ORBITAL PSEUDOTUMOR CAN MIMIC GRAVES' OPHTHALMOPATHY

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Abstract

Context. Orbital pseudotumor (OP) is a benign inflammatory process of the orbit with a large polymorphous lymphoid infiltrate, associated with fibrosis in variable amounts, localized or diffuse. Graves' ophthalmopathy (GO) is the most common cause of proptosis, unilateral or bilateral.

Case report. We report a patient with unilateral proptosis who was initially treated with antithyroid drugs for an euthyroid Graves disease, but the extension of the investigation informed this. The MRI findings (inflammation of fat, muscle and the left lacrimal gland) in conjunction with the biopsy informed the initial diagnostic and confirmed the OP.

Conclusions. Orbital pseudotumor is a rare disorder that can image and clinically mimics some inflammatory disease especially Graves' ophthalmopathy. Orbital MRI represents the most important test for diagnostic. A negative TRAb in euthyroid cases of proptosis can be a serious starting point for investigating an OP.

Key words: orbital pseudotumor, Graves' ophthalmopathy, differential diagnosis, TRAb, MRI.

INTRODUCTION

Orbital pseudotumor (OP), nonspecific orbital inflammation (NSOI), also known as idiopathic orbital inflammation and orbital inflammatory syndrome represent a common cause of painful orbital mass in adults (1). OP is a benign inflammatory process of the orbit with a large polymorphous lymphoid infiltrate, associated with fibrosis in variable amounts (2). This inflammation can be localized or diffuse. The localized inflammation occurs in the extraocular muscles (orbital myositis), lacrimal gland (dacryoadenitis), sclera (scleritis), uvea (uveitis), and the superior orbital fissure and cavernous sinus (Tolosa-Hunt syndrome). If the inflammation is diffuse, it involves the orbital fatty tissues (2).

After thyroid eye disease and orbital lymphoma

OP is the third most common orbital disease (1). OP can both radiologically and clinically mimic a malignant process or a Basedow' disease. It is a diagnosis of exclusion after all other causes of inflammation have been eliminated. The treatment is based on surgery, steroids, chemotherapeutic agents and irradiation (3).

The etiology and pathogenesis of OP are not known at present. Some data demonstrated infectious and immune-mediated etiologies. Differential diagnosis of Graves' disease has to exclude OP, Cushing's syndrome, obesity, idiopathic myositis and cellulitis, granulomatous disorders, primary or metastatic tumors, fistulas in the cavernous portion of the carotid artery and other vascular conditions (4).

Graves' ophthalmopathy (GO) is the most common cause of proptosis, unilateral or bilateral. Hyperthyroidism can be associated or not with GO (1, 5). In some cases, the diagnostic of GO is not very clear because orbital imaging like computed tomography (CT) or magnetic resonance imaging (MRI) describe orbital inflammation masses and thyrotropin-receptor antibodies (TRAb) as normal with their high specificity and sensitivity in Graves' disease. The objective of this paper is to present a rare inflammatory cause of exophthalmos.

CASE PRESENTATION

This case report presents a patient with unilateral exophthalmos, who was initially diagnosed with GO, but the final diagnosis was that of orbital pseudotumor.

In October 2015, a 28-year-old man was admitted in Endocrinology Department for evaluation of unilateral proptosis in the left eye, which had developed 2 months before, associated with intermittent diplopia with progressive worsening.

Clinical examination revealed: BMI = 26.58 kg/m², skin and mucous normal colored, blood pressure 120/70 mmHg, pulse 74/min, mild thyroid hypertrophy

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(goiter grade II) with slightly firm texture, surface regular, mobile, painless on palpation; we observed an evident proptosis in the left eye, associated with mild swelling, redness, and normal eye movements; no pain, diplopia or goiter.

Thyroid function tests revealed: TSH = 0.5 μ IU/mL (normal value: 0.4-4), FT4 = 1.43 ng/dL (normal value: 0.89-1.76), TRAb = 1.63 UI/L (normal value: 0-1.75), IgG4 = 0.52 g/L (normal value: 0.052-1.250), negative antithyroglobulin and antithyroid peroxidase antibodies. The normal value of TRAb was unusual for the clinical signs and we repeat the measurement but it was also normal (TRAb = 1.43 UI/L).

Ophthalmological evaluation revealed visual acuity (VA): VA-right eye = 1/2 cc, VA-left eye = 2/3cc; intraocular pressures (IOP) was IOP- right eye = 18mmHg, IOP- left eye = 22mmHg; funduscopy showed bilateral optic disc pallor and the right eye presented flat papilla, contoured, normal colored macula with increased reflex, vessels look normal, left eye had excavated papilla, slightly pale, contoured macula with low reflex and normal vessels. Exophthalmometry described: right eye 21mm, left eye 27mm measured by Hertel's exophthalmometer; also the ophthalmologic examination described conjunctival injection, and mild chemosis with mild exposure keratitis (Fig. 1).

Orbital MRI showed internal, external and lower left muscle thickening as loading homogeneous contrast iv administration, with proptosis; slight increase in volume of the left lacrimal gland compared to the straight homogeneous hypervascular

administration of intravenous contrast. The conclusion of MRI was a left retrobulbar myositis with chronic inflammatory infiltrate with important left proptosis; also the left lacrimal gland was hypertrophic with mild inflammation (Fig. 2).

The extensive investigations revealed normal complete blood count, kidney and liver function tests. Urine analysis was normal. ECG, X-ray chest and abdominal ultrasound were normal. Collagen profile was in normal limits and Venereal Disease Research Laboratory (VDRL) and anti-neutrophil cytoplasmic autoantibody (ANCA) were negative.

Thyroid ultrasound showed a mild hypertrophy of the thyroid with hypoechogenicity, normal vascularity with small inflammatory lymph nodes on neck.

The case was interpreted as a GO with no clear thyrotoxicosis and treated with methimazole 10 mg/day for 2 months, based on the relative low TSH. After this period the thyroid hormonal tests were in normal limits (euthyroidism), but the patient accused proptosis, diplopia, redness and swelling of the left eye. TRAb and antithyroid antibodies were in normal limits.

The reevaluation of the case decided the need for a retrobulbar biopsy of the external rectus muscle from the left eye. The result of biopsy showed chronic inflammatory infiltrate, and the striated muscle sample was normal, excluding GO. There were described muscle fibers of uniform appearance without dystrophic changes or atrophy, lymphocytic inflammatory infiltrate, minimal hyperemia and moderate interstitial edema, without atypia in the examined material (Fig. 3).

Figure 1. Left proptosis and important inflammatory signs (A,B,C - before treatment, October 2015).

Figure 2. Left retrobulbar myositis with MRI isointense images of the left mass (A, B, C) and hypertrophy of left lacrimal gland (D).

Figure 3. Histopathological result (A,B) with reduced chronic inflammatory infiltrate in muscle sample, muscle fibers of uniform appearance without dystrophic changes or atrophy (HE 40x, 100x).

Figure 4. Improvement of eye signs after methylprednisolone treatment (January 2016).

Based on the clinical evolution and histopathological examination correlated with MRI examination, there was established the diagnosis of orbital pseudotumor associated with mild diffuse goiter.

The treatment started with 500 mg intravenous methylprednisolone and after 5 infusions, we observed a marked improvement of ocular clinical signs (Fig. 4).

After 5 months and another cure of 5 infusions with intravenous methylprednisolone 500mg the ocular sign decreased in intensity, the proptosis had reduced to 20 mm on the right and 21 mm on left side. The patient is presently in remission.

DISCUSSION

GO is an inflammatory disorder of the orbit that occurs in association with autoimmune thyroid disease (6, 7). The diagnosis is based on clinical and usual hormonal evaluation in thyrotoxic patient with bilateral proptosis. This is difficult in an euthyroid patient with unilateral proptosis when CT scanning or MRI of the orbits are indicated, identifying an orbital mass lesion, an infiltrative process, idiopathic orbital inflammation (pseudotumor), or other orbital abnormality. If the

imaging is compatible with GO, the elevated TRAb is useful for diagnosis in euthyroid patient (7).

In 1903, Gleason, Busse and Hochheim first described a new condition known as orbital pseudotumor (OP) or idiopathic orbital inflammatory disease (5, 8). OP is a benign inflammation, non-infectious, space-occupying orbital lesion with no identifiable local or systemic etiology, involving any orbit structure (myositis, dacryoadenitis, perineuritis, tendonitis, episcleritis, and localized mass) (1, 5).

Some reserchers have tried to identify the pathogenesis of this inflammation, but it is still not clear. They described a real association with infection, trauma, surgery and with autoimmune disorders (Crohn's disease, Sjögren's syndrome, Behçet's disease, lupus, rheumatoid arthritis, diabetes mellitus, myasthenia gravis, and ankylosing spondylitis) suggesting an immune-mediated process (5, 9).

OP occurs more often in the third to sixth decades with no strong sex predilection (5). Our case presents a young man without a specific medical history with abrupt onset of ocular symptoms, with proptosis and other inflammatory signs such as swelling and erythema. Unilateral presentation is more typical than bilateral form which is not uncommon. Similar data was reported by Caminha LSC *et al.* in 2011 in a young woman (39 years old) with initial diagnostic of Graves' orbitopathy and 7 years later, the relapse of the ocular signs revealed an unilateral OP in the left eye (5).

The medical history, laboratory investigation, the response to steroid therapy and histopathological analysis, represent important diagnostic steps (10). Most studies demonstrated that the diagnosis of OP is an exclusion diagnostic (5).

The positive diagnosis is difficult but after

excluding an active thyroid ophthalmopathy, the biopsy and imaging evaluation including high-resolution CT or contrast-enhanced MRI can identify this disease.

The biopsy is difficult to perform if the imaging evaluation cannot identify a distinct mass to biopsy or the lesion is unapproachable. It is absolutely necessary for diagnosis if the patient complains about neurologic deficits, or in case of no responsiveness to steroid therapy or persistent imaging abnormalities (2). The biopsy results usually describe pleomorphic inflammatory cell infiltration with reactive fibrosis. Some studies demonstrated that a sclerotic description has an aggressive prognosis (8). Biopsy should be performed to rule out any other underlying pathology (11).

In evaluation of our case the retrobulbar biopsy of the external rectus muscle from the left eye demonstrated chronic inflammatory infiltrate, and the striated muscle sample was normal, excluding Graves' ophthalmopathy. We identified muscle fibers of uniform appearance without dystrophic changes or atrophy, lymphocytic inflammatory infiltrate, minimal hyperemia and moderate interstitial edema, without atypia in the examined material. Similar data was also described by Chaudhry IA *et al.* in 2008 (12).

For a positive diagnosis the orbital imaging is very important because it revealed details about the localisation, extension and the inflammation characteristics. The CT or MRI can describe diffuse orbital mass, uveoscleral thickening, contrast enhancement of Tenon's potential space, proptosis and optic nerve and extraocular muscle enlargement. The CT examination can identify a focal or diffuse mass with a clear infiltration of retrobulbar fat (5).

On MRI, the frequent description in OP is the presence of a hypointense lesion in T1 and in T2-weighted images with a relative isointense T2 signal. Some data described an important postcontrast enhancement (5, 13). The MRI of orbit can describe the magnitude of inflammation by evaluation of the proptosis, optic nerve thickening, uveal-scleral thickening, lacrimal gland infiltration and the enlargement of ocular muscles with muscle tendon. In Graves' ophthalmopathy, the MRI modifications are frequently bilateral and involved the inflammation of orbital fat and muscle with no sheath enlargement (spindle-shaped) (5,12-14).

The MRI examination in our patient described internal, external and lower left muscle thickening as loading homogeneous contrast iv administration, with proptosis; slight increase in volume of the left

lacrimal gland compared to the straight homogeneous hypervascular administration of intravenous contrast. Other papers sustain that the lacrimal gland appears diffusely enlarged with preservation of its shape with possible blurring at the gland margins with expansion along lateral orbital wall and lateral rectus muscle (2, 5). MRI is a useful diagnostic test to exclude orbital tumors like astrocytoma or lymphoproliferative diseases (15).

OP responses rapidly to steroids with a clear improvement of the symptoms and imaging. In 2003, Yuen and Rubin reported that 69% of the cases were treated with steroids alone, 12% with steroids and radiation therapy and 9% with steroids and non-steroids antiinflammatory drugs; of these, 24 patients had treatment failures with steroid dependence and steroid intolerance occurring in 33% (8).

Our patient responded very efficiently to steroids in pulse-therapy and the clinical signs rapidly decreased. This type of intravenous therapy is very efficient in serious forms with optic nerve dysfunction. Some papers reported good results after non-steroids antiinflammatory drugs or even spontaneous remission after a few weeks (5). The same data presented recurrence rates of about 25%-52% because incomplete resolution and recurrence are possible (5, 8).

The particularity of our case is that initially it was considered a Graves' ophthalmopathy with euthyroidism but the normal TRAb and MRI findings (inflammation of fat, muscle and the left lacrimal gland) in conjunction with the biopsy infirmed the initial diagnostic and confirmed the OP.

In conclusion, an unilateral proptosis in any patient had to be completely investigated by orbital imaging by MRI and if the results are non-conclusive, biopsy is needed.

Our case demonstrated the importance of TRAb assay to exclude Basedow' disease. Also the orbital imaging investigations and in selected cases the biopsy represent important steps to identify a possible OP. Orbital MRI represent the most important test for diagnostic.

Orbital pseudotumor is a rare disorder that radiologically and clinically can mimic Graves' ophthalmopathy, a malignant orbital disease or other inflammatory process.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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