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7 **Unilateral Graves' Orbitopathy in a patient with Marine-Lenhart Syndrome**

8 *A case report*

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15 16 **Abstract**

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

26 **Keywords:** Graves' disease; Unilateral proptosis; Thyroid Eye Disease; Graves' orbitopathy;
27 Marine-Lenhart syndrome.

28

29 **Introduction**

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

33

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

41

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

49

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

53

54 **Case Report**

55 A 36-year-old Omani male patient presented to the Endocrinology outpatient department (OPD)
56 of Sultan Qaboos University Hospital, Muscat, Oman, in 2022 as a referral from ophthalmology
57 OPD with a thirteen- month history of isolated right eye proptosis and redness. He revealed that
58 during the previous few months, he experienced sweating, non-frequent palpitations, tremors,
59 shortness of breath, diarrhea, along with generalized weakness. There was no weight loss or

60 decrease in appetite. He had no other symptoms or signs suggestive of systemic disease or other
61 autoimmune diseases. There is no family history of thyroid disease.

62
63 On physical examination, he had tachycardia (114 beats/ minute), blood pressure of (120/78),
64 respiratory rate was 18 breaths/ minute, and oxygen saturation was 99% in ambient air. He was
65 not restless and had no tremors. He was obese, with a BMI of 36Kg/m². He had right eye
66 proptosis, a normal pupil, and erythematous conjunctive with intact intraocular muscles
67 movement. He did report double vision. The left eye examination was normal. He had a palpable
68 right thyroid lobe with no palpable nodules. No cervical lymphadenopathy was noted.
69 Cardiovascular examination revealed normal heart sounds with no added sounds or murmurs.
70 The clinical picture was consistent with thyroid-associated orbitopathy.

71
72 Laboratory investigations showed a slight increase of C-reactive protein (CRP) 8 mg/L (normal:
73 0-5 mg/L). The thyroid function test revealed free thyroxine (FT4) at 25.0 pmol/L (normal: 13.1-
74 21.3) and thyroid-stimulating hormone (TSH) at 0.08 mIU/L (normal: 0.27- 4.20). The anti-
75 thyroid receptor antibody was 2.94 IU/L (normal range 0-1.75).

76
77 A thyroid ultrasound showed a right thyroid nodule with TI-RADS score 3, measuring 3.9 cm [
78 Figure 1A]. FNA of the right thyroid nodule showed atypia of undetermined significance/
79 Follicular lesion of undetermined significance (AUS/FLUS). ATc-99 test reported a single hot
80 nodule inside the upper pole of the right thyroid lobe, coinciding with the ultrasound thyroid
81 finding, with high total thyroid radiotracer uptake of 5.5% (normal range 1-4%) [Figure 1B]. A
82 CT scan of the orbit without contrast was obtained, which showed severe right proptosis and a
83 normal left orbit [Figure 2 A1, A2] with moderate to severe enlargement of right orbital
84 extraocular muscles predominately involving medial, superior rectus and to a lesser extent
85 inferior rectus. Enlarged muscles with relative preservation of tendon resulting in characteristics
86 “coke bottle” morphology.

87
88 He was initially managed with a tapering course of Prednisone for a month with no
89 improvements in Graves’ orbitopathy. Subsequently, he received two doses of intravenous
90 Rituximab (1000 mg with two weeks’ intervals). He did not have a significant improvement. He

91 was started on a trial of high-dose intravenous glucocorticoids therapy because Teprotumumab
92 was not available in the country. The course consists of 6 doses of IV Methylprednisolone (0.5 g
93 per week for a six weeks) lead by 6 doses of 0.25 g per week, IV Methylprednisolone for six
94 weeks with an increasing dosage equivalent to 4.5 g. He reported a noticeable improvement in
95 his ophthalmopathy, in particular, his eye redness. Post-treatment CT scan of the orbits without
96 IV contrast showed an interval improvement of the right eye proptosis and right extraocular
97 muscles hypertrophy, keeping with good response (interval improvement in the size of the right
98 orbital extraocular muscles compared to the previous study) [Figure 2 B1, B2]. Outcome and
99 follow-up six months after IV rituximab and methylprednisolone, the eye symptoms and signs
100 improved specifically his double vision disappeared. Thyroid function test normalized [FT4 17.8,
101 TSH 1.81] and the TSH receptor antibodies became negative. Additionally, the patient was
102 directed to a thyroid surgeon for total thyroidectomy for histopathological confirmation and
103 definitive treatment.

104
105 A consent for publication was obtained from the patient.

107 **Discussion**

108 Graves' disease is an autoimmune illness characterized by elevated levels of FT4 and
109 triiodothyronine (FT3) and a diffuse goiter.¹⁴Thyroid nodules can accompany Graves' disease;
110 while most are hypoactive, a small percentage can be hyperactive.⁸Consequently, patients may
111 have thyrotoxicosis because of each Graves' disease and hyperfunctioning nodular goiter or a
112 single toxic nodule. This form of Graves' disease is known as Marine-Lenhart syndrome.^{9, 10, 14}
113 In recent study from Japan showed prevalence of 0.26% in Japanese populations.¹⁵There are no
114 clear criteria for the diagnosis. The anti-thyroid medications were effective in treating one case
115 of Marine-Lenhart syndrome with a solitary toxic nodule.³ In Japan RAI therapy was used in
116 treatment of 18 patients, however there was high prevalence of hypothyroidism due to because of
117 increase RAI uptake.¹⁵

118
119 Another symptom of Graves' disease is Graves' orbitopathy (GO), also known as thyroid-eye
120 disease. An individual suffering from GO may experience a number of physical and mental

121 disabilities as well as loss of vision. The symptoms of which can start at the same time as the
122 symptoms of hyperthyroidism.⁸ Though, GO can develop even if the thyroid function is normal.

123
124 The disease is typically accompanied by exophthalmos, lid retraction, and diplopia, and appears
125 bilaterally and symmetrically.⁹ There are, however, some patients who show symptom in an
126 asymmetric or unilateral manner. There is a limited amount of literature available regarding
127 actual unilateral GO, and the information that does exist is quite diverse. Despite this, there is
128 no definitive explanation or data available for this manifestation. It has been reported that a small
129 percentage of patients, ranging from 9% to 15%, experience pure unilateral GO.¹⁶⁻¹⁸ The severity
130 and activity of Graves' orbitopathy can be indicated by its asymmetry, according to a recent
131 cross-sectional study conducted by the European Group on Graves' orbitopathy. This finding is
132 important as it highlights the need for proper management and monitoring of the disease.²⁰ Our
133 patient was assessed and found to have moderate to severe thyroid eye disease based on
134 EUGOGO classification for disease activity and severity.

135
136 The autoimmune process that causes the growth of the orbital contents in an asymmetric and
137 unilateral GO appears to be comparable to those that cause bilateral illness in terms of
138 pathogenesis. However, structural variations, mechanical, circulatory, and inflammatory
139 variables may also play roles in the emergence of asymmetric disease. Soroudi et al. theorized
140 that the asymmetrical expansion of orbital contents may be caused by the uneven distribution of
141 antigen or inflammatory processes, albeit this was not investigated in any studies to date.
142 Furthermore, there have been suggestions that there could potentially be variances in structure
143 that lead to distinct blood circulation or lymphatic drainage patterns.¹⁴ It has also been
144 hypothesized that unilateral triggers like infections or variances in the ability for adipogenesis
145 may be caused by the flexibility of the orbital septae or other local variables.²⁰ Previous studies
146 have explored the effects of sleeping positions on asymmetric GO, but their findings did not
147 reveal any significant correlation.¹⁹ The precise mechanisms continue to be a mystery despite
148 prior postulations. Therefore, more research is required to better understand asymmetric GO and
149 reveal the causes of asymmetry. This might offer additional insights into GO development and
150 management. Finally, some limitation of this case is availability of tissue diagnosis and repeat
151 uptake scan after treatment.

152

153 **Conclusion**

154 Physician should be aware of the link between unilateral orbitopathy and Graves' disease,
155 despite the lack of a robust pathophysiology explanation supported by strong evidence.

156 Thyrotoxicosis should be treated along with orbitopathy as part of the overall therapy plan.

157 Marine-Lenhart syndrome is a distinct variant of Graves' disease that has been recognized by
158 medical professionals, albeit it is quite rare. Moreover, it is picked up incidentally and usually
159 does not impact the treatment.

160

161 **Authors' Contribution**

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

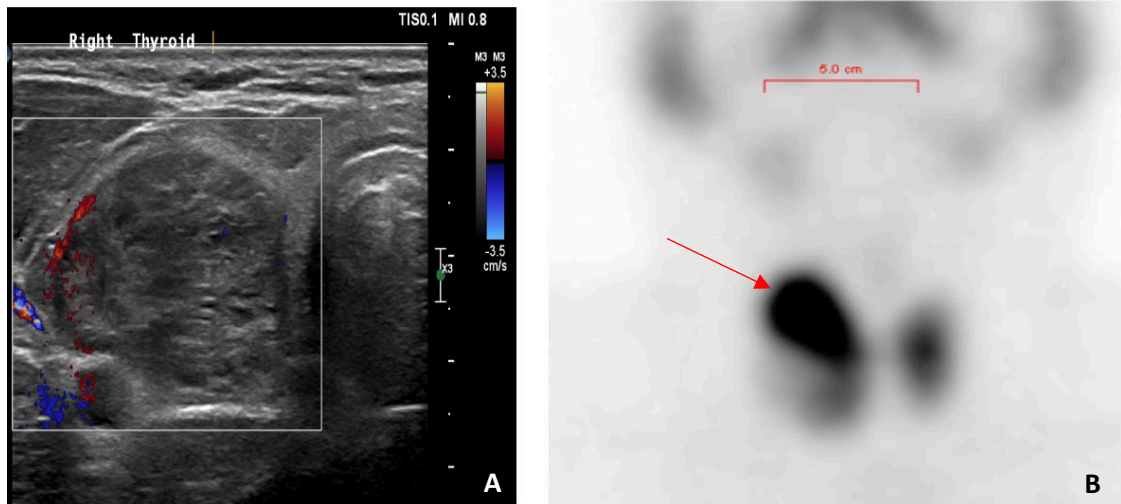
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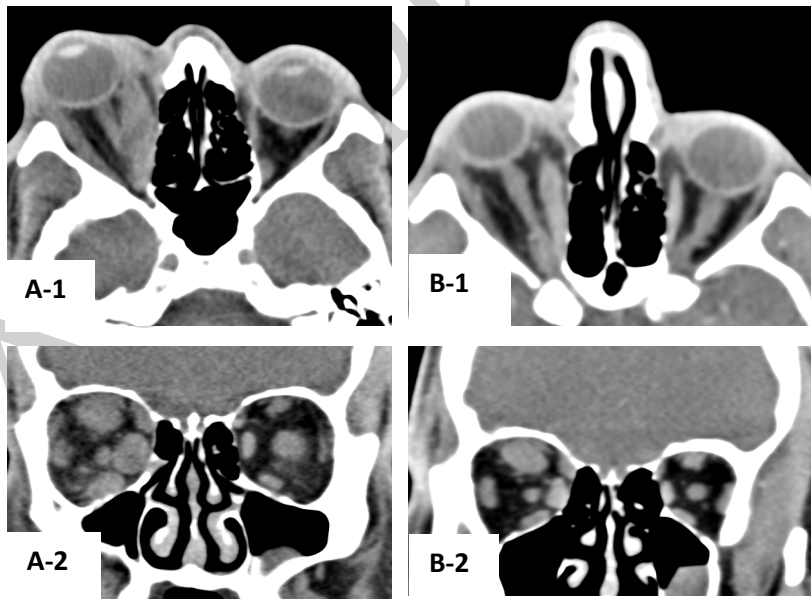
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216



217
218 **Figure 1:** Thyroid Ultrasound (A) showing right thyroid nodule and Tc-99 thyroid scan (B) right
219 hot nodule with increased total tracer uptake.

220



221
222 **Figure 2:** CT scan of orbits showing good response to treatment, pretreatment (A1- A2), post-
223 treatment (B1- B2).