CASE REPORT

UDC: 616.441-008.61:[617.7:616-006.44
DOI: 10.2298/VSP1405510H

Orbital lymphoma associated with Graves' disease: A case report

Orbitalni limfom udružen sa Gravesovom bolesti

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

***Clinic for Endocrinology, ‡Clinic 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 occurence 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 decompression 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 polychemiotherapy 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.

Apstrakt

Uvod. Zbog ispoljavanja bilateralnog egzoftalmusa i periorbitalnih edema udruženih sa hipertireoidizmom najčešće se inicijalno postavlja sumnja na Gravesovu oftalmopatiju. Ipak, Gravesova orbitopatija kod 20% bolesnika može prethoditi ispoljavanju hipertireoidizma i predstavljati diferncijalnodijagnostički problem, naročito ako je unilateralna. Takođe, i pored primene intenzivne farmakološke terapije, kod 3% bolesnika sa Gavesovom orbitopatijom može doći do progresije bolesti koja u ozbiljnim slučajevaima zahteva zračnu ili operativnu terapiju. Prikazan je bolesnik sa Gravesovom bolešću, inicijalno ispoljenom bilateralnom orbitopatijom sa progresivnim pogoršanjem unilateralnog egzoftalmusa, uzrokovanog B-ćelijskim nehočkinskim, limfomom orbite marginalne zone. **Prikaz bolesnika.** Kod bolesnika, starog 64 godine, sa 3-godišnjom evolucijom bilateralne Gravesove orbitopatije i hipertireoze, predominantno levostrano unilateralno ispoljilo se pogoršanje egzoftalmusa, rezistentno na primenjenu glukokortikoidnu terapiju, zbog čega je učinjena levostrana dekompresija orbite. Godinu dana nakon operativnog lečenja ponovo se razvio značajan egzoftalumos levog oka, što je pobudilo sumnju na drugu etiologiju. Ultrazvučni pregled orbite ukazao je na primarni limfom orbite, što je CT skenom i biopsijom tumorskog tkiva potvrđeno. Detaljna ispitivanja ukazala su na B-ćelijski nehočkinski limfom marginalne zone, proširenog IV – B-b CS, IPI 3 (infiltracija koštane srži: m+orbita+). Nakon primenjene polihemioterapije i radijacione terapije orbite ostvarena je kompletna remisija bolesti. **Zaključak.** Mada Gravesova bolest jeste najčešći razlog bilateralne orbitopatije progresivno pogoršanje orbitopatije zahteva detaljnu analizu u cilju isključivanja drugih ređih etiologija.

Ključne reči:
egzoftalmus; dijagnoza, diferencijalna; gušavost, egzoftalmička; histološke tehnike.

Correspondence to: Snežana Kuzmić-Janković, Clinic for Endocrinology, Military Medical Academy, Crnotravska 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 [1]. It tipically presents as proptosis, eyelid inflammation and chemosis, motility disturbances and in severe cases, decreased visual acuity [2]. Orbital imaging clasically shows well-defined extraocular muscle swelling, usually *musculus rectus medialis* and inferor, and periocular fat tissue edema [3]. 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 [4]. Reach lymphocytic infiltration might be a predisposing risk factor for the later development of a malignant lymphocyte clone and orbital lymphoma [5].

We reported a patient with unilateral, low-grade marginal zone B-cell lymphoma simulating unilateraly 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 serume TSH level: 0.02 μIU/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.

An initial bilateral enlargement of the thyroid gland of hypoechogenic texture without nodules, but with highly increased vascularisation was verified by thyroid ultrasound. Ophthalmological examination confirmed the bilateral proptosis predominantly to the left eye, oculus sinister (OS) 24 mm, oculus dexter (OD) 20 mm (base 107 mm).

The diagnosis of Graves' disease with associated ophthalmopathy was made, and the patient was placed on propylthiouracil treatment without applying any therapy specific for orbitopathy.

Over the next year, antithyroid therapy application ensured a stable thyroidmetabolic status with the TSH level of 1.23 μIU/L, normal values of free thyroxine iodine fractions. Inspite of achiving 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 suspectable to orbital lymphoma (Figure 1). The

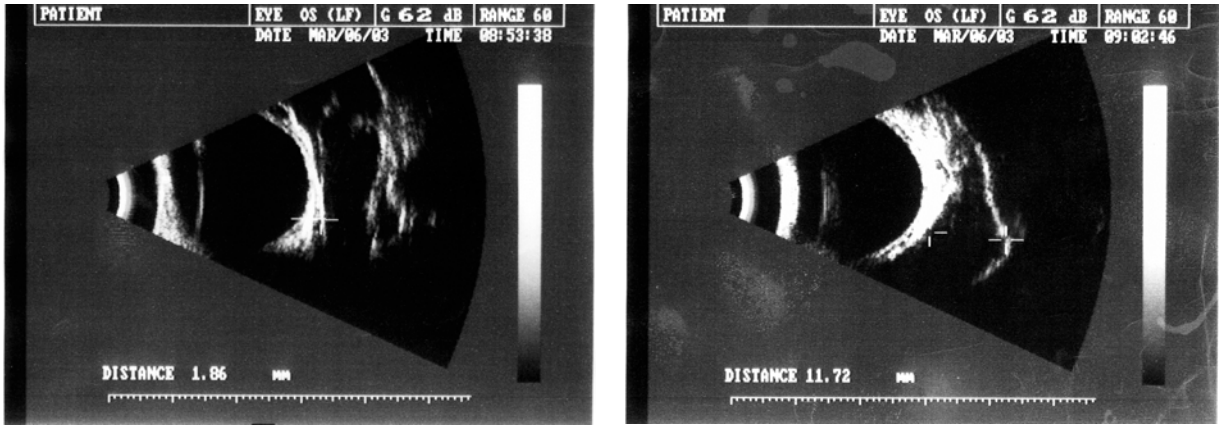


Fig. 1– Ultrasound of the left eye showing hypoechoic lesion of the lateral wall of the left orbit with low reflectability and internals septations.

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 × 16 mm nodule localized to the exterior wall of the left orbit, and another one of 15 × 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

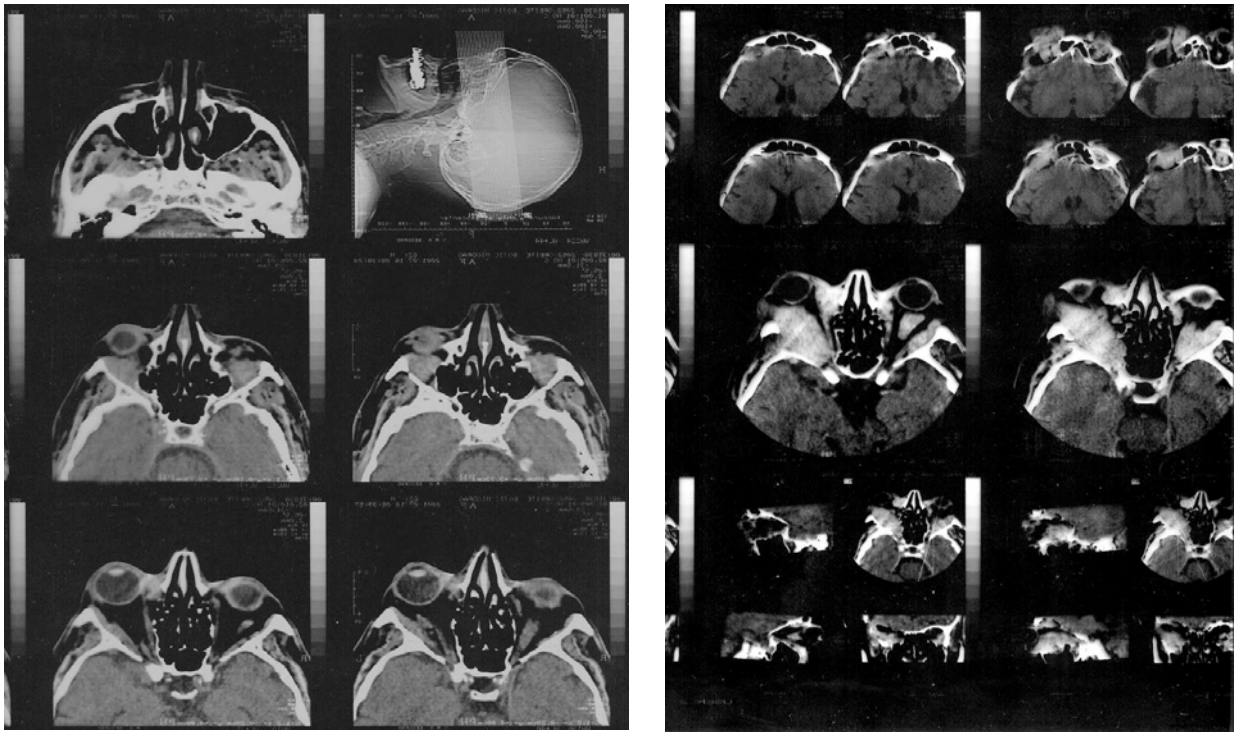


Fig. 2 – Computed tomography depicting protrusion of the left bulb with tumor mass lesion diameter 3.8 × 1.6 cm of the lateral wall of the left orbit. The lesion is strongly enhanced after contrast injection.

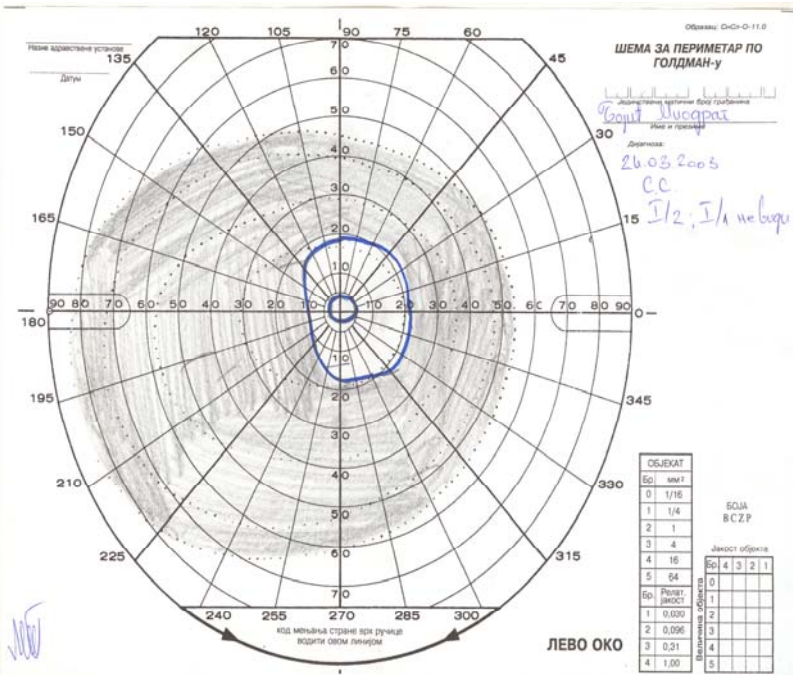


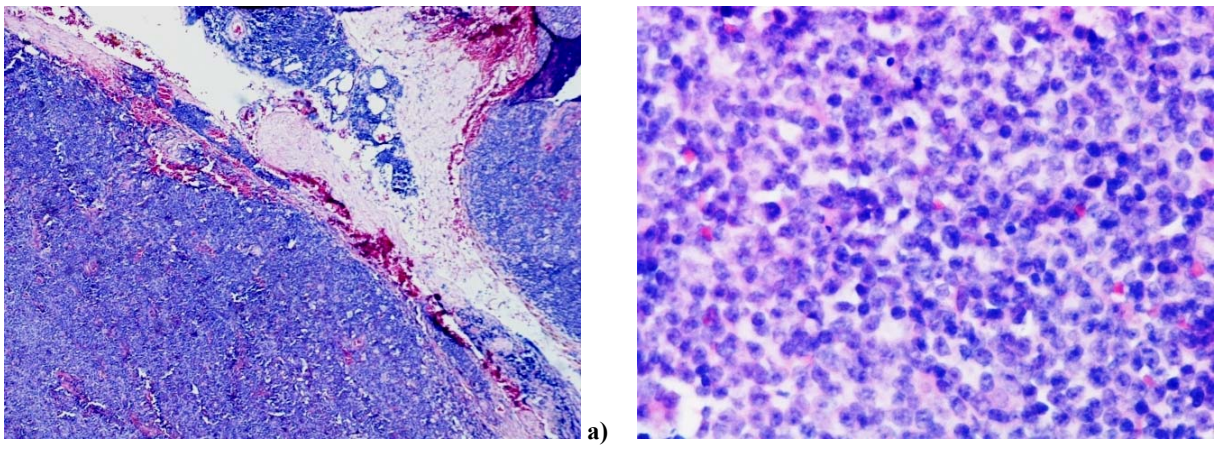
Fig. 3 – Goldmann visual field testing indicated the concentric visual field narrowing up to 30 degrees from the point of fixation to the right, and 15 degrees from the fixation point on the left.

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 μV (normal values); VEP o. sin – latent conductivity rate of 129 m/sec / 7.16 μV, 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%, CD-43 cells of 43% and the dispersed small CD3-positive lymphocyte cells. Staging of the disease including haed, 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-.

Esophagogastroscopy revealed grade 1 and grade 2 esophageal varices extending 25 cm from the top of the esophagus; a spontaneous Mallory Weis tear at 1 h and 11 h; a friable, polypoid mass about 5 mm in diameter confined to the posterior wall of the stomach subcardially, at the distance of 43 cm. Some 16 years before, the patient underwent Bilroth surgery, when a biopsy sample was taken from the stoma.

The council of doctors decided on the CHOP chemotherapy regimen followed by the radiation therapy for the orbit. Due to the expressed myelosuppression, the orbital radiation therapy was terminated after the completion of the second chemotherapy cycle, but it was reinitiated as soon as the bone marrow was recovered, and applied along with the chemotherapy. The remission in the patient was maintained after the two years of the initial treatment.



a) b)

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) Hight 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).

Discussion

Orbital lymphoma and lymphoma of the orbital adnexa are relatively rare conditions, and account for approximately 0.1% of all lymphomas [5]. The prevelance 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 prevelance of the previous thyroid disease (in 5.0% of patients), whilst the autoimmune thyroid disease was confirmed in 2.5% of the patients, TRO was seen in 1.6 percent of cases. The average latency period of TRO before the diagnosis of periocular lymphoma assessed to be 17.5 years (11–27 years), and in the majority of patients it was identified as marginal zone lymphoma [5].

In the presented case, the period of the development of Graves' disease and lymphoma was markedly short. Even though it was the case of an extended disease (IV B-b), it was initially manifested as a localized, unilateral condition involving the left periocular area. So, a question arises whether the disease was present at the time when the orbital decompression surgery was performed, since the biopsy included only the right *musculus rectus medialis* and not the periocular fat tissue. However, despite the well-preserved thyroid function and metabolism, the first systemic manifestations of lymphoma in the form of the weight loss, weakness and adinamia were observed by the end of 2002, i.e. seven months after the orbital decompression surgery. It, therefore, may be assumed that the primary localization of

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 hyperfunctioning 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 sugestive 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 thyrod 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, difusse 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 polychemiotherapy and radiotherapy. Complications occured after second cycle of chemiotherapy, 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 encertainty, 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.

R E F E R E N C E S

1. *Lacey B, Chang W, Rootman J.* Nonthyroid causes of extraocular muscle disease. Surv Ophthalmol 1999; 44(3): 187−213.
2. *Boyce PJ.* Orbital lymphoma masquerading as thyroid ophthalmopathy. J Am Optom Assoc 1998; 69(10): 666−73.
3. *Abdullah A, Elsamaloty H, Patel Y, Chang J.* CT and MRI findings with histopathologic correlation of a unique bilateral orbital mantle cell lymphoma in Graves' disease: a case report and brief review of literature. J Neurooncol 2010; 97(2): 279−84.
4. *Bahn RS, Dutton CM, Natt N, Joba W, Spitzweg C, Heufelder AE.* Thyrotropin receptor expression in Graves' orbital adipose/connective tissues: potential autoantigen in Graves' ophthalmopathy. J Clin Endocrinol Metab 1998; 83(3): 998−1002.
5. *Nutting CM, Shah-Desai S, Rose GE, Norton AP, Plowman PN.* Thyroid orbitopathy possibly predisposes to late-onset of periocular lymphoma. Eye 2006; 20(6): 645−8.
6. *Bartalena L, Brogioni S, Valeriano R, Nardi M, Cartei F, Bogazzi F,* et al. Non-autoimmune hyperthyroidism associated with isolated bilateral ocular lymphomamimicking Graves' disease with ophthalmopathy: a cause of misdiagnosis. J Endocrinol Invest 1995; 18(10): 817−9.
7. *Buescu A, Teixeira P, Coelho S, Donangelo I, Vaisman M.* Orbital lymphoma misdiagnosed as Graves' ophthalmopathy. Endocir Pract 2001; 7(2): 110-−2.
8. *Payne JF, Shields CL, Eagle RC, Shields JA.* Orbital lymphoma simulating thyroid orbitopathy. Ophthal Plast Reconstr Surg 2006; 22(4): 302−4.
9. *Woolf DK, Ahmed M, Plowman PN.* Primary Lymphoma of the Ocular Adnexa (Orbital Lymphoma) and Primary Intraocular Lymphoma. Clin Oncology 2012; 24(5): 339−44.
10. *Stark JJ, Newsom RW, Roman J, Larocque JC, Richardson DW.* Orbital MALT lymphoma in a patient with Graves' ophthalmopathy: a unique observation. Cancer Invest 2005; 23(7): 593−5.

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