Unilateral Graves’ Orbitopathy in a patient with Marine-Lenhart Syndrome

A case report

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Abstract
Thyroid eye disease (TED) is the most common symptoms of Graves’ disease. This condition commonly manifests bilaterally and symmetrically. The most prominent symptoms are lid retraction, exophthalmos, and diplopia. Rarely, individuals with Graves’ disease may show asymmetrical or unilateral eye symptoms. Marine-Lenhart syndrome is a variant of Graves’ disease with occasional hyperactive nodules. We introduce a 36-year-old Omani male patient who presented to the endocrinology outpatient department of Sultan Qaboos University Hospital, Muscat, Oman, in 2022 with unilateral eye proptosis and was subsequently found to have Graves’ disease. This case presents a rare Graves’ disease variant with unilateral goiter and orbitopathy.

Keywords: Graves’ disease; Unilateral proptosis; Thyroid Eye Disease; Graves ‘orbitopathy; Marine-Lenhart syndrome.
Introduction

Graves’ disease is an autoimmune condition resulting in thyroid hyperactivity. It is usually associated with high levels of thyroid hormones and the presence of thyrotropin receptor antibodies (TRAb).

Graves’ orbitopathy is an immune-mediated process that expands fibroblast in the extraocular muscles within the constrained space of the bony orbits in patients with Graves’ disease.\(^1\)\(^,\)\(^2\) This condition is usually bilateral and symmetrical. The most dominant symptoms are lid retraction, exophthalmos, and diplopia.\(^3\) Graves’ orbitopathy can occur without a hyperactive thyroid. The link between these two is supported by evidence suggesting an autoimmune link or a direct metabolic effect.\(^4\)\(^-\)\(^7\) Marine-Lenhart syndrome is a combination of Graves’ disease and hyperfunctioning nodules. This has been described in the literature mostly in case reports.\(^8\)\(^-\)\(^10\)

Marine-Lenhart syndrome was first reported in 1911 by D. Marine and C.H. Lehart. It is characterized by the following criteria: (I) Enlarged thyroid with poorly functioning nodules. (ii) The nodules demonstrate reduced radioiodine uptake. (iii) The nodules are resistant to radioiodine treatment and may require higher doses. (iv) After radioiodine treatment, there may be a return of function in the nodule, and (v) The nodule is benign.\(^11\) Marine-Lenhart syndrome is described as a subvariant of Graves’ disease.\(^12\) The condition has a prevalence of 0.8–2.7% in patients with Graves’ disease.\(^13\)

Here, we described a case of Marine-Lenhart syndrome with unilateral thyroid orbitopathy and Graves’ disease. In previous studies, the association of Marine-Lenhart syndrome with unilateral orbitopathy and Graves’ disease is uncommon.

Case Report

A 36-year-old Omani male patient presented to the Endocrinology outpatient department (OPD) of Sultan Qaboos University Hospital, Muscat, Oman, in 2022 as a referral from ophthalmology OPD with a thirteen-month history of isolated right eye proptosis and redness. He revealed that during the previous few months, he experienced sweating, non-frequent palpitations, tremors, shortness of breath, diarrhea, along with generalized weakness. There was no weight loss or
decrease in appetite. He had no other symptoms or signs suggestive of systemic disease or other autoimmune diseases. Three is no family history of thyroid disease.

On physical examination, he had tachycardia (114 beats/minute), blood pressure of (120/78), respiratory rate was 18 breaths/minute, and oxygen saturation was 99% in ambient air. He was not restless and had no tremors. He was obese, with a BMI of 36 kg/m². He had right eye proptosis, a normal pupil, and erythematous conjunctive with intact intraocular muscles movement. He did report double vision. The left eye examination was normal. He had a palpable right thyroid lobe with no palpable nodules. No cervical lymphadenopathy was noted.

Cardiovascular examination revealed normal heart sounds with no added sounds or murmurs. The clinical picture was consistent with thyroid-associated orbitopathy.

Laboratory investigations showed a slight increase of C-reactive protein (CRP) 8 mg/L (normal: 0-5 mg/L). The thyroid function test revealed free thyroxine (FT4) at 25.0 pmol/L (normal: 13.1-21.3) and thyroid-stimulating hormone (TSH) at 0.08 mIU/L (normal: 0.27-4.20). The anti-thyroid receptor antibody was 2.94 IU/L (normal range 0-1.75).

A thyroid ultrasound showed a right thyroid nodule with TI-RADS score 3, measuring 3.9 cm [Figure 1A]. FNA of the right thyroid nodule showed atypia of undetermined significance/Follicular lesion of undetermined significance (AUS/FLUS). ATc-99 test reported a single hot nodule inside the upper pole of the right thyroid lobe, coinciding with the ultrasound thyroid finding, with high total thyroid radiotracer uptake of 5.5% (normal range 1-4%) [Figure 1B]. A CT scan of the orbit without contrast was obtained, which showed severe right proptosis and a normal left orbit [Figure 2 A1, A2] with moderate to severe enlargement of right orbital extraocular muscles predominately involving medial, superior rectus and to a lesser extent inferior rectus. Enlarged muscles with relative preservation of tendon resulting in characteristics "coke bottle" morphology.

He was initially managed with a tapering course of Prednisone for a month with no improvements in Graves’ orbitopathy. Subsequently, he received two doses of intravenous Rituximab (1000 mg with two weeks' intervals). He did not have a significant improvement. He
was started on a trial of high-dose intravenous glucocorticoids therapy because Teprotumumab was not available in the country. The course consists of 6 doses of IV Methylprednisolone (0.5 g per week for a six weeks) lead by 6 doses of 0.25 g per week, IV Methylprednisolone for six weeks with an increasing dosage equivalent to 4.5 g. He reported a noticeable improvement in his ophthalmopathy, in particular, his eye redness. Post-treatment CT scan of the orbits without IV contrast showed an interval improvement of the right eye proptosis and right extraocular muscles hypertrophy, keeping with good response (interval improvement in the size of the right orbital extraocular muscles compared to the previous study) [Figure 2 B1, B2]. Outcome and follow-up six months after IV rituximab and methylprednisolone, the eye symptoms and signs improved specifically his double vision disappeared. Thyroid function test normalized [FT4 17.8, TSH 1.81] and the TSH receptor antibodies became negative. Additionally, the patient was directed to a thyroid surgeon for total thyroidectomy for histopathological confirmation and definitive treatment.

A consent for publication was obtained from the patient.

Discussion

Graves’ disease is an autoimmune illness characterized by elevated levels of FT4 and triiodothyronine (FT3) and a diffuse goiter. Thyroid nodules can accompany Graves’ disease; while most are hypoactive, a small percentage can be hyperactive. Consequently, patients may have thyrotoxicosis because of each Graves’ disease and hyperfunctioning nodular goiter or a single toxic nodule. This form of Graves’ disease is known as Marine-Lenhart syndrome. In recent study from Japan showed prevalence of 0.26% in Japanese populations. There are no clear criteria for the diagnosis. The anti-thyroid medications were effective in treating one case of Marine-Lenhart syndrome with a solitary toxic nodule. In Japan RAI therapy was used in treatment of 18 patients, however there was high prevalence of hypothyroidism due to because of increase RAI uptake.

Another symptom of Graves’ disease is Graves’ orbitopathy (GO), also known as thyroid-eye disease. An individual suffering from GO may experience a number of physical and mental
disabilities as well as loss of vision. The symptoms of which can start at the same time as the 
symptoms of hyperthyroidism.\textsuperscript{8} Though, GO can develop even if the thyroid function is normal. 

The disease is typically accompanied by exophthalmos, lid retraction, and diplopia, and appears 
bilaterally and symmetrically.\textsuperscript{9} There are, however, some patients who show symptom in an 
asymmetric or unilateral manner. There is a limited amount of literature available regarding 
actual unilateral GO, and the information that does exists is quite diverse. Despite this, there is 
no definitive explanation or data available for this manifestation. It has been reported that a small 
percentage of patients, ranging from 9\% to 15\%, experience pure unilateral GO.\textsuperscript{16-18} The severity 
and activity of Graves’ orbitopathy can be indicated by its asymmetry, according to a recent 
cross-sectional study conducted by the European Group on Graves’ orbitopathy. This finding is 
important as it highlights the need for proper management and monitoring of the disease.\textsuperscript{20} Our 
patient was assessed and found to have moderate to severe thyroid eye disease based on 
EUGOGO classification for disease activity and severity.

The autoimmune process that causes the growth of the orbital contents in an asymmetric and 
unilateral GO appears to be comparable to those that cause bilateral illness in terms of 
pathogenesis. However, structural variations, mechanical, circulatory, and inflammatory 
variables may also play roles in the emergence of asymmetric disease. Soroudi et al. theorized 
that the asymmetrical expansion of orbital contents may be caused by the uneven distribution of 
antigen or inflammatory processes, albeit this was not investigated in any studies to date. 
Furthermore, there have been suggestions that there could potentially be variances in structure 
that lead to distinct blood circulation or lymphatic drainage patterns.\textsuperscript{14} It has also been 
hypothesized that unilateral triggers like infections or variances in the ability for adipogenesis 
may be caused by the flexibility of the orbital septae or other local variables.\textsuperscript{20} Previous studies 
have explored the effects of sleeping positions on asymmetric GO, but their findings did not 
reveal any significant correlation.\textsuperscript{19} The precise mechanisms continue to be a mystery despite 
prior postulations. Therefore, more research is required to better understand asymmetric GO and 
reveal the causes of asymmetry. This might offer additional insights into GO development and 
management. Finally, some limitation of this case in availability of tissue diagnosis and repeat 
uptake scan after treatment.
Conclusion

Physician should be aware of the link between unilateral orbitopathy and Graves’ disease, despite the lack of a robust pathophysiology explanation supported by strong evidence. Thyrotoxicosis should be treated along with orbitopathy as part of the overall therapy plan. Marine-Lenhart syndrome is a distinct variant of Graves’ disease that has been recognized by medical professionals, albeit it is quite rare. Moreover, it is picked up incidentally and usually does not impact the treatment.

Authors’ Contribution

AF managed the patient and follow-up. ZSS and OSS collected the data and provided the images. AA and AO drafted the manuscript. FB and SKR edited the manuscript and arranged the references. AA and AO revised the manuscript. All authors approved the final version of the manuscript.

References


**Figure 1:** Thyroid Ultrasound (A) showing right thyroid nodule and Tc-99 thyroid scan (B) right hot nodule with increased total tracer uptake.

**Figure 2:** CT scan of orbits showing good response to treatment, pretreatment (A1- A2), post-treatment (B1- B2).