Case Report / Olgu Sunumu

Hypercalcemia due to Graves' disease in a patient with thyroid hemiagenesis

Tiroid hemiagenezili bir hastada Graves hastalığına bağlı hiperkalsemi

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Thyroid hemiagenesis is a rare anomaly due to failure of development of one thyroid lobe during embryological life. A lot of thyroid disorders may accompany thyroid hemiagenesis. In this report, we present a case of thyroid hemiagenesis, who had moderate hypercalcemia due to Graves' disease. A 43-year-old woman presented with weight loss of more than 5 kg within one month, heat intolerance, and increased sweating. For the past month, she had been troubled by intermittent symptoms of vomiting, thirst, and constipation. On examination, she had tachycardia with no signs of dehydration. Pulse rate was 110 per minute. She had fine tremor, proximal muscle weakness, and asymmetric smooth goiter and hyperplasia in the right thyroid gland. Thyroid function tests confirmed the diagnosis of hyperthyroidism. Although hypercalcemia may be detected in patients with thyrotoxicosis, to the best of our knowledge, this is the first case report of thyroid hemiagenesis accompanying hypercalcemia due to thyrotoxicosis.

Key Words: Graves' disease; thyroid hemiagenesis; thyroid ultrasonography.

Tiroid hemiagenezisi embriyolojik yaşam sırasında bir tiroid lobunun gelişim yetersizliğine bağlı nadir bir anomalidir. Birçok tiroid hastalığı tiroid hemiagenezisine eşlik edebilir. Bu yazıda Graves' hastalığına bağlı orta düzeyde hiperkalsemisi olan bir tiroid hemiagenezisi olgusu sunuldu. Kırk üç yaşında bir kadın bir ay içinde 5 kg'dan fazla kilo kaybı, sıcağa tahammülsüzlük ve aşırı terleme yakınması ile kliniğimize başvurdu. Son ay içinde belirli aralıklarla kusma, susama ve kabızlık semptomları vardı. Muayenesinde dehidrasyon bulguları olmaksızın taşikardisi olduğu saptandı. Nabız dakikada 110 idi. Hafif titremesi ve proksimal kas zayıflığı olan hastada tiroid glandın sağ lobunda hiperplazi ve asimetrik düz guatr saptandı. Tiroid fonksiyon testleri hipertiroidizm tanısını doğruladı. Hiperkalsemi tirotoksikozlu hastalarda saptanabilmesine karşın, yaptığımız literatür taramasına göre, hastamız tirotoksikoza bağlı hiperkalsemiye eşlik eden ilk tiroid hemiagenezisi olgusudur.

Anahtar Sözcükler: Graves hastalığı; tiroid hemiagenezis; tiroid ultrasonografisi.

Thyroid hemiagenesis is a rare congenital anomaly, which develops due to failure of embryologic development of a lobe of the thyroid gland.[1] It more often affects the left thyroid lobe. The isthmus may be present in approximately half of the cases, and looks like a hockey stick on imaging studies.[2] Several accompanying thyroid disorders including follicular and papillary neoplasms, Graves'

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disease, Hashimoto's thyroiditis, lymphocytic thyroiditis, subacute thyroiditis, nodular goiter, hyperfunctioning adenoma, and ectopic thyroid tissue have been reported.[1-5]

Thyrotoxicosis can cause sufficient bone resorption to increase serum calcium.[6] Although mild hypercalcemia may occur commonly in patients with thyrotoxicosis, moderate or severe hypercalcemia during the course of thyrotoxicosis is relatively rare.[7,8] Here we report a case of thyroid hemiagenesis with Graves' disease, who also had moderate hypercalcemia. The patient was evaluated in terms of hypercalcemia etiology, but no other cause was found. Hypercalcemia was established to be due to thyrotoxicosis, and it resolved after successful treatment of thyroid dysfunction.

CASE REPORT

A 43-year-old woman presented with weight loss of more than 5 kg within one month, heat intolerance, and increased sweating. For the past month, she had been troubled by intermittent symptoms of vomiting, thirst, and constipation. On examination, she had tachycardia with no signs of dehydration. Pulse rate was 110 per minute. She had fine tremor, proximal muscle weakness, and asymmetric smooth goiter accompanied by a large right lobe.

Thyroid function tests confirmed the diagnosis of hyperthyroidism. Thyroid stimulating hormone was below 0.004 μIU/ml (normal: 0.4-5.0), free thyroxine 2.94 ng/dl (normal: 0.8-1.9), and free triiodothyronine 5.49 pg/ml (normal: 1.57-4.71). Antithyroglobulin antibody and antithyroid peroxidase antibody titers were elevated, whereas TSH receptor antibody (TRAb) titer was normal. To investigate persistent vomiting laboratory tests were performed Table 1, revealing an elevated serum calcium of 13.7 mg/dl (normal: 8.5-10.2), a normal serum phosphorous of 3.6 mg/dl (normal: 2.5-4.8), and a normal serum albumin of 3.7 g/dl (normal: 3.5-5.2). Repeat serum calcium was 13.6 mg/dl. Ionized calcium was also elevated at 7.4 mg/dl (normal: 4.5-5.3). Serum creatine was 1.6 mg/dl (normal: 0.8-1.4), and alkaline phosphatase 346 U/L (normal: 34-240). Further blood tests demonstrated parathyroid hormone (PTH) as 3 pg/ml (normal: 12-72) and 25-hydroxy vitamin D3 as 45 ng/ml (normal: 7.6-75). Urinary calcium excretion was increased to 377 mg/day (normal: 100-300).

Therapy with both propranolol 20 mg and propylthiouracil 100 mg three times daily was initiated. Hypercalcemia was managed by hydration with intravenous normal saline infusion and intravenous furosemide 20 mg every eight hours for three days. Serum calcium decreased to 11.2 mg/dl rapidly. Subsequent monitoring showed that serum calcium rose back to a relatively high level of 13.6 mg/dl when intravenous therapy was stopped (Table 1). Workup investigations to exclude other causes of hypercalcemia were done. In presence of low serum PTH level, it was unlikely that the hypercalcemia was caused by hyperparathyroidism.

Table 1. Laboratory findings of the patient at admission (day 0) and after antithyroid therapy

	Day 0	Day 21	Day 120
Ca (mg/dl)	13.7	11.2	9.4
P (mg/dl)	3.6	3.7	4
ALP (U/L)	346	–	180
U_{Ca} (mg/day)	377	365	168
25-OH D_3 (ng/ml)	45	–	–
PTH (pg/ml)	3	–	–
PTHrP (pmol/L)	0.28	–	–
FT3 (pg/ml)	5.49	3.9	3.08
FT4 (ng/dl)	2.94	2.14	1.36
TSH (μIU/ml)	0.004	0.004	5.12
TRAb (U/L)	3.8	–	–
ATPO (U/L)	135	–	–
ATG (U/L)	160	–	–

Ca: Calcium (normal: 8.5-10.2 mg/dl); P: Phosphorous (normal: 2.5-4.8 mg/dl); ALP: Alkaline phosphatase (normal: 34-240 U/L); U_{Ca}: Urinary calcium excretion (normal: 100-300 mg/day); 25-OH D_3: 25-hydroxy vitamin D_3 (normal: 7.6-75 ng/m); PTH: Parathyroid hormone (normal: 12-72 pg/ml); PTHrP: Parathyroid hormone related peptide (normal: 0 -1.3 pmol/L); FT3: Free triiodothyronine (normal: 1.57-4.71 pg/ml), FT4: Free thyroxine (normal: 0.8-1.9 ng/dl); TSH: Thyroid stimulating hormone (normal: 0.4-5.0 uIU/ml); TRAb: Thyroid stimulating hormone receptor antibody (normal: 0-9 U/L); ATPO: Antithyroid peroxidase antibody (normal: 0-50 U/L); ATG: Antithyroglobulin antibody (normal: 0-50 U/L).

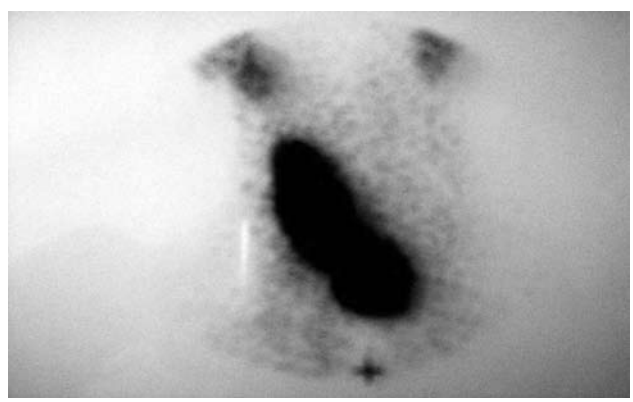

Fig. 1. *Technetium-99 m sestamibi scan showing homogeneous uptake only in the right lobe and isthmus.*

Serum electrophoresis was negative for monoclonal proteins. Parathyroid hormone related peptide was 0.28 pmol/L (normal: 0-1.3). She indicated no symptoms of peptic ulcer, and there was neither exogenous vitamin D intake nor family history of endocrinopathy. No recent history of immobilization was noted. Hematological examinations revealed normocellular bone marrow biopsy. Bone scintigraphy showed no evidence for metastasis. Computed tomography of thorax and abdomen did not reveal any malignancy or granulomatous disease.

Thyroid ultrasonography demonstrated a slightly enlarged right lobe of thyroid gland and confirmed absence of the left lobe. Technetium-99 m (Tc-99m) sestamibi imaging of thyroid was obtained to identify the cause hyperthyroidism. Thyroid scan showed asymmetric thyroid gland with only right lobe (Fig. 1). Technetium-99m uptake was increased. Isthmus was present. Increased vascularity of right thyroid lobe was observed by color doppler. These results suggested that the patient's hyperthyroidism was due to TRAb negative Graves' disease. Serum calcium level started to decrease as overt hyperthyroid state improved and became normal when the patient's free thyroid hormones returned to normal with antithyroid drug therapy.

DISCUSSION

Thyroid hemiagenesis is a rare anomaly, in which a lobe of the thyroid gland fails to develop. The incidence and prevalence of thyroid hemiagenesis in the general population are unknown.[3] Although several papers revealed ratios varying widely between 1:20 and 1:9073, a systematic ultrasound study in 2845 normal school children conducted by Shabana et al.[9] showed that the estimated prevalence of thyroid hemiagenesis is 0.02%. In another study, Maiorana et al.[10] investigated thyroid hemiagenesis prevalence by neck ultrasound in 24032 unselected 11- to 14-year-old schoolchildren, and found a prevalence of 0.05%. Actually, thyroid hemiagenesis is most frequently diagnosed during examination for other thyroid disorders, especially for hyperthyroidism.[2,5]

The diagnosis of thyroid hemiagenesis can be done by ultrasonography and Tc-99m pertechnetate scintigraphy.[5] Although scintigraphy may also detect accompanying ectopic thyroid tissue, which may be not detected by ultrasound, this technique is less sensitive to distinguish several conditions mimicking thyroid hemiagenesis such as autonomously functioning nodules with suppression of remaining thyroid gland, infiltrative disorders, and unilateral inflammation of one lobe.[3,11] As in our case, the possibility of Graves' thyrotoxicosis with hemiagenesis should be considered in the differential diagnosis of autonomously functioning nodules by thyroid scan. Thyroid ultrasound is simple, safe, and cost-effective, gives accurate results, and does not expose patients to radiation.[3] However, as in our case, where accompanying thyroid disorder is also present, using both techniques gives more information.

The cause of the abnormal development leading to thyroid hemiagenesis is not known. The thyroid gland develops from a duct-like invagination of the primitive pharynx endoderm. It expands ventrally along the thyroglossal duct line, and at the end of the second month, the thyroid rudiment acquires the bilobed structure. It is believed that a defect during embryogenesis leads to failure of thyroid gland to become bilobed. In fact, most people have asymmetric thyroid glands with right lobes being larger than left lobes. Some authors suggest that this difference may underlie the pathogenesis of the anomaly. Factors affecting lobulation process are also unknown. Although a genetic component is suggested by several reports from monozygotic twins and affected families, no responsible gene is demonstrated in patients with thyroid hemiagenesis. Similarly, there is inadequate data for environmental factors.[12,13]

In addition to thyroid hemiagenesis and Graves' disease, relatively severe hypercalcemia was detected in our patient. Intensive investigations did not lead to any underlying cause for elevated serum calcium level, and hypercalcemia was explained by thyrotoxicosis. Thyrotoxicosis is a well known cause of hypercalcemia due to increased bone resorption caused by elevated free thyroid hormones.[6,8] However, the incidence of moderate or severe hypercalcemia is very low in hyperthyroidism. Hypercalciuria developing due to suppression in serum PTH level and low intestinal calcium absorption due to the decrease in serum 1.25-dihydroxy vitamin D3 level are believed to be responsible for the mild course of hypercalcemia in hyperthyroid patients.[7,14] Treatment of the thyrotoxicosis with beta blockers and antithyroid agents resolves hypercalcemia, as in our case.

In conclusion, thyroid hemiagenesis is a rare anomaly of the thyroid gland. Various thyroid disorders may be seen among patients with thyroid

hemiagenesis. Although accompanying Graves' disease has been reported in patients with hemiagenesis, to the best of our knowledge, this is the first case of thyroid hemiagenesis associated with hypercalcemia due to thyrotoxicosis.

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