

Marine-Lenhart Syndrome: Role of Iodinated Contrast Administration, Case Report and A Review of Literature

Mark Chambers DVM, MD^{1,2}, Mazhar Khan MD¹, Constance Chen MD³, Steven Secrest CNMT, RT¹ and Sing-Yung WU, MD, PHD^{1,2*}

¹Department of Radiology/Nuclear Medicine, VA Medical Center, Long Beach, California.

²Department of Radiological Sciences, University of California, Irvine, California.

³Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine; VA Long Beach Healthcare System.

*Correspondence:

Sing-yung Wu, MD, PhD, 5901 7th Street (Station 114), VA Medical Center, Long Beach, CA 90822-5201, Tel: 562-900-8588; Fax: 562-826-5121.

Received: 16 October 2020; **Accepted:** 03 November 2020

Citation: Mark Chambers DVM, Mazhar Khan, Constance Chen, et al. Marine-Lenhart Syndrome: Role of Iodinated Contrast Administration, Case Report and A Review of Literature. J Med - Clin Res & Rev. 2020; 4(11): 1-5.

ABSTRACT

Objective: High iodine load in vulnerable populations, including the elderly, increases the risk of iodine-induced thyroid dysfunction. We report a case of an elderly patient presented with the Marine-Lenhart syndrome, defined as the coexistence of Graves' disease and autonomous thyroid nodule(s) that result in biochemical hyperthyroidism. In the present case the thyrotoxic state occurred following a chest CT angiogram.

Methods: Clinical, laboratory, and radiographic data are presented as well as a review of the literature.

Results: A 73 y male has been euthyroid until after a chest CT angiogram. He presented to the endocrine service with thyrotoxic symptoms, including palpitation and weight loss. Suppressed TSH and elevated free T4 were found six weeks after the angiogram with a positive thyroid-stimulating immunoglobulin. A thyroid ultrasound examination revealed a solid nodule in the medial right lobe where a hot nodule was found on I-123 thyroid scan with a highly elevated 24-hour uptake. He received radioiodine therapy after 2 months of treatment of methimazole.

Conclusion: This case demonstrates the occurrence of Marine-Lenhart syndrome in an older man, likely due to exposure to an excess iodine load. As the elderly represent a group at increased risk of iodine-induced thyroid dysfunction, it is advised to monitor serum thyroid function following the administration of iodinated contrast media in older individuals.

Keywords

Hyperthyroidism, Marine-Lenhard Syndrome, Iodinated Contrast, Elderly Patients, Subclinical Hyperthyroidism.

Introduction

The Marine-Lenhart syndrome refers to the coexistence of Graves' disease and a superimposed autonomous thyroid nodule that result in biochemical hyperthyroidism. Mechanisms underlying this syndrome include somatic constitutively activate mutations in the TSH receptors and the presence of anti-TSH receptor autoantibodies. The present case is an unusual report in an elderly

patient of Marine-Lenhart syndrome, and the administration of iodinated contrast may play a role in the mechanism of its onset.

Case Report

A 73-yrs male (as shown in Table, Patient A) has been euthyroid until after a chest CT angiogram on 3/31/2018. He presented to the endocrine service with thyrotoxicosis, including palpitation and weight loss. Suppressed TSH (0.01 mIU/L, reference range, 0.55-0.78 mIU/L and elevated free T4 (3.8 ng/dL, reference range, 0.67-1.52 ng/dL) were found on May 18, six weeks after the angiogram with a positive thyroid-stimulating immunoglobulin (TSI), 458%

Patient (age/sex)	Time after CT-Contrast	TSH (.55-4.78 mIU/L)	FT4 (.67-1.52, ng/dL)	TSI Ab ($\geq 140\%$ baseline)	RAIU (4h,3-20% 24h,8-35%)	Thyroid Scan/US (see below)	Treatment
A. 73/M	1.5 month	0.01	3.8	458%	36% (4h); 57.5% (24h)	Patchy \uparrow uptake with a hot nodule	RAI therapy after 2 months treatment of MMI
B. 70/M* * Ref (1)	<16 month	0.01	1.9	93%	24.6% (4h); 53.9% (24h)	Diffuse \uparrow uptake with hot nodule	No therapy, spontaneous recovered 12 months later

Table 1: Two cases of iodinated contrast- induced Marine-Lenhart syndrome, the current patient (A): time after a contrast CT, serum thyroid function, serum antibody titers, thyroid imaging studies and treatment in comparison with a similar case (patient B) with negative TSI reported recently [1].

(reference range $<140\%$). A thyroid ultrasound examination revealed a 1.8x1.3x2.1 cm solid nodule in the medial right lobe where a hot nodule was found on an I-123 thyroid scan with an elevated 24-hour uptake of 57.5% (reference range, 8 – 35%). He received radioiodine therapy after two months of treatment of methimazole.

The Table shows a summary of the patient's serum thyroid function tests, in comparison with another similar elder patient with iodinated contrast-induced coexistence of thyrotoxicosis and autonomous nodule with a negative TSI [1]. Figure 1, a thyroid I-123 nuclear scan on 6/27/2018, showed a patchy increased uptake bilaterally and a hot thyroid nodule in the right lower lobe corresponding to a solid nodule on thyroid ultrasound examination. Figure 2 showed a thyroid ultrasound examination on 5/17/2018. The images include the long sagittal (left) and trans-axial (right) images. There is a 1.8 x 1.3 x 2.1 cm predominantly solid nodule in the medial right lower lobe, and a 2.5x1.0x2.2 cm hypoechoic nodule in the posterior right lobe. The left lobe is diffusely nodular. On the ultrasonic examination, 18 months after radioiodine therapy (999 MBq), both nodules became unidentifiable, while the overall thyroid volume reduced to 20% of original size.

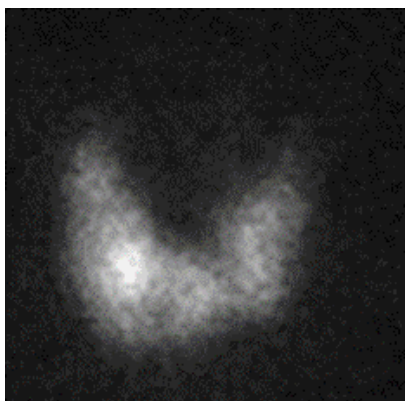


Figure 1: I-123 thyroid scan on 6/27/2018 showed a slightly patchy increased uptake bilaterally (57.5% at 24 h) and a hot thyroid nodule in the right lower lobe corresponding to a solid nodule on thyroid ultrasound examination.

Discussion

Thyroid-stimulating antibody-positive toxic goiter (Graves' disease) and toxic nodular goiter both result in biochemical hyperthyroidism, but by different pathophysiologic mechanisms.

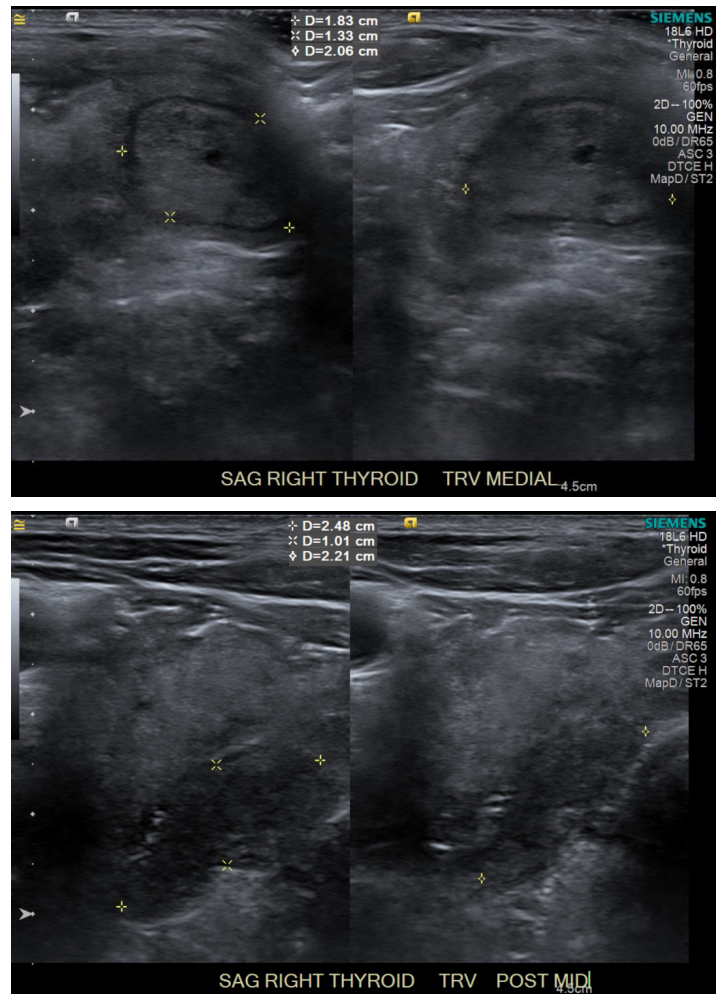


Figure 2: Thyroid ultrasound examination on 5/17/2018. The image is the sagittal (long) and trans-axial images (Upper) There is a 1.8x1.3x2.1 cm predominantly solid nodule in the medial right lower lobe. (Lower) a 2.5x1.0x2.2 cm hypoechoic nodule in posterior lower right lobe.

The original report of Marine-Lenhart syndrome, the coexistence of these two entities, was published over a century ago [2] and reported the concurrent development of both in the same patient has been described in several more recent reports [3-6], including our prior case study [1].

In the present report, we describe a case in which both Graves' disease and an autonomous thyroid nodule were likely exacerbated simultaneously by exposure to an excess iodine load that occurred

1.5 months before in a chest angiogram study. This patient was unlike the prior one (patient B in Table) reported recently that was somewhat unusual that the exposure was remote, occurring 22 months before the diagnosis of hyperthyroidism [1]. The other interesting point is the positive TSI antibody found in the present patient compared to the negative titer in the last case [1]. The difference in TSI titer between these two individuals may be correlated with the difference in the clinical course between these two patients. The present patient was treated with radioiodine I-131 after two months of therapy with methimazole while the other patient with negative TSI titer reverted to the euthyroid state spontaneously after refusing recommended treatment [1,7].

Toxic nodular disease (Plummer's Disease) is often produced by the development of nodular thyroid disease, including the growth of established nodules, new nodule formation, and development of autonomy over time [7,8]. This disease prevails in elderly patients, and is postulated that the autonomous functioning thyrocytes originate more often in the iodine-deficient region over a long period. Mechanisms in the development of thyroid nodules involve cellular mutations. Currently, more than 30 oncogenes may be involved in the development of nodules, e.g., RAS, BRAF, and RET/PTC, etc. [9]. When the mass of mutated cells becomes sufficient and iodine supply is increased, the subject may become thyrotoxic [10]. In fact, it has been suggested that iodine-induced hyperthyroidism may also occur in "latent" Graves' disease as in the present cases [11,12].

Thyroid nodules associated with Graves' disease have been reported with the incidence between 13 to 34% (mean 23.5%), most of which are cold nodules in a retrospect review of 1733 patients (13-17). The incidence of Graves' disease accompanied by a single hot nodule, as shown in our two patients, ranges from 1 to 2.7% and represents a rare form of Marine-Lenhart syndrome [3,4]. Most reported cases among Graves' disease with hyperfunctioning nodules are multiple.

In the two elderly patients who may have latent Graves' disease with or without detectable TSI antibody in conjunction with a nodular goiter might be responsible for developing Marine-Lenhart syndrome induced by excess iodine after intravenous administration of radiocontrast media. As shown in the scan (Figure 1), the slightly patchy appearance may be associate with some follicular degeneration in contrast with the homogeneously increased uptake in the remaining thyroid gland outside the hot nodule in a prior report [1], despite the suppressed level of TSH in these cases, are consistent with the underlying Graves' disease.

A large controlled study found an association between radiocontrast administration and incident hyperthyroidism in the euthyroid patient population [18]. In some susceptible individuals, the elderly with nodular goiter, as in the present case, the use of these iodine-containing substances can result in thyroid dysfunction due to the high iodine load. In certain circumstances, iodine excess can result in adverse thyroidal effects after only a single exposure to an

iodine-rich substance, as demonstrated in the present cases [1,19]. Iodine-induced hyperthyroidism (the Jod-Basedow phenomenon) was observed to be more common among patients with endemic goiter treated with iodine supplementation than in individuals without goiter [7,8]. Furthermore, iodine-induced hyperthyroidism in euthyroid patients with nodular goiter in iodine-sufficient areas has also been reported when iodine supplementation is excessive [10].

The use of iodinated contrast agents in diagnostic radiologic studies is a common source of excess iodine exposure in many patients [20]. A single dose of iodinated contrast can contain up to 13,500 µg of free iodine and 15–60 g of bound iodine [18,20]. Following the exposure to an iodinated contrast agent in a CT examination, iodine stores remain elevated and provide a continuous pool for 1 - 2 months [21-23]. In euthyroid, healthy adults without previous thyroid or renal disease, urinary iodine content did not return to baseline in a study with a small number of older participants over 75 days [21] following exposure to the contrast agent. A Turkish study of 101 patients found a small increased risk of subclinical hyperthyroidism (6%) at up to 8 weeks after the iodine exposure [24,25]. A German study of 788 patients who underwent coronary angiography found only two male patients did not belong to a risk group, although older (55 and 68 yrs) developed overt hyperthyroidism in 4 weeks after exposure to contrast media [26]. In the large case-control study in the Boston area found that patients without pre-existing hypothyroidism or hyperthyroidism who received a single iodinated contrast dose had a 2–3-fold increased risk of developing either incident hyperthyroidism (including overt hyperthyroidism) or overt hypothyroidism at a median of 9 months following exposure, compared with patients who did not receive the high iodine load [18]. A similar finding of 1.6 to 2.0 times the odds of developing incident thyroid dysfunction, including hyperthyroidism, was found in a community-based cohort of ambulatory patients [27]. However, in an elderly population (70 – 96 yrs of age), iodine-induced thyrotoxicosis following contrast radiography was found in 7 of 28 cases of hyperthyroidism in a geriatric hospital [21]. This patient's age distribution is closer to our VA patient population (52.2% of VA-veterans are age 65 or older) in the 2015 Rand study with the source from 2006-2012 analysis [28].

Iodine-induced thyroid dysfunction is a potential consequence in patients with nodular goiters and elderly patients [26]. Undiscovered and untreated hyperthyroidism is a dangerous clinical condition; it may lead to multiple organ involvement and even a life-threatening cardiac event [12,29–32].

Guidelines from the Contrast Media Safety Committee of the European Society of Urogenital Radiology advocate that high-risk patients are monitored for thyroid dysfunction following iodinated contrast use [33]. In the recent ACR Manual on Contrast Media stated: "Some patients with hyperthyroidism or other thyroid diseases (especially when present in those who live in iodine-deficient areas) may develop iodine-provoked delayed

hyperthyroidism. This effect may appear 4 to 6 weeks after the IV contrast administration in some of these patients. This can occur after the administration of any iodinated contrast media. It is usually self-limited.” [34]. This guideline appears to have ignored some of the relevant data, especially in the elderly at-risk and critically-ill patients in ICU. This issue may deserve a closer evaluation, especially in the VA elderly population.

Radioiodine and thionamides are both effective treatment for Graves' hyperthyroidism. Radioiodine had been the therapy of choice in the United States, selected by 60 percent of thyroid specialists who responded to a survey in 2011 [35]. Data subsequently have shown that long-term antithyroid drug use is safe [36], and an updated analysis using insurance claims data in the United States suggests that antithyroid drugs are used as initial therapy for 60 percent of patients, while only 33 percent of patients receive radioiodine [37].

Our prior reported case with the co-occurrence of Graves' disease and a functional nodule did not continue to retain autonomy following the spontaneous remission of the Graves' disease after the iodine pool had returned to baseline [1]. We are not aware of any case report of iodine-induced as shown in these two cases or spontaneous remission of hyperthyroid state in Marine-Lenhart syndrome, as demonstrated in our prior report [1]. In susceptible patients, especially elderly patients with nodular goiters and prior history of iodine-induced hyperthyroidism should be counseled regarding the risk, as demonstrated in the present patients. Prophylactic treatment with anti-thyroid medication and/or beta-blocker may be considered before exposure to contrast agents even though it may not routinely be recommended because of the side effects of these drugs in the low-risk general patient population. To recognize the self-limiting nature of radio-contrast induced hyperthyroidism, especially in TSI negative patients, is important in order to avoid over-treatment as demonstrated in our prior report [1]. Thus, in iodine-induced hyperthyroidism, thionamides is the preferred treatment as compared with RAI ablative therapy.

There is an association of thyroid cancer in patients with Graves' disease [38,39]. However, an autonomously functioning papillary thyroid cancer in Marine-Lenhart syndrome nodule is rare [40,41].

Conclusion

We present a hyperthyroid patient diagnosed with Marine-Lenhart Syndrome, defined as the coexistent presentation of Graves' disease and an autonomous thyroid nodule, following administration of an iodinated contrast load.

This case illustrates the mechanism turning on both toxic nodule and under Graves' hyperthyroidism simultaneously by a single switch: the excess supply of iodine. It also demonstrates the importance of monitoring elderly patients, a group at increased risk for developing iodine-induced thyroid dysfunction. Such patients should be closely monitored following the administration of iodinated contrast media, which represents an increasingly common source of excess iodine exposure. The present case also

illustrated iodine load may play a role in the mechanism of onset of both Graves' hyperthyroidism and an autonomous toxic nodule.

Reference

1. Wu SY, Leung AM, Chambers MD, et al. Coexistent Presentation of Graves' Disease and a Potentially Autonomous Thyroid Nodule Following Administration of an Iodinated Contrast Load. *J Clin Translat Endocrinol: Case Report*. 2018.
2. Marine D, Lenhart CH. Further observations and experiments on the so-called thyroid carcinoma of the brook trout (*salvelinus fontinalis*) and its relation to endemic goitre. *J Exp Med*. 1911; 13: 455-475.
3. Balmes E, Burcea A, Belgun M, et al. Marine-Lenhart syndrome: Case report and literature review. *Acta Endocrinologica*. 2007; 3: 201-208.
4. Biersack HJ, Biermann K. The Marine-Lenhart syndrome revisited. *Wien Klin Wochenschr*. 2011; 123: 459-462.
5. Cakir MJ. Letter to the editor: diagnosis of Marine-Lenhart syndrome. *Thyroid*. 2004; 14: 555.
6. Takei M, Ishii H, Sato Y, et al. A case of Marine-Lenhart syndrome with a negative TSH receptor antibody titer successfully treated with a fixed, low dose of I¹³¹. *Case Reports Endocrinology*. 2014.
7. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid*. 2016; 26: 1343-1421.
8. Midgley J EM, R Larisch, JW Dietrich, et al. Heterogenous biochemical expression of hormone activity in subclinical/overt hyperthyroidism and exogenous thyrotoxicosis. *J Clin Translat Endocrinology*. 2020; 100219.
9. Nikiforov YE, Molecular analysis of thyroid tumors. *Modern Pathology*. 2011; 24: 534-543.
10. Stanbury JB, Ermans AE, Bourdoux P, et al. Iodine-Induced Hyperthyroidism: Occurrence and Epidemiology. *Thyroid*. 1998; 8: 83-100.
11. Braverman LE, Cooper DS. *Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text*. 2012; 250.
12. Brotfain E, Koyfman L, Frenkel A, et al. Iodine-Induced Hyperthyroidism—An Old Clinical Entity That Is Still Relevant to Daily ICU Practice: A Case Report. *Case Reports in Endocrinology*. 2013; 2013: 792745.
13. Lamata Hernández F, Sánchez Beorlegui J, Artigas Marco MC, et al. Graves' disease with associated thyroid nodules (nodular Graves' disease). Clinical, diagnostic and therapeutic considerations. *An Med Interna*. 2003; 20: 403-409.
14. Mishra A, Mishra SK. Thyroid nodules in Graves' disease: implications in an endemically iodine deficient area. *J Postgrad Med*. 2001; 47: 244-247.
15. Kraimps JL, Bouin-Pineau MH, Marechaud R, et al. Multicentre study of thyroid nodules in patients with Graves' disease. *Br J Surg*. 2000; 87: 1111-1113.

16. Carnell NE, Valente WA. Thyroid nodules in Graves' disease: Classification, characterization, and response to treatment. *Thyroid*. 1998; 8: 647–652.
17. Cantalamessa L, Baldini M, Orsatti A, et al. Thyroid nodules in Graves' disease and the risk of thyroid carcinoma. *Arch Intern Med*. 1999; 159: 1705-1708.
18. Rhee CM, Bhan I, Alexander EK, et al. Association between iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism. *Arch Intern Med*. 2012; 172: 153–159.
19. Pramyothin P, Leung AM, Pearce EN, et al. Clinical problem-solving. A hidden solution. *N Engl J Med*. 2011; 365: 2123–2127.
20. Lee SY, Rhee CW, Leung AW, et al. A Review: Radiographic iodinated contrast media-induced thyroid dysfunction, *J Clin Endocrinol Metab*. 2015; 100: 376-383.
21. Nimmons GL, Funk GF, Graham MM, et al. Urinary iodine excretion after contrast computed tomography scan: implications for radioactive iodine use. *JAMA Otolaryngol Head Neck Surg*. 2013; 139: 479–482.
22. Padovani RP, Teresa S Kasamatsu, Claudia CD Nakabashi, et al. One month is sufficient for urinary iodine to return to its baseline value after the use of water-soluble iodinated contrast agents in post-thyroidectomy patients requiring radioiodine therapy. *Thyroid*. 2012; 22: 926–930.
23. Lee SY, Chang DL, He X, et al. Urinary iodine excretion and serum thyroid function in adults after iodinated contrast administration. *Thyroid*. 2015; 25: 471-477.
24. Martin FI, Tress BW, Colman PG, et al. Iodine-induced hyperthyroidism due to nonionic contrast radiography in the elderly. *Am J Med*. 1993; 95: 78–82.
25. Ozkan S, Oysu AS, Kayata K, et al. Thyroid functions after contrast agent administration for coronary angiography: a prospective observational study in euthyroid patients. *Anadolu Kardiyol Derg*. 2013; 13: 363–369.
26. Hintze G, Blombach O, Fink H, et al. Risk of iodine-induced thyrotoxicosis after coronary angiography: an investigation in 788 unselected subjects. *Eur J Endocrinol*. 1999; 140: 264–267.
27. Rhee CM, Lynch KE, Zandi-Nejad K, et al. Iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism in a community-based cohort. *Endocrinol Stud*. 2013.
28. Assessment A (Demographics). *Rand Cooperation Study for US Department of Veterans Affairs*. 2015; 109.
29. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med*. 1994; 331:1249-1252.
30. Parle JV, Maisonneuve P, Sheppard MC, et al. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet*. 2001.
31. Sgarbi JA, Matsumura LK, Kasamatsu TS, et al. Subclinical thyroid dysfunctions are independent risk factors for mortality in a 7.5-year follow-up: the Japanese-Brazilian thyroid study. *Eur J Endocrinol*. 2010; 162: 569-577.
32. Alkhuja S, Pyram R, Odeyemi O. In the eye of the storm: Iodinated contrast medium induced thyroid storm presenting as cardiopulmonary arrest. *Heart Lung*. 2013; 42: 267–269.
33. van der Molen AJ, Thomsen HS, Morcos SK. Contrast Media Safety Committee, European Society of Urogenital Radiology (ESUR) Effect of iodinated contrast media on thyroid function in adults. *Eur Radiol*. 2004; 14: 902–907.
34. Ellis JH, Cohan RH, Davenport MS, et al. ACR Committee on Drugs and Contrast Media, ACR Manual on Contrast Media. Version 10.2. 2016; 7.
35. Burch HB, Burman KD, Cooper DS. A 2011 survey of clinical practice patterns in the management of Graves' disease. *J Clin Endocrinol Metab*. 2012; 97: 4549.
36. Azizi F, Malboosbaf R. Safety of long-term antithyroid drug treatment? A systematic review. *J Endocrinol Invest*. 2019; 42: 1273.
37. Brito JP, Payne S, Singh Ospina N, et al. Patterns of Use, Efficacy, and Safety of Treatment Options for Patients with Graves' Disease: A Nationwide Population-Based Study. *Thyroid*. 2020; 30: 357.
38. Kim WB, Han SM, Kim TY, et al. Ultrasonographic screening for detection of thyroid cancer in patients with Graves' disease. *Clin Endocrinol (Oxf)*. 2004; 60: 719–725.
39. Gerenova J, Buyschaert M, de Burbure CY, et al. Prevalence of thyroid cancer in Graves' disease: A retrospective study of a cohort of 103 patients treated surgically. *Eur J Intern Med*. 2003; 14: 321–325.
40. Uludag M, Aygun N, Ozel A, et al. A rare presentation of autonomously functioning papillary thyroid cancer: malignancy in Marine-Lenhart syndrome nodule. *Case Rep Surg*. 2016.
41. Haugen BR, Alexander EK, Bible KC et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016; 26: 1-133.