Case Report

Graves Disease Following Subacute Thyroiditis in a Chinese Man

Souad Al-Bacha, MD, Sharon Wu Lahiri, MD *

Department of Internal Medicine, Division of Endocrinology, Diabetes, Bone and Mineral Disorders, Henry Ford Health System, Detroit, Michigan

A R T I C L E   I N F O

Article history:
Received 13 August 2021
Received in revised form 6 October 2021
Accepted 11 October 2021
Available online 20 October 2021

Key words:
Graves disease
subacute thyroiditis
Chinese
HLA typing
thyroid-stimulating immunoglobulin
TSH receptor autoantibody

A B S T R A C T

Background/Objective: The development of Graves disease (GD) after subacute thyroiditis (SAT) is rare, with approximately 31 reported cases, of which only 5 occurred in men. We describe a case of GD diagnosed based on newly elevated thyroid-stimulating immunoglobulin (TSI) and thyroid-stimulating hormone (TSH) receptor autoantibody (TRAb) levels after SAT. Case Report: A 32-year-old Chinese man presented with right anterior neck pain, swelling, sore throat, cough, and fever. He had a diffuse tender goiter but no proptosis, lid lag, or stare. His TSH level was 0.03 mIU/mL (normal range [NR] 0.45-5.33 mIU/mL), serum free thyroxine (FT4) level was 2.40 ng/dL (NR 0.61-1.44 ng/dL), total triiodothyronine (TT3) level was 113 ng/dL (NR 87-178 ng/dL), TSI level was <0.10 IU/L (NR < 0.10 IU/L), and erythrocyte sedimentation rate was 21 mm/h (NR < 15 mm/h). After 7 weeks of prednisone, the symptoms resolved, FT4 level was 0.95 ng/dL, and TT3 level was 91 ng/dL. At 11 weeks after SAT onset, the TSH level was <0.01 mIU/mL, TT3 level was 257 ng/dL, FT4 level was 3.03 ng/dL, TSI level was 1.94 IU/L, then 3.42 IU/L 2 weeks later, TRAb level was 8.72 IU/L (NR < 2 IU/L), and erythrocyte sedimentation rate was 4 mm/h. After 1 month of methimazole, the FT4 level was 1.32 ng/dL and TT3 level was 110 ng/dL. Genetic testing revealed human leukocyte antigen-B35 and DRB1*15:01 positivity. Discussion: GD after SAT is thought to be due to the activation of thyroid autoimmunity induced by SAT in genetically susceptible individuals. Conclusions: This case illustrates the induction of thyroid autoimmunity after SAT, resulting in GD, supporting TSI and/or TRAB testing if hyperthyroidism recurs. The presence of HLA alleles associated with SAT and GD suggests a genetic contribution to the development of thyroid autoimmunity. © 2021 AACE. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Subacute thyroiditis (SAT) is a self-limited inflammation of the thyroid, typically followed by the return of normal thyroid function. Persistent hypothyroidism is rare, but recurrent SAT can occur in up to 20% of cases. Graves disease (GD) after SAT is rare, with only approximately 31 cases described in the literature, and has been reported to occur in <1% of patients presenting with GD or SAT in a Japanese study.2-15 Thyroid antigen release in patients with SAT is thought to trigger thyroid autoimmunity and GD.2 Certain human leukocyte antigen (HLA) genes are associated with susceptibility to either GD or SAT alone, but there are inadequate data regarding associations between specific HLA alleles and the risk of GD after SAT.16-18 Herein, we report a 32-year-old Chinese man who developed elevated thyroid-stimulating immunoglobulin (TSI) and thyroid-stimulating hormone (TSH) receptor autoantibody (TRAb) levels after SAT and was found to be positive for HLA-B35 and DRB1*15:01.

Case Report

An otherwise healthy 32-year-old Chinese man presented virtually to his primary care physician on January 19, 2021, with about a 7-day history of right anterior neck pain and swelling, sore throat, cough, fatigue, and a temperature of 37.5 °C. He reported no recent travel, exposure to ill individuals, or SARS-CoV-2 vaccination. He reported no past medical or surgical history or family history of autoimmune disease or cancer. His mother had thyroid
nODULES. Testing for SARS-CoV-2 RNA yielded a negative result, and a 7-day course of amoxicillin was prescribed. He returned virtually on January 26, 2021, because of worsening anterior neck pain, cough, chest tightness, and a fever (39°C). Chest x-ray revealed no radiographic evidence of acute cardiopulmonary process. Laboratory testing (day 1) revealed a TSH level of 0.03 mIU/mL (normal range [NR] 0.45-5.33 mIU/mL), serum free thyroxine (FT4) level of 2.40 ng/dL (NR 0.61-1.44 ng/dL), serum free triiodothyronine level of 3.9 pg/mL (NR 2.5-4.4 pg/mL), total triiodothyronine (TT3) level of 113 ng/dL (NR 87-178 ng/dL), TSI level of <0.10 IU/L (NR < 0.10 IU/L), and thyroid peroxidase antibody (TPO Ab) level of 3 IU/mL (NR < 9 IU/mL). Computed tomography of the neck showed a diffusely enlarged and heterogeneous-appearing thyroid gland. Thyroid ultrasound demonstrated a diffuse mild increase in vascularity, as determined using color flow Doppler, and estimated the thyroid size to be 50 mL in volume.

He presented in-person to the endocrinology department on February 1, 2021, with the same symptoms and a 13-pound weight loss. On physical examination, his heart rate was 123 beats/min, thyroid was diffusely enlarged and mildly tender bilaterally, and skin was warm and slightly moist. He had no proptosis, chemosis, periorbital edema, lid lag, or stare. Prednisone was initiated at 30 mg daily, propranolol 20 mg three times daily, and ibuprofen 200 to 400 mg daily was taken from day 7 to 13 until testing (day 14) revealed a C-reactive protein level of 4.3 mg/dL and TT3 level of 227 ng/dL. Methimazole at 10 mg every 6 to 8 hours were initiated. Testing (day 7) showed a FT4 level of 0.55 IU/L resulted in a sensitivity of 98.5%.20 Operating characteristic analysis of this assay found that a threshold of <0.10 IU/L yielded the criteria for SAT.11

Prednisone was taken for 7 weeks. On day 56, the FT4 level was 0.95 ng/dL, the TT3 level was 91 ng/mL, and he reported no symptoms. On day 77, testing revealed a TSH level of <0.01 mIU/mL, TT3 level of 257 ng/dL, and FT4 level of 3.03 ng/dL. He reported no neck pain or fever but noted occasional palpitations and mild heat intolerance. Prednisone was restarted for 2 days, before the treatment was changed to methimazole (day 79). The TSI level was 1.94 IU/L, increasing to 3.42 IU/L 2 weeks later. The TPO Ab level was 805 IU/mL and TRAb level was 8.72 IU/L (NR < 2 IU/L). The C-reactive protein level and ESR were 0.1 mg/dL and 4 mm/h, respectively. The 24-hour radioactive iodine uptake (RAIU) was 66.2% (NR 10%-30%), and thyroid scan showed diffuse homogeneous radiotracer uptake throughout the thyroid and pyramidal lobe. Ultrasound estimated the thyroid size to be 34 mL in volume, with an increase in vascularity—as determined using color Doppler imaging—similar to a prior study. His symptoms resolved, FT4 level was 1.32 ng/dL, and TT3 level was 110 ng/dL 1 month after starting methimazole. HLA testing revealed HLA-B35 and -DRB1*15:01 allele positivity. Testing for additional HLA variants (HLA-B*46:01, -B*18:01, -DPB1*05:01, DQB1*05:02, -DQB1*06:04, -DRB1*01, -DRB1*03:01, -DRB1*14:03, and -DRB1*16:02) yielded negative results.

**Discussion**

The diagnoses of SAT and GD in our patient were based on previously published criteria.10,11 The criteria for the diagnosis of SAT include elevated ESR and either painful and tender goiter or ultrasound findings consistent with SAT in addition to 1 or 2 additional criteria (depressed RAIU, transient hyperthyroidism, fine aspiration needle biopsy findings consistent with SAT, and absent or low titers of thyroid autoantibodies).11,13 Our patient had a painful tender goiter, elevated ESR, transient hyperthyroidism, and absent thyroid autoantibodies, fulfilling the criteria for SAT.11

GD is typically diagnosed based on the classic findings of moderate-to-severe hyperthyroidism, the presence of a symmetrically enlarged thyroid gland, and recent onset of orbitopathy.10 If this constellation of signs is absent, TRAb measurement, RAIU determination, or ultrasonography to measure thyroidal blood flow is recommended.10,12 Either TRAb or TSI measurement are the recommended initial test for GD because of their excellent sensitivity (96%-97%) and specificity (99%), cost effectiveness, and timely return of results.10 In our patient, GD diagnosis was based on the elevated TSI and TRAb levels and supported by the elevated RAU and absent ESR. The IMMULITE 2000 TSI assay (Siemens Healthcare, Llanberis, UK) was used for all TSI measurements in this case. This is an automated chemiluminescent immunosassay that uses recombinant human TSH receptors to selectively detect stimulating TRAbs.20 Receiver-operating characteristic analysis of this assay found that a threshold of 0.55 IU/L resulted in a sensitivity of 98.6% and specificity of 98.5%.20 The Kronus TRAb enzyme-linked immunosorbent assay kit (Star, Idaho) was used for the semiquantitative determination of the TRAb level in this patient. The clinical sensitivity and specificity of this assay was 85% and 100%, respectively.

![Laboratory data and treatment over time.](image)

Normal reference ranges are in parentheses. CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; FT4 – free thyroxine; TPO Ab – thyroid peroxidase antibody; TRAb – TSH receptor autoantibody; TSH – thyroid-stimulating hormone; TSI – thyroid-stimulating immunoglobulin; TT3 – total triiodothyronine.)
We identified 14 publications reporting 31 cases of GD after SAT (Table). Demographics, features used to diagnose SAT and GD, including antibody status, and genetic test results were compared. The criteria for SAT, including tender goiter and either elevated ESR and/or low RAIU, were documented in 29 of 31 cases (93.5%); histologic findings of SAT were reported in 4 of the 31 cases (13%).

Table
Graves Disease Following Subacute Thyroiditis: Summary of Case Report Data From the Literature. A Modification of the Table From Nakano et al

| Case   | Author, year, country | Sex | Age (y) | Race | SAT to GD (mo) | Elevated ESR | 24-h RAIU | Thyroid-directed auto-Ab | HLA typing |
|--------|----------------------|-----|---------|------|---------------|--------------|-----------|--------------------------|------------|
| 1      | Sheets, 1955, USA    | F   | 37      | White| 7             | Yes          | 12%       | 80%                      | SAT, GD    |
| 2      | Perloff, 1956, USA   | M   | 19      | White| 0.5          | Yes          | 13%       | 80%                      | SAT, GD    |
| 3      | …                    | …   | …       | …    | …             | …            | …         | …                        | …          |
| 4      | …                    | …   | …       | …    | …             | …            | …         | …                        | …          |
| 5      | …                    | …   | …       | …    | …             | …            | …         | …                        | …          |
| 6      | …                    | …   | …       | …    | …             | …            | …         | …                        | …          |
| 7      | Werner, 1979, USA    | F   | 50      | Black| 8            | Yes          | 12%       | 80%                      | SAT, GD    |
| 8      | Wartofsky and Schaaf, 1987, USA | F   | 34      | Black| 3            | Yes          | 12%       | 80%                      | SAT, GD    |
| 9      | …                    | …   | …       | …    | …             | …            | …         | …                        | …          |
| 10     | Fukuoka et al, 1992, Japan | F   | 45      | White| 5            | Yes          | 12%       | 80%                      | SAT, GD    |
| 11     | …                    | …   | …       | …    | …             | …            | …         | …                        | …          |
| 12     | Bartalena et al, 1996, Italy | F   | 57      | White| 4            | Yes          | 12%       | 80%                      | SAT, GD    |
| 13     | Bennedbaek et al, 1996, Denmark | F   | 49      | White| 6            | Yes          | 12%       | 80%                      | SAT, GD    |
| 14     | Gronenberger et al, 1998, France | M   | 46      | White| 5            | Yes          | 12%       | 80%                      | SAT, GD    |
| 15-20  | Iitaka et al, 1998, Japan | 1M/5F | 50 ± 9 | 5 to 48| Yes          | 12%       | 80%                      | SAT, GD    |
| 21     | Iitaka et al, 2001, Japan | M   | 45      | White| 18           | Yes          | 12%       | 80%                      | SAT, GD    |
| 22     | Wang and Renedo, USA | F   | 56      | White| 12           | Yes          | 12%       | 80%                      | SAT, GD    |
| 23     | Nakano et al, 2011, Japan | M   | 43      | White| 5            | Yes          | 12%       | 80%                      | SAT, GD    |
| 24     | …                    | …   | …       | …    | …             | …            | …         | …                        | …          |
| 25     | …                    | …   | …       | …    | …             | …            | …         | …                        | …          |
| 26     | …                    | …   | …       | …    | …             | …            | …         | …                        | …          |
| 27     | …                    | …   | …       | …    | …             | …            | …         | …                        | …          |
| 28     | …                    | …   | …       | …    | …             | …            | …         | …                        | …          |
| 29     | …                    | …   | …       | …    | …             | …            | …         | …                        | …          |

(continued on next page)
31 reported cases (26%) of GD after SAT.6-11,15 Of these 8 patients, 6 were positive for HLA-B35 and 4 were positive for HLA alleles associated with GD (HLA-BW46, -DRB1*03, and -DR3).6-9,11,15-17 Currently, there are inadequate data to determine the association between certain HLA profiles and the risk of GD after SAT, and genetic testing is not recommended as part of the evaluation of hyperthyroidism10; however, more HLA testing in these rare cases may reveal specific correlations.

With regard to demographics, 26 of the 31 reported cases (84%) were women over the age of 40 years, similar to what has been seen in cases in which GD or SAT occurs alone.1-9,11,13-15 Race was not documented in all the cases, but reports originated from many different countries. We did not find documentation of the Chinese race in any of the reported cases or any reports originating from China. To our knowledge, ours is the first reported case of GD after SAT in a Chinese man.

Conclusion

This case of SAT followed by GD in a Chinese man with HLA positivity for HLA-B35 and -DRB1*03 highlights the utility of checking the TSI and/or TRAb levels to diagnose GD in cases of recurrent hyperthyroidism after SAT. Elevated TSI and/or TRAb levels after SAT support autoimmune thyroid activation by SAT as a mechanism of GD development. Genetic factors, specifically the presence of HLA alleles associated with GD or SAT, may increase susceptibility to the development of thyroid autoimmunity after SAT; however, because of the rarity of these cases and inadequate HLA data, a correlation between this risk and specific HLA alleles cannot be made. This case adds to the few reported cases of this rare occurrence in men, provides support for the use of TSI and/or TRAb testing to detect the autoimmune activation of the thyroid and GD after SAT, and adds to the literature on HLA alleles detected in these rare cases.

Acknowledgments

The authors thank Karla Passalacqua, PhD, Henry Ford Hospital, for her editorial assistance.

Author Contributions

S.A. researched the data, contributed to writing the manuscript, and reviewed the manuscript. S.W.L. researched the data, wrote the manuscript, and reviewed and edited the manuscript. S.W.L. is the guarantor of this work and, as such, had full access to all the sections of the manuscript and references and takes responsibility for the integrity and accuracy of this paper.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Stasiak M, Lewinski A. New aspects in the pathogenesis and management of subacute thyroiditis. Rev Endocr Metab Disord. 2021;1-3.
2. Nakano Y, Kurihara H, Sasaki J. Graves’ disease following subacute thyroiditis. Tohoku J Exp Med. 2011;225(4):301–309.
3. Sheets RF. The sequential occurrence of acute thyroiditis and thyrotoxicosis. *J Am Med Assoc*. 1955;157(2):139–140.
4. Perloff WH. Thyrotoxicosis following acute thyroiditis: a report of 5 cases. *J Clin Endocrinol Metab*. 1956;16(4):542–546.
5. Werner SC. Graves’ disease following acute (subacute) thyroiditis. *Arch Intern Med*. 1979;139(11):1313–1315.
6. Wartofsky L, Schaad M. Graves’ disease with thyrotoxicosis following subacute thyroiditis. *Am J Med*. 1987;83(4):761–764.
7. Fukata S, Matsuzuka F, Kobayashi A, Hirai K, Kuma K, Sugawara M. Development of Graves’ disease after subacute thyroiditis: two unusual cases. *Acta Endocrinol (Copenh)*. 1992;126(6):495–496.
8. Bartalena L, Bogazzi F, Pecori F, Martino E. Graves’ disease occurring after subacute thyroiditis: report of a case and review of the literature. *Thyroid*. 1996;6(4):345–348.
9. Bennedsen FN, Gram J, Hegedus L. The transition of subacute thyroiditis to Graves’ disease as evidenced by diagnostic imaging. *Thyroid*. 1996;6(5):457–459.
10. Grunenberger F, Chenard MP, Weber JC, Jaech D, Schlenger JL. Relapse of Graves’ disease after subacute thyroiditis. *Thyroid*. 1998;8(8):683–685.
11. Iitaka M, Momotani N, Hisaoka T, et al. TSH receptor antibody-associated thyroid dysfunction following subacute thyroiditis. *Clinical Endocrinol*. 1998;48(4):445–453.
12. Iitaka M, Kakinuma S, Yamanaka K, et al. Induction of autoimmune hypothyroidism and subsequent hyperthyroidism by TSH receptor antibodies following subacute thyroiditis: a case report. *Endocr J*. 2001;48(2):139–142.
13. Wang X, Renedo MF. Graves’ disease occurring after hyperparathyroidism and subacute thyroiditis. *Endocr Pract*. 2004;10(6):509–511.
14. Dow A, Azer P, Yu R. Subacute thyroiditis metamorphosing into Graves’ disease. *Endocrinol Nutr*. 2014;61(3):171–172.
15. Halilgiren B, Planck T, Asman P, Lantz M. Presence of thyroid-stimulating hormone receptor antibodies in a patient with subacute thyroiditis followed by hypothyroidism and later Graves’ disease with ophthalmopathy: a case report. *Eur Thyroid J*. 2015;4(3):197–200.
16. Shin DH, Baek JC, Kim HJ, et al. HLA alleles, especially amino-acid signatures of HLA-DPB1, might contribute to the molecular pathogenesis of early-onset autoimmune thyroid disease. *PLoS One*. 2019;14(5):e0216941.
17. Chu X, Yang M, Song ZJ, et al. Fine mapping MHC associations in Graves’ disease and its clinical subtypes in Han Chinese. *J Med Genet*. 2018;55(10):685–692.
18. Yeo PP, Chan SH, Aw TC, et al. HLA and Chinese patients with subacute (De Quervain’s) thyroiditis. *Tissue Antigens*. 1981;17(2):249–250.
19. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid*. 2016;26(10):1343–1421.
20. Tozzoli R, D’Aurizio F, Villalta D, Giovannelli L. Evaluation of the first fully automated immunoassay method for the measurement of stimulating TSH receptor autoantibodies in Graves’ disease. *Clin Chem Lab Med*. 2017;55(1):58–64.