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OPIS PRZYPADKU CASE REPORT

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Marine-Lenhart syndrom

Zespół Marine-Lenharta

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Słowa kluczowe
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Summary

Hyperthyroidism affects about 2% of adult population. The most common underlying causes are, dependant on dietary iodine supply, Graves' disease and toxic nodular goiter. The occurrence of thyroid nodules in patients with Graves' disease is greater than in general population and the majority of them are non-functioning ones. The coexistence of Graves' disease and a solitary or multiple autonomous thyroid nodules is extremely rare and is called Marine-Lenhart syndrome. The aim of this paper is to present a case of Marine-Lenhart syndrome and to analyze similar cases reported in PubMed since 2000. A 40-year-old woman who was previously diagnosed to have autonomous thyroid nodule was admitted to the Outpatient Endocrinology Department of Medical Centre of Postgraduate Education after seven years with signs and symptoms of severe hyperthyroidism in the course of Graves' disease. The following diagnostic steps and treatment strategy were presented and discussed. Other reported cases of Marine-Lenhart syndrome were also discussed. All analyzed cases showed that the diagnosis of the syndrome may be difficult due to fluctuating scintigrafical character of the nodules and thyroid parenchyma. Therefore, strict clinical follow-up as well as the assessment of serum anti-TSH receptor antibodies and thyroid imaging procedures: scintigraphy and ultrasonography are all necessary to make the right diagnosis and choose the appropriate treatment strategy.

Streszczenie

Nadczynność tarczycy dotyczy ok. 2% populacji. Najczęstszymi jej przyczynami, w zależności od podaży jodu, są choroba Gravesa i Basedowa oraz wole guzowate nadczynne. U pacjentów z chorobą Gravesa i Basedowa obserwuje się częstsze występowanie guzków tarczycy niż w populacji ogólnej, większość z nich stanowią guzki nieczynne hormonalnie. Do rzadkości należy współistnienie choroby Gravesa i Basedowa oraz pojedynczego lub mnogich guzków autonomicznych nazywane zespołem Marine-Lenharta – dotyczy jedynie 2,4-4,1% osób z chorobą Gravesa i Basedowa. Celem pracy jest prezentacja przypadku pacjentki z zespołem Marine-Lenharta oraz analiza podobnych przypadków dostępnych w bazie PubMed od 2000 roku.

Czterdzistoletnia kobieta ze zdiagnozowanym w przeszłości guzkiem autonomicznym tarczycy została przyjęta do Poradni przy Klinice Endokrynologii CMKP w Warszawie z objawami ciężkiej nadczynności tarczycy w przebiegu choroby Gravesa i Basedowa. W artykule przedstawiono i przedyskutowano kolejne kroki diagnostyczne i metody leczenia. Przeanalizowano także inne dostępne w piśmiennictwie przypadki zespołu Marine-Lenharta. Wskazują one na trudności diagnostyczne wynikające ze zmienności obrazu scyntygraficznego guzków oraz miąższu tarczycy. Dlatego dokładna obserwacja kliniczna w połączeniu z oceną stężenia przeciwciał przeciwko receptorowi dla TSH oraz metodami obrazowania tarczycy – ultrasonografią i scyntygrafią – są niezbędne do postawienia właściwego rozpoznania i wdrożenia właściwego leczenia.

Conflict of interest
Konflikt interesów
None
Brak konfliktu interesów

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INTRODUCTION

Hyperthyroidism affects about 2% of adults. The most common causes are Graves' disease and toxic nodular goiter. The prevalence of these two disorders depends mainly on dietary iodine supply: Graves' disease predominates in populations with adequate iodine intake, whereas toxic nodular goiter occurs more often in iodine-deficient areas. Poland like many European

countries suffered from moderate to mild iodine deficiency but became iodine-sufficient from 1997 when iodine prophylaxis program was reestablished. Due to the long-lasting insufficient iodine supply toxic nodular goiter is responsible for 30-40% cases of hyperthyroidism in Poland and typically affects older population (1).

The above disorders lead to hyperthyroidism through different pathomechanisms. In Graves' disease which has an autoimmune origin, the excessive production of thyroid hormones is caused by thyroid-stimulating immunoglobulins (TSI), while in toxic nodular goiter – by acquired activating mutation of TSH-receptor or protein G. The coexistence of both disorders, known as Marine-Lenhart syndrome, is extremely rare.

Herein we present a case of a 40-year-old woman with Marine-Lenhart syndrome who was admitted to the Outpatient Endocrinology Department of Medical Centre of Postgraduate Education. We also discuss similar cases reported in PubMed since 2000.

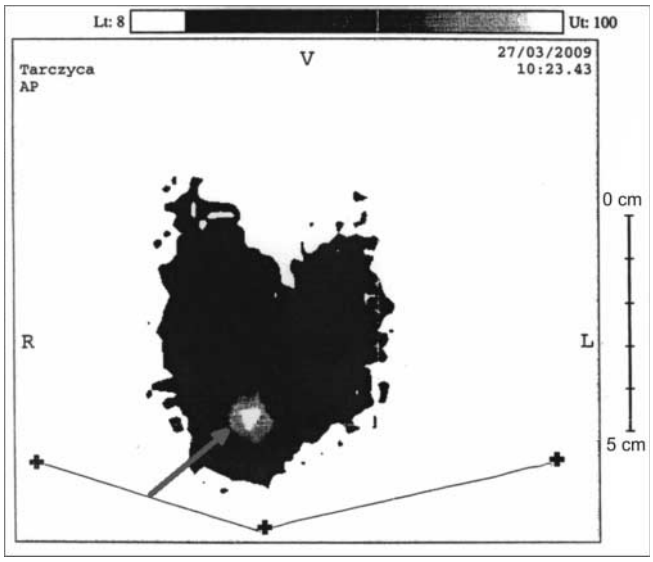

Fig. 1. Thyroid scintigraphy with ^{99m} technetium in March 2009: a hot nodule in the lower pole of the right thyroid lobe (arrow)

CASE PRESENTATION

A forty-year-old woman with a family history of autoimmune diseases (rheumatoid arthritis in mother, psoriasis in son) was admitted to the Outpatient Endocrinology Department of Medical Centre of Postgraduate Education in April 2016 with signs and symptoms of hyperthyroidism. Seven years before, based on the abnormal thyroid function tests (TFTs) (tab. 1), thyroid ultrasound and ^{99m}Tc thyroid scan (fig. 1) she was diagnosed to have subclinical hyperthyroidism due to a solitary autonomously-functioning nodule with diameter of 16 mm in the right thyroid lobe. The patient was feeling well and she abandoned the further medical surveillance until 2016 when she started to complain of progressive fatigue, muscles weakness, sweating, tremor, anxiety, heart palpitations, diarrhea and weight loss. TFTs established in February 2016 demonstrated the signs of severe hyperthyroidism (tab. 1) and treatment with thiamazole 30 mg daily and propranolol 60 mg daily was instituted. Two weeks later the allergic skin reaction to thiamazole had occurred, thus therapy was discontinued and propylthiouracil 300 mg daily was started. Then, ultrasound-guided fine-needle aspiration biopsy (FNAB) of the right thyroid lobe nodule was performed and showed benign cytology (category 2 according to the Bethesda System for Reporting Thyroid Cytopathology).

Tab. 1. Thyroid function tests

	March 2009	February 2016	Admission to Outpatient Clinic, April 2016	June 2016
TSH, uIU/mL n.: 0.35-4	0.047	0.016	0.003	< 0.005
fT4, pmol/l n.: 12-22	18	> 100	35.74	15.31
fT3, pmol/l n.: 3.95-6.8	5.63	> 50	8.47	7.43
TRAb, IU/l n.: < 1.8			10.25	
a-TPO, IU/ml n.: < 60			> 1300	
a-Tg, IU/ml n.: < 60			116.1	

At admission to the Outpatient Endocrinology Department in April 2016 physical examination of the patient revealed blood pressure of 140/80 mmHg, regular heart rate of 70 bpm, moist skin, enlarged thyroid gland with a palpable nodule in the bottom of the right lobe and vascular murmur over the whole thyroid gland. TFTs revealed overt hyperthyroidism and significant elevation of anti-thyroid autoantibodies: anti-peroxidase (a-TPO), anti-thyroglobulin (a-Tg) and thyrotropin receptor antibodies (TRAbs) (tab. 1). The ultrasound scans showed thyroid enlargement (thyroid right lobe volume 27 ml, thyroid left lobe volume 21.2 ml), heterogenic echotexture with small hypoechogenic areas, diffusely increased vascularity on Color-Doppler examination. In the lower part of right thyroid lobe there was a mixed partially solid and cystic nodule, soft on elastography, with diameter of 23 mm and volume of 4.8 ml (fig. 2a-c). Thyroid ^{131}I scintigraphy revealed increased iodine uptake (T_{24} ^{131}I – 71.2%) with a cold area corresponding to the right lobe nodule and intensive iodine accumulation in the rest of thyroid parenchyma (fig. 3). At admission the patient was treated with propylthiouracil 250 mg daily and propranolol 60 mg daily, both in 3 divided doses. Then propylthiouracil was reduced to 150 mg daily and one month later a significant decrease in thyroid hormones levels was observed (tab. 1). Eventually surgical treatment was performed after euthyroidism was obtained and levothyroxine substitution was started afterwards. Histopathological examination revealed hyperplastic thyroid epithelium with moderate lymphocytic infiltration characteristic to Graves' disease and hyperplastic thyroid nodule of the right thyroid lobe.

DISCUSSION

Graves' disease is an autoimmune thyroid disease characterized by hyperthyroidism and diffuse hypervascular goiter caused by TSI, occasionally associated

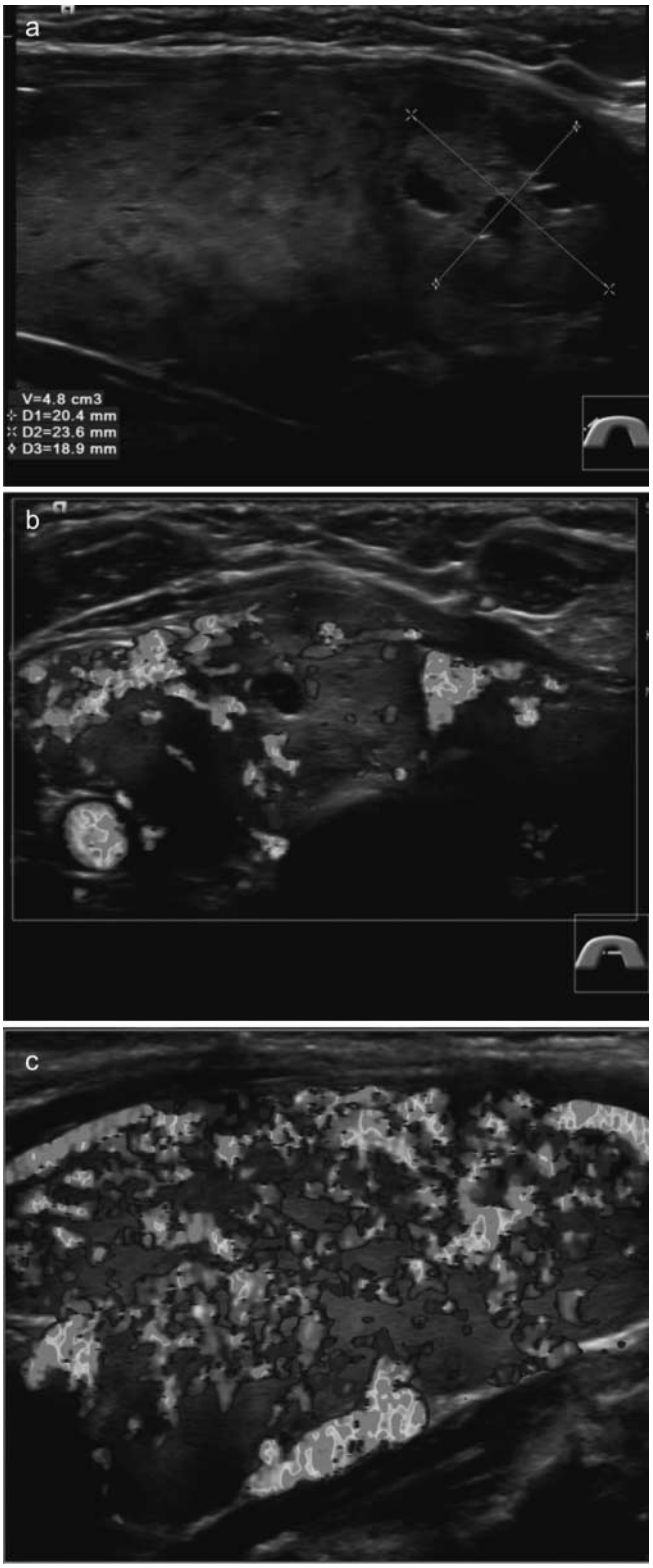

Fig. 2a-c. Thyroid ultrasound scans in April 2016. Heterogenic echotexture of parenchyma with small hypoechogenic areas (a), diffusely increased vascularity on Color-Doppler examination (c), complex solid and cystic lesion in the right thyroid lobe with a peripheral-central flow pattern (a, b)

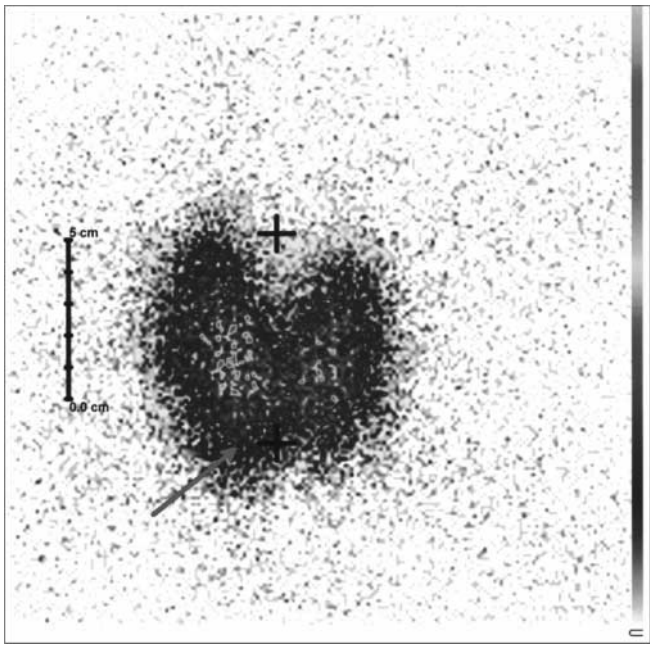

Fig. 3. Thyroid scintigraphy with ^{131}I in April 2016: a cold nodule in the lower pole of the right thyroid lobe (arrow)

with orbitopathy, dermopathy and acropachy. It is the most common cause of hyperthyroidism in areas with normal and high iodine supply with the peak incidence occurring between the 2nd and 4 th decade of life. On the other hand, toxic nodular goiter has a completely different, non-autoimmune etiology. Due to the somatic activating mutation of TSH-receptor or protein G, monoclonal proliferation of hyperfunctioning thyreocytes is initiated which consequently leads to hyperactive nodule formation acting independently of TSH. It is a common cause of hyperthyroidism in areas with insufficient iodine supply, develops over years and affects usually patients over forty years old. In Graves' disease the prevalence of palpable thyroid nodules is estimated by 15-30% in comparison to 5 to 9% in general population (2, 3). Almost half of them are solitary hormonally inactive nodules (4). The coexistence of Graves' disease and hyperfunctioning thyroid nodules in form of a solitary toxic adenoma or toxic multinodular goiter occurs very rarely – it affects 2.7 to 4.1% of patients with Graves' disease (4). The simultaneous occurence of Graves' disease and autonomous thyroid nodules was first described by American surgeons David Marine and Carl H. Lenhart, who published their research on histopathology and iodine content of thyroid gland in exophthalmic goiter in 1911 (5). D. Marine and C.H. Lenhart were the first who noticed, that in patients with Graves' disease not only thyroid parenchyma but also some thyroid nodules can accumulate iodine intensively. The above pathology known as Marine-Lenhart syndrome may take different clinical forms – the two disorders may appear simultaneously or one after another. In the first form the radioisotope accumulation in thyroid parenchyma and thyroid nodules is similar – the thyroid nodules are scintigrafically "warm". In the second variant when thyrotoxicosis is once caused by autonomous thyroid nodules and once by Graves' disease the radioisotope thyroid scan can demonstrate "hot" nodules with absent tracer uptake in thyroid parenchyma, or cold nodules with hyperactive

surrounding thyroid tissue. The phenomenon of fluctuating character of thyroid nodules from scintigrafically "hot" to scintigrafically "cold" remains unclear but we can hypothesize that the explanation may be the low expression of sodium/iodide symporter (NIS) in some of hyperfunctioning thyroid nodules. When Graves' disease remains in remission the autonomous thyroid nodules are scintigrafically "hot". In the phase of active Graves' disease when thyroid gland is overstimulated by TSI, the iodine accumulation in thyroid parenchyma where NIS expression is higher is more avid than in thyroid nodules–thyroid nodules become scintigrafically "cold".

The latter clinical form of Marine-Lenhart syndrome was observed in the presented case. In 2009, at the age of 33 our patient was diagnosed with autonomous solitary thyroid nodule, an unusual cause of hyperthyroidism in the young woman, which probably resulted from iodine deficiency in Poland before 1997. In 2016 the severe exacerbation of hyperthyroidism was caused by Graves' disease and then the previously "hot" thyroid nodule became scintigrafically "cold". Although, in 2016 the clinical presentation was very suggestive for Graves' disease and high serum TRAb titers and ^{131}I thyroid scan confirmed initial diagnosis, the thyroid ultrasonography was also of a great diagnostic value.

The ultrasound image of thyroid in active Graves disease is characterized by diffuse gland enlargement (lobes sagittal dimension) with rounded lobes poles, decreased, heterogenous echogenicity and increased vascularity, demonstrating a "thyroid inferno" pattern on Color-Doppler. All above features were revealed on ultrasound examination of our patient.

In the presented case the treatment strategy was thyroidectomy after obtaining euthyroid state with antithyroid drug therapy and potassium-iodide solution preparation shortly before surgery. Radical treatment in the presented case was the treatment of choice due to the high serum TRAbs concentration, significant initial T_3-toxicosis and goiter volume of nearly 50 ml. Surgical treatment was preferred to ^{131}I therapy because of the insufficient radioiodine accumulation in thyroid nodule and the risk that one of the two underlying causes of hyperthyroidism would not be successfully treated.

Whereas over a dozen cases of Marine-Lenhart syndrome can be found in world literature, the case we have presented above is the second in Polish literature. The first report published by Górowski et al. in 1990 also described a patient presenting different patterns of hyperthyroidism over time (6). Initially the patient was diagnosed with Graves' disease manifesting with hyperthyroidism, moderate orbitopathy and vascular goiter with a concurrent scintigrafically "cold" thyroid nodule. Five years after the effective treatment with thiamazole was completed the patient developed hyperthyroidism due to the autonomous thyroid nodule (previously "cold" nodule became "hot"), which was treated with ^{131}I. Several months after radioiodine therapy hyperthyroidism with orbitopathy, vascular goiter and increased ^{131}I uptake in the whole thyroid parenchyma with cold area corresponding to the previous hot nodule recurred. In both cases: the present one and the one described previously a long-term observation and scintigraphy evaluation over time were essential for establishing the right diagnosis.

We have analysed case reports of Marine-Lenhart syndrome dated from 2000 available in PubMed considering epidemiology, pathophysiology, diagnosing and treatment strategies (4, 7-26). Concluding from the reports the course of Marine-Lenhart syndrome may be various, leading to misdiagnosis and treatment failure.

Marine-Lenhart syndrome affects women more often and appears mainly in the 5th decade of life. However, we have found cases of an adolescent girl (7) as well as of an elderly woman (8). The majority of the described hyperthyroid patients had concomitant Graves' disease and autonomously functioning thyroid nodules at the same time – this is the classic Marine-Lenhart syndrome. There were also several reports documenting the development of Graves' disease with elevated TRAbs after radioiodine treatment for toxic nodular goiter in previously aTPO-positive patients (9, 10). Giuffrida et al. discusses the pathophysiology of such cases emphasizing the hypothesis that cell damage caused by radioiodine therapy can trigger the autoimmune process against TSH receptors in patients who are genetically prone to autoimmune disorders (11). Both Giuffrida and Schmidt (9) are of the opinion that the risk of developing post-radioiodine immunogenic hyperthyroidism (estimated by Schmidt to be 1.1% in general population) increases approximately ten-fold by elevated a-TPO at baseline.

Surprisingly, the cases of the autonomous toxic nodules development after previous ^{131}I treatment for Graves' disease were also described (11, 12). In the analyzed material we have found three cases of thyroid carcinoma in Marine-Lenhart syndrome, all of them were papillary thyroid cancers (13-15). Although one of the Marine-Lenhart syndrome characteristic is its benignity on histological examination the cases listed above indicate the possibility of coexistence of the syndrome and thyroid carcinoma. It is well-known that both palpable and non-palpable thyroid nodules are more frequent in Grave's disease. Belfiore et al. have analyzed the frequency of thyroid nodules and thyroid cancer in Graves' disease, reporting nodules prevalence as 30-50% (depending on the population and iodide supply) and cancer prevalence as 1.7-2.5%, which is eight-to-ten-fold higher than in general population (27). According to the current knowledge serum thyrotropin (TSH) concentration is an independent risk factor of the differentiated thyroid cancer development and the dependence is linear (28). One can hypothesize that TSI in Graves' disease may play a similar mitogenic role as TSH in thyroid cancerogenesis.

Although the malignancy risk in thyroid nodules is about 4 to 6.5% it decreases significantly to less than

1% in hyperfunctioning nodules (29). Concluding from that, malignancy in the Marine-Lenhart syndrome is extremely rare but should be taken into account especially in multinodular goiter and fine-needle aspiration biopsy should be performed according to recommendations (30).

The majority of patients in the analyzed publications were treated with radioiodine. Only four of them (26.7%) including carcinoma cases underwent surgery. Here we should point that the authors did not report on eventual hyperthyroidism relapses after radioiodine treatment. As Braga-Basaria (16, 19) emphasizes, patients with Marine-Lenhart syndrome may require higher doses of ^{131}I and should be prepared for multistage treatment.

CONCLUSIONS

In conclusion, clinical imaging plays a significant role in diagnosing Marine-Lenhart syndrome. The ultrasound is essential for thyroid nodules detection while scintigraphy is pivotal in defining their functional status. The therapy of choice in Marine-Lenhart syndrome is a radical treatment. Surgery is preferred in young patients. By choosing ^{131}I treatment we should be aware of the need for higher and repeated radioiodine doses.

BIBLIOGRAPHY

1. Jastrzębska H, Bednarczuk T, Kochman M: Nadczynność tarczycy. [W:] Zgliczyński W (red.): Wielka Interna. Endokrynologia. Część I. Wyd. 1, Medical Tribune, Warszawa 2011: 256-273.
2. Pellegriti G, Mannarino C, Russo M et al.: Increased mortality in patients with differentiated thyroid cancer associated with Graves' disease. J Clin Endocrinol Metab 2013; 98(3): 1014-1021.
3. Cakir M: Case report: Marine-Lenhart syndrome. J Natl Med Assoc 2005; 97: 1036-1038.
4. Carnell NE, Valente WA: Thyroid nodules in Graves' disease: classification, characterization, and response to treatment. Thyroid 1998; 8(7): 571-576.
5. Marine D, Lenhart CH: Pathological anatomy of exophthalmic goiter. Arch Intern Med 1911; 8(3): 265-316.
6. Górowski T, Jastrzębska H, Makowska A: Niezwykły przebieg zespołu Marine-Lenharta. Endokrynol Pol 1990; 41: 495-499.
7. Şen Y, Cimbek EA, Yuca SA: Marine-Lenhart syndrome in a young girl. J Pediatr Endocrinol Metab 2014; 27(1-2): 189-191.
8. Brahma A, Beadsmoore C, Dhatariya K: The oldest case of Marine-Lenhart syndrome? JRSM Short Rep 2012; 3(4): 21.
9. Schmidt M, Gorbrauch E, Dietlein M et al.: Incidence of post radioiodine immunogenic hyperthyroidism/Graves' disease in relation to a temporary increase in thyrotropin receptors antibodies after radioiodine therapy for autonomous thyroid tissue. Thyroid 2006; 16(3): 281-288.
10. Custro N, Nanci A, Scafi di V: Relapses of hyperthyroidism in patients treated with radioiodine for nodular toxic goiter: relation to thyroid autoimmunity. J Endocrinol Invest 2003; 26(2): 106-110.
11. Giuffrida G, Giovinazzo S, Certo R et al.: An uncommon case of Marine-Lenhart syndrome. Arq Bras Endocrinol Metabol 2014; 58(4): 398-401.
12. Joven MH, Anderson RJ: Marine-Lenhart syndrome. Endocrine 2015; 49(2): 570-571.
13. Scherer T, Wohlschlaeger-Krenn E, Bayerle-Eder M et al.: A case of simultaneous occurrence of Marine-Lenhart syndrome and a papillary thyroid microcarcinoma. BMC Endocr Disord 2013; 13: 16.
14. Atmaca H, Çolak R, Yazici Z et al.: Marine-Lenhart syndrome with papillary thyroid carcinoma. J Res Med Sci 2015; 20(4): 412-415.
15. 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; 2016: 8740405.
16. Braga-Basaria M, Basaria S: Marine-Lenhart syndrome. Thyroid 2003; 13(10): 991-991.
17. El-Kaissi S, Kotowicz MA, Goodear M et al.: An unusual case of Marine-Lenhart syndrome. Thyroid 2003; 13(10): 993-994.
18. Cakir M: Diagnosis of Marine-Lenhart syndrome. Thyroid 2004; 14(7): 555.
19. Braga-Basaria M, Basaria S: Marine-Lenhart syndrome. Thyroid 2004; 14(12): 1107-1107.
20. Chatzopoulos D, Iakovou I, Moralidis E: Marine-Lenhart syndrome and radioiodine-131 treatment. Thyroid 2007; 17(4): 373-374.
21. Biersack HJ, Biermann K: The Marine-Lenhart syndrome revisited. Wien KlinWochenschr 2011; 123(15-16): 459-462.
22. Harisankar CN, Preethi GR, Chungath BB: Hybrid SPECT/CT evaluation of Marine-Lenhart syndrome. Clin Nucl Med 2013; 38(2): 89-90.
23. Damle NA, Mishra R: Identifying Marine-Lenhart syndrome on a ^{99m}Tc-pertechnetate thyroid scan. Indian J Endocrinol Metab 2013; 17(2): 366.
24. Mohan JR, Santhosh S, Sood A et al.: Pertechnetate thyroid scan in Marine-Lenhart syndrome. Indian J Nucl Med 2013; 28(2): 125-126.
25. 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 I^{131}. Case Rep Endocrinol 2014; 2014: 423563.
26. Avci E, Narci H: Coexistence of Graves' disease and toxic adenoma: a rare presentation of Marine-Lenhart syndrome. J Ayub Med Coll Abbottabad 2015; 27(1): 248-250.
27. Belfiore A, Russo D, Vigneri R, Filetti S: Graves' disease, thyroid nodules and thyroid cancer. Clin Endocrinol (Oxf) 2001; 55(6): 711-718.
28. Boelaert K, Horacek J, Holder RL et al.: Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. J Clin Endocrinol Metab 2006; 91(11): 4295-4301.
29. Hegedus L: Clinical practice. The thyroid nodule. N Engl J Med 2004; 351(17): 1764-1771.
30. Haugen B, Alexander E, Bible K et al.: 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016; 26(1): 1-133.

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