Orbital lymphoma associated with Graves’ disease: A case report

Zoran Hajduković*, Snežana Kuzmić-Janković*, Tamara Klijaković-Avramović†, Leposava Sekulović‡, Ljiljana Tukić§

*Clinic for Endocrinology, †Clinical for Ophthalmology, ‡Institute of Radiology, §Clinic for Haematology, Military Medical Academy, Belgrade; †Faculty of Medicine of the Military Medical Academy, University of Defence, Belgrade, Serbia

Abstract

Introduction. The presence of bilateral exophthalmos and palpebral, periorbital edema associated with hyperthyroidism is most often considered as an initial sign of Graves' ophthalmopathy. However, in up to 20% of cases, Graves' ophthalmopathy might precede the occurrence of hyperthyroidism, which is very important to be considered in the differential diagnosis, especially if it is stated as unilateral. Among other less common causes of non-thyroid-related orbitopathy, orbital lymphoma represents rare conditions. We presented of a patient with Graves’ disease, initially manifested as bilateral orbitopathy and progressive unilateral exophthalmos caused by the marginal zone B-cell non-Hodgkin lymphoma of the orbit. Case report. A 64-year-old man with the 3-year history of bilateral Graves’ orbitopathy and hyperthyroidism underwent the left orbital de-compression surgery due to the predominantly left, unilateral worsening of exophthalmos resistant to the previously applied glucocorticoid therapy. A year after the surgical treatment, a substantial exophthalmos of the left eye was again observed, signifying that other non-thyroid pathology could be involved. Orbital ultrasound was suggestive of primary orbital lymphoma, what was confirmed by orbital CT scan and the biopsy of the tumor tissue. Detailed examinations indicated that the marginal zone B-cell non-Hodgkin lymphoma extended to IV – B-b CS, IPI 3 (bone marrow infiltration: m+ orbit+). Upon the completion of the polichemiotherapy and the radiation treatment, a complete remission of the disease was achieved. Conclusion. Even when elements clearly indicate the presence of thyroid-related ophthalmopathy, disease deteriorating should raise a suspicion and always lead to imaging procedures to exclude malignancy.

Key words: exophthalmos; diagnosis, differential; graves disease; histological techniques.

Correspondence to: Snežana Kuzmić-Janković, Clinic for Endocrinology, Military Medical Academy, Crnogravska 17, 11 000 Belgrade, Serbia. E-mail: janko47@open.telekom.rs
Introduction

Thyroid-related orbitopathy (TRO) is the most common cause of extraocular muscle abnormality. It typically presents as proptosis, eyelid inflammation and chemosis, motility disturbances and in severe cases, decreased visual acuity. Orbital imaging classically shows well-defined extraocular muscle swelling, usually *musculus rectus medialis* and inferior, and periorcular fat tissue edema. Its strong association with autoimmune thyroid disease and chronic lymphocytic infiltration suggests shared antigens for both conditions with frequent serum antibodies against thyroid-stimulating hormone (TSH) receptors, thyroglobulin and thyroid microsomal antibodies. Reach lymphocytic infiltration might be a predisposing risk factor for the later development of a malignant lymphocyte clone and orbital lymphoma.

We reported a patient with unilateral, low-grade marginal zone B-cell lymphoma simulating unilaterally worsening TRO.

Case report

A 64-year-old man, presented with an excessive lacrimation and discrete palpebral edema with bilateral conjunctival suffusion in November 1999. He was treated for the bilateral conjunctivitis. Steroid/antibiotic eyedrops administered for the presumptive diagnosis of allergic conjunctivitis did not relieve his symptoms. By the end of January 2000, the patient developed the manifestations of hypermetabolism, observed in the form of anxiety, insomnia, sporadic palpitations, tachycardia and weight loss. The patient was seen by an endocrinologist who diagnosed Graves' disease with associated ophthalmopathy.

An objective examination revealed marked periocular swelling, conjunctival hyperemia and chemosis, bilateral exophthalmos with considerable proptosis of the left eye but without any motility disturbances.

The first grade diffuse goiter was determined by palpation; it was more consistent and avascular, whilst the heart rate was 88 beats per minute. Other clinical findings were found to be within normal ranges. Evaluation of thyroid function evidenced hyperthyroidism with suppressed serum TSH level: 0.02 mIU/mL, and T4: 191 nmol/L (60.0–120.0 nmol/L); T3: 3.9 nmol/L (0.6–2.1 nmol/L). The thyroid-specific antibody test was not carried out at the time of diagnosis due to technical reasons.

Over the next year, antithyroid therapy application ensured a stable thyroidmetabolic status with the TSH level of 1.23 mIU/L, normal values of free thyroxine iodine fractions. Inspite of achieving the euthyreoid status, the gradual progression of proptosis of the left eye was evident, (OS 26 mm, OD 20 mm, base 107 mm) and the ultrasound and computed tomography (CT) scan of the orbit revealed a marked enlargement of the inferior, medial and lateral rectus muscles bilaterally and more pronounced on the left eye, along with the enlargement of the retrobulbar fat tissue compressing the left bulbous and displacing it downwards. The same findings were confirmed by magnetic resonance imaging (MRI). Upon the completion of the corticosteroid therapy, the regression of the exophthalmos was achieved, but, in May 2002, the exophthalmos was seen to progress on the left side again. Measurements by Hertel exophthalmometry at the base were 107 mm – OS 28 mm, OD 20 mm. Due to the possible damage to the left optical nerve, the orbital decompression surgery was performed. The definite histopathological findings of a part of the ocular muscle showed the lymphocytic infiltration specific to Graves’ disease. The patient’s postoperative recovery went well, with the expected regression of the left-sided exophthalmos.

In December 2002, left eyeball protrusion was observed to progress again.

The orbital ultrasound findings indicated the presence of the retrobulbar tumor mass of a low reflectability, with a lobular appearance and internal septations, which by their characteristics were susceptible to orbital lymphoma (Figure 1).
orbital CT scan demonstrated the protrusion of both globes of the eyes, more pronounced on the left one, and the extraocular muscles' enlargement with the two nodules, one $38 \times 16$ mm nodule localized to the exterior wall of the left orbit, and another one of $15 \times 10$ mm in diameter found in the medial angle (Figure 2). The tumor grew and extended around the surrounding anatomical structures (nervus opticus sinister) which resulted in a concentric narrowing of the left view field (Figure 3).

The controlled laboratory test results showed that the erythrocyte sedimentation rate was 50 mm/hr, fibrinogen level was 5.2 g/L, haptoglobin level was 4.34 g/L, low immunoglobulin levels were – IgG 4.56 (8–17) g/L, IgA (1–4.90) 0.731 g/L, IgM (0.5–3.2) 0.441 g/L. Other laboratory findings were within the reference ranges. The chest x-ray and the ECG were normal. The serum levels of T3: 1.50 nmol/L; T4 : 95.3 nmol/L; TSH: 0.95 μIU/mL were also within the normal limits. The Goldman visual field testing

![Computed tomography](image1)

**Fig. 2** – Computed tomography depicting protrusion of the left bulb with tumor mass lesion diameter $3.8 \times 1.6$ cm of the lateral wall of the left orbit. The lesion is strongly enhanced after contrast injection.

![Goldmann visual field testing](image2)

**Fig. 3** – Goldmann visual field testing indicated the concentric visual field narrowing up to 30 degrees from the point of fixation to the right, and 15 degrees from the fixation point on the left.

indicated the concentric visual field narrowing up to 30 degrees from the point of fixation to the right, and 15 degrees from the fixation point on the left. The visual evoked potentials (VEP) o. dex – latent conductivity ratio of 115 m/sec / 6.64 \( \mu V \) (normal values); VEP o. sin – latent conductivity rate of 129 m/sec / 7.16 \( \mu V \), what was the sign of prolonged conductivity due to the compression of the left optical nerve. The Hess-Lancaster test was within normal ranges, as well.

The biopsy of tumor changes protruding from the left bulbus confirmed a non-Hodgkin B-cell, marginal zone lymphoma, with a low degree of malignancy (low grade type). Histopathology disclosed several nodular lymphoid infiltrate, also within orbital fat tissue, small to medium sized atypical lymphocytic cell population, nearly monomorphic centrocellular images, with focally distributed sheets of small lymphocyte cells, scattered clear-cell monocytoid like lymphocyte, and a few histiocytic cells in periphery (Figures 4a and b). Mitotic index, Ki-67 was low, bellow 10%. The immunophenotyping analysis of the tumor cells demonstrated the CD-79 alfa expression, CD20-positive in the percentage of over 80%, CD43 cells of 43% and the dispersed small CD3-positive lymphocyte cells. Staging of the disease including head, neck, chest, abdomen and small pelvis CT scans were whitin the normal ranges, but the biopsy of the bone marrow confirmed bone marrow infiltration by the small lymphocyte cells of some 95% with the immunophenotypisation: CD20+, CD3-, CD5-, CD43-, CD 23-, and Cyclin dl, what indicated the spreading of the disease: IV B –b CS (m+ orbit+) IPI 3-.

Discussion
Orbital lymphoma and lymphoma of the orbital adnexa are relatively rare conditions, and account for approximately 0.1% of all lymphomas. The prevalence is more frequent in patients with previous several autoimmune diseases such as Hashimoto thyroiditis and Graves disease, Sjögren’s syndrome and coeliac disease.

The study that included 369 patients with periocular lymphoma (1979–1999 year) found a considerably higher prevalence of the previous thyroid disease (in 5.0% of pa-

![Fig. 4 – a) Histopathology of the lid biopsy tissue showing diffuse inflammation and invasion by atypical monomorphyc lymphocyte cells [May-Grünwald-Giemsa (MCG), ×20]; b) High power magnification of the biopsy revealing tightly packed, homogenous small to medium sized lymphocytes. Many of cells showed neoplastic appearance with clear nuclei containing multiple nucleoli (monocytoid like lymphocytes) (MCG, ×20).](image)

Lymphoma was initially the periorbital tissue with further progression of the disease. Bartalena et al. 6 also described a case of bilateral exophthalmos, in a patient wrongly assumed that it was Graves’ disease, even though it was the case of a non-autoimmune thyroid disorder, i.e. an autonomously hyper-functioning adenoma and subclinical hyperthyroidism, that could not cause bilateral ophthalmopathy. Since the previous treatment of Graves’ ophthalmopathy proved to be unsuccessful, some other etiologies as possible causes were considered, but only after exophthalmos deterioration 7, 8. Similarly, in our case, the patient had a previously confirmed Graves’ disease with histopathologically proven lymphocytic infiltration of the muscles, but the clinical presentation and progression of exophthalmos was suggestive of some extrathyroidal causes. Morphological imaging, first ultrasound and than orbital CT scan and MRI, also biopsy of the tumor mass, confirmed orbital lymphoma.

Within typical manifestations and biochemical evidence of hyperthyreoidism, bilateral ocular inflammation is likely to be interpreted as Graves’ ophthalmopathy. A review of 1,849 cases of orbital muscle enlargement revealed thyroid orbitopathy in 95% and other muscle disease in 5%. The three leading causes of non TRO were nonspecific myositis (43%), dural and carotid cavernous fistula (22%) and neoplasms (18%). Intramuscular lymphoma was seen in 0.2% 9.

About 85% of primary orbital lymphomas are low-grade, such as marginal zone lymphomas, diffuse lymphoplasmocytic or follicle cell lymphomas 9. The majority of patients had localized, IE stage diseases, with good prognosis after the completion of the local radiation therapy for the orbit 10.

In this case, the patient has a systemic spread of low-grade marginal zone B-cell lymphoma and received a combination of polychemotherapy and radiotherapy. Complications occurred after second cycle of chemotherapy, but after recovery and continuing the combined therapy, the complete remission and favourable outcome was achived.

**Conclusion**

Even when the elements clearly indicate the presence of the thyroid-related ophthalmopathy, disease deterioration, especially unilaterally, should raise a suspicion and always lead to imaging procedures to exclude malignancy. Biopsy and adequate pathological sampling will be needed to make the diagnosis of lymphoma. In case of uncertainty, regular and timely referral to the endocrinologist and ophthalmologist is mandatory.

Even though orbital lymphoma is localized in the majority of described studies, in-depth examination is required to be conducted to ascertain the degree of the disease in all cases.

**REFERENCES**


Received on October 30, 2012. Revised on March 25, 2013. Accepted on March 26, 2013.