

Interdisciplinary correlations in non-Hodgkin malignant lymphomas of the ocular annexes – case reports

Corelații interdisciplinare în limfoamele maligne non-Hodgkin ale anexelor globului ocular – prezentări de caz

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Abstract

Ocular annexes lymphomas are malignancies which occur in the conjunctiva, eyelids, lacrimal gland and orbit. Ocular annexes lymphoma is primarily a disease of older adults, with a slight female preponderance. Most lymphomas are low-grade B-cell lymphomas, with marginal zone lymphoma being by far the most common type. Marginal zone lymphoma typically involves the ocular annexes primarily, whereas other types of low-grade B-cell lymphoma often involve the ocular annexes secondarily. High-grade B-cell lymphomas only occasionally involve the ocular annexes, and T-cell lymphoma, NK-cell lymphoma, and Hodgkin lymphoma are only rarely encountered at this site.

The aim of the two cases presented in this paper is to discuss the diagnostic and therapeutic problems in non-Hodgkin malignant lymphoma with ophthalmologic extension and to underline the importance of para-clinical investigations in early diagnosis of this neoplasm. The clinical features, histopathological findings and differential diagnosis of lymphoproliferative lesions of the ocular annexes are discussed.

Keywords: non-Hodgkin lymphoma (NHL), ocular annexes, conjunctivitis

Rezumat

Majoritatea limfoamelor maligne non-Hodgkin sunt localizate în nodulii limfatici, dar se pot întâlni și la nivelul orbitei, conjunctivei, pleoapelor, glandei lacrimale și foarte rar intraocular. Limfomul anexelor oculare este de obicei o afecțiune a pacienților vârstnici, cu o ușoară preponderență la sexul feminin. Majoritatea limfoamelor sunt cu celule B de grad mic, limfomul zonei marginale fiind de departe cea mai frecventă formă întâlnită. Acesta afectează de obicei primar anexele oculare, pe când alte tipuri de limfom apar secundar la acest nivel. Limfoamele cu celule B de grad înalt apar ocazional la nivelul anexelor oculare, limfomul cu celule T, limfomul cu celule NK și limfomul Hodgkin sunt rar întâlnite la acest nivel.

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Lucrarea de față își propune abordarea problemelor de diagnostic și tratament în două cazuri de limfom malign non-Hodgkin cu localizare secundară oftalmologică și sublinierea importanței investigațiilor paraclinice în diagnosticul precoce al acestei malignități. Sunt discutate aspectele clinice și histopatologice întâlnite în leziunile limfoproliferative de la nivelul anexelor oculare.

Cuvinte-cheie: limfom malign non-Hodgkin, anexe oculare, conjunctivită

Introduction

The non-Hodgkin's lymphomas (NHLs) comprise a heterogeneous collection of lymphoproliferative malignancies, which are most common in people aged over 55 years. Diffuse large B-cell lymphoma is the most common type of NHL, accounting for approximately 30% of all new patients. Follicular lymphoma is the second most common NHL sub-type, and accounts for a further 22% of cases. While the incidence of most other cancers is decreasing, that of NHL is increasing steadily. During the 1970's and 1980's, worldwide NHL incidence rose by 3-4% per year (1). This rise has slowed in the 1990's, but an annual increase of 1-2% is still being recorded. Over the last five years, the introduction of monoclonal antibodies, and specifically the anti-CD20 monoclonal antibody, rituximab, has radically changed treatment of B-cell NHL (1).

Lymphoid neoplasms of the ocular adnexa include lymphomas of the conjunctiva, lacrimal glands, eyelids and orbit. The new "W.H.O. Classification of Tumours of Haemopoietic and Lymphoid Tissues" is the most suitable for subdividing the ocular adnexal lymphomas (2).

The pathogenetic role of several microorganisms is different in ocular adnexal malignancies. Chronic antigen stimulation is implicated as a causative agent in the development of some mature B-cell proliferations; for example, there are associations involving *Helicobacter pylori* with gastric or conjunctival MALT (Mucosa Associated Lymphoid Tissue) lymphoma and *Chlamydia psittaci* with ocular adnexal lymphoma (3). Unlike cervical cancer where a single infectious agent, human papilloma virus is found in greater than 99% of le-

sions, multiple organisms may play a role in the etiology of certain ocular adnexal neoplasms by acting through similar mechanisms of oncogenesis. However, similar to other human malignancies, the role of infectious agents in ocular adnexal neoplasms is most likely as a cofactor to genetic and environmental risk factors (4).

Conjunctival lymphoma should be included in the differential diagnosis of chronic conjunctivitis. Persisting signs and symptoms of conjunctivitis not responding to standard treatment should prompt biopsy (5, 6). Conjunctival low-grade lymphoma may share similar clinical features with allergic conjunctivitis. Ophthalmologists should be concerned that primary conjunctival low-grade malignant lymphoma can be misdiagnosed as allergic conjunctivitis (7).

Conjunctival lymphomas have different treatment options compared to other adnexal lymphomas: radiotherapy (external beam radiation), brachytherapy, cryotherapy, intralesional interferon injections, systemic rituximab, and observation. Radiotherapy that has been demonstrated to be highly effective for both low and high-grade tumors, can however be associated with a high percentage of short-term side effects and long-term complications. Brachytherapy can provide local tumor control, but can also cause many complications. Cryotherapy may be used in certain tumor locations, but has a high recurrence rate. Both interferon and rituximab show promising results for treating low-grade tumors while avoiding the complications associated with radiotherapy (8).

Rituximab is the first monoclonal antibody to consistently improve survival rates of patients with a malignant disease. Its excellent efficacy in combination with cytotoxic chemotherapy, together with its favorable toxicity pro-

file, establishes rituximab as an indispensable component of modern standard immunochemotherapy (9).

Clinical Case I

A 60 years old female presented with weakness, fatigue, upper and lower left eyelids oedema, bilateral laterocervical and sub-mandibular lymph-nodes. From the associated diseases we noticed hypothyroidism. Ophthalmologic examination identified a 3/2 cm tumor on the lower left eyelid adherent to tarsus and conjunctival lymph stasis (*Figure 1*).

Three years before, the patient had deglutition dysfunction for solid foods, blepharoconjunctivitis, painless, firm, nonadherent sub-mandibular lymph-nodes, hypertrophy of tonsils, especially on the right side. The presumptive diagnosis was non-Hodgkin malignant lymphoma of the tonsil, but the histopathological examination of the biopsy did not confirm it. Two months later, she presented multiple bilateral laterocervical lymph-nodes. The histopathological diagnosis after the right amigdalectomy: non-Hodgkin malignant lymphoma with B cells, grade 2. The cells were CD45 (common leucocytes antigen LCA) positive, CD20 (marker for B cells) positive, and CD3 (T



Figure 1. Case I. Non-Hodgkin malignant lymphoma of the lower eyelid

cells marker) negative. Computer tomography: lymphadenopathies in the superior interazygoscaval space and in the aortopulmonary window. Magnetic Resonance Imaging: the increasing of the caliber in the upper and lower left eyelids with high signal T2 and STIR, without intracranial secondary determinations and without intraorbital space-occupying lesion. Differential diagnosis is made with allergies, renal oedema, Meibomian gland carcinoma, orbital cellulitis, eyelid phlegmon and chronic dacryocystitis. The histopathological examination of the eyelid biopsy confirmed non-Hodgkin malignant lymphoma with B cells (*Figures 2a, 2b*).

The disease presented periodic remissions under chemotherapy. A full healing was not expected in the systemic malignancy, and the patient died because of the systemic complications.

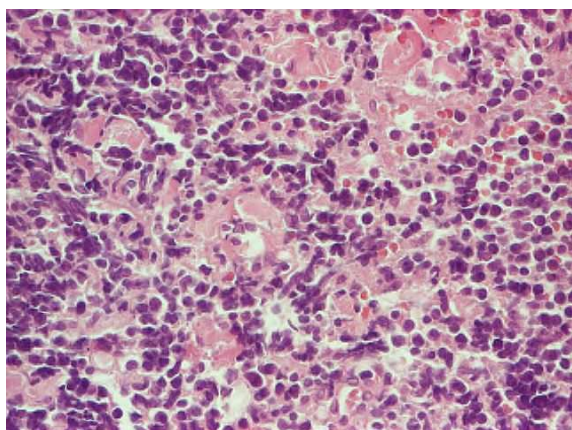


Figure 2a. Case I. Non-Hodgkin malignant lymphoma of the eyelid (HE 20x)

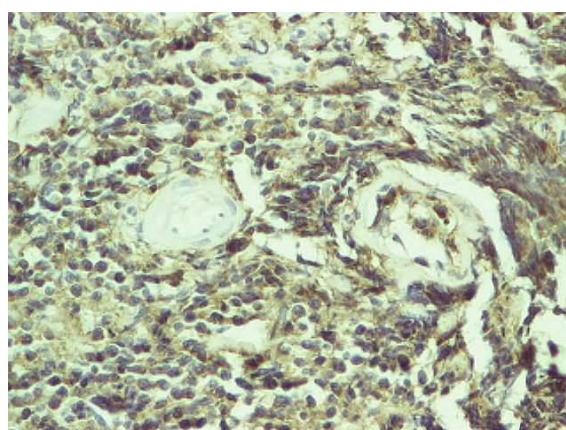


Figure 2b. Case I. Non-Hodgkin malignant lymphoma of the eyelid. Immunohistochemical staining CD20+ (20x)

Clinical case II

A 32 years old female was admitted in August for a chronic redness of the right eye, which have been present since May. From the medical history we found out that in March the patient suffered a cervical conization for Exacerbated Dysplasia CIN III (Cervical Intraepithelial Neoplasia), H-SIL (High Grade Squamous Intraepithelial Lesion) and that she was under topical treatment with antibiotics and corticosteroids drops for chronic conjunctivitis.

Ophthalmologic examination identified a 12/5 mm "salmon-coloured" subconjunctival infiltrate, in the inferior part of the right eye (Figure 3).

The lesion was suspected to be a malignant non-Hodgkin conjunctival lymphoma, but the positive diagnosis could only be ascertained histologically.

Differential diagnosis is made especially with the following diseases: chronic conjunctivitis, allergic conjunctivitis, conjunctival papilloma, conjunctival haemangioma, conjunctival lymphangioma, conjunctival naevus, malignant conjunctival tumors (epithelioma, melanoma, lymphosarcoma, reticulosarcoma), telangiectatic granuloma.

The histopathological examination of the conjunctival biopsy showed a follicular pro-

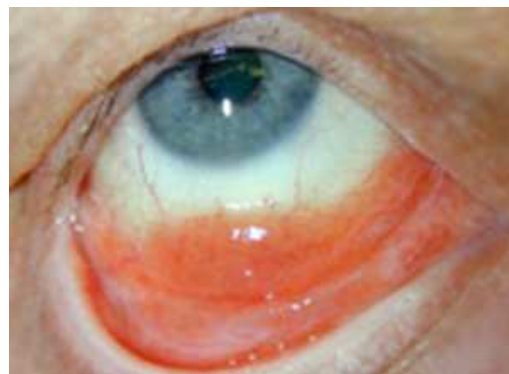


Figure 3. Case II. Conjunctival non-Hodgkin malignant lymphoma

liferation of large B lymphocytes which enlarged the follicular centers, and an intense proliferation of follicular dendritic cells (revealed with CD21). Immunohistochemical staining revealed that tumor cells were intensely positive for CD20, pax-5, CD19, bc16, mildly positive for bc12 and negative for CD10 and CD43. The proliferation index was very high and the expression of p27 was lost. The expression of p53/p21 pointed to the fact that there was no mutation on p53.

Histopathological diagnosis: Conjunctival follicular lymphoma grade 3a.

The patient was admitted to the Haematological Clinic for further investigations and special treatment.

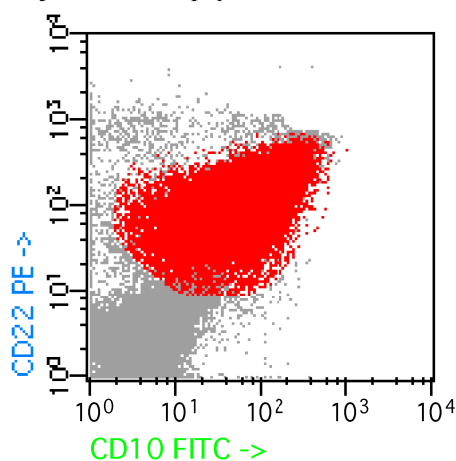


Figure 4a. Case II. Immunophenotyping of bone marrow by flow cytometry.

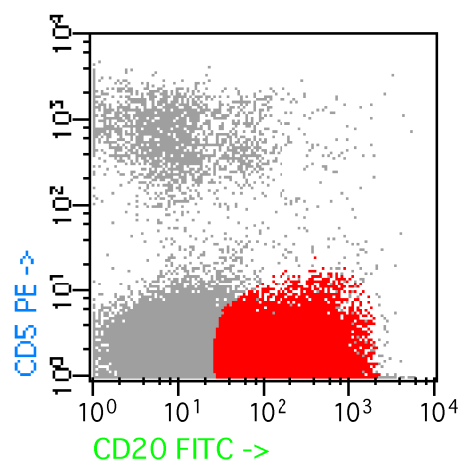


Figure 4b. Case II. Immunophenotyping of bone marrow by flow cytometry.

Immunophenotyping by flow-cytometry of the bone marrow: 51% lymphoid population with following markers: CD19+, CD22+, CD10+(83%), CD20+, HLA-DR+, CD5-, CD23-, FMC7+(6.5%). Conclusion: Follicular non-Hodgkin lymphoma (Figures 4 a,b).

Discussions

For the first case, the disease started with ophthalmologic symptoms (eyelid oedema of unknown etiology), and the diagnosis was established after approximately 1 year, following histopathological examination of the right tonsil. The biopsy of the left eyelid tumor confirmed the suspicion of non-Hodgkin malignant lymphoma with ophthalmologic extension.

Specialty literature quotes:

- association of non-Hodgkin malignant lymphoma of the ocular adnexa with *Chlamydia psittaci* infection and the regression of lymphoma after doxycycline treatment (10, 11, 12).
- thyroid orbitopathy predisposes to local lymphoma (13, 14).

The following aspects came into our attention in the second case:

- non-Hodgkin malignant lymphoma appeared on a 32 years old female patient, while the age reported in the specialty literature is over 55 years (1).
- conjunctival non-Hodgkin malignant lymphoma was treated as a chronic conjunctivitis, a frequent confusion reported by many authors (5, 7).

The expression of bc1 2 is weak in tumor cells, but this aspect is a characteristic of the follicular high grade lymphoma. Morphology of tumor cells, expansion of dendritic cells and the high expression of bc1 6 support the diagnosis of follicular lymphoma. The lack of p27 expression predicts an unfavorable outcome in aggressive lymphoma.

The case remains dependant on other techniques for a final diagnosis: PCR for IgH and FISH for bc1 2 translocation.

Malignant systemic lymphoma can have secondary intraocular determinations. The flow-cytometry of the aspiration fluid from anterior eye chamber is a very useful method for diagnosis in such cases.

Conclusions

The extraganglionic localizations of the non-Hodgkin lymphomas cases are rare. The capacity of the lymphoma recurrence even during the specific treatment underlines the high-grade malignancy of the tumor (15).

The treatment of eyelid modifications resumes to specific systemic treatment of the non-Hodgkin lymphoma without surgical intervention (16).

Any suspected eyelid or conjunctival change must be investigated not only from an ophthalmic point of view but also by following the general clinic aspect.

The biopsy is a very useful and efficient method in the examination of the suspected lesions of the ocular adnexa.

The prognosis of the patients with non-Hodgkin lymphomas of the ocular adnexa is being influenced in a great part by the moment of diagnosis and the therapeutical methods applied.

The early diagnosis of this malignant disease needs a prompt interdisciplinary collaboration; clinical findings must be rapidly correlated with the para-clinical investigations, the latter being of a great importance in establishing the stage of the tumor, the best therapy, and the prognosis.

Very attentive and long-term systemic follow-up of the patients is required, because related systemic lymphoma can manifest many years later.

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