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Case Report

THYROID-ASSOCIATED OPHTHALMOPATHY IN A HYPOTHYROID PATIENT

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SUMMARY – Thyroid-associated ophthalmopathy (TAO) is an autoimmune disorder of the orbit that occurs predominantly in Grave's hyperthyroidism, while it is an uncommon clinical finding in patients with Hashimoto's thyroiditis (HT) and hypothyroidism. We report the case of a 62-year-old female patient who presented with left eyelid edema, proptosis, diplopia, and lateral paralysis of the left eye. Magnetic resonance imaging of the orbits showed retrobulbar mass in the left orbit with hyperintense signals within left medial rectus muscle, offsetting but not infiltrating the optic nerve. An ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) scan revealed pathological ^{18}F-FDG uptake of expansive mass within rectus medialis muscle of the left eye (SUVmax=11.0) and similar findings in the right eye (SUVmax=7.1). It also displayed increased glucose metabolism in the thyroid gland (SUVmax=6.4). Laboratory findings showed increased thyrotropin level, while thyroid-stimulating-hormone-receptor antibodies were negative. The patient was diagnosed with HT and TAO, so levothyroxine therapy was introduced. Gradual improvement of TAO symptoms was attained a year later. Diplopia subsided and the patient regained complete eye movements. In conclusion, correction of hypothyroidism can significantly improve symptoms of TAO. Additional value of this case report lies in ^{18}F-FDG PET/CT images displaying increased metabolic activity, which can advance clinical evaluation; however, further research is needed.

Keywords: *Thyroid-associated ophthalmopathy; Hashimoto's thyroiditis; hypothyroidism; Magnetic resonance imaging; ^{18}F-FDG PET/CT*

Introduction

Thyroid-associated ophthalmopathy (TAO) or Graves' ophthalmopathy (GO) is the most common autoimmune disorder of the orbital retrobulbar tissue and is closely associated with autoimmune thyroid disease. It affects females more frequently, with a four to

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one female to male ratio, as the age-adjusted incidence rate stands at 16 cases *per* 100,000 population *per* year for females and 2.9 cases *per* 100,000 population for males[1]. It predominates as an extrathyroidal manifestation of Graves' hyperthyroidism. It is clinically relevant in 25%-50% of patients with Graves' disease (GD), while subclinical presentation can be detected on orbital imaging in more than 70% of patients with GD[2,3]. However, TAO may also develop in euthyroid and hypothyroid patients with chronic lymphocytic (Hashimoto's) thyroiditis, where the incidence has been reported at only 4.3%[4]. In this specific subgroup of patients, TAO is usually less severe and asymmetric, with 70% of cases manifesting mild symptoms and 20% of patients having unilateral ocular involvement[4,5]. Euthyroid and hypothyroid patients are usually tested positive for thyroid-stimulating hormone receptor antibodies (TRAb) specific to GD, and are thus diagnosed as euthyroid or hypothyroid GD. Only a few cases of Hashimoto's thyroiditis TAO with negative TRAb have been reported[5,6]. Herein, we report a case of a biochemically hypothyroid patient with negative TRAb who developed unilateral TAO of moderate severity.

Case Report

A 62-year-old Caucasian female patient presented to an oncology specialist with progressive left eye proptosis, left upper eyelid swelling, corneal dryness, diplopia, and lateral paralysis of the left eye (Fig. 1).

A year before, the patient was diagnosed with breast cancer of the left mammary gland. She was administered four cycles of neoadjuvant chemotherapy and subsequently underwent left mastectomy with dissection of the left axilla, followed by adjuvant chemotherapy, external radiotherapy and hormone therapy.

The patient was referred to magnetic resonance imaging (MRI) of the orbits, which depicted biconvex, retrobulbar, well-limited formation in the left orbit, with signal hyperintensity on postcontrast T1-weighted images (Fig. 2), as well as on fluid attenuated inversion recovery (FLAIR) and short tau inversion recovery (STIR) sequences (Fig. 3). The mass was situated within the left medial rectus muscle, indented into the adipose tissue of the orbit, slightly offsetting but not infiltrating the optic nerve. In the right orbit, less significant findings were seen as discrete right lateral rectus muscle enlargement. These results suggested dysthyroid ophthalmopathy, although the patient had no past medical history of thyroid disease. Additional investigations were required, so the patient was referred to the Department of Nuclear Medicine.

An 18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) scan revealed pathological ^{18}F-FDG uptake in the expansive mass within the medial rectus muscle of the left eye (maximum standard unit value (SUVmax)=11.0), and similar findings in the right eye (SUVmax=7.1) (Fig. 4a). The same scan also indicated an increased glucose metabolism in the thyroid gland (SUVmax=6.4) (Fig. 4b).

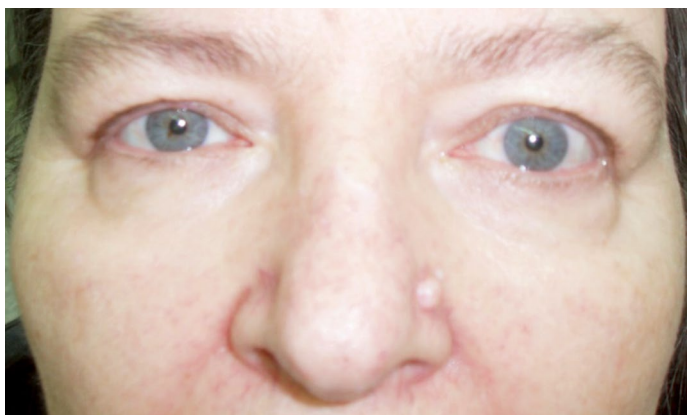

Fig. 1. Patient's eyes on first appointment presenting left eye proptosis.

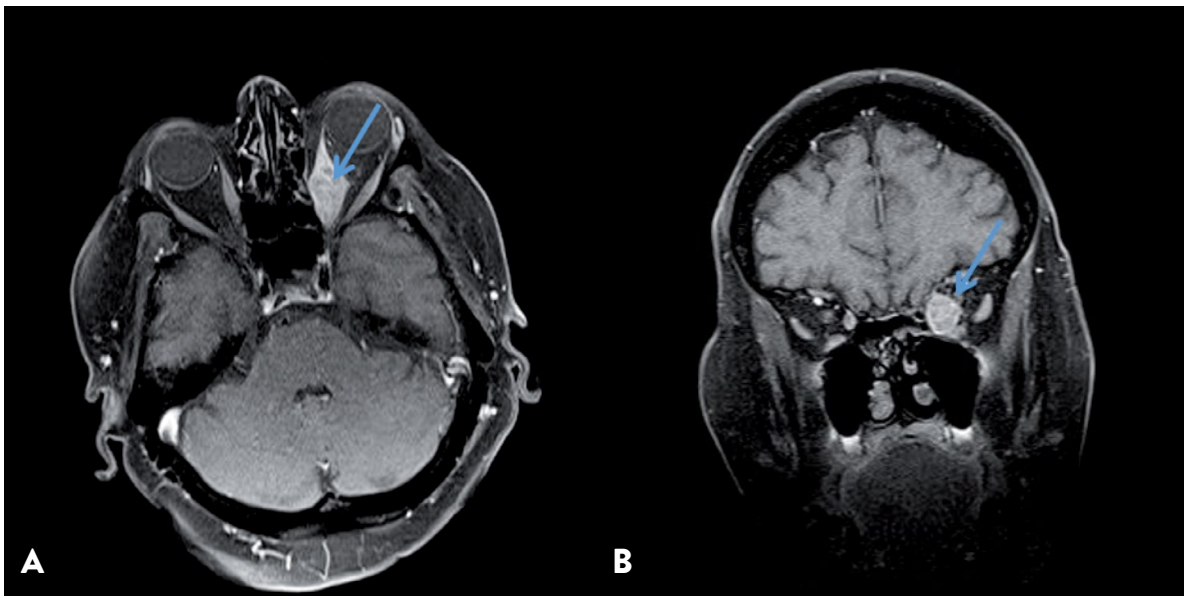

Fig. 2. Retrobulbar formation in the left orbit with signal hyperintensity on MRI postcontrast T1-weighted images: (a) axial plane; (b) coronal plane.

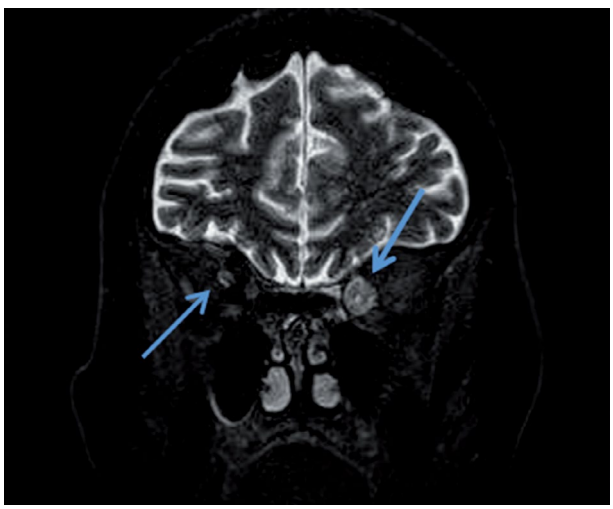

Fig. 3. The mass within the left medial rectus muscle and discrete enlargement of the right medial rectus muscle on MRI short tau inversion recovery (STIR) sequences in coronal plane.

Laboratory investigations used electrochemiluminescence immunoassay (ECLIA) and showed increased thyroid-stimulating hormone (TSH) levels, as well as substantially high anti-thyroid-peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibody levels, while TRAb were negative. Ultrasound examination demonstrated a thyroid gland of total volume of 10 mL (weight estimated at 11 grams), appearing in a diffuse parenchyma pattern with no focal nodes.

The patient was diagnosed with chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), subclinical hypothyroidism and TAO of moderate severity. Thus, levothyroxine therapy was introduced. Gradual medication dosage calibration was achieved within a year, with optimal dose becoming 125 μg of levothyroxine *per* day *per os*, and TSH levels dropped to reference values. The patient also used eye lubricants topically and reported gradual improvement of TAO symptoms, i.e., reduced corneal dryness and visual disturbance. However, palpebral edema did not diminish substantially. On follow-up 12 months later, diplopia subsided, and the patient regained complete eye movements.

Discussion

The successful outcome of the presented case indicates that prompt correction of hypothyroidism by thyroid hormone replacement therapy can significantly

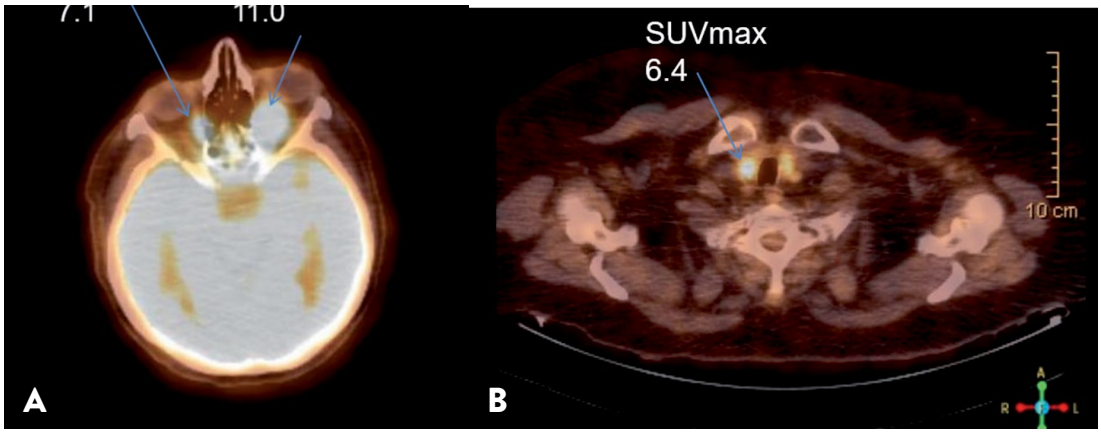

Fig. 4. [18]F-FDG PET/CT scan: (a) increased [18]F-FDG uptake in the expansive mass within bilateral medial rectus muscles; (b) increased [18]F-FDG uptake in the thyroid gland.

improve symptoms of TAO and render surgical interventions unnecessary, even if clinical manifestations are marked to a smaller extent, with less soft-tissue involvement and more asymmetric disease. Since hypothyroid patients with TAO are scarcely reported in the literature, there are no clear guidelines for treatment. According to the European Group on Graves' Ophthalmopathy (EUGOGO), it is recommended that all patients with GO, after initial assessment, be referred to a physician with clinical experience in managing thyroid-associated ophthalmopathy[7]. Using EUGOGO classification of the severity of ophthalmopathy and clinical activity score, our patient was diagnosed with a moderate form of the illness without sufficient impact on daily life to justify the risks of immunosuppression or surgical intervention. Therefore, the recommended measures of restoration and maintaining euthyroidism were employed.

The particularity of this case is a TRAb negative TAO patient. In a study by Khoo *et al.*, the prevalence of euthyroid and hypothyroid patients was only 0.7% and 0.2%, respectively, among 1021 patients with GO, yet TRAb were detectable in all patients[8]. Another study by Eckstein *et al.* found TRAb levels 6 months after GO onset were considerably lower in euthyroid and hypothyroid compared to hyperthyroid patients[9]. Both studies affirmed that TRAb titers are very low in these patients, and the availability of a sensitive assay technique is, therefore, an invaluable diagnostic tool. We discuss that negative TRAb results in our patient might not be significant since standard assays were used.

Additional value of this case report lies in [18]F-FDG PET/CT images displaying increased metabolic activity in the enlarged extraocular muscles and thyroid gland. PET is a noninvasive method used not only in diagnosis and staging of malignancies, but also in assessing some forms of inflammation. Due to a radiolabeled analog to glucose, [18]F-FDG, utilized as a quantitative metabolic marker of glucose uptake, which is often increased in malignancies and inflammation, it may be helpful in detecting cases in which clinical assessment is not precise enough. This technique is also proven efficient in detecting early inflammation prior to structural changes in the tissue because it computes tissue functionality independent of any structural changes[10-12]. Since patients with GO have increased 18-FDG uptake compared to patients without GO, it can advance clinical evaluation of TAO[13]. However, one paper observed a lack of correlation between 18-FDG myofiber uptake and inflammation score or muscle diameter[12]. Since no meta-analyses have been reported on this subject, we conclude that further research is needed to justify the use of FDG in detection and clinical evaluation of TAO.

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Sažetak

DISTIREOIDNA OFTALMOPATIJA U BOLESNICE U HIPOTIREOZI

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Distireoidna oftalmopatija je autoimuni poremećaj orbite koji se javlja pretežno kod Gravesove hipertireoze, dok je neuobičajen klinički nalaz u bolesnika s Hashimotovim tireoiditisom i hipotireozom. Prikazujemo slučaj 62-godišnje bolesnice s edemom lijevog kapka, proptozom, diplopijom i lateralnom paralizom lijevog oka. Magnetska rezonanca orbita pokazala je retrobulbarnu masu u lijevoj orbiti s hiperintenzivnim signalima unutar lijevog medijalnog ravnog mišića, ali bez infiltracije lijevog optičkog živca. Ispitivanje tehnikom 18-fluorodeoksiglukoza pozitron emisijska tomografija/kompjutorizirana tomografija (^{18}F-FDG PET/CT) otkrilo je patološku akumulaciju ^{18}F-FDG u ekspanzivnoj masi unutar medijalnog ravnog mišića lijevog oka (SUVmax=1,0) te sličan nalaz u desnom oku (SUVmax=7,1). Također, pojačan metabolizam glukoze nađen je i u štitnjači (SUVmax=6,4). Laboratorijski su nalazi pokazali povećanu razinu tireotropina, dok su antitijela na receptore tireotropina bila negativna. Bolesnici je dijagnosticiran Hashimotov tireoiditis i distireoidna oftalmopatija te je uvedena terapija levotiroksinom. Na kontrolnom pregledu godinu dana kasnije vidljivo je poboljšanje simptoma oftalmopatije – nestanak diplopije uz vraćanje potpunog pokreta očiju. Zaključno, ispravljanje hipotireoze može značajno poboljšati simptome distireoidne oftalmopatije. U prikazu ovoga slučaja ističemo ulogu PET/CT-a s ^{18}F-FDG koji je ukazao na povišenu metaboličku aktivnost ne samo u orbitalnoj regiji, nego i u štitnjači, što je unaprijedilo kliničku dijagnozu i daljnji terapijski postupak distireoidne oftalmopatije, no potrebna su daljnja istraživanja.

Ključne riječi: *Distireoidna oftalmopatija; Hashimotov tireoiditis; Hipotireoza; Magnetska rezonanca; ^{18}F-FDG PET/CT*