunctival hyperemia
Orbit - painless palpable mass generally in the superolateral quadrant

- proptosis, ptosis, diplopia, restrictions of ocular movement

Lacrimal gland – dystopia - inferomedially displaced eyeball.
Eyelids – Swelling/prolapse
General signs – preauricular/ cervical/ inguinal lymphadenopathy, abdominal mass

The **differential diagnosis** of orbital lymphoma includes the following[17]:
Conjunctival lymphoma - allergic or chronic conjunctivitis or nasolacrimal duct obstruction - they do not respond to standard medical treatment (antibiotics, glucocorticoids, and nonsteroidal anti-inflammatory drugs)

Orbital lymphoma

- Pseudotumor
- Orbital metastases
- Diffuse lymphangioma
- Lacrimal adenoma

[15] Coupland SE, Damato B. Understanding intraocular lymphomas. ClinExpOphthalmol. 2008;36(6):564–578. [PubMed]

[16] Hata, M., Miyamoto, Ogino, K., Sumiyoshi, & Yoshimura. (2013). Conjunctivalextranodal marginal zone lymphoma of mucosa-associated lymphoid tissue in the fornix: Do not overlook conjunctival lymphomas. Clinical Ophthalmology, 663. doi:10.2147/opth.s40551; Hormigo A, DeAngelis LM. Primary ocular lymphoma: clinical features, diagnosis, and treatment. Clin Lymphoma. 2003;4(1):22–29.[PubMed]; Bardenstein D. Ocular adnexal lymphoma: classification, clinical disease, and molecular biology. OphthalmolClin North. 2005;18:187–197. doi: 10.1016/j.ohc.2004.11.001.[PubMed][CrossRef]

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- Cavernous hemangioma
- Lymphoid lesions of the orbit (benign reactive lymphoid hyperplasia, atypical lymphoid hyperplasia)

Positive diagnosis[18]

All patients with ocular lymphoma need a complete workout to exclude systemic lymphoma:

- History and physical examination
- Dilated fundus examination
- Thorough examination of opposite orbit as well as the oral cavity and oropharynx
- Complete blood count, biochemistry profile
- Fine-needle aspiration and biopsy
- Liver function tests, renal function tests
- Chest x-ray
- Computed tomography (CT) and magnetic resonance imaging (MRI) of orbit, abdomen, thorax, and pelvis
- Bone marrow aspiration

Imaging[19]

Computed tomography

- moderately well-defined orbital mass, which molds to the adjacent ocular structures without bony destruction
- usually homogeneous in density, either isodense or slightly hyperdense when compared with the density of the extraocular muscles
- the lesion is usually extraconal, calcifications are rarely seen
- it may exhibit any of the following four patterns: retroocular, anterior preseptal, lacrimal gland involvement, or extension of an adnexal lesion.
- heterogeneous lesions, with bony destruction, are indicative of high-grade lymphomas, which are usually accompanied by pain
- bilateral lesions are usually a sign of systemic disease

Magnetic resonance imaging

- conjunctival disease can be missed
- the orbital mass appears isointense or hypointense on a T1-weighted MRI scan and isointense to hyperintense on a T2-weighted scan.

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- hypointense T2-weighted images are suggestive of high-grade lymphomas

Contrast-enhanced imaging techniques
Contrast-enhanced CT/MRI scans reveal mild to moderate enhancement of the lesion, and when this is seen in T1-weighted images, high cellularity of the lymphoma can be expected. It can provide differential diagnosis with other types of expansive orbital lesions.

PET-CT – greater susceptibility than CT (86% vs 72%) in systemic disease detection

Other tests
- Lumbar puncture - obtaining CSF for cytology if CNS lymphoma is suspected
- Bone marrow biopsy –stadialization of systemic lymphomas

Orbital biopsy
- essential to confirm the diagnosis
- incisional most frequently, because complete excision is difficult due to its diffuse character

Treatment[20]
There are four main treatment options for orbital lymphoma: surgery, radiotherapy, chemotherapy, and immunotherapy.

Surgery
- both diagnostic and therapeutic
- surgery as the sole treatment modality often ends with a relapse of disease - the location of the tumor makes it difficult for the surgeon to achieve both complete excision and preservation of ocular function and aesthetics.

Radiotherapy[21]
- the most common and preferred treatment modality – because most orbital lymphomas are localized.
- to reduce the chance of recurrence - the entire orbit must be encompassed in the radiation field no matter of how much of the orbit is involved
- doses of 25 to 35 Gy are considered to be curative for low-grade tumors, and 30 to 40 Gy for the high-grade varieties.
- the higher doses, especially greater than 35 Gy, are associated with significant complications:
    - conjunctivitis and dry eye - the most common acute side effects
    - keratitis and corneal ulceration.
    - cataract - the most frequent delayed side effect
    - radiation retinopathy

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Chemotherapy

- currently, there is no indication for use of chemotherapy in solitary orbital lymphomas, except in diffuse large B-cell lymphoma.
- reserved for - disseminated disease - tumors categorized as stage II or higher
- it may be administered either after surgery or in combination with radiation
- may be used in monotherapy (cyclophosphamide, chlorambucil) or combination therapy (CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone) and CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone))
- significant side effects include myelosuppression and congestive heart failure

Immunotherapy

- neoplastic cells of MALT lymphomas have been shown to express the antigen CD20 on their surfaces.
- Rituximab is a chimeric monoclonal antibody that is directed against CD20 leading to cell destruction
- high rate of relapse
- recently, combination therapy consisting of rituximab and chlorambucil has shown promising results in newly diagnosed cases of orbital lymphoma

Conjunctival lymphoma[22]

- local radiotherapy
- in some cases, a spontaneous regression after biopsy has been observed

Primary Orbital lymphoma[23]

- radiotherapy as monotherapy is very effective
- bilateral orbital disease, in the absence of systemic disease, is not an indication for chemotherapy
- approximately 50% of orbital lymphomas are limited to orbit at the time of diagnosis -> in cases where there is no evidence of systemic involvement, low doses (1500-3000 cGy) are used (with globe shielding to minimize post-radiotherapy ocular complications)
- massive orbital lesions -> radiotherapy + chemotherapy simultaneously

Secondary orbital lymphoma[24]

- are histologically more aggressive -> chemotherapy + systemic immunotherapy +/- local radiotherapy
- ongoing studies to replace chemotherapy with immunotherapy with Monoclonal Antibodies – Rituximab, Ibritumomab, Epratuzumab

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- antiangiogenic drugs eg. Talidomide - currently under investigation for use in the treatment of lymphoma (slows cancer growth)

Follow –up[25]

- Although they have an indolent evolution, B-cell lymphomas may recur in extraganglionar locations including ocular adnexa, lungs, bone marrow
- Medical visits need to be scheduled once every three months for two years, then every six months for the subsequent three years, and then every year, and must include a complete history, physical examination, and radiological investigations, if indicated – CT scan, mode B ultrasound, orbital MRI
- **Warning!** - residual fibrosis of extraocular muscles can be confused with a relapse of the disease
- The prognosis depends upon the histology, grade and stage and treatment modality used, the overall five-year survival rate is approximately 60%.

Major **prognostic criteria** for orbital lymphomas include[26]:

- tumor location
- stage and grade of the disease at the moment of the diagnosis
- immunohistochemical markers
- *serum LDH*levels - commonly *elevated* in lymphoproliferative disorders
- systemic disease

Conjunctival lymphoma - has the lowest rate of extraorbitalextension and the best vital prognosis

Orbital lymphoma

- in 50% of cases is not associated with systemic disease at presentation
- 20-25% develop systemic disease within 5 years
- with radiotherapy the survival rate at 5 years is 70%
- the majority of relapses occur within the first 2 years of treatment

Visual prognosis– impaired vision in:

- untreated or aggressive cases, with severe ptosis, corneal complications or optic neuropathy
- post radiotherapy complications:
    - Cataracts

[25] Hata, M., Miyamoto, Ogino, K., Sumiyoshi, & Yoshimura. (2013). Conjunctivalextranodal marginal zone lymphoma of mucosa-associated lymphoid tissue in the fornix: Do not overlook conjunctival lymphomas. Clinical Ophthalmology, 663. doi:10.2147/opth.s40551; Ahmed AH, Foster CS, Shields CL. Association of Disease Location and Treatment With Survival in Diffuse Large B-Cell Lymphoma of the Eye and Ocular Adnexal Region. JAMA Ophthalmol. 2017;135(10):1062-1068

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- Keratitis
- Optic neuropathy
- Retinopathy

CLINICAL CASES

Primary orbital lymphoma

Case 1

T. A., male, 57 year old, no important familial or personal medical history

Simptoms - The appearance, three years ago, of a painless left orbital mass [Fig.1], which has progressively increased in size, causing diplopiabegining 6 months ago

Signs:LE: Upgaze diplopia,proptosis, orbital and palpebral mass of about 3.5 / 1 cm, renitent content, polilobate, dystopia with inferolateral displacement of the globe [Fig.2]

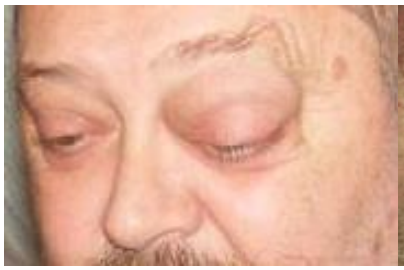

Figure 1- left orbital mass

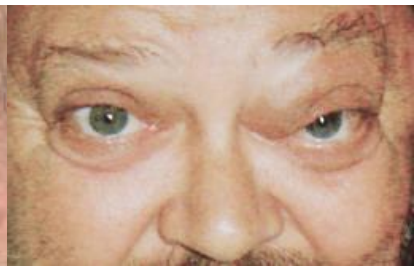

Figure 2 – orbital mass that causes dystopia

LE fundus examination – normal, no optic disc edema, no retinal changes

Imaging - MRI with contrast: left orbital mass of approximately 13 mm length and 34 mm diameter, irregular contour, invades superior and lateral rectus muscle, levator muscle, lacrimal gland and superior ophthalmic vein.

Surgery: incisional biopsy

Histopathological examination - B cell non-Hodgkin's lymphoma

The patient is then sent to the haematology department where chemotherapy is started, with favorable evolution [Fig.3]

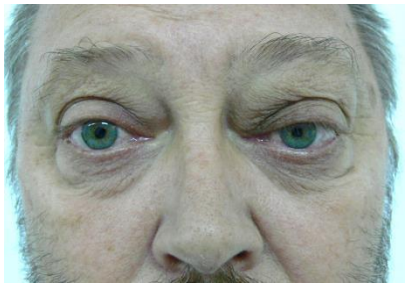

Figure 3 – Good outcome after treatment – regression of signs

Case 2
C. C. male, 67 year old., no familialmedical history
Personal medical history – Lateral cervical adenopathyfor about 2 weeks
Simptoms - the appearance, 1 month ago, of a painless conjunctival massin the left inferior fornix, that progressively increased in size despite the local antibiotic and anti-inflammatory treatment
Signs:LE:pink conjunctivalmass in the inferior fornix, soft consistency, mobile, that invades the surrounding connective tissue, about 1 cm long [Fig.4]

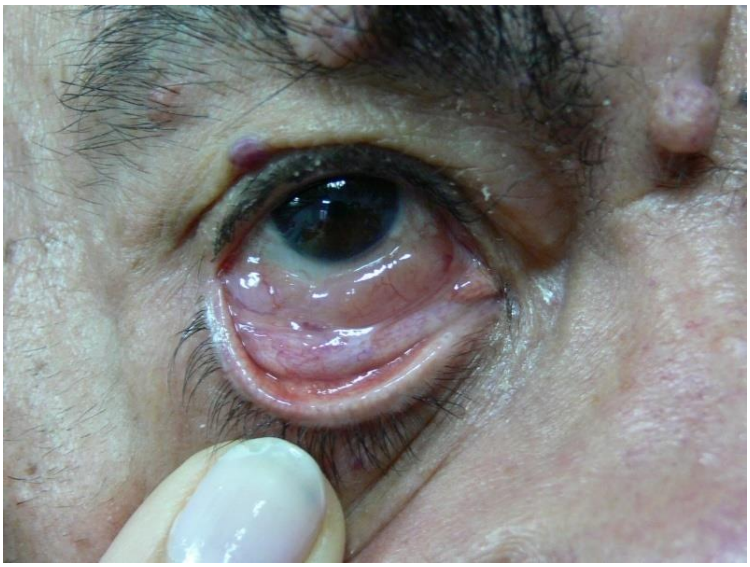

Figure 4 - Conjunctival tumor located in the fornix

Surgery: Incisional biopsy
Histopathological examination: B-cell non-Hodgkin's lymphoma
Secondary orbital lymphoma
Case 1
C.E. female, 85 year old, no familialmedical history
Personal medical history - Non-Hodgkin B-cell Lymphoma diagnosed one and a half years ago - refuses chemotherapy for personal reasons
Simptoms - the appearance for about 2-months, of a painless, palpable upper eyelid mass that progressively increased in size invading about 2/3 of the eyelid, causing ptosis
Signs:LE: Upper eyelid mass of approximately 1.5 / 2.5 cm with broad implantation base, which determines the mechanical ptosis [Fig.5]

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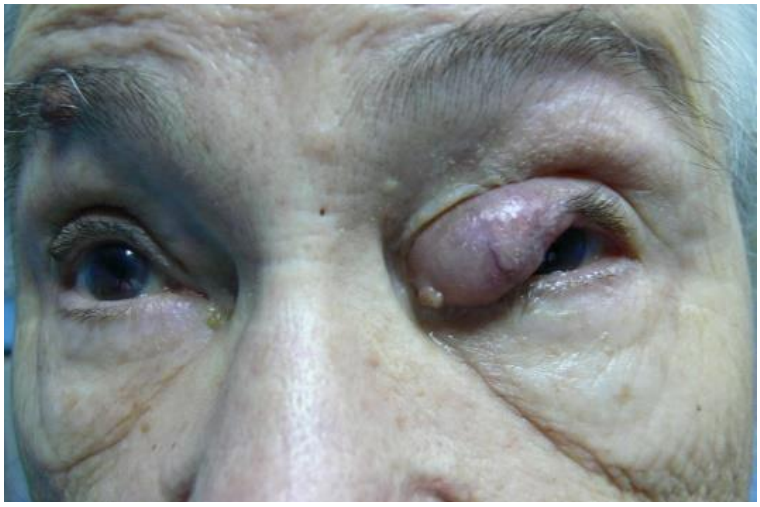

Figure 5 - Upper eyelid tumor with mechanical ptosis

Surgery:excision of the upper eyelid tumor, reconstruction of the upper eyelid using the Cutler-Beard technique [Fig.6,7]

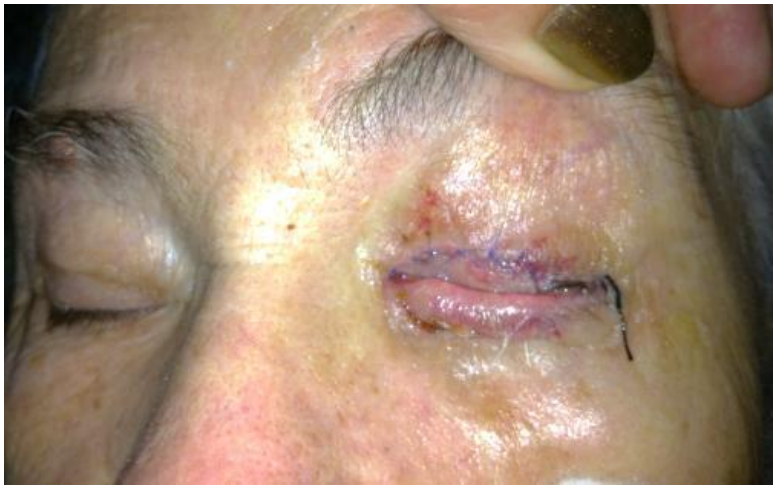

Figure 6 – First day after surgery - Cutler-Beard technique

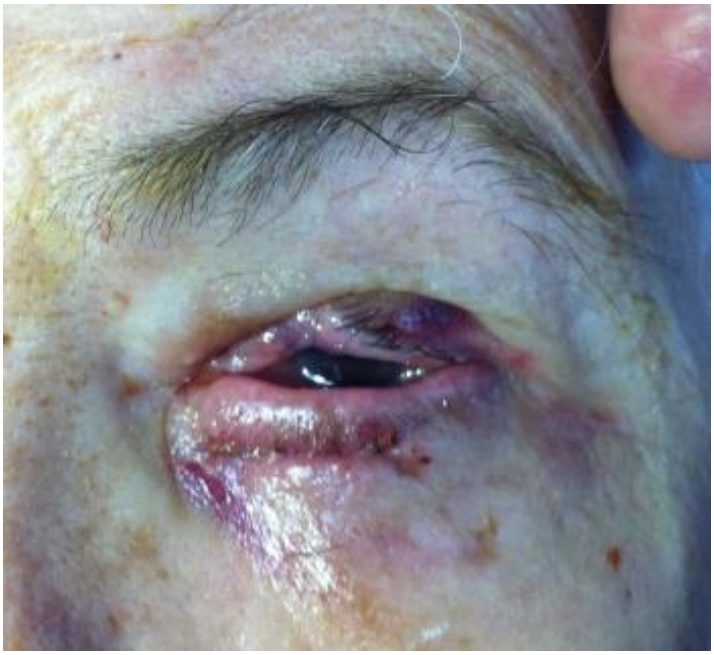

Figure7 – One month after surgery – the palpebral fissure is opened

Histopathological examination: B-cell non-Hodgkin's lymphoma
The patient is advised to the haematology department where treatment for systemic non-Hodgkin's B-cell lymphoma is started, with favorable evolution

Case 2
C.I., male, 56 years old
Personal medical history - Non-Hodgkin B-cell Lymphoma diagnosed 6 years ago. Initially with chemotherapy (Vincristin, MabThera, Endoxan and Fludara), stops treatment for personal reasons 5 years after the diagnosis
Simptoms- 6 months after cessation of treatment, it claims the appearance of a lateral canthal mass that has increased rapidly in sizeinvading the upper and lower eyelid [Fig.8]
Signs: RE - lateralcanthal mass of approximately 7 cm comprising ½ external lower and upper eyelid, deep tumoral invasion - including the palpebral and bulbar conjunctiva up to the limbus in the lateral quadrants

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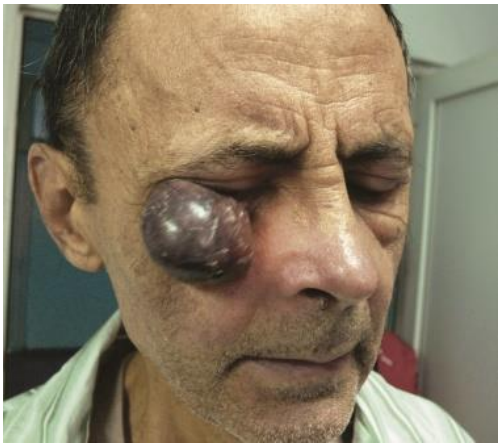


Figure 8 – Massive tumor invading the lower lid and lateral canthus

Surgery: tumor excision – lateral half of the upper and lower eyelid, lateral canthus, lateral quadrants af the conjunctiva up to the limbus, reconstruction using skin grafts and oral mucosa, blepharoraphy [Fig.9-11]

Figure 9 – Excised tumor

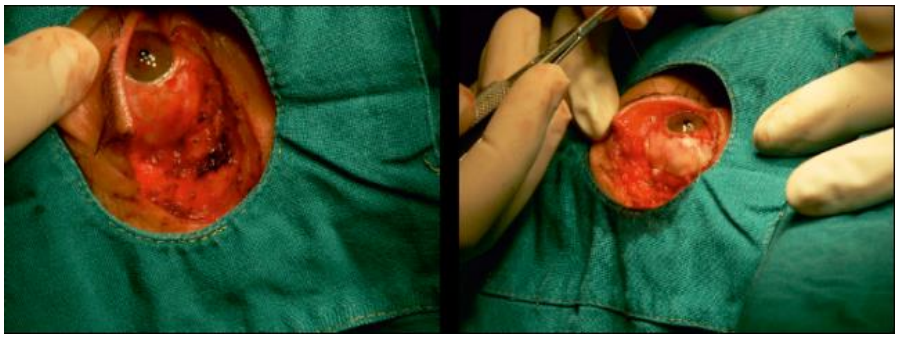


Figure 10 – The remaining coloboma following the tumoral excision

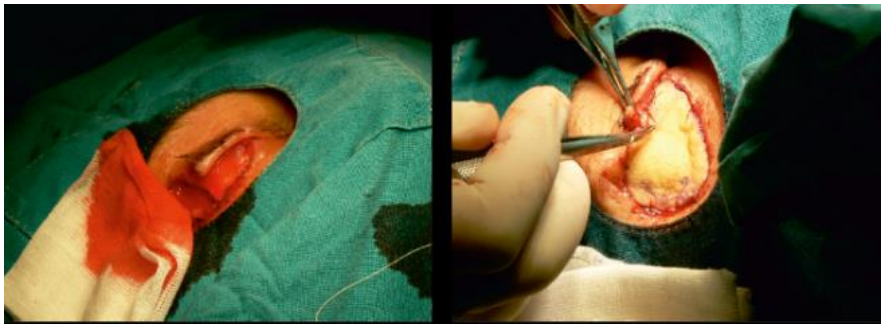


Figure 11 – Reconstruction using oral mucosa and a full thickness skin graft

Histopathological examination: B-cell non-Hodgkin's lymphoma
6 weeks postop - good ocular motility, good functional and aesthetic result [Fig.12 a, b]

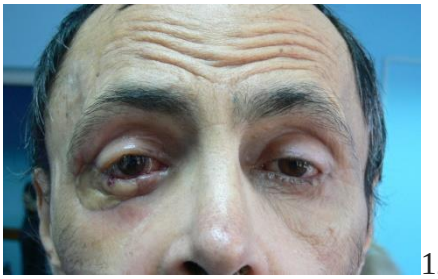
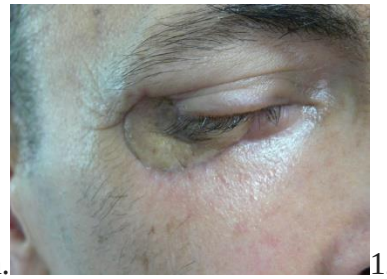

12a.

12b.

Figure 12 (a+b) – 6 weeks after surgery

IN CONCLUSION, we note that in the last 3 years we have found an increase in the incidence of these cases in the clinic, but at the moment it is difficult to estimate if this is due to the increase of the incidence of orbital B cell lymphoma or the increase of addressability to the physician on the background of improving health education.
Also, the palpebral or conjunctival tumors represent only the "tip of the iceberg" and, postoperatively, patients require haematological surveillance for systemic damage and specialized treatment.
A good collaboration between the ophthalmologist and the hematologist is necessary because orbitallymphoproliferations have special characteristics and prognosis.

Disclosure
The authors report no financial conflicts of interests in this work.

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