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【 CASE REPORT 】

Two Cases of Transiently Elevated Serum CEA Levels in Severe Hypothyroidism without Goiter

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Abstract:
Carcinoembryonic antigen (CEA), the level of which is known to increase in both patients with gastrointestinal cancers and those with non-neoplastic conditions, is one of the most widely-used tumor markers. Hypothyroidism is a common endocrinological disorder in which CEA levels can rise, and is sometimes overlooked as a diagnosis in the absence of typical symptoms or thyroid enlargement. We report the cases of two patients with non-goiterous severe hypothyroidism with markedly elevated CEA levels that effectively decreased with levothyroxine replacement therapy alone. Hypothyroidism should be considered as an important cause of unexplained high serum CEA levels in order to avoid unnecessary medical examination.

Key words: carcinoembryonic antigen, hypothyroidism

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Introduction

Carcinoembryonic antigen (CEA) is a glycoprotein with a molecular weight of approximately 200,000, which was first extracted from colon cancer tissue in 1965 (1). CEA is overexpressed in adenocarcinoma cells in gastrointestinal cancers; thus, it is used mainly as a serological biomarker for malignant tumors. However, the CEA levels can also increase with certain metabolic disorders, including smoking, aging, and obstructive lung disease (2-4); thus, it is important to clarify the reason for elevated serum CEA levels.

Hypothyroidism is a common endocrinological disorder, and is caused by a variety of functional or structural disorders of the thyroid gland, including Hashimoto's thyroiditis. Hypothyroidism has a number of signs, and can be misdiagnosed for long periods before becoming apparent (5), especially in patients lacking goiter. Hypothyroidism is also an important cause of inappropriate CEA elevation (6).

We herein report two cases of severe hypothyroidism with minimal symptoms and the absence of thyromegaly, in which the patients' highly elevated CEA levels were effectively reduced by levothyroxine administration alone.

Case Reports

Case 1

A 62-year-old woman was referred to our hospital from a nearby clinic for an examination to determine the cause of mild liver dysfunction. Her only symptom was lower leg edema. A screening blood analysis revealed an elevated CEA level, which had not been pointed out previously (21.3 ng/mL); endoscopy and abdominal ultrasonography revealed no abnormalities. 18F-deoxyglucose positron emission tomography showed no abnormal accumulation, including in the thyroid gland. An endocrinological analysis showed the excessive elevation of thyroid-stimulating hormone (TSH); the patient was therefore referred to our department. With the exception of dyslipidemia, the patient had no relevant medical history and her only medication or health supplement was rosuvastatin calcium; she had not been taking supplemental iodine. She had smoked 20 cigarettes per day for 20 years (from age 20-40 years), but she had stopped smoking after that. She did not consume alcohol regularly, and had no allergies. There was no family history of thyroid dis-

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Table. **Laboratory Test Results for Patient 1 and Patient 2 on Admission.**

Variable	Reference range	Case 1	Case 2
Thyroid stimulating hormone (μU/mL)	0.33-4.05	146	170
free T3 (pg/mL)	2.30-4.00	0.340	<0.026
free T4 (ng/dL)	0.97-1.69	0.172	0.087
Anti-thyroglobulin antibody (IU/mL)	<28	91	22
Anti-thyroid peroxidase antibody (IU/mL)	<16	156	553
TSH receptor antibody (IU/L)	<2.0	8.6	NA
Thyroid stimulating antibody (%)	<120	100	NA
TSH-stimulation blocking antibody (%)	<31.7	97.8	NA
Carcinoembryonic antigen (ng/mL)	<5.0	21.3	26.9
Carbohydrate antigen 19-9 (U/mL)	<37.0	16.0	NA

NA: not assessed

ease or malignancy.

On physical examination, her thyroid gland was not palpable from the body surface, and there was no tenderness. Non-pitting edema was observed in both lower legs. Her weight, height, and body mass index were 58.9 kg, 154 cm, and 24.8 kg/m^2, respectively. Laboratory testing revealed severe hypothyroidism and mild liver dysfunction with the following values: TSH, 146 μIU/mL; free-T3, 0.340 pg/mL; free-T4, 0.172 ng/dL; aspartate aminotransferase, 61 IU/mL; and alanine aminotransferase, 41 IU/mL (Table). Although the patient was positive for anti-thyroid peroxidase, anti-thyroglobulin, and TSH-receptor antibody, the thyroid gland showed remarkable atrophy. An additional analysis was negative for thyroid-stimulating antibody and strongly positive for TSH-stimulation blocking antibody. We therefore diagnosed the patient with hypothyroidism secondary to atrophic thyroiditis (Table).

We started hormone replacement therapy with levothyroxine, which gradually but effectively improved the patient's hypothyroidism and liver dysfunction; this was followed by the normalization of the patient's CEA level to 4.2 ng/mL (Figure a). Thereafter, the patient's CEA levels remained within the normal range.

Case 2

A 65-year-old woman was diagnosed with hypertension and a chest "shadow" was found on radiography during a routine health examination. She was referred to our hospital for further examination, which revealed pericardial effusion, severe hypothyroidism (TSH, 170.2 μU/mL; free-T4, 0.087 ng/dL; free-T3:, undetectable); and high CEA (26.9 ng/mL) (Table). She was diagnosed with myxedema heart disease secondary to hypothyroidism and was referred to our department. She had no subjective symptoms or suggestive medical history, and neither she nor her family had a history of thyroid disease. Her thyroid gland was not obviously enlarged and was barely palpable. She was a current smoker (12 cigarettes per day for 45 years) and consumed 20 g of alcohol per day. Thyroid ultrasound revealed mild thyroid gland enlargement, heterogenous low echoic parenchyma, and multiple small nodules. A blood analysis was positive for anti-thyroid peroxidase antibody. No malignant tumors were found in a whole-body examination, including computed tomography and endoscopy. We diagnosed the patient with primary hypothyroidism and started levothyroxine replacement therapy. After replacement therapy, although there was no change in her smoking status, both her TSH and CEA levels gradually decreased; however, her CEA level did not reach the normal range (Figure b).

Neither of the patients has developed a malignant tumor to date.

Discussion

Several different tumor markers are now widely used in the diagnosis and management of malignancies. CEA is one of the most widely-used markers and increases in gastrointestinal cancer as well as other types of carcinoma, including thyroid (7), breast (8), and lung (9) cancers. However, the CEA level may also rise in patients with non-neoplastic conditions such as inflammatory diseases of the glandular epithelium because CEA is also produced in the normal mucosal epithelium (in particular the oral cavity, large intestine, stomach, bronchus, biliary tract, and other locations). Furthermore, because CEA is metabolized in the liver (10), the CEA level can increase in patients with biliary obstruction and certain metabolic disorders (11). The CEA level has also been reported to increase during summer months and to show a certain degree of fluctuation (12). For these reasons, it is important to discriminate between cancer-related CEA elevation and non-neoplastic conditions.

Hypothyroidism is an endocrinological disorder associated with the elevation of certain tumor marker levels. Amino et al. reported a significantly high frequency of CEA positivity in hypothyroid patients with Hashimoto's disease, and that hormone replacement therapy reduced CEA levels in hypothyroid patients (6). Indeed, the CEA levels of our 2 cases drastically decreased. In case 2, the CEA level remained relatively high, even after levothyroxine treatment. We judged that CEA did not normalize due to her smoking habit, as no malignancies were detected. Other studies revealed that hypothyroidism was associated with an increased

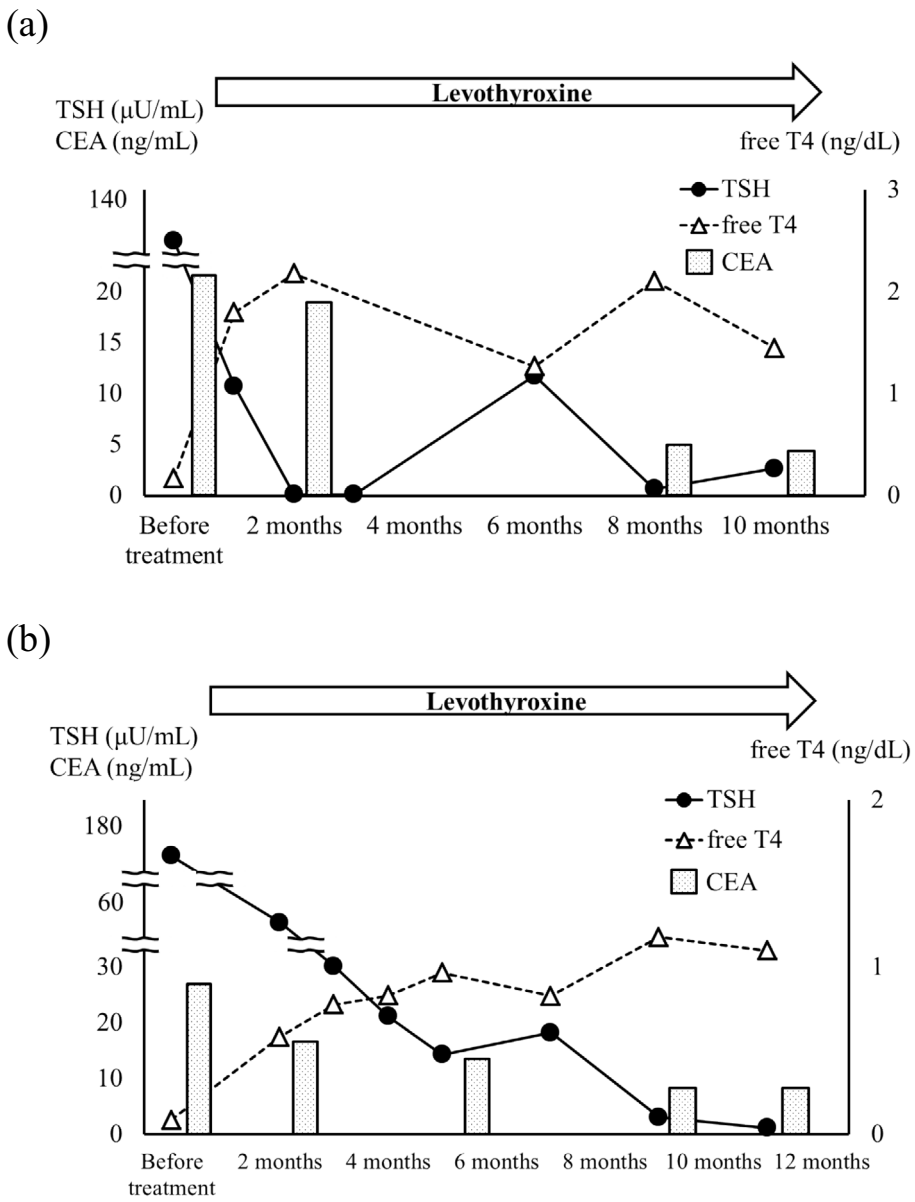

Figure. **(a) The clinical course of patient 1. Levothyroxine replacement therapy alone normalized both the CEA level and thyroid function. (b) The clinical course of patient 2. As in the case of patient 1, the treatment of the hypothyroidism reduced the serum CEA level.**

CEA level, as well as increased cancer antigen 125, cancer antigen 15-3, and alpha-fetoprotein levels in comparison to euthyroid and hyperthyroid patients (13). The mechanism underlying these inappropriate elevations remains unclear. In addition, it has been reported that the carbohydrate antigen 19-9 level, but not the CEA level, was increased in a patient with hypothyroidism (14). However, the reason for the discrepancies among reports remains unclear. In general, tumor marker elevation is assumed to be caused by their overexpression or due to decreased metabolism. With regard to CEA, it has been suggested that hypothyroidism affects the CEA metabolism or clearance by the liver because CEA is metabolized and excreted by the liver (6, 10).

Hypothyroidism includes a variety of symptoms; however, typical symptoms and signs of hypothyroidism may be present in only 20% of patients when they are first seen (15). Thus, it is often difficult to diagnose hypothyroidism in the absence of typical symptoms and obvious thyroid swelling, such as atrophic thyroiditis or drug-induced hypothyroidism. Indeed, the hypothyroidism of our two patients was found incidentally, and we would not have diagnosed hypothyroidism without thyroid function testing because there was no (or minimal) thyroid enlargement. Because of the lack of symptoms, our first patient underwent unnecessary whole-body medical examination until hypothyroidism was diagnosed.

In conclusion, we herein described two cases of hypothyroidism without massive thyroid enlargement and with marked CEA elevation that responded to the administration of levothyroxine. Our cases illustrate the importance of remembering that hypothyroidism can cause the elevation of tumor marker levels and that it may be a cause of unex-

plained high serum CEA levels.

The authors state that they have no Conflict of Interest (COI).

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