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CASE REPORT

Early Massive Fibrosis of a Single Extraocular Muscle Causing Severe Unilateral Euthyroid Graves' Ophthalmopathy in a Patient with Hypercholesterolemia Who Smokes

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Background: Graves' ophthalmopathy (GO) is an autoimmune manifestation of orbit affecting approximately 25% of patients with Graves' disease (GD). Autoreactive T cells involved in thyroid autoimmunity can recognize the thyroid-stimulating receptor (TSHr) expressed in orbital tissues of GO patients. Clinical manifestations of GO are rather different depending on the presence of some risk factors, such as smoking, hyperthyroidism duration, age, biological activity of anti-TSHr antibodies (TSH-R-Ab) and metabolic diseases.

Case Presentation: Here, we present a rare case of euthyroid single muscular GO in a 50-year-old patient who was a smoker and had dyslipidemia for several years. The patient experienced a very rapid and severe depression of ocular motility of the right eye that caused uncorrectable and constant diplopia, severely affecting his quality of life. He was euthyroid, and TSH-R-Ab plasmatic levels were only slightly elevated. Intravenous corticosteroid pulse therapy was partially effective, and two rounds of wall orbital surgical decompression were necessary. Massive mono-muscular fibrosis was evidenced by biopsy of the right inferior rectus muscle.

Conclusion: Severe unilateral, mono-muscular GO in a euthyroid Graves' patient was found to be sustained by rapid and massive fibrosis of the inferior rectus muscle of the right orbit. Clarification of the pathogenetic mechanisms of these GO clinical forms requires further studies.

Keywords: Graves' ophthalmopathy, massive fibrosis, smoke, hypercholesterolemia

Background

GO is an autoimmune extrathyroid manifestation of Graves' disease and the most common cause of GD exophthalmos. GO is characterized by retroocular fat expansion, inflammatory infiltration and possibly fibrosis of extraocular muscles in chronic states. GO presents in mild forms in almost 85% of cases. The moderate to severe and severe forms present in 5–6% and 2% of cases, respectively, and asymmetrical GO forms are observed in approximately 15% of cases.[1] Euthyroid GO has a prevalence of 0.02/10.000 cases and potentially qualifies as a rare condition.[2]

Case Presentation

We report a rare case of euthyroid unilateral GO with early massive mono-muscular fibrosis in a 50-year-old male patient. The patient had a family history of cardiovascular disease, type 2 diabetes mellitus, and myasthenia gravis but no family or personal history of thyroid autoimmune disease. The patient was a smoker of 20 cigarettes a day from the age of 30 and presented dyslipidemia for several years. Since June 2020, he experienced rapid and progressive swelling of the soft tissues in the right orbit, moderate pain during ocular globe movements, redness of eyelids and diplopia. Visual

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acuity was normal in both eyes. In October 2020, the patient was evaluated in our outpatient clinic. Moderate right orbit active inflammation was confirmed by Clinical Activity Score 3/7 (CAS),[3] and eyelid edema was moderate. The eyelid aperture was 14 mm in the right orbit and 10 mm in the left orbit, and the Hertel measurements were 24 mm and 18 mm in the right and left orbits, respectively. In addition, the patient presented a severe reduction in elevation, persistent depression in the primary position of the right ocular globe (Figure 1) and constant diplopia, as scored according to the Gorman score.[4] The quality of life evaluated by Graves' Ophthalmopathy quality of life questionnaire (GO-QOL)[5] was reduced in both appearance and functional subscales. However, the functional subscale was reduced with respect to the appearance subscale, as the values were 12.5 and 50, respectively (considering 0 = worse condition and 100 = the best health state). Visual acuity was normal, and color vision by Ishihara tables was 16/17 and 17/17 in the right and left eyes, respectively. Evaluation of extraocular muscles by computer tomography (CT) scan (contiguous 1.25 mm thick slices, 200 mA, 120 kV, pitch 0.5) showed severe enlargement of the lower rectal body to the edge of the insertion tendon in the right orbit. Remarkably, the morphology of the other extraocular muscles in both orbits was normal (Figure 2A and B). The muscle orbit area ratio measured in the right eyes was 0.25 Autocad units (in-house method; vn $\leq$ 0.20±0.03).[6] Thyroid function was normal with a slight increase in TSH-R-Ab: 1.75 mU/l (n.v. < 1.5 mU/l). The amplitude of the p100 wave was slightly reduced by electrophysiology evaluation in the right eye. A thyroid ultrasound scan of the thyroid gland showed a thyroiditis pattern. Biochemical and clinical evaluations were negative for hematological or other systemic diseases. Routine clinical tests were normal, but the total cholesterol levels that were 220 mg/dl, triglyceride levels were 297 mg/dl, and high-density lipoprotein cholesterol (HDL) levels were 38 mg/dl.

The patient was treated by intravenous corticosteroid pulse therapy (Solumedrol; Pfizer, Karlsruhe, Germany) with a cumulative dose of 4500 mg over 12 weeks, leading to the resolution of inflammatory signs and symptoms. However, GO-QOL, Hertel measurements and diplopia remained unchanged; in contrast, electrophysiology evaluation and visual acuity worsened. Two-wall orbital surgical decompression plus parenteral glucocorticoids was chosen as the second-line

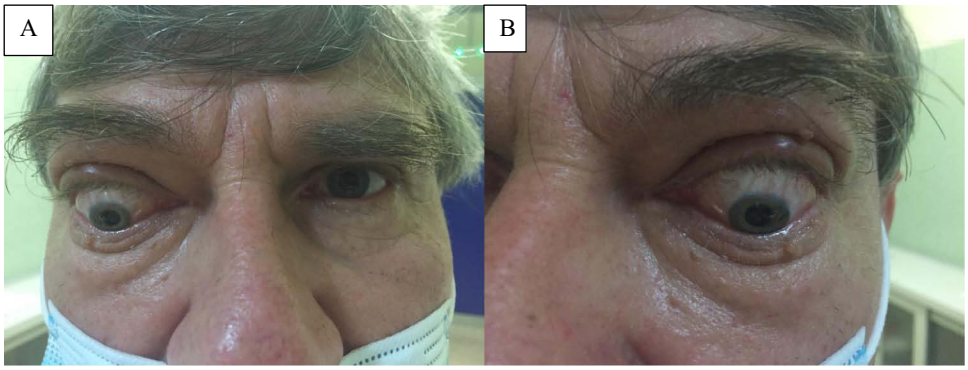

Figure 1 Early asymmetrical orbits involvement and constant depression in primary position of the right ocular globe (**A** and **B**).

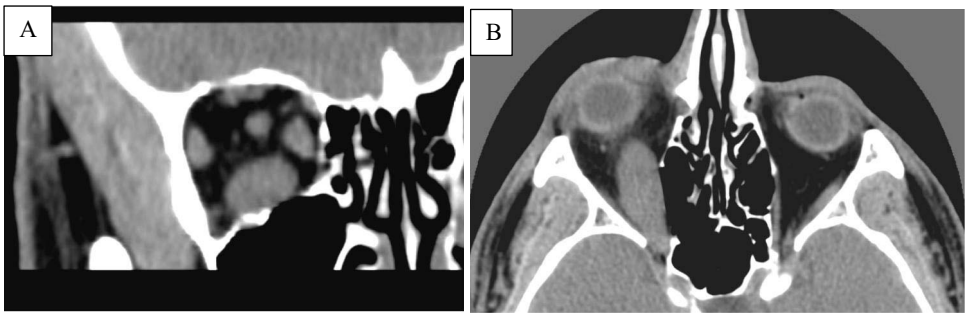

Figure 2 Coronal (**A**) and axial (**B**) CT slices shows massive enlargement of inferior rectus in right orbit.

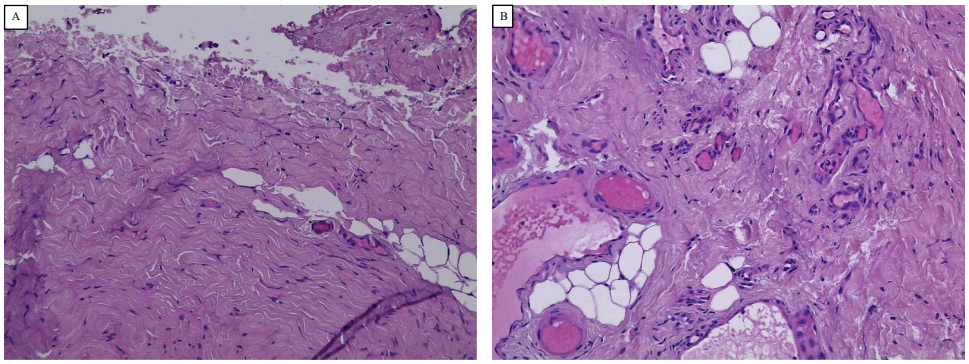

Figure 3 Photos at 100x (**A**) and 200x (**B**) magnification of right inferior rectus biopsy show diffuse fibrosis, fibroblast proliferation and adipose tissue infiltration inside intermyofibrillar space.

treatment for GO. In that context, a biopsy of the right inferior rectus muscle revealed massive fibrosis with adipose tissue infiltration of this extraocular muscle (Figure 3A and B).

Discussion

Graves' ophthalmopathy is diagnosed by inflammatory involvement of orbital soft tissues and an established diagnosis of Graves' disease (GD). The diagnosis of GO is often delayed due to different clinical presentations; in fact, GO can occur within 12 months or several years after hyperthyroidism, before hyperthyroidism or in euthyroid patients in approximately 10% of cases. Approximately 5–15% of GO patients present asymmetrical involvement of the orbits.[1] Bilateral enlargement of the inferior rectus muscle is seen in most patients, and this is followed by medial and superior rectus muscle involvement. In our patient, we diagnosed a severe enlargement of the right inferior rectus (IR) and very early evidence of massive fibrosis in the same muscle. Enlarged muscles are apparently an early phenomenon in GO. However, IR involvement is less frequently observed in mono-muscular GO, and increases in fat mass and muscle fibrosis occur relatively late.[6,7] In the early stages of GO, autoimmune inflammation is mainly related to cell-mediated immunity, whereas in the later stages, it is related to humoral immunity. B cells in fact act by inducing autoantibodies and promoting fibrosis by secreting cytokines.[7] These data support the evidence that fat expansion is a late phenomenon in the orbits of GO patients.[8] Fat expansion causes hemodynamic decompensation, an increase in intraorbit pressure and, in rare cases, optic neuropathy. Leucocyte infiltration and glycosaminoglycan (GAG) deposition contribute further to remodeling of the orbit environment. In our patient, elevation of the right eye was dramatically reduced, and a constant depression of the ocular globe appeared very quickly despite normal thyroid function with a very slight increase in TSH-R-Ab. Asymmetric or, more rarely, mono-muscular involvement of extraocular muscles might be related to differences between fibroblast phenotypes and cytokine profiles in muscles and/or fat compartments,[9] This includes different orbital T-cell subsets during the course of the disease and peroxisome proliferator activator receptor-γ polymorphisms or modulation of 11β-hydroxysteroid dehydrogenase-1.[7] Another possibility to be considered in this case is immunoglobulin G4 (IgG4)-related ophthalmic disease; however, the data about fibrosis involvement of the intraorbital soft tissues of GO related to IgG4 are rather conflicting.[10] Unfortunately, we were not able to dose plasmatic IgG4 levels in our patient at that time.

The vascular and bone anatomy of orbits might play a role in allowing appropriate or not appropriate intraorbit fluid circulation and/or oxygenation during GO autoimmune reactions and soft tissue remodeling.[11,12] In our case, a determinant role of smoke should be considered. Our patient was a smoker for several years, and smoking is a well-known risk factor for GO presentation and exacerbation. Moreover, individuals who smoke have more severe GO than those who do not smoke. This is due to increased hyaluronan secretion and adipogenesis in the orbital fibroblasts (OFs) of smokers.[13] In our patient, smoking both directly and indirectly may have played a role. Chronic hypoxia could be considered an indirect mechanism to explain the massive and very early fibrosis of the IR of our patient. In fact, extraocular muscles need a large amount of oxygen and contain numerous mitochondria that are sensitive to hypoxia.[14] Chronic low-grade localized hypoxia could redirect local macrophages to promote a high degree of inflammation and

fibrosis in only one extraocular muscle at an early stage of the disease when cell-mediated immunity is expected to cause inflammation and enlargement of the muscles of the orbit with a low amount of fibrosis. However, smoking could affect GO clinical presentation and evolution through a direct toxic effect and trauma from heat through the medial orbit wall, which is very tiny[15] and very close to IR. Dyslipidemia is associated with low-grade inflammation and an increased risk of GO in patients with elevated total and low-density lipoprotein cholesterol levels (RR: 1.28; P=0.03), and CAS was found to be higher (P=0.02) in patients with high total cholesterol levels.[16] Moreover, in patients with GO and very high levels of LDLc, corticosteroid efficacy can be reduced.[17] In our patient, dyslipidemia was diagnosed for several years and never treated. Thus, it could have contributed to the peculiar clinical presentation of GO. Notably, thyroid function was normal and stable during the early and fast functional deterioration of the right inferior rectus and remained stable during the entire observation period. It has been shown that thyroid hormones attenuate mitochondrial apoptosis in alveolar epithelial cells, and although oxidative processes are increased during hyperthyroidism, a direct role of thyroid hormones in counteracting fibrosis processes of extraocular muscles in patients with GO cannot be excluded.[18] Unfortunately the period of clinical follow-up was limited and we were not able to study the others clinical characteristic as choroidal thickness variations usefully to diagnose active GO in euthyroid patients[19,20]. Finally, we cannot exclude that the presentation of this rare phenotype of GO may be affected by potential molecular peculiarities of anti–thyrotropin-receptor antibodies or other molecular abnormalities;

Based on these observations, future studies are needed to establish whether these GO forms have a distinct pathophysiology.

Conclusions

In this rare case, severe unilateral, mono-muscular GO in a euthyroid Graves' patient was found to be sustained by massive fibrosis of the inferior rectus muscle. We hypothesize that other unilateral GOs may share similar pathogenetic mechanisms, the clarification of which requires further studies.

Ethics Statement

All the procedures performed in the study involving human participants were in accordance with the ethical standards of the Trust and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Being a retrospective investigation, ethical approval was not required.

Informed Consent

Written informed consent was obtained from the participant for the publication of this case report and any potentially identifying images/information.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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