A rare case of early massive monomuscular fibrosis causing severe unilateral euthyroid Graves' ophthalmopathy in a smoker patient with dyslipidemia

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Case report

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Abstract

Background

Graves’ ophtahlmopathy (GO) is an autoimmune manifestation of orbit affecting about 25% of patients with Graves’ disease (GD). Autoreactive T cells involved in thyroid autoimmunity can recognize the thyroid stimulating receptor (TSHr) expressed in orbit tissues of GO patients. Clinical manifestations of GO are rather different depending of the presence of some risks factors as smoke, 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 years old patient, he was smoker and had dyslipidemia from several years. The patient experienced a very rapid and severe depression of ocular motility of the right eye that causes an uncorrectable and constant diplopia severely affecting his quality of life. He was euthyroid and TSH-R-Ab plasmatic levels were only slightly elevated. Intravenous corticosteroids pulse therapy was partially effective and two rounds of wall orbital surgical decompression was necessary. A massive mono-muscular fibrosis was evidenced by biopsy of right inferior rectus muscle.

Conclusions

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 right orbit, the clarification of pathogenetic mechanisms of these GO clinical forms requires further studies.

Introduction

GO is an autoimmune extra thyroid 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, moderate to severe and severe forms in 5-6% and 2%, respectively; asymmetrical GO forms are observed in about 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. He was a smoker of 20 cigarettes a day from the age of 30 and presented dyslipidemia from several years. Since June 2020 he experienced a rapid and progressive swelling of the soft tissues in the right orbit, moderate pain during

ocular globe movements, redness of eyelids and diplopia. Visual acuity was normal in both eyes. In October 2020 he was evaluated in our outpatients' clinics. A moderate right orbit active inflammation was confirmed by Clinical Activity Score 3/7 (CAS) [3], eyelid edema was moderate. Eyelid aperture was 14 mm in the right orbit and 10 mm in the left orbit, while Hertel measurements were 24mm and 18mm in the right and left orbit respectively. In addition, the patient presented a severe reduction of elevation, persistent depression in primary position of the right ocular globe (Fig.1 A-B) and constant diplopia, as scored according to Gorman score [4]. Quality of life evaluated by Graves' Ophthalmopathy quality of life questionnaire (GO-QOL) [5] was reduced in both appearance and functional sub-scales, however, functional sub-scale was rather reduced respect the appearance subscale: 12.5 vs 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 the left eye, respectively. Evaluation of extraocular muscles by computer tomography (CT) scan (contiguous 1.25mm thick-slices, 200mA, 120kV, 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 (Fig. 2 A-B). Muscles orbit area ratio measured in right eyes was 0.25 Autocad Units (in house method; vn ≤ 0.20±0.03) [6]. Thyroid function was normal with a slight increase of TSH-R-Ab: 1.75mU/l (n.v. < 1.5mU/l). Amplitude of p100 wave was slightly reduced by electrophysiology evaluation in the right eye. Thyroid ultrasound scan of thyroid gland showed a thyroiditis pattern. Biochemical and clinical evaluations were negative for hematological or other systemic diseases. Routine clinical tests were normal except total cholesterol levels that were 220 mg/dl, triglycerides 297 mg/dl, and high-density lipoprotein cholesterol (HDL) 38 mg/dl.

The patient was treated with intravenous corticosteroids pulse therapy (Solumedrol; Pfizer, Karlsruhe, Germany) with a cumulative dose 4500 mg in 12 weeks leading to the resolution of inflammatory signs and symptoms. However GO-QOL, Hertel measurements and diplopia remained unchanged and required two rounds of wall orbital surgical decompression. In that context, a biopsy of right inferior rectus muscle revealed a massive fibrosis with adipose tissue infiltration of the intermiofibrillar space (Fig. 3 A-B).

Discussion

Graves' ophthalmopathy is diagnosed by inflammatory involvement of orbit soft tissues and 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 after several years from hyperthyroidism, before hyperthyroidism or in euthyroid patients in about 10% of cases. 5–15% of GO patients presents asymmetrical involvement of the orbits [1]. Bilateral enlargement of the inferior rectus muscle is seen in most patients, followed by medial and superior rectus muscle involvement. In our patient we diagnosed a severe enlargement of right inferior rectus (IR) and a 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 increasing in fat mass and muscles fibrosis occurs relatively late [6–7]. In the early stages of GO the autoimmune inflammation is mainly related to cell-mediated immunity, whereas in the later stages it is related to humoral immunity involving Graves' IgG

binding to TSH receptor that is overexpressed in differentiated orbital fibroblast [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, increment of intra-orbit pressure and in rare cases optic neuropathy. Leucocyte infiltration and glycosaminoglycans (GAGs) deposit contribute further to remodeling of the orbit environment. In our patient elevation of the right eye was dramatically reduced and a constant depression of ocular globe appeared very quickly despite normal thyroid function with a very slight increase of 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 compartment [9], to different orbital T cell subsets during the course of the disease and to peroxisome proliferator activator receptor-γ polymorphisms or modulation of 11β-hydroxysteroid dehydrogenase-1 [7]. Vascular and bone anatomy of orbits might play a role allowing an appropriate or not appropriate intra-orbit fluids circulation and/or oxygenation during GO autoimmune reaction and soft tissues remodeling [10–11]. In our case, a determinant role of smoke should be considered. Our patient was a smoker from several years and smoking is a well-known risk factor for GO presentation and exacerbation. Moreover, smokers have more severe GO than no smokers, owing to hyaluronan secretion and adipogenesis that are increased in orbital fibroblasts (OF) of smokers [12]. In our patient, smoke both directly and indirectly may have played a role. Chronic hypoxia could be considered an indirect mechanism to explain massive and very early fibrosis of the IR of our patient. In fact, extraocular muscles need large amount of oxygen and contain numerous mitochondria that are sensitive to hypoxia [13]. 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, smoke could affect GO clinical presentation and evolution through a direct toxic effect and trauma from heat through the medial orbit wall that is very tiny [14] and very close to IR. Dyslipidemia is associated to low-grade inflammation and to an increased risk of GO in patients with elevated total and low density lipoprotein cholesterol (RR: 1.28; P = 0.03), and CAS was found higher (P = 0.02) in patients with high total cholesterol [15]. Moreover, in patient with GO and very high levels of LDLc, corticosteroid efficacy can be reduced [16]. In our patient, dyslipidemia was diagnosed from several years and never treated, thus it could have contributed to the peculiar clinical presentation of GO. Noteworthy, thyroid function was normal and stable during the early and fast functional deterioration of right inferior rectus and remained stable during the entire observation period. It has been shown that thyroid hormones attenuate mitochondria apoptosis in alveolar epithelial cells and although oxidative processes are increased during hyperthyroidism, a direct role of thyroid hormones to counteracting fibrosis processes of extraocular muscles in patients with GO cannot be excluded [17]. 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.

Declarations

Ethics approval and consent to participate

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.

Consent for publication

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

Availability of data and materials

Data and materials are available at Endocrinology Unit – Department of Clinical and Experimental Medicine – University of Catania.

Competing interests

The authors declare that they have no conflict of interest.

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Author contributions

RL and GF participated in the acquisition and analysis of data, RL wrote the manuscript. AB participated in the conceptualization and editing of the manuscript. RL, AB and FF reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

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Figures

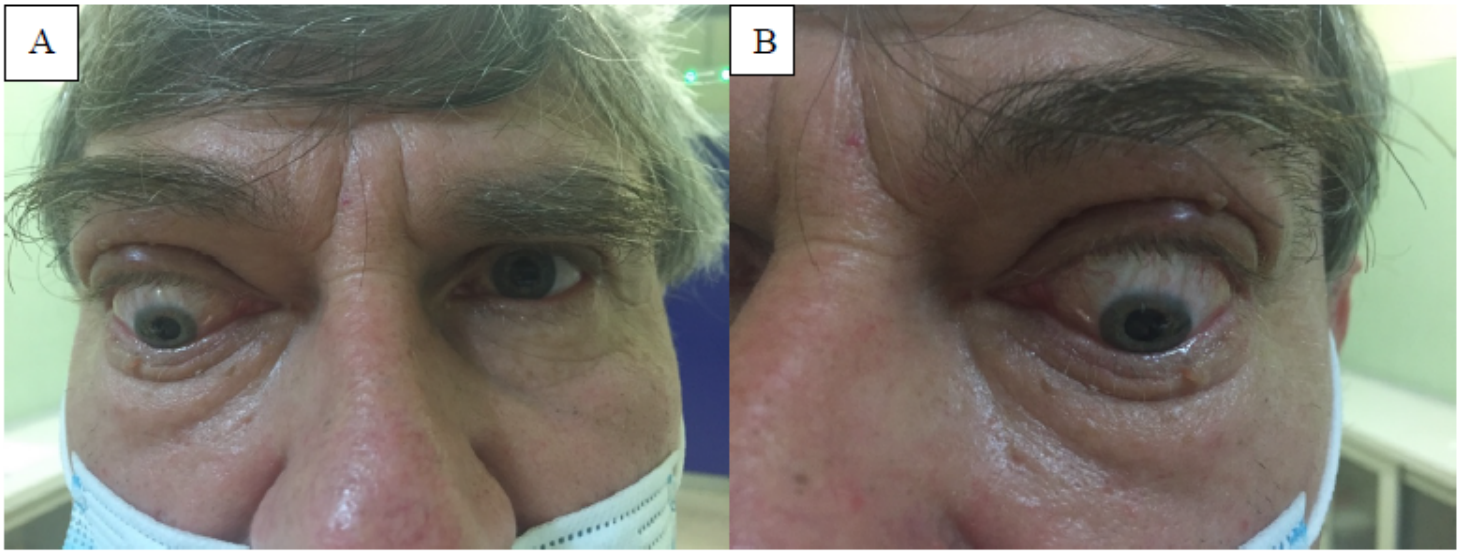

Figure 1

early asymmetrical orbits involvement and constant depression in primary position of the right ocular globe (A-B)

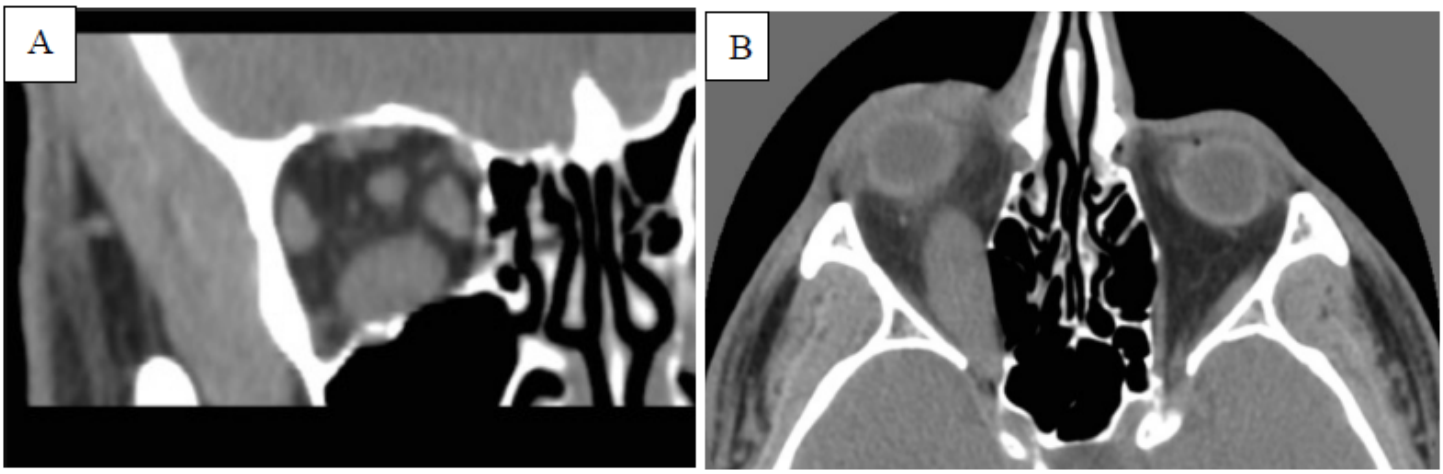

Figure 2

coronal (A) and axial (B) CT slices shows massive enlargement of inferior rectus in left orbit.

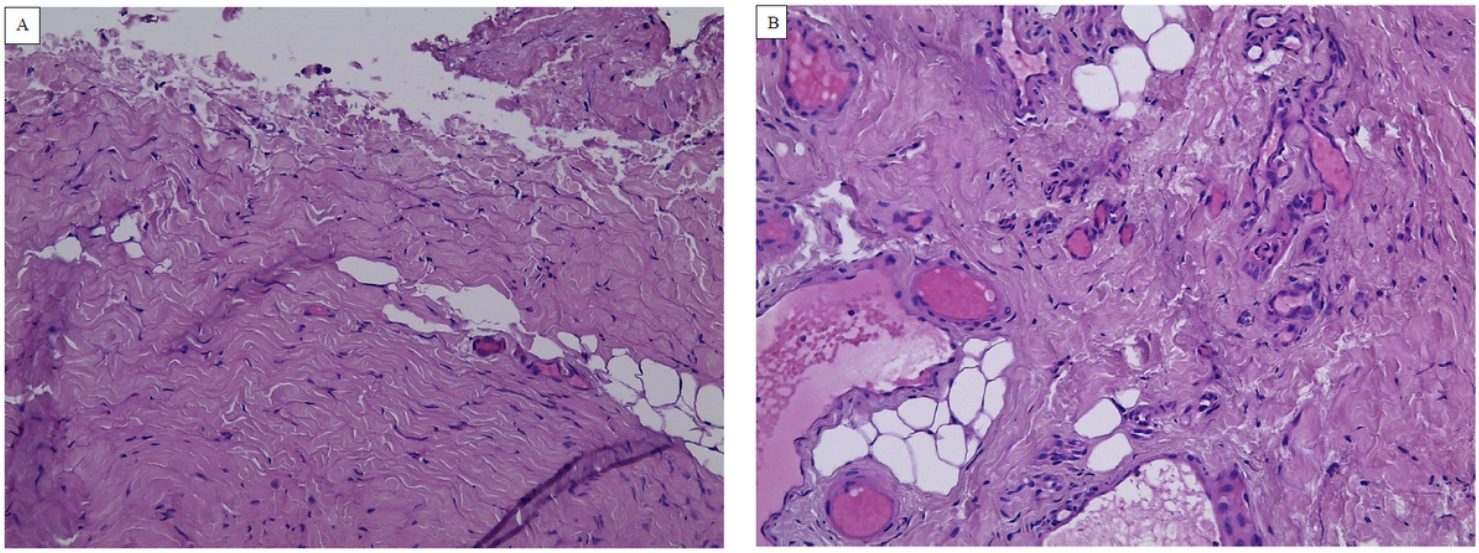

Figure 3

photos at 100x (A) and 200x (B) magnification of rigth inferior rectus biopsy show diffuse fibrosis, fibroblast proliferation and adipose tissue infiltration inside intermiofobrillar space.