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Case Report

Induction of TSH Receptor Antibody and Hyperthyroidism in Metastatic Follicular Thyroid Carcinoma

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Abstract

It has been reported that patients with metastatic thyroid carcinoma develop hyperthyroidism even after total thyroidectomy, but those with positive anti-TSH Receptor Antibody (TRAb) were rare. A 68-year old male developed tumor in the middle of sternum in 2015. Histopathological findings of resected tumor suggested a metastatic thyroid carcinoma. Thyroid ultrasound revealed the presence of a solid nodule in the left lobe. The fine needle aspiration cytology confirmed follicular thyroid carcinoma. Total thyroidectomy was performed, followed by external beam radiation therapy to the metastasis in the sternum and left rib. Subsequently, levothyroxine replacement was initiated and serum thyroid hormone levels were maintained within the normal range. Since serum thyroid hormone levels gradually increased one year after total thyroidectomy, levothyroxine was discontinued. However, serum thyroid hormone levels further increased over the normal range. TRAb was present and antithyroid agent was initiated. Iodine scintigraphy revealed the accumulation in the sternum, clavicular, rib and spine without accumulation to the thyroid bed. This is an unusual case of induction of TRAb-positive hyperthyroidism in the course of development of follicular carcinoma-derived bone metastases. An analysis of Human Leukocyte Antigen (HLA) revealed that he had HLA-DPB1*05:01, a Graves' disease-specific susceptible gene. The presence of susceptible HLA allele for Graves' disease might be responsible for his potential to provoke TRAb-induced hyperthyroidism.

Keywords: TSH receptor antibody; Hyperthyroidism; Follicular thyroid carcinoma; Human leukocyte antigen

Introduction

Thyroid cancer occurs in Graves' disease with a frequency of around 2% [1,2]. On the other hand, Yoshimura et al. [3] reported that metastatic thyroid carcinoma develop hyperthyroidism in parallel with an increased metastatic volume even after total thyroidectomy and summarized 45 similar cases. So far, there have been around 50 reported cases of hyperthyroidism in the metastatic thyroid carcinoma [4-6]. It is thought that a low capability of thyroid hormone production per tumor cell may cause thyrotoxicosis only after the metastatic tumor had grown very large in size [7]. Besides, in some cases with metastatic thyroid carcinoma, anti-TSH Receptor Antibodies (TRAb) were detected even after total thyroidectomy and, as with Graves' disease, could be associated with development of hyperthyroidism [3-6,8-13]. In the present case, total thyroidectomy was made for follicular thyroid carcinoma with bone and lung metastasis, and hyperthyroidism developed several years after total thyroidectomy when thyroid autoantibodies including TRAb became positive. In this context, we examined patient's Human Leukocyte Antigen (HLA) typing to clarify whether our patient possesses susceptible or resistant HLA alleles for the development of autoimmune hyperthyroidism.

Case Presentation

A 68-year old male, who had been suffering from type 2 diabetes, was disabled by lumbar disc herniation and amputation of left foot due to diabetic gangrene. He developed tumor in the middle of sternum in March, 2015 (Figure 1A). Histopathological findings of resected tumor suggested a metastatic thyroid carcinoma (Figure 1B). Thyroid ultrasound revealed the presence of a solid nodule in the left lobe (Figure 2A). A diagnosis of follicular thyroid carcinoma was made by the fine needle aspiration cytology. As shown in Figure 3, at this time, serum thyroid hormone levels were normal (free T3: 2.9 pg/mL [normal range; 2.1-4.1], free T4: 1.3 ng/dL [normal range; 0.9-1.7]) and thyroid autoantibodies against Thyroid Peroxidase (TPOAb) and purified Thyroglobulin (TgAb) were not present. Total thyroidectomy was performed in July, 2015. The histopathological findings of the left nodule confirmed follicular thyroid carcinoma, and remnant thyroid tissue showed no abnormality. He could not receive Radioactive Iodine-131 (RAI) therapy because of his disability. Instead, external beam radiation therapy was subsequently made towards the metastasis in the sternum and left rib. Levothyroxine replacement was then initiated and serum thyroid hormone levels were maintained within the normal range. Since serum thyroid hormone levels gradually increased along with marked increase in serum thyroglobulin one year after total thyroidectomy, levothyroxine was discontinued. However, serum thyroid hormone levels further increased over the normal range. Therefore, he was admitted for detailed examination in January, 2018.

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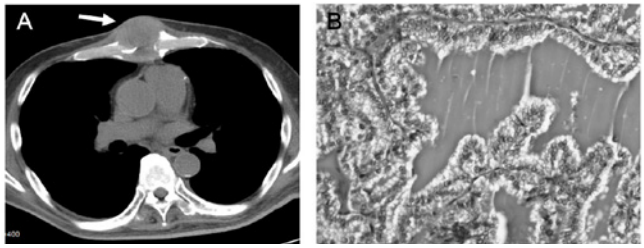

Figure 1: Computed Tomography (CT) of the chest revealed a tumor in the middle of the sternum (A). Histopathological findings of resected tumor suggested a metastatic thyroid carcinoma (B; Hematoxylin and eosin staining, x200).

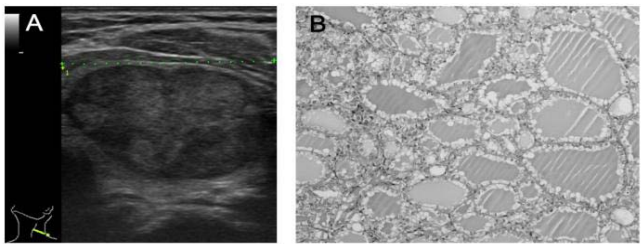

Figure 2: Thyroid ultrasound revealed the presence of a hypoechoic solid nodule, 2.5 x 3.8 x 6.0 cm in size, in the left lobe with a heterogeneous echo texture (A). The histopathological findings of the left nodule confirmed follicular thyroid carcinoma (B; Hematoxylin and eosin staining, x100).

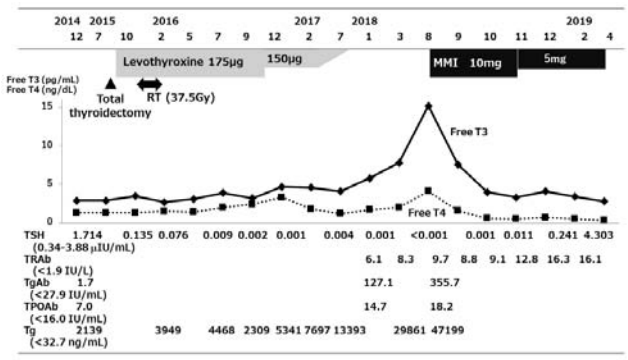

Figure 3: Clinical course. Changes in serum free T3, free T4, and TSH following total thyroidectomy and external beam Radiation Therapy (RT) combined with levothyroxine replacement. Around one year after thyroidectomy, serum Thyroglobulin (Tg) was remarkably increased, suggesting enlargement of metastatic lesions. Together with tumor growth, anti-TSH Receptor Antibody (TRAb) became positive and hyperthyroidism appeared. Serum thyroid hormone levels were normalized by antithyroid agent (thiamazole: MMI). TPOAb: thyroid peroxidase antibody, TgAb: thyroglobulin antibody.

At admission, TRAb, TPOAb and TgAb were present (Figure 3). ^{123}I scintigraphy revealed the strong accumulation of radioactive iodine in the multiple bone metastases towards sternum, clavicular, rib and spine without accumulation in the thyroid bed (Figure 4). This is thought to be an unusual case of induction of TRAb-positive hyperthyroidism in the course of development of follicular thyroid carcinoma-derived bone metastases, and antithyroid agent was initiated. So far, thyroid hormone levels have been well controlled by antithyroid agent.

We examined his HLA typing whether he has susceptible genes

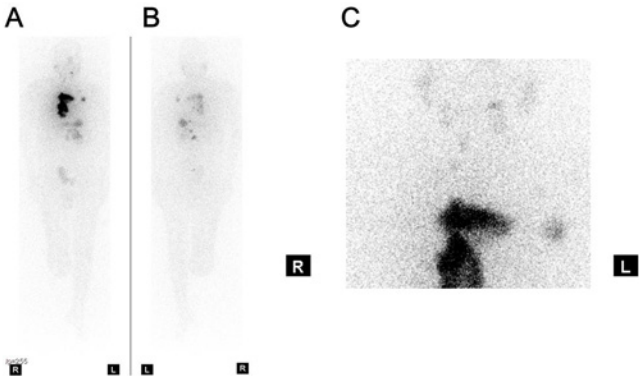

Figure 4: Anterior (A) and posterior (B) view of ^{123}I scintigraphy showed a massive uptake of the tracer in the metastatic lesions including the sternum, clavicular left rib and spine. There was no accumulation in the thyroid bed (C).

Table 1: HLA DNA typing in this patient.

A:	310102	2402
B:	5101	5201
C:	0304	1202
DRB1:	090102	150201
DPB1:	090101	**0501**
DQA1:	030201	010301
DQB1:	030302	060101

HLA: Human Leukocyte Antigen

for Graves' disease. As shown in Table 1, he had one of the most common HLA haplotypes in Japanese population (HLA-A*24:02, B*52:01, C*12:02, DRB1*15:02, DQB1*06:01, and DPB1*09:01) [14]. It is of interest that he had one of the Graves' disease-specific susceptible class II molecules, HLA-DPB1*05:01 [15-17].

Discussion

As shown in Table 2, there have been 12 reported cases of TRAb-positive hyperthyroidism associated with thyroid carcinoma-derived bone metastases [3-6,8-13]. All cases received thyroidectomy with or without RAI therapy. Most cases are caused by follicular carcinoma, and onset after total or subtotal thyroidectomy is ranged from 15 to 120 months with exception of one case in which hyperthyroidism had already been present before thyroidectomy. Thus, basically, Graves' disease was not present before development of bone metastases. In the present case, thyroid function was normal, and TgAb and TPOAb were not detected before total thyroidectomy. Furthermore, at thyroidectomy, there was no histopathological sign of Graves' disease in the remnant thyroid tissue. Although we did not examine TRAb in the beginning, the above mentioned findings indicate that Graves' disease was not evident before thyroidectomy.

Susceptibility and resistance to the development of Graves' disease is known to depend on the genetic background. He has one of the most common HLA haplotypes in Japanese population (HLA-A*24:02, B*52:01, C*12:02, DRB1*15:02, DQB1*06:01, and DPB1*09:01) [14], which showed protective effects against the development of Graves' disease [16]. On the other hand, he has the Graves' disease-specific susceptible class II molecule, HLA-DPB1*05:01 [15-17]. Interestingly, the presence of HLA-DPB1*05:01

Table 2: Metastatic thyroid carcinoma exhibiting hyperthyroidism with TRAb.

Author	Year	Age	Sex	history of Graves	Carcinoma type	Onset of hyperthyroidism after thyroidectomy (months)	Metastasis	Treatment for Graves	TRAb after treatment
[8]	1970	49	female	possible*	follicular	96 (subtotal)	pelvis	RAI	decrease
		58	female	possible*	follicular	12 (subtotal)	pelvis, rib	RAI	decrease
		60	male	unknown	trabecular	48 (subtotal?)	lung	RAI	decrease
[9]	1979	67	male	none	follicular	120 (total)	lung	RAI	decrease
[10]	1984	70	female	unknown*	follicular	before (total)	lung, humerus, scapula, spine	RAI	decrease
[11]	1994	48	female	none	follicular	15 (total with RAI)	lung, bone (sternum, spine, pelvis, skull, femur, humerus)	RAI	decrease
[12]	1997	49	female	none	follicular	108 (total)	lung	MMI+RAI	decrease
[3]	1997	53	male	none	follicular	93 (total) 79 (RAI)	lung, bone (pelvis, femur)	MMI+RAI	decrease
[4]	2000	62	female	unknown	follicular	48 (total)	lung	EBRT+chemo	decrease
[5]	2001	56	female	unknown	follicular	79 (hemi) 1 (total)	lung	MMI+RAI	decrease
[13]	2002	70	female	none	follicular	96 (hemi)	skull, spine, ilium	MMI+RAI	decrease
[6]	2017	57	female	none	follicular	48 (total with RAI)	lung, skull	MMI+RAI	decrease
Our case	2020	68	male	none	follicular	30 (total with EBRT)	sternum, rib, spine, lung	MMI	stable

RAI: Radioactive Iodine-131 therapy, EBRT: External Beam Radiation Therapy

*Hyperthyroidism was present before thyroidectomy or RAI. TRAb was measured after thyroidectomy.

is crucial for the development of Graves' disease in the presence of resistant HLA-DR13 [16]. Therefore, it is possible that susceptible HLA-DPB1*05:01 in this patient is epistatic to protective HLA alleles. To the best of our knowledge, this is the first report demonstrating the presence of susceptible HLA alleles for Graves' disease in the patients with TRAb-positive hyperthyroidism, analogous to Graves' disease, in the follicular thyroid carcinoma-derived multiple bone metastases.

One may criticize why TRAb-positive hyperthyroidism did not develop before thyroidectomy under genetic background of Graves' disease. The production of TRAb in Graves' disease is often influenced by the immunological fluctuations such as allergic rhinitis and sarcoidosis [18,19]. In this context, the reason for the production of TRAb after total thyroidectomy is thought to be as follows: (1) stress by surgery or RAI may alter immunological homeostasis and trigger the production of TRAb [6]. (2) RAI may induce the release of thyroid antigens, resulting in the stimulation of autoimmunity [20]. (3) TSH receptor in metastatic tumors functions as an antigen of TRAb [3].

Despite any reasons, thyroid stimulating antibodies are known to increase cAMP in human follicular thyroid carcinoma [21]. Since ^{123}I scintigraphy showed the strong accumulation of radioactive iodine in the multiple bone metastases without accumulation in the thyroid bed, TRAb could accelerate the production of thyroid hormone in the metastatic lesions. In this case, hypersecretion of thyroid hormone appears to be parallel with an increase in serum thyroglobulin level. Therefore, hyperthyroidism may largely depend on the increase in metastatic volume [3]. However, the appearance of TRAb suggests that thyroid stimulating antibody at least additionally contribute to his hyperthyroidism.

Conclusion

We first examined susceptible HLA alleles for Graves' disease in the patients with TRAb-positive hyperthyroidism following the follicular thyroid carcinoma-derived multiple bone metastases. More data should be accumulated to clarify whether the genetic background similar to Graves' disease is responsible for TRAb production and the subsequent development of hyperthyroidism in the metastatic follicular thyroid carcinoma.

Acknowledgment

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References

1. Hancock BW, Bing RF, Dirmikis SM, Munro DS, Neal FE. Thyroid carcinoma and concurrent hyperthyroidism: a study of ten patients. Cancer. 1977; 39: 298-302.
2. Staniforth J, Erdirimanne S, Eslick G. Thyroid Carcinoma in Graves' Disease: A Meta-Analysis. Int J Surg. 2016; 27: 118-125.
3. Yoshimura Noh J, Mimura T, Kawano M, Hamada N, Ito K. Appearance of TSH receptor antibody and hyperthyroidism associated with metastatic thyroid cancer after total thyroidectomy. Endocr J. 1997; 44: 855-859.
4. Cobin RH. Thyroid carcinoma and Graves' disease. Endocr Pract. 2000; 6: 264-267.
5. Suzuki K, Nakagawa O, Aizawa Y. A case of pulmonary metastatic thyroid cancer complicated with Graves' disease. Endocr J. 2001; 48: 175-179.
6. Aoyama M, Takizawa H, Tsuboi M, Nakagawa Y, Tangoku A. A case of metastatic follicular thyroid carcinoma complicated with Graves' disease after total thyroidectomy. Endocr J. 2017; 64: 1143-1147.
7. Aiyoshi Y, Ogata E. Report on a case of functioning thyroid carcinoma provoking thyrotoxicosis with review of literature. Endocrinol Jpn. 1978; 25: 623-629.
8. Valenta L, Lemarchand-Béraud T, Němec J, Griessen M, Bednár J. Metastatic thyroid carcinoma provoking hyperthyroidism, with elevated circulating thyrostimulators. Am J Med. 1970; 48: 72-76.
9. Snow MH, Davies T, Smith BR, Ross WM, Evans RG, Teng CS, et al. Thyroid stimulating antibodies and metastatic thyroid carcinoma. Clin Endocrinol (Oxf). 1979; 10: 413-418.

10. Chapman CN, Sziklas JJ, Spencer RP, Bower BF, Rosenberg RJ. Hyperthyroidism with metastatic follicular thyroid carcinoma. J Nucl Med. 1984; 25: 466-468.

11. Kasagi K, Takeuchi R, Miyamoto S, Misaki T, Inoue D, Shimazu A, et al. Metastatic thyroid cancer presenting as thyrotoxicosis: report of three cases. Clin Endocrinol (Oxf). 1994; 40: 429-434.

12. Katz SB, García AJ, Niepomniszcze H. Development of Graves' disease nine years after total thyroidectomy due to follicular carcinoma of the thyroid. Thyroid. 1997; 7: 909-911.

13. Ishihara T, Ikekubo K, Shimodahira M, Iwakura T, Kobayashi M, Hino M, et al. A case of TSH receptor antibody-positive hyperthyroidism with functioning metastases of thyroid carcinoma. Endocr J. 2002; 49: 241-245.

14. Nakaoka H, Mitsunaga S, Hosomichi K, Shyh-Yuh L, Sawamoto T, Fujiwara T, et al. Detection of Ancestry Informative HLA Alleles Confirms the Admixed Origins of Japanese Population. PLoS One. 2013; 8: e60793.

15. Chen PL, Fann CS, Chu CC, Chang CC, Chang SW, Hsieh HY, et al. Comprehensive genotyping in two homogeneous Graves' disease samples reveals major and novel HLA association alleles. PLoS One. 2011; 6: e16635.

16. Ueda S, Oryoji D, Yamamoto K, Noh JY, Okamura K, Noda M, et al. Identification of Independent Susceptible and Protective HLA Alleles in Japanese Autoimmune Thyroid Disease and Their Epistasis. J Clin Endocrinol Metab. 2014; 99: 379-383.

17. Inaba H, De Groot LJ, Akamizu T. Thyrotropin Receptor Epitope and Human Leukocyte Antigen in Graves' Disease. Front Endocrinol (Lausanne). 2016; 7: 120.

18. Takeoka K, Hidaka Y, Hanada H, Nomura T, Tanaka S, Takano T, et al. Increase in serum levels of autoantibodies after attack of seasonal allergic rhinitis in patients with Graves' disease. Int Arch Allergy Immunol. 2003; 132: 268-276.

19. Makino S, Yagi C, Naka M, Hirose S, Fujiwara M, Ohbayashi C. A case of Graves' disease developing with exacerbation of sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2019; 36: 318-324.

20. Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G, Tørring O. TSH-receptor Autoimmunity in Graves' Disease After Therapy With Anti-Thyroid Drugs, Surgery, or Radioiodine: A 5-year Prospective Randomized Study. Eur J Endocrinol. 2008; 158: 69-75.

21. Filetti S, Belfiore A, Amir SM, Daniels GH, Ippolito O, Vigneri R, et al. The role of thyroid-stimulating antibodies of Graves' disease in differentiated thyroid cancer. New Engl J Med. 1988; 318: 753-759.