Original Article
Turk J Endocrinol Metab. 2020;24:144-148

Frequency of Thyroid Antibodies at the Diagnosis of Subacute Thyroiditis

Subakut Tiroidit Hastalığında Tanı Sırasında Tiroid Antikor Sıklığı

Muhammed Erkam SENCAR, Murat ÇALAPKULU, Davut SAKIZ*, Sema HEPSEN, Pınar AKHANLI, İlknur ÖZTÜRK ÜNSAL, Erman ÇAKAL

University of Health Sciences Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Endocrinology and Metabolism, Ankara, TURKEY
*Mardin State Hospital, Clinic of Endocrinology and Metabolism, Mardin, TURKEY

Abstract

Objective: Although subacute thyroiditis (SAT) is not an autoimmune disease, the presence of antithyroid antibodies has been reported in this disease too. This study aims to determine the frequency of antithyroid antibodies at the time of diagnosis of SAT. **Material and Methods:** Quantitative measurements of antithyroid peroxidase antibody (anti-TPO), antithyroglobulin antibody (anti-Tg), and thyroid-stimulating hormone (TSH) receptor autoantibodies (TRAb) were made in 76 patients at the diagnosis of SAT. Cytopathological examination and iodine uptake test was performed to exclude Graves' disease and Hashimoto's disease in suspected patients. Multiple multinuclear giant cells and granulomatous formations, including epithelioid histiocytes, were the cytological findings employed to support the diagnosis of SAT in suspicious cases. **Results:** The median erythrocyte sedimentation rate and C-reactive protein levels were found to be 49 mL/hour (21-130) and 54 mg/L (8-179), respectively. TSH, free T4, and free T3 levels were determined to be 0.01 mIU/L (0.003-5.2), 1.98 ng/dL (0.78-6.1) and 5.51 ng/L (3.07-14), respectively. During the initial presentation, 88% of the patients were hyperthyroid, and 9% of the patients were euthyroid. Anti-TPO and anti-Tg antibody levels were detected to be above the assay-specific cut-off in 11.8% and 10.5% of SAT patients, respectively, at the time of diagnosis. Elevated TRAb was detected in 6.6% of all SAT patients. The median anti-TPO, anti-Tg, and TRAb levels of antibody-positive patients were 55 IU/mL (38-1.078), 163 IU/mL (5.5-876), 5 IU/L (1.9-23), respectively. **Conclusion:** Although uncommon, antibody positivity can also be observed in SAT disease. This study has proved that the previous studies claiming the absence of thyroid antibodies in SAT are flawed. SAT must be considered while assessing the differential diagnosis of Graves' and Hashimoto's disease.

Keywords: Subacute thyroiditis; antithyroid peroxidase antibody; antithyroglobulin antibody; TSH receptor autoantibody

Özet

Amaç: Subakut tiroidit (SAT) otoimmün bir hastalık olmamasına rağmen antitiroid antikorlarının pozitif olabileceği literatürde bildirilmiştir. Bu çalışmanın amacı, SAT'de tanı anında antitiroid antikorlarının sıklığını belirlemektir. **Gereç ve Yöntemler:** Toplam 76 SAT hastasının antitiroid peroksidaz antikoru (anti-TPO), antitiroglobulin antikoru (anti-Tg) ve TSH reseptörü otoantikorlarının [receptor autoantibodies (TRabs)] tanı anında kantitatif ölçümleri yapıldı. Tanısı şüpheli hastalarda Graves ve Hashimoto hastalığını dışlamak için radyoiyot uptake testi ve sitopatolojik inceleme yapıldı. Sitolojik incelemede çok çekirdekli dev hücrelerin ve epiteloid histiyosit içeren granülomatöz oluşumların saptanması şüpheli vakalarda SAT tanısını desteklemek için kullanıldı. **Bulgular:** Ortalama eritrosit sedimentasyon hızı ve C-reaktif protein düzeyleri sırasıyla 49 mL/saat (21-130) ve 54 mg/L (8-179) olarak saptandı. TSH, serbest T4 ve serbest T3 düzeyleri sırasıyla 0,01 mIU/L (0,003-5,2), 1,98 ng/dL (0,78-6,1) ve 5,51 ng/L (3,07-14) olarak saptandı. İlk başvuru anında hastaların %88'i hipertiroidik, %9'u ötiroid idi. Tanı anında hastaların sırasıyla %11,8 ve %10,5'inde anti-TPO ve anti-Tg antikorlarının pozitif olduğu saptandı. Hastaların %6,6'sında TRAb pozitifliği saptandı. Antikor düzeyi pozitif olan hastaların medyan anti-TPO, anti-Tg ve TRAb seviyeleri sırasıyla 55 IU/mL (38-1.078), 163 IU/mL (5,5-876) ve 5 IU/L (1,9-23) olarak saptandı. **Sonuç:** Sık olmasa da antitiroid antikor pozitifliği SAT hastalarında da görülebilir. Bu çalışma, SAT'de tiroid antikorlarının saptanamayacağını iddia eden önceki çalışmaların hatalı olduğunu kanıtlamıştır. Bu nedenle SAT hastalığı, Graves ve Hashimoto hastalıklarının ayırıcı tanısında göz önünde bulundurulmalıdır.

Anahtar kelimeler: Subakut tiroidit; antitiroid peroksidaz antikoru; antitiroglobulin antikoru; TSH reseptörü otoantikoru

Address for Correspondence: Muhammed Erkam SENCAR, University of Health Sciences Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Endocrinology and Metabolism, Ankara, TURKEY/TÜRKİYE
Phone: +90 533 732 52 20 **E-mail:** erkamsencar@gmail.com

Peer review under responsibility of Turkish Journal of Endocrinology and Metabolism.

Received: 12 Feb 2020 **Received in revised form:** 03 May 2020 **Accepted:** 14 May 2020 **Available online:** 20 May 2020

DOI: 10.25179/tjem.2020-74287

Introduction

Subacute thyroiditis (SAT) is a rare type of thyroiditis presenting with severe neck pain, besides a tender, firm, and enlarged thyroid gland (1). Subacute thyroiditis is thought to be caused by a post-viral inflammatory process (1-3). Subacute thyroiditis is a diagnosis based on clinical and laboratory findings (4). SAT clinically presents with thyrotoxicosis, followed by a short euthyroidism phase and then a hypothyroidism phase, which is mostly transient before remission (3,4) Thyroid antibodies help differentiate SAT from Hashimoto's disease and Graves' disease. The literature presents only limited data on the frequency of antithyroid antibodies in subacute thyroiditis. Some reviews also report that subacute thyroiditis lacks thyroid antibodies, unlike Hashimoto's and Graves' disease (3,5,6). Though subacute thyroiditis is not an autoimmune disease, the release of antigens due to the destruction of the thyroid gland may increase serum antithyroid antibody concentrations (2). The main purpose of the present study was to determine the frequency of thyroid antibodies at the time of diagnosis of subacute thyroiditis.

Material and Methods

A total of 76 subjects were diagnosed with SAT at the Diskapi Yildirim Beyazit Training and Research Hospital, Department of Endocrinology and Metabolism, between January 2019 and December 2019. SAT diagnosis was made based on clinical findings (severe neck pain, a tender, stiff and enlarged thyroid gland, and fever), thyroid ultrasonography findings, and laboratory test results including thyroid function tests (TFT), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Cytopathological examination and iodine uptake test was performed to exclude Graves' and Hashimoto's disease in suspected patients. The cytopathological findings of multiple multinuclear giant cells and granulomatous formations, including isolated epithelioid histiocytes, supported the diagnosis of SAT in suspicious cases. While significant radioactive iodine uptake is expected in Graves's disease, low radioactive iodine uptake by the thyroid backs the diagnosis of SAT. Thyroid ultrasound suggestive of SAT typically shows hypoechoic areas with blurred borders and reduced vascularization while that of Graves' disease demonstrates diffusely extended hypoechogenicity and marked hypervascularity. At the time of diagnosis, the TSH receptor autoantibody (TRAb) test, antithyroid peroxidase antibody (anti-TPO) test, and anti-thyroglobulin antibody (anti-Tg) test were performed in all the patients in addition to the TFT, ESR, and CRP.

Subjects were excluded from the study if they were diagnosed with Hashimoto's thyroiditis or Graves' disease, had any known thyroid diseases or had previously used levothyroxine or antithyroid drugs. TFT and thyroid antibodies were evaluated using an automated, direct chemiluminescent immunoassay (Beckman Coulter, CA, USA). Normal ranges were defined as TRAb: 0-1.5 IU/L, anti-TPO: 0-35 IU/mL, anti-Tg: 0-4 IU/mL, TSH: 0.38-5.33 mIU/L, fT3: 2.28-4 ng/L, and fT4: 0.60-1.25 ng/dL. The study was conducted following the Declaration of Helsinki. Approval of the institutional review board was obtained from the local ethics committee (declaration no: 57/03, approval date: 17/12/2018). Informed consent was obtained from all the study participants.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 21, Chicago, USA). Categorical data were summarized as frequencies and percentages (%). Continuous factors with normal distribution were defined as mean±standard deviation, while non-normally distributed factors were defined as median (range) values.

Results

A total of 76 SAT patients, including 54 (71%) females and 22 (29%) males, were evaluated to determine the thyroid antibody frequency. The mean age of subjects was 42 (20-75). The median ESR and CRP levels were obtained to be 49 mL/hour (21-130) and 54 mg/L (8-179), respectively. TSH, fT4, and fT3 levels were found to be 0.01 mIU/L (0.003-5.2), 1.98 ng/dL (0.78-6.1), and 5.51 ng/L (3.07-14), respectively. In the initial presentation, 88% of the study participants were hyperthyroid, and 9% of

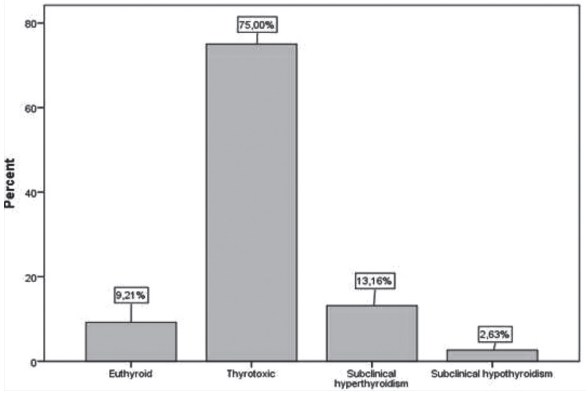

Figure 1: Clinical conditions of patients at the time of diagnosis.

the patients were euthyroid (Figure 1). Subclinical hypothyroidism was determined in two patients at the time of diagnosis. Mean anti-TPO, anti-Tg, and TRAb levels were 2.4 IU/mL (0.1-1078), 0.9 IU/mL (0.9-876), and 0.3 IU/L (0.1-23.7), respectively at the onset of SAT. At the time of diagnosis, anti-TPO and anti-Tg antibody levels were detected to be above the assay-specific cut-off in 9 (11.8%), and 8 (10.5%) SAT patients, respectively (Figure 2). Both anti-TPO and anti-Tg antibodies were positive in 4 subjects. Positive TRAb level was detected in 5 (6.6%) SAT patients; these patients were excluded from Graves' disease by cytological confirmation and iodine uptake test (Figure 3). The median anti-TPO, anti-Tg, and TRAb levels of patients with antibody levels above the assay-specific cut-off were 55 IU/mL (38-1078), 163 IU/mL (5.5-876), and 5 IU/L (1.9-23), respectively.

Discussion

As subacute thyroiditis manifests with thyrotoxicosis, the laboratory findings may be misunderstood for Graves' disease. Acute exacerbation of chronic thyroiditis can also be clinically confused with SAT (7). Thyroid antibodies are valuable in differentiating SAT from Hashimoto's disease and Graves' disease. Some reviews and textbooks state that circulating thyroid antibodies are absent or present in low amounts in subacute thyroiditis (3,5). The absence of thyroid antibodies is thought to be one of the typical signs of SAT. The present study determined anti-TPO and anti-Tg positivity to be >10% in SAT patients. Except for a few patients, antibody titers were not as high as that in Hashimoto's disease. The limitation of this study lies in the time interval between the onset of symptoms and the diagnosis of SAT, which is not known. Although all thyroid antibodies were measured at the time of diagnosis, it was not possible to speculate about the time gap in antibody occurrence. Recent studies have shown that the rate of antibody positivity may be higher than that deliberated at the time of diagnosis. Stasiak et al. also reported that antibodies can be positive in one-third of SAT patients and that the incidence of patients with atypical findings is gradually increasing (8). Contrary to the previous studies, Stasiak also found that TRAb may be positive in 6% of these patients (8); this is in accordance with the present study results, which observed TRAb positivity in approximately 6.6% of all SAT patients. In a study conducted to determine the antibody prevalence in SAT patients, the anti-Tg positivity rate was determined to be 52%, while anti-TPO positivity was 15.6%

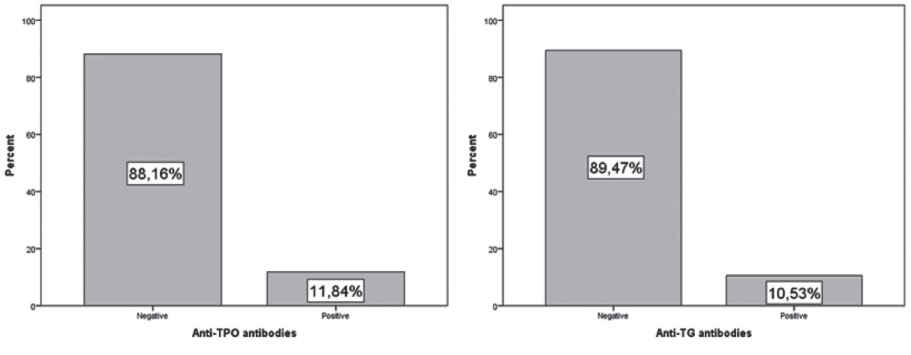

Figure 2: Frequencies of anti-TPO and anti-TG at the time of diagnosis in subacute thyroiditis.

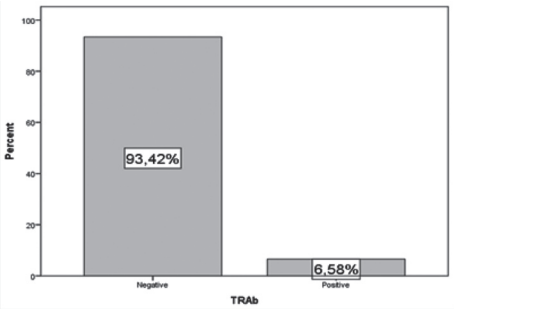

Figure 3: Frequencies of TRAb at the time of diagnosis in subacute thyroiditis.

(9). Nishihara also determined that anti-Tg antibody titers decreased and disappeared over time after SAT resolution. Anti-Tg positivity in SAT patients can be attributed to the antigens that arise due to thyroid damage in the early phase of SAT. Latrofa showed that the Anti-Tg epitope pattern in SAT is different from that in Hashimoto's disease and that the anti-Tg release in SAT disease is transient, with no autoimmune significance (10). It has been hypothesized that patients with autoimmune thyroid disease who have anti-TPO positivity may also develop subacute thyroiditis (8,11) Recently published studies have established that the clinical importance of overlapping of SAT and autoimmune thyroid disease is that autoimmunity has been demonstrated to increase the rate of permanent hypothyroidism after SAT (12-16). Until recently, an increase in the level of TRAb, just like anti-TPO and anti-Tg, was not expected in patients with SAT. Previous studies have proved that the release of thyroid antigens after SAT can stimulate TRAb-producing B cells or helper T cells, which may play a role in thyroid dysfunction after SAT disease (17,18). The literature reports incidences of the development of Graves' disease after SAT and of the co-existence of TRAb with SAT (19-22). Thus, the view that thyroid antibodies are absent in SAT disease is now unreasonable. Hence, antibody-positive SAT patients must be followed up for chronic thyroiditis and Graves' disease.

Conclusion

Although uncommon, antibody positivity can also be observed in SAT disease and must be considered in the differential diagnosis of Graves' and Hashimoto's diseases.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Muhammed Erkam Sencar, Murat Çalapkulu; Design: Muhammed Erkam Sencar, Murat Çalapkulu; Control/Supervision: Erman Çakal, İlknur Öztürk Ünsal; Data Collection and/or Processing: Muhammed Erkam Sencar, Murat Çalapkulu, Pınar Akhanlı, Sema Hepsen, Davut Sakız; Analysis and/or Interpretation: Muhammed Erkam Sencar, Murat Çalapkulu, Davut Sakız; Literature Review: Muhammed Erkam Sencar; Writing the Article: Muhammed Erkam Sencar; Critical Review: Erman Çakal; References and Fundings: Muhammed Erkam Sencar; Materials: Muhammed Erkam Sencar.

References

1. Volpé R. 7 Subacute (de Quervain's) thyroiditis. Clin Endocrinol Metab. 1979;8:81-95. [Crossref]
2. Volpé R, Row VV, Ezrin C. Circulating viral and thyroid antibodies in subacute thyroiditis. J Clin Endocrinol Metab. 1967;27:1275-1284. [Crossref] [PubMed]
3. Hennessey Jv. Subacute thyroiditis. In: Feingold KR, Anawalt B, Boyce A, et al., eds. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2020 Feb 11]. [PubMed]
4. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN, Walter MA. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016;26:1343-1421. [Crossref] [PubMed]
5. Shrestha RT, Hennessey J. Acute and subacute, and Riedel's thyroiditis. In: Feingold KR, Anawalt B, Boyce A, et al., eds. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2020 Feb 11]. [PubMed]

6. Nishihara E, Ohye H, Amino N, Takata K, Arishima T, Kudo T, Ito M, Kubota S, Fukata S, Miyauchi A. Clinical characteristics of 852 patients with subacute thyroiditis before treatment. Intern Med. 2008;47:725-729. [Crossref] [PubMed]
7. Kon YC, DeGroot LJ. Painful Hashimoto's thyroiditis as an indication for thyroidectomy: clinical characteristics and outcome in seven patients. J Clin Endocrinol Metab. 2003;88:2667-2672. [Crossref] [PubMed]
8. Stasiak M, Michalak R, Stasiak B, Lewinski A. Clinical characteristics of subacute thyroiditis is different than it used to be - current state based on 15 years own material. Neuro Endocrinol Lett. 2019;39:489-495. [PubMed]
9. Nishihara E, Amino N, Kudo T, Kohsaka K, Ito M, Fukata S, Nishikawa M, Nakamura H, Miyauchi A. Moderate frequency of anti-thyroglobulin antibodies in the early phase of subacute thyroiditis. Eur Thyroid J. 2019;8:268-272. [Crossref] [PubMed] [PMC]
10. Latrofa F, Ricci D, Montanelli L, Altea MA, Pucci A, Pinchera A, Vitti P. Thyroglobulin autoantibodies of patients with subacute thyroiditis are restricted to a major B cell epitope. J Endocrinol Invest. 2012;35:712-714. [Crossref] [PubMed]
11. Jabeen S, Masood MQ. Subacute thyroiditis evolving into Hashimoto thyroiditis. AACE Clin Case Rep. 2018;4:e297-e299. [Crossref]
12. Hnilica P, Nyulassy S. Plasma cells in aspirates of goitre and overt permanent hypothyroidism following subacute thyroiditis. Preliminary report. Endocrinol Exp. 1985;19:221-226. [PubMed]
13. Tikkanen MJ, Lamberg BA. Hypothyroidism following subacute thyroiditis. Acta Endocrinol (Copenh). 1982;101:348-353. [Crossref] [PubMed]
14. Gozariu L, Stroe M, Vladutiu T, Yepez-Escobar NG, Simionescu L, Szantay I, Dumitru E, Florescu O. Late hypothyroidism following subacute thyroiditis. Exp Clin Endocrinol. 1986;87:48-52. [Crossref] [PubMed]
15. Sencar ME, Calapkulu M, Sakiz D, Hepsen S, Kus A, Akhanli P, Ozturk Unsal I, Kizilgul M, Ucan B, Ozbek M, Cakal E. An evaluation of the results of the steroid and non-steroidal anti-inflammatory drug treatments in subacute thyroiditis in relation to persistent hypothyroidism and recurrence. Sci Rep [Internet] 2019 [cited 2020 Feb 11];9(1). [Crossref] [PubMed] [PMC] [Link]
16. Görges J, Ulrich J, Keck C, Müller-Wieland D, Diederich S, Janssen O. Long-term outcome of subacute thyroiditis. Exp Clin Endocrinol Diabetes. Off J Ger Soc Endocrinol Ger Diabetes Assoc. 2019 Sep 23. [Crossref] [PubMed]
17. Iitaka M, Momotani N, Hisaoka T, Noh JY, Ishikawa N, Ishii J, Katayama S, Ito K. TSH receptor antibody-associated thyroid dysfunction following subacute thyroiditis. Clin Endocrinol (Oxf). 1998;48:445-453. [Crossref] [PubMed]
18. Fatourechi V, Aniszewski JP, Fatourechi GZE, Atkinson EJ, Jacobsen SJ. Clinical features and outcome of subacute thyroiditis in an incidence cohort: Olmsted County, Minnesota, study. J Clin Endocrinol Metab. 2003;88:2100-2105. [Crossref] [PubMed]
19. Wartofsky L, Schaaf M. Graves' disease with thyrotoxicosis following subacute thyroiditis. Am J Med. 1987;83:761-764. [Crossref] [PubMed]
20. Werner SC. Graves' disease following acute (subacute) thyroiditis. Arch Intern Med. 1979;139:1313-1315. [Crossref] [PubMed]
21. 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;126:495-496. [Crossref] [PubMed]
22. Hallengren B, Planck T, Åsman 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;4:197-200. [Crossref] [PubMed] [PMC]