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Case Report

Recurrent Subacute Thyroiditis in a Patient With Human Leukocyte Antigen–associated Predisposition to Graves Disease

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ABSTRACT

Background: Subacute thyroiditis (SAT) followed by Graves disease (GD) is a rare condition. We report the case of a patient with recurrent SAT with human leukocyte antigen (HLA)–associated predisposition to GD.

Case Report: A 28-year-old Japanese woman presented with neck pain and hyperthyroidism symptoms. We observed elevated C-reactive protein and thyroid hormone levels, along with a high erythrocyte sedimentation rate. Further, anti–thyroid-stimulating hormone receptor antibody was undetected, and thyroid glands were heterogeneous and hypoechoic. These findings confirmed a diagnosis of SAT. The patient was treated with prednisone (starting dose, 30 mg), and clinical and laboratory data suggested an improvement. Six months later, the patient presented with recurrent clinical and biochemical features of hyperthyroidism (thyroid-stimulating hormone level, 0.003 mIU/mL; free thyroxine level, 3.14 ng/dL; and TSH receptor–stimulating autoantibodies, 220%). The patient was diagnosed with GD and was successfully treated with methimazole. Eleven years later, the patient was diagnosed with simultaneous SAT and GD. HLA-typing revealed that the patient possessed characteristic alleles associated with susceptibility to GD, such as *HLA-DRB1*04:03* and **15:01*, *DQB1*03:02:01* and *06:02:01*, and *HLA DPB1*05:01* alleles.

Discussion: The occurrence of SAT may trigger thyroid antigen release and lead to the onset of GD in patients who are genetically predisposed to this autoimmune disorder.

Conclusion: For certain patients, the diagnosis of GD should be considered in case of recurrent hyperthyroidism and history of resolved SAT.

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Introduction

Subacute thyroiditis (SAT) is an inflammatory disorder characterized by the destruction of follicular epithelial cells.¹ Thyrotoxicosis during Graves disease (GD) is caused by thyroid-stimulating hormone (TSH) receptor–stimulating autoantibodies (TRAb).¹ The excess production of thyroid hormone is not a self-limited dysfunction and requires treatment with antithyroid drugs, radioisotopes, or thyroidectomy.¹ SAT is an uncommon disorder that mainly affects women aged 40 to 50 years and is characterized by

neck pain, tender diffuse thyroid goiter, and elevated inflammatory markers.¹ SAT is also characterized by initial hyperthyroidism, followed by a gradual decline in thyroid function, with an eventual restitution to normal thyroid function.²

The underlying causes of SAT and GD are unrelated; thus, the occurrence of GD after SAT is rare.³ Herein, we present a rare case of recurrent SAT followed by the development of GD. Furthermore, we have thoroughly reviewed the literature for articles describing previous cases and discuss the possible mechanisms triggering the recurrence of SAT and GD in our case.

Case Report

A 28-year-old Japanese woman was referred to our hospital by her primary care physician for fever, neck pain, and palpitations. At presentation, the patient had a regular pulse rate of 106 beats/min, and her body temperature was 38.5 °C. She had no history of undergoing head/neck irradiation, immune therapy, or having an upper airway infection. The patient's white blood cell count was

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FT4, free thyroxine; GD, Graves disease; HLA, human leukocyte antigen; SAT, subacute thyroiditis; TRAb, anti-TSH receptor antibody; TSH, thyroid-stimulating hormone.

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Table 1
Trends in Laboratory Findings for the First Episode

	Baseline	2 months	3 months	6 months	8 months	3.5 years
	Subacute thyroiditis			Graves		
TSH, mIU/mL (0.50-5.00)	<0.001	0.006	0.10	0.003	0.003	1.32
FT4, ng/dL (0.85-1.51)	2.76	1.43	1.36	3.14	1.64	1.30
CRP, mg/dL (0-0.5)	9.0	0.012	0.012	0.021	0.017	...
ESR, mm/h	74	...	5	4	...	5
TRAb, % (<15%)	0.4
TSAb, % (0%-180%)	220	...	160
Medications						
PSL	30 mg	10 mg	5 mg	None
MMI	15 mg	10 mg	None

Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; FT4 = free thyroxine; MMI = methimazole; PSL = prednisolone; TRAb = anti-TSH receptor antibody; TSAb = thyroid-stimulating antibody; TSH = thyroid-stimulating hormone.

normal (8040 cells/ μ L), whereas her C-reactive protein (CRP) level (9.0 mg/dL; 0-0.5 mg/dL) and erythrocyte sedimentation rate (ESR) (74 mm/h; 0-15 mm/h, normal levels) were elevated. Both free triiodothyronine (6.34 pg/mL; 2.63-3.94 pg/mL) and free thyroxine (FT4) (2.76 ng/dL; 0.85-1.51 ng/dL) levels were elevated, whereas TSH (<0.001 μ IU/mL; 0.500-5.00 μ IU/mL) was undetected. We obtained negative results for thyroglobulin antibody (<0.1 U/mL; 0-0.7 U/mL), thyroperoxidase antibody (<0.1 U/mL; 0-0.1 U/mL), and endocrinologist realize the TRAb second (0.4%; <15%). Ultrasonography of the thyroid gland revealed heterogeneous and hypochoic areas consistent with SAT. The patient was diagnosed with SAT and received prednisolone (30 mg/day); subsequently, her neck pain and fever subsided. The prednisolone dose was reduced by 5 mg every 2 weeks, and it was discontinued after 3 months. Then, almost all parameters, including FT4 (1.36 ng/dL), CRP (0.012 mg/dL), and ESR (5 mm/h) levels, returned to normal; however, TSH levels remained suppressed despite her not receiving antithyroid medications (Table 1).

After 6 months, the FT4 levels were elevated (3.14 ng/dL) and TSH was suppressed (0.00358 μ IU/mL), with elevated thyroid-stimulating antibodies (220%; 0%-180%), undetectable thyroglobulin (<0.1 U/mL), and thyroperoxidase antibodies (3.1 U/mL); CRP and ESR levels were normal, and ^{99m}Tc-pertechnetate uptake homogeneously increased by 4.96% (0.4%-3.0%), indicating GD. Therefore, methimazole (15 mg) was started. The methimazole dose was gradually reduced and was discontinued after 4 years because the patient became clinically and biochemically euthyroid with negative TRAb. At 1 year after discontinuation, TSH and FT4 levels remained within a normal range. We regarded this as a remission of GD and stopped following up the case.

At 11 years after treatment completion, the patient experienced fever, palpitations, neck pain, tachycardia, and weight loss again. At presentation, her heart rate was 100 beats/min and her body temperature was 38.5 °C. The thyroid gland was diffusely enlarged, and

she presented with resting tremor. Laboratory analyses showed a normal white blood cell count (7000 cell/ μ L), elevated CRP levels (2.1 mg/dL), and increased ESR levels (61 mm/h). Free triiodothyronine (20.27 pg/mL) and FT4 (7.53 ng/dL) levels were elevated, whereas TSH was undetected (Table 2). Additionally, we obtained negative results for TRAb: third (<0.8 IU/L; <2 IU/L). Thyroid ultrasonography revealed hypochoic areas indicative of decreased vascularity. The patient was treated with prednisolone (30 mg/day), after which her symptoms rapidly improved. The prednisolone dose was reduced by 5 mg every 2 weeks (Table 1). At 1 month after treatment initiation, the FT4 levels remained high (>7.7 ng/dL), although the CRP levels (<0.005 mg/dL) and ESR levels (4 mm/h) returned to normal. The patient was treated with 50-mg potassium iodide. At 2 months after treatment initiation, the thyroid hormone levels improved (FT4 level, 1.37 mg/dL); therefore, potassium iodide administration was discontinued. Three months later, the patient complained of sweating and tremors. Her TSH level was 0.005 mIU/mL and FT4 level was 3.0 ng/dL, whereas TRAb level was elevated (7.7 IU/L). Thyroid ultrasonography revealed diffuse heterogeneity with increased vascularity on color Doppler flowmetry, consistent with GD. We elected to resume methimazole to treat GD.

Because genetic susceptibility to both SAT and GD has been linked to certain human leukocyte antigen (HLA) subtypes, we performed HLA-typing to investigate whether the patient had a genetic predisposition to these diseases.⁴⁻⁶ HLA-typing results revealed that the patients had *HLA-DRB1*04:03* and **15:01*, *DQB1*03:02:01* and *06:02:01*, and *HLA-DPB1*05:01* alleles.

Discussion

Here, we describe a rare case, in which SAT was followed by GD. The patient had recurrent SAT and GD for 11 years after SAT was diagnosed.

Table 2
Trends in Laboratory Findings for the Second Episode

	Baseline	1 months	2 months	3 months	4 months	5 months	6 months
	Subacute thyroiditis			Graves			
TSH, mIU/mL	<0.001	0.005	0.005	0.005	0.005	0.005	0.005
FT4, ng/dL	7.53	>7.7	1.37	3.0	2.37	1.7	0.94
CRP, mg/dL	2.19	<0.015	<0.015	<0.015	<0.015	<0.015	<0.015
ESR, mm/h	61	4	4	2	2	3	2
TRAb (<2 IU/L)	0.08	7.7
Medications							
MMI	15 mg	15 mg	15 mg	10 mg
PSL	30 mg	20 mg	10 mg	None
KI	...	50 mg

Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; FT4 = free thyroxine; KI = potassium iodide; MMI = methimazole; PSL = prednisolone; TRAb = anti-TSH receptor antibody; TSH = thyroid-stimulating hormone.

The concurrence of GD and SAT is extremely rare, and only few cases have been described in the literature.^{4,5,7} In 2011, Nakano et al³ reviewed 33 cases of SAT; of these, 7 cases were followed by GD. Since then, a few cases have been reported. The period between SAT and GD onset reportedly ranges between 1 and 8 months.³ Hoang et al⁷ presented the first known case of GD and SAT occurring simultaneously. In the present case, GD first occurred 6 months following SAT onset; in the second recurrence, the period between SAT onset and GD was only 1 month. The patient tested negative for TRAb during the first assessment of SAT; however, she became positive for TRAb the second time, during which antibodies were assessed. Therefore, we concluded that GD did not occur simultaneously with SAT.

A damaged thyroid tissue may lead to the release of antigens. Therefore, we hypothesized that the destructive effect of SAT on the thyroid tissue may contribute to an increase in TRAb levels after the disease. Reportedly, SAT triggers the autoimmune system to produce TRAb and results in thyroid dysfunction in approximately 2% of patients.⁶ Thus, in our case, TRAb positivity may be attributed to SAT-induced thyroid autoimmunity, although glucocorticoid therapy for SAT might have some effects on this phenomenon. The intervals between SAT and GD episodes 1 and 2 seem to be approximately 6 months and 1 to 2 months, respectively. Since it was already exposed to an antigen of the thyroid tissue, the interval in episode 2 might have been shortened.

However, transient detection of TRAb does not always induce GD.¹ The patient had a family history of SAT but not autoimmune thyroiditis. Genetic susceptibility to both SAT and GD has been linked to HLA subtypes, whereas predisposition to SAT has been linked to *HLA-B*35* alleles.^{8–11} More recently, *HLA-B*18:01*, *DRB1*01*, and *C*04:01* have also been associated with genetic predisposition to SAT.¹² After analyzing the risk of SAT recurrence, Stasiak et al¹³ have shown that the recurrence was HLA-dependent and that the determining factor was the presence of *HLA-B*18:01* and *HLA-B*35*. In the present case, the patient had *HLA-DRB1*04:03* and **15:01*, *DQB1*03:02:01* and *06:02:01*, and *HLA-DPB1*05:01* alleles. Several studies have identified links between GD and distinct HLA alleles according to ethnicity. Although *HLA-DRB1*04:03* and **15:01*, and *DQB1*03:02:01* and *06:02:01* have not been reported to be associated with GD, *HLA-DPB1*05:01* has been associated with GD susceptibility in the Japanese population.¹⁴ Our HLA-typing results showed that this patient had HLA-associated predisposition to GD but not to SAT.

It remains unclear whether SAT can reoccur after complete recovery. In contrast, GD recurrence is common.¹ In this case, the patient might have developed SAT independently of her HLA alleles. We posit that SAT may have triggered thyroid antigen release and led to the development of GD in an individual that was already genetically predisposed to the disease. It remains unknown whether the patient has other genes linked to SAT predisposition.

In addition, we suggest that the persistently high blood levels of thyroid hormone after SAT remission are indicative of GD.

Conclusion

Based on the case presented herein, the occurrence of GD after SAT is rare and may be linked to HLA-associated genetic susceptibility to GD.

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Disclosure

The authors have no multiplicity of interest to disclose.

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