VERSITA

Cent. Eur. J. Med. • 6(6) • 2011 • 826-829
DOI: 10.2478/s11536-011-0081-6

Central European Journal of **Medicine**

Orbital lymphoma mimicking Graves' ophthalmopathy: a case report

Case Report

Barbara Wolyniak[1], Anna Lewczuk[1], Lukasz Obolonczyk[1*], Hanna Majewska[2], Krzysztof Sworczak[1]

[1] *Department of Endocrinology and Internal Medicine, Medical University of Gdansk, 80-809 Gdansk, Poland*

[2] *Department of Pathology, Medical University of Gdansk, 80-809 Gdansk, Poland*

Received 12 May 2011; Accepted 18 July 2011

Abstract: Orbital tumor is a rare presentation of lymphoma. Unspecific symptoms, local infiltration, chronic progression may mimic other more common orbital diseases and often make the diagnosis difficult. We report a case of orbital non-Hodgkin lymphoma initially diagnosed as Graves' disease. A 65-year-old woman was admitted to the Department of Endocrinology with a diagnosis of a left eye tumor. On admission, apart from the tumor, exophthalmos and the upper eyelid proptosis were present. The lesion had been observed for two years before hospitalization. Due to the muscle infiltration, as detected on computed tomography scanning and magnetic resonance imaging, Graves' disease was suggested. The thyroid function was normal. Further diagnosis performed during hospitalization revealed lymphoplasmacytic lymphoma. Lymphoma may manifest as a localized orbital tumor without extraorbital or constitutive symptoms. Rare orbital diseases, among others lymphoproliferations, should be taken into account in the differential diagnosis of exophthalmos.

Keywords: *Lymphoma • Ophthalmopathy • Exophthalmos • Graves' disease • Tumor • Orbit*

1. Introduction

Ocular lymphomas are very rare orbital tumors. Lymphoid proliferations in the orbit are usually divided into inflammatory pseudotumors, reactive lymphoid hyperplasias, atypical lymphoid hyperplasias and lymphomas [1]. There are two groups of orbital lymphomas. Ocular adnexal lymphomas are usually benign, not associated with HIV infection, and are generally treated with radiotherapy. Intraorbital lymphomas, which are central nervous system lymphomas, are a high grade malignancy that occur mainly in HIV-infected patients and are treated with chemotherapy [2,3]. Clinically, an orbital lymphoma usually appears as a pink coloured, conjunctival mass, with conjunctival hyperemia, exophthalmos, and a palpebral or orbital tumour [3,4]. Because symptoms are unspecific, with local infiltration only and the condition has a low prevalence, ocular lymphoma can be misdiagnosed.

We present a case of a woman with orbital lymphoma diagnosed after almost three years' follow-up of Graves' ophthalmopathy.

2. Case Report

A 65-year-old woman was admitted for the first time to the Department of Endocrinology in October 2008, with a diagnosis of left eye tumor. The tumor had appeared 2 years previously as a small, painless nodule localized in the medial part of the lower eyelid. The pathological mass had enlarged slowly. After one year of observation, exophthalmus of the left eye occurred with concomitant diplopia and retrobulbar pain. In 2006, computed tomography (CT) scanning revealed enlargement of the lateral rectus muscle in the right orbit and the inferior rectus muscle in the left orbit (1.6 and 1.4 cm in widths, respectively). Additionally, a small lump of tissue (6 x 3 mm) was identified behind the left eyeball

* *E-mail: przepona@wp.pl*

Table 1. Causes of intraorbital soft tissue mass.

Inflammatory lesions	Graves' ophthalmopathy, pseudo-tumor of the orbit, benign reactive hyperplasia, sarcoidosis, systemic lupuserythematosus, Sjögren's syndrome, Churg-Straussvasculitis, polyarteritis nodosa
Lymphoproliferative diseases	multiple myeloma, Waldenstrom's macroglobulinemia, granulocytic sarcoma, lymphoma
Primary orbital neoplasias	cavernous angioma, optic nerve sheath menigioma, opticnerve glioma, neurofibroma, fibrous histiocytoma, haemangiopericytoma, arteriovenous communication, lymphangioma, mucocele, shwannoma, dermoid tumor
Metastases	breast cancer, lung cancer, thyroid cancer, renal cancer, uterine cancer, carcinoid tumor, melanoma, neuroblastoma
Fungal and viral infections	Mucor, Rhizopus, Aspergillus, Herpes Zoster

with evident contrast enhancement. The fine needle biopsy revealed lymphocytic infiltration described as a chronic inflammatory infiltrate of the lower tarsus region. Further follow-up was suggested by the treating ophthalmologists. However, between 2006 and 2008, no other diagnostic procedures and treatment were carried out. The tumor slowly enlarged, and exophthalmos and extraocular motility problems increased. In January 2008, magnetic resonance imaging (MRI) revealed bilateral pathological orbital masses. In the right orbit, the pathological mass measured 16 x 20 mm and moulded lateral rectus muscle. In the left orbit, the tumor size was 24 x 14 mm, moulded inferior rectus muscle and protruded from the orbit. Both lesions were hyperintense in T2-weighted scans and after contrast dye administration they were well defined (Figure 1). Myositis, pseudotumor and thyroid ophthalmopathy were suggested at that time. Fine needle biopsy was performed once more. A cytological diagnosis of benign lymphoid hyperplasia was rendered, supported by immunohistochemistry showing a mixture of B- and T-cell lymphocytes [CD20(+), CD-3(+), CD-43(-)]. Despite the radiological suggestion of thyroid ophthalmopathy, systemic steroid therapy was not initiated, as characteristic features of Graves' disease were absent. Levels of thyroid hormones were within normal values and thyroid autoantibodies (anti-TSH receptor, anti-thyroid peroxidase, anti-thyroglobulin) were negative. Positive radionuclide uptake on somatostatin receptor scintigraphy at the tumor site and slightly elevated chromogranin A level (123.5 ng/ml; referent range <100) suggested a neuroendocrine tumor. Because the symptoms progressed with occurrence of the left upper eyelid ptosis and other diagnostic problems, the patient was admitted to our clinic.

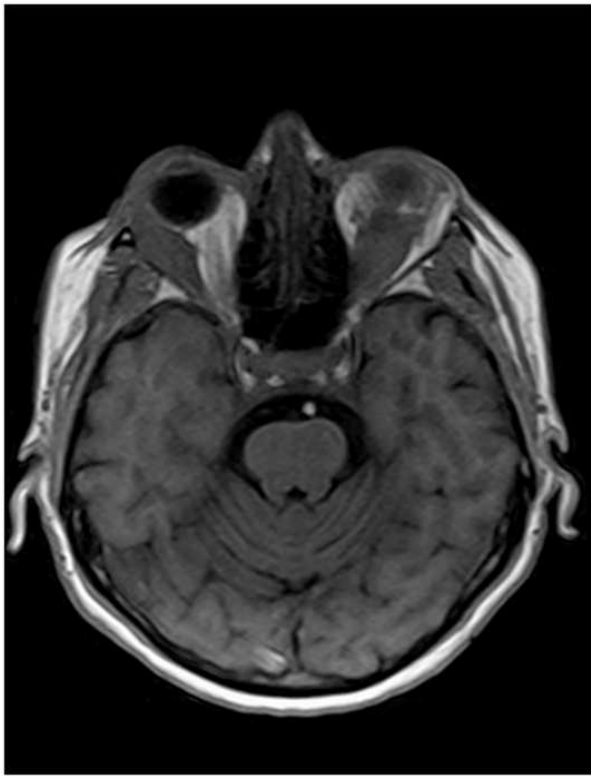
On admission, the patient was in good condition, with a Karnofsky scale 90%. Physical examination revealed a tumor of the left lower eyelid with exophthalmos and upper eyelid ptosis. Neither lymphadenopathy nor signs of hyperthyroidism were observed. Blood tests revealed a slightly increased erythrocyte sedimentation rate (26 mm/h), and levels of C-reactive protein (5.10 mg/dl), lactate dehydrogenase (230 U/l) and dyslipidemia. A chest X-ray and ultrasonography of her abdomen were normal. A skull X-ray revealed no abnormalities. On the repeated MRI in November 2008, inferior rectus muscle infiltration in the left orbit was present with a density similar to that of muscles. Its dimensions were 28 x 18 x 50 mm, and the anterior portion of the tumor extended extraorbitally (15 mm). No pathological mass was observed in the right orbit. Open surgical biopsy revealed lymphoplasmocytic lymphoma. The lymphoma phenotype was CD 20(+) CD79a(+), VS38c (+ in scattered plasma cells), CD3(-), CD43(+/-) (Figure 2). The patient was admitted to the outpatient hematological clinic and was treated using the CHOP regimen. Three months later she was in good condition, and the mass under left eye had partially regressed.

3. Discussion

Primary orbital non-Hodgkin lymphoma (NHL) represents 10% of all orbital tumors, less than 1% of all NHLs and 5%–15% NHLs of all extranodal sites [2,3,5-7]. Most (95%–100%) originate from the B-cell lineage and are low grade lymphomas (80%) [1-3,7,8]. Among all lymphomas involving the orbit, marginal zone B-cell (mucosa-associated lymphoid tissue, MALT) lymphoma is the most common (26%–80%) [1-5,7-10], although lymphoplasmacytic lymphomas predominated in a series of older patients, [2]. MALT lymphoma is followed by other subtypes, i.e., follicular, lymphoplasmacytic, mantle-cell lymphoma, diffuse B-cell lymphoma and rarely, anaplastic large cell lymphoma, or T-cell lymphoma [2-5,7,8]. The prevalence of each lymphoproliferation is not constant in the published series [2]. Although orbital lymphoproliferative disorders appear generally in the fifth or seventh decade of life, they may manifest at any age, and occur more often in women than in men [1,3-5,8].

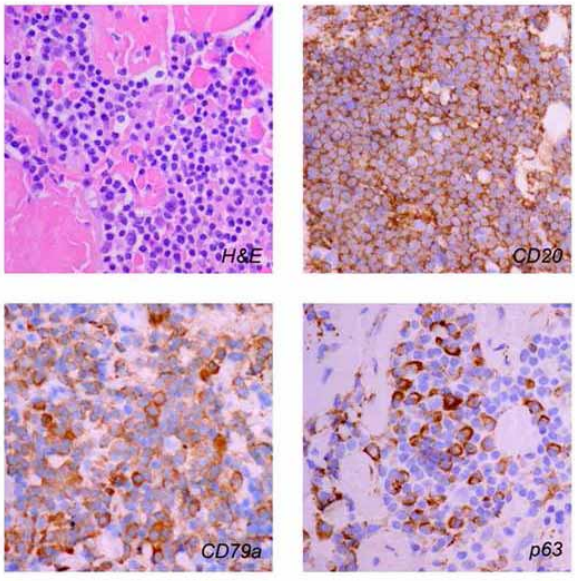
The most frequent ophthalmic symptoms of lymphoma are a pink-coloured, conjunctival mass or conjunctival hyperemia (32%), exophthalmos (27%), palpebral or orbital mass (19%), visual acuity reduction and ptosis (6%) and diplopia (2%) [2-4,7]. If the lymphoma

Figure 1. The mass in the right orbit measured 16 x 20mm and moulded lateral rectus muscle. In the left it measurred 24 x 14mm, moulded inferior rectus muscle and protruded from the orbit. The structures were hyperintense in T2 sequences and after contrast dye administration well defined.



infiltrates the conjunctiva, the lesion may appear as a smooth, pink/salmon patch [1,5]. Lymphomas usually locate in the lacrimal gland and other intraorbital areas, in particular in its anterior and superior portion [1,4]. Proptosis is more common in mono than bi-ocular disease [1]. If lymphoma occurs bilaterally (3%–25%), [1-4,7,8] the morphology and immunohistochemistry are the same on both sides [2,7]. The symptoms usually have a chronic, progressive course [5,7,8]. Systemic disease may develop in about 15%–33% of patients with localized orbital lymphoma [5,11]; approximately 20%–40% of patients present with extraorbital symptoms at the onset of disease [4,5,7]. Development of systemic disease is generally associated with bilateral involvement [7,11]. It also depends on the histological type of lymphoma (more frequent in high grade NHL) and the primary location (more frequent in lymphoma of the lacrimal gland and eyelid than conjunctiva and deep orbit) [3-5,7]. Orbital lymphoma usually metastasizes to the lymph nodes (34%), skin (19%), bone marrow (11%) and spleen (10%) [5,9]. The mean time between the onset of symptoms and diagnosis is approximately 4 to 6 months [4]. After diagnosis of lymphoma, the stage

Figure 2. Lymphoplasmacytic lymphoma of the orbit. The lymphoma infiltrates were composed of mononuclear cells surrounded by homogenous eosinophilic masses. Immunohistochemical staining showed expression of CD20 and CD79a antigen in the neoplastic lymphocytes and, in addition, expression of p53 in the cells showing plasmacytic differentiation (all the pictures magnification 400x).



of the disease has to be assessed [2,3]. Patients with recognized lymphoid hyperplasia must be followed up because of risk of progression to lymphoma [12]. On an MRI, orbital lymphoma presents as a hyperintense mass in relation to fat tissue on T2-weighted images and is brighter in relation to T1-weighted images. Inflammatory orbital masses are isotense to fat tissue on T2-weighted images and become hypointense or unchanged in relation to T1 images [5]. The tumor usually surrounds structures within the orbital cavity. The infiltration of extraocular muscles, as described in our case, is very rare in orbital lymphoma. Bone destruction, typical of paranasal sinus lymphoma, was also not observed in our case [1].

Lymphoma may develop in the setting of reactive or inflammatory hyperplasia. Differentiation between benign and malignant lymphoproliferation requires a histopathologic and immunohistochemical examination [1,12]. Proper diagnosis is important because of the difference in possible treatments and prognosis [2,7]. In some situations, immunohistochemical methods may be unreliable; then, a cytogenetic analysis is required [12].

The differential diagnosis of orbital lymphoma must include infiltrative ophthalmopathy. Patients with suspected Graves' disease who present with a typical medical history, blood tests and in most cases bilateral ophthalmopathy (85%) aren't problematic for

endocrinologists. However, unilateral ophthalmopathy may cause a diagnostic concern that needs to be differentiated from several conditions, e.g., inflammatory lesions (pseudo-tumor of the orbit, benign reactive hyperplasia, sarcoidosis, systemic lupus erythematosus, Sjögren's syndrome, Churg-Strauss vasculitis, polyarteritis nodosa) [8], lymphoproliferative diseases (multiple myeloma, Waldenstrom's macroglobulinemia, granulocytic sarcoma) [13], other orbital tumors (cavernous angioma, optic nerve menigioma, fibrous histiocytoma, haemangiopericytoma, arteriovenous communication, lymphangioma, mucocele), metastases to the orbit (breast, lung, thyroid, kidney, uterine cancer; carcinoid tumor; melanoma; neuroblastoma) and fungal and viral infections (Mucor, Rhizopus, Aspergillus, Herpes Zoster) [8]. Table 1 summarizes causes of intraorbital pathological masses (Table 1).

Generally, lymphomas originating from the conjunctiva and retro-bulbar tissue have a better prognosis than those developing from the lacrimal gland and the eyelid [5]. Prognostic criteria for orbital lymphoma involve the anatomic location of the tumor, the stage of disease at first presentation, the lymphoma subtype in REAL classification and other determining factors such as tumor growth rate and serum lactate dehydrogenase level [14]. Likewise, complete remission after primary radiotherapy and older age are good prognostic features [5].

4. Conclusion

We present the case to emphasize problems involved in evaluation of orbital tumors. Clinical local symptoms and muscular changes presented on a CT or MRI could suggest Graves' disease, although in the present case the thyroid gland function was normal. Repeated biopsies produced a diagnosis of lymphoma. It is important to remember that lymphoma may manifest as a localized orbital tumor without general and extraorbital symptoms, will require treatment and will have a favorable prognosis.

References

[1] Fedor R., Skorin R., Malignant lymphoma of the orbit. A case report, Optometry today,2005,http://www.optometry.myzen.co.uk/articles/docs/dd8d10f44977a672b9942f0322dbb5a7_fedor20050715.pdf

[2] Bednaruk-Mlynski E., Czupryn A., Jassem J., MALT-type orbital lymphoma: a case report and the review of the literature, Onkologia w Praktyce Klinicznej, 2007, 1, 32-35

[3] Decaudin D., de Cremoux P., Vincent-Salomon A., Dendale R., Lumbroso-Le Ruic., Ocular adnexal lymphoma: a review of clinicopathologic features and treatment options, Blood, 2006, 108, 1451-1460

[4] Rey-Porca C., Perez-Encinas M., Gonzalez F., Orbital lymphomas. Presentation of nine cases, Arch. Soc. Esp. Oftalmol., 2008, 83, 95-104

[5] Schick U., Lermen O., Unsold R., Hassler W., Treatment of primary orbital lymphomas, Eur. J. Haematol., 2004, 72, 186-192

[6] Narayanan G., Ratheesan K., Madhavan J., Rajan B., Primary orbital lymphoma – A review of 25 cases from India, Journal of Clinical Oncology, 2004, Supplement, 6721

[7] Nutting C.M., Jenkins C.D., Norton A.J., Cree I., Rose G.E., Plowman P.N., Primary orbital lymphoma, The Hematology Journal, 2002, 3, 14-16

[8] Terpos E., Theocharis S., Panitsas F., Revelos K., Tsionos K., Karkantaris C:., Anaplastic primary orbital lymphoma: report of a case and review of the literature, Haema., 2002, 7, 370-373

[9] Rosado M.F., Byrne G.E., Ding F., Fields K.A., Ruiz P., Dubovy S.R., et al., Ocular adnexal lymphoma: a clinicopathologic study of a large cohort of patients with no evidence for an association with Chlamydia psittaci, Blood, 2006,107, 467-472

[10] Lagoo A.S., Haggerty C., Kim Y., Hammons M., Neufeld K., Redher C., et al., Morphologic features of 115 lymphomas of the orbit and ocular adnexa categorized according to the World Health Organization classification: are marginal zone lymphomas in the orbit mucosa-associated lymphoid tissue-type lymphomas?, Arch. Pathol. Lab. Med., 2008, 132, 1405-1416

[11] Demirci H., Shields C.L., Karatza E.C., Shields J.A., Orbital lymphoproliferative tumors analysis of clinical features and systemic involvement in 160 cases, Ophthalmology, 2008, 115, 1626-1631

[12] Lowen M.S., Saraiva V.S., Martins M.C., Burnier Jr. M.N., Immuohistochemical profile of lymphoid lesions of the orbit, Can. J. Ophthalmol., 2005, 40, 634-639

[13] Brisbane J.U., Lessell S., Finkel H.E., Neiman R.S., Malignant lymphoma presenting in the orbit: A clinicopathologic Study of Rare Immunoglobulin-Producing Variant, Cancer, 1981, 47, 548-553

[14] Coupland S.E., Hummel M., Stein H., Ocular adnexal lymphomas: five case presentations and a review of the literature, Surv. Ophtalmol., 2002, 47, 470-490