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Unilateral thyroid-associated ophthalmopathy as an initial presentation of euthyroid Graves' disease

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Abstract
Unilateral exophthalmos (EO), although most frequently seen with Graves' disease (GD), has a large differential diagnosis that includesorbital pseudo tumor, lymphoma, sarcoidosis, and IgG4-related disease. Although Graves' ophthalmopathy (GO) is usually associated with hyperthyroidism, it has been estimated that up to 20 % of patients are euthyroid.[1, 2] Thyroid Eye Disease (TED) is the most frequent extrathyroidal manifestation of Graves' disease, and results from an increased volume of orbital tissues (connective and adipose tissue, interstitial enlargement of extraocular muscles) within the enclosed space of the bony orbits. Although excellent review articles have been published on TED, it remains a pathogenetic enigma and a therapeutic dilemma. Once initiated, the orbital immune process frequently assumes a momentum of its own, leading to non-specific but nonetheless harmful consequences such as tissue hypoxia, oxygen free radical damage, and fibrogenic tissue remodeling.
Thyroid Eye Disease is a self-limiting disease with active and static phases. The initial active inflammatory phase usually lasts For 6–24 months, but may sometimes continue for several years.
Exophthalmos, probably the most widely known symptom of TED, occurs in 20–30% of patients with Graves' disease and up to 40–70% of patients with TED. In the majority of patients both eyes are equally affected, although often in an asymmetric manner. Pure unilateral ophthalmopathy is rare, with 5% to 11% of cases showing no progression to bilateral disease.

Keywords: exophthalmos, unilateral, ophthalmopathy, showing, Thyroid

1. Introduction
The most common cause of bilateral and unilateral exophthalmos among adults is Graves' disease. Unilateral exophthalmos, although frequently seen in connection with thyroid diseases, has a much larger differential diagnosis than bilateral exophthalmos. With unilateral presentation one should think of orbital pseudotumour, orbital cellulites, cavernous sinus thrombosis, or intraorbital neoplasms.
Graves' ophthalmopathy (GO) usually is associated with Graves' hyperthyroidism (GH) although the temporal relation to thyroid disease is not consistent. It has been estimated that 77% of GO patients are hyperthyroid, 21% euthyroid, and 2% hypothyroid.

Case presentation
We present a case of a 49-year-old male with a past medical history of HCV cirrhosis (stage IV) and HTN who suddenly developed right eye proptosis and diplopia since awakening one morning and presented for evaluation four months later. He had been wearing a patch over his right eye to treat his diplopia. Associated symptoms included right eye pain/pressure/tearing and headaches that were exacerbated upon not wearing the eye patch. He denied trauma to the eye, flashes, floaters, curtain-like visual obscuration, transient vision loss, eye redness, foreign body sensation, dry eye, recent illnesses, fevers, night sweats, and hyperthyroid symptoms. He endorsed fluctuating weight changes, occasional shortness of breath, and easy bleeding/bruising attributed to decompensated liver cirrhosis. Family history was pertinent for lymphoma and stomach cancer in both parents. Patient was a former smoker with a 15-pack year smoking history. He denied history of radiation to the head, neck, and face. His physical exam revealed proptosis of the right eye with mild lack of convergence and inability to up gaze on the right eye. Examination of the thyroid gland and other systems was unremarkable.
Initial MRI orbit showed enlargement of the right inferior, medial, and lateral rectus muscles with enhancement. At this time, differential diagnoses included orbital pseudotumor, thyroid eye disease, lymphoma, sarcoidosis, metastatic malignancy, and IgG4 disease. Given extensive family history of cancer, CT abdomen/pelvis was ordered which was negative for malignancy. CT orbit was ordered for further evaluation which showed right eye proptosis with fusiform enlargement of the right extraocular muscle bellies predominantly involving the inferior rectus muscle suggestive of thyroid eye disease.
Initial labs showed leucopenia, thrombocytopenia, and transaminitis which are typical findings in cirrhotic patients. ANA and ANCA negative, and ESR mildly elevated (14 mm/HR). Patient was noted to have elevated total T4 (14.1 mcg/dL), total T3 (231 ng/dL), and positive TSI (200%). Free T4 (1.06 ng/dL) and TSH (1.25 mIU/L) were normal. IgG (2060 mg/dL) and ACE (108 U/L) were elevated. Patient was diagnosed with Euthyroid Graves Ophthalmopathy due to positive TSI which is highly specific for Graves' disease. Total T3 and T4 were elevated

in the setting of increased TBG in the setting of liver disease. Free T3, T4, and TSH were normal and patient was without hyperthyroid symptoms so anti-thyroid medications were not initiated. He was started on Prednisone that started with 80mg daily for two weeks, followed by an additional seven-week taper. During follow up visit in 3 months the patient continued to remain clinically and chemically euthyroid.

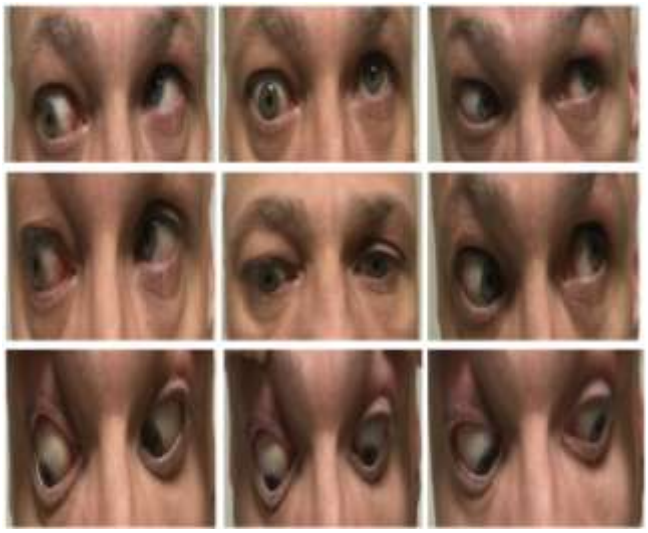

Fig 1

Discussion

Graves' ophthalmopathy (GO) is a chronic inflammatory disease of the orbits typically affecting women in their productive years of life. GO classically occurs in patients with Graves' hyperthyroidism, but 5–10% of patients have hypothyroidism or normal thyroid function. Individuals with GO and normal thyroid status are said to have euthyroid Graves' ophthalmopathy (EGO), the diagnosis of which is supported by the presence of one or more thyroid-specific antibodies, namely antibodies to thyroid peroxidase (TPOAb) and the TSH receptor (TRAbs). TRAbs, the pathological hallmark of Graves' disease, are present in virtually every patient with the disease, and thus, the occurrence of GO in the absence of thyroid dysfunction and positive thyroid antibodies is a cause of diagnostic uncertainty. We report a case of GO without thyroid dysfunction and positive thyroid antibodies at presentation. This condition occurs in approximately 5% of the cases of GO and refers to the occurrence of ophthalmopathy in the absence of current or past history of hyperthyroidism. Patients with EGO typically have relatively mild disease, characterized by unilateral or asymmetrical disease and lesser degrees of soft tissue inflammation and muscle involvement than patients exposed to hyperthyroidism. However, regardless of the degree of thyroid dysfunction or orbital involvement, it is unusual for GO to occur in the absence of abnormal thyroid function. However, a patient with orbital symptoms in the absence of thyroid disease and positive autoantibodies presents a diagnostic dilemma, and the clinician may be tempted to attribute such cases to non-thyroid causes. Our report illustrates the importance of a thorough clinical and radiological evaluation and close monitoring of long-term thyroid status in such individuals.

Conclusion

Our case illustrates the importance of a thorough evaluation required to determine the etiology of unilateral EO. The diagnosis of euthyroid GO is supported in our patient by presence of TSI that binds to TSH receptor on orbital fibroblasts, that plays a role in development of thyroid-associated ophthalmopathy [4]. Patients with euthyroid GO typically have mild, asymmetric disease, and lesser degrees of soft tissue/muscle inflammation [3]. ACE levels are non-specific for ocular sarcoidosis, which typically presents as uveitis, dry eye or orbital granulomas [5]. IgG4-related disease typically causes proptosis by involvement of lacrimal gland, extraocular muscles or other pseudo-tumor. While its diagnosis is typically made from biopsy findings, elevated IgG4 levels supports the diagnosis [6]. The treatment for all above conditions include glucocorticoids and timely management can prevent further complications [4, 7, 8].

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