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Araştırma Makalesi / Research Article

A Single-Center Experience in the Diagnosis and Treatment of Subacute Thyroiditis: Should Steroids Always Be the First Choice?

Subakut Tiroidit Tanı ve Tedavisinde Tek Merkez Deneyimi: Steroidler Her Zaman İlk Seçenek mi Olmalıdır?

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Abstract

We aimed to evaluate the clinical and laboratory findings of our patients with subacute thyroiditis (SAT) and their responses to the treatments given. Twenty SAT patients and 31 healthy controls were included in this retrospective case-control study. The clinical and laboratory data were obtained from the file records. The patient group consisted predominantly of women. The thyroid function tests and acute phase reactants of the patient group were different than the controls, as expected. The platelet count and alkaline phosphatase levels were found to be significantly higher in the patient group. Remission was achieved in 17 patients with non-steroidal anti-inflammatory drug (NSAID) treatment, five of the patients were administered steroid treatment in another center, and switched to NSAIDs by us. Only one patient switched from NSAIDs to steroids. Two patients were switched to acetylsalicylic acid treatment due to moderate transaminase elevation. One of the patients was in the 16th week of pregnancy and took NSAID treatment due to her appropriate trimester. Remission was achieved in all patients with the treatments we administered, and no recurrence was observed in any patient. SAT may be encountered by clinicians from different specialties in daily practice. Referral of the patient to an internist or an endocrinologist is important in terms of timely diagnosis and right treatment. Since SAT shows a self-limiting feature, clinicians should not be in a hurry to administer steroids, NSAID option should always be considered.

Keywords: Subacute thyroiditis; non-steroidal anti-inflammatory drug treatment; permanent hypothyroidism; acetylsalicylic acid; pregnancy

Özet

Subakut tiroiditli (SAT) hastalarımızın klinik ve laboratuvar bulgularını ve verilen tedavilere yanıtlarını değerlendirmeyi amaçladık. Bu retrospektif vaka kontrol çalışmasına 20 SAT hastası ve 31 sağlıklı kontrol dahil edildi. Klinik ve laboratuvar veriler dosya kayıtlarından elde edildi. Hasta grubu ağırlıklı olarak kadınlardan oluşuyordu. Hasta grubunun tiroid fonksiyon testleri ve akut faz reaktanları beklendiği üzere kontrol grubundan farklıydı. Hasta grubunda trombosit sayısı ve alkalen fosfataz düzeyleri anlamlı olarak yüksek bulundu. Non-steroid antiinflamatuar ilaç (NSAİİ) tedavisi ile 17 hastada remisyon sağlandı, hastaların beşine başka bir merkezde steroid tedavisi başlanmıştı ve tarafımızca NSAİİ'lere geçildi. Sadece bir hasta NSAİİ tedaviden steroide geçti. İki hastada orta derecede transaminaz yüksekliği nedeniyle asetilsalisilik asit tedavisine geçildi. Hastalardan biri gebeliğinin 16. haftasındaydı ve uygun trimester nedeniyle NSAİİ tedavisi aldı. Uyguladığımız tedaviler ile tüm hastalarda remisyon sağlandı ve hiçbir hastada nüks görülmedi. SAT, günlük pratikte farklı uzmanlıklardan klinisyenlerin karşısına çıkabilir.Hastanın iç hastalıkları veya endokrinoloji uzmanına sevki zamanında tanı ve doğru tedavi açısından önemlidir. SAT kendi kendini sınırlayıcı bir özellik gösterdiğinden klinisyenlerin steroid tedavisi konusunda aceleci olmaması gerekir, NSAİİ tedavi seçeneği her zaman düşünülmelidir.

Anahtar Kelimeler: Subakut tiroidit; non-steroid antiinflamatuar ilaç tedavisi; kalıcı hipotiroidi; asetilsalisilik asit; gebelik

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1. Introduction

Subacute thyroiditis (SAT) is a self-limiting inflammatory disease of the thyroid gland. Its prevalence has been reported as 24-35/100000 (1,2). The diagnosis is made by clinical features, and laboratory and imaging studies. In cases where the diagnosis is uncertain, fine needle aspiration biopsy (FNAB) shows infiltration with neutrophils, lymphocytes, histiocytes, and giant cells, deterioration in the structure of thyroid follicles, and necrosis in thyroid follicular cells. However, the FNAB is generally rarely used. After the thyroiditis resolves fibrosis may occur, but gland histology mostly returns to normal (3).

It is thought that SAT is not associated with thyroid autoimmunity. Human leukocyte antigen (HLA)-B*35 positivity had been found higher in patients with SAT than in the general population, thus it can be said that cellular immunity is predominant in SAT (4). In the etiology of the disease, it is thought that viral antigens or antigens resulting from virus-caused tissue damage bind to the HLA-B*35 molecule in macrophages, and cytotoxic T lymphocytes are activated thereafter. Thyroiditis is triggered when activated cytotoxic T lymphocytes target thyroid follicle cells with similar antigenic structure. Histopathological absence of viral inclusion bodies in the thyroid tissue suggests immunological damage rather than direct viral invasion (3).

Inflammation of the thyroid gland in SAT causes damage to the thyroid follicles and proteolysis of the thyroglobulin stored in the follicles. As a result, uncontrolled large amounts of thyroxine (T4) and triiodothyronine (T3) enter the systemic circulation and cause thyrotoxicosis. The state of hyperthyroidism continues until the thyroglobulin stores are depleted, and because of the high thyroid hormone concentration in the peripheral circulation, thyrotropin (TSH) is suppressed by the feedback mechanism, and new hormone synthesis pauses. As the inflammation subsides, the thyroid follicles regenerate and thyroid hormone synthesis and release begin again. Before thyroid hormone secretion returns to normal, there may be a transient period of hypothyroidism and associated increased TSH secretion. In addition, hypothyroidism may be permanent in 15% of the patients (1,5).

The patients' complaints at presentation are mostly neck pain, tenderness in the thyroid lodge, and symptoms related to thyrotoxicosis. Fatigue, weakness, anorexia, and myalgia are common. Usually, both thyroid lobes are affected, but unilateral involvement can also be seen. In some patients, the inflammation may start on one side and then spread to the other side. About half of the patients have symptoms and signs of hyperthyroidism, and fever may also be present. In addition, an increased erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level is typical in laboratory investigation. A low uptake of radioiodine in the scintigraphic evaluation helps confirm the diagnosis. Thyroid ultrasonography (USG) may be useful in distinguishing cystic and/or solid lesions in clinically atypical patients. Demonstration of decreased blood flow during the hyperthyroid phase of SAT with color Doppler sonography is very useful in distinguishing it from Graves' disease (2,3,6). Patients' complaints at the beginning can be confusing for the clinician, and if the preliminary diagnosis of SAT does not come to mind, it can easily be missed, and the patients could take unnecessary medication. The main element of the treatment is non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), or corticosteroid drugs to suppress inflammation. Also, antithyroid treatment is useless in SAT, so if the etiology of hyperthyroidism in a patient is not well defined it can result in unnecessary antithyroid use. In the treatment period, the patients should be well managed in terms of the effectiveness of the treatments and the problems encountered during the treatment.

In this study, we aimed to evaluate the clinical and laboratory findings of patients presenting with SAT and their responses to different treatments given.

2. Materials and Methods

Study population

The current study is a retrospective observational study. Twenty patients with SAT, diagnosed in the Internal Medicine and Endocrinology outpatient clinics, and 31 healthy control subjects were included. The demographic characteristics of the patients, their complaints at presentation, conditions that cause delay in diagnosis, laboratory and imaging tests, treatments given, response to treatment, relapse, and permanent hypothyroidism situations were evaluated from the file records. In addition, the laboratory findings of the patients at admission were compared with the data of the healthy control group.

The study was approved by the Eskisehir Osmangazi University Ethics Committee (Approval No: 40, dated 15 Feb 2022). The study was carried out in accordance with the statement of the Helsinki Declaration. Informed consent was obtained from each participant.

Laboratory measurements

Complete blood count parameters were determined on a Sysmex XN 9100 (Sysmex Corporation, Kobe, Japan) hematology analyzer. Erythrocyte sedimentation rate (ESR) was studied in a fully automated Vacuplus ESR-120 (Ankara, Turkey) analyzer by the Westergren method. Serum C-reactive protein (CRP) levels were measured by immunoturbidimetric method, thyrotropin (TSH), free triiodothyronine (fT3), free thyroxine (fT4), anti-thyroglobulin antibodies (TgAb), and anti-thyroid peroxidase antibodies (TPOAb) were analyzed by electrochemiluminescence immunoassay (ECLIA) in a Cobas 8000 (c702 and e801) autoanalyzer (Roche Diagnostics, Mannheim, Germany).

Statistical Analysis

Statistical analyses of the data were performed with the IBM SPSS Statistics 21.0 package program. The relevance of data to normal distribution was surveyed with the Shapiro-Wilk test. Continuous data were presented as mean± standard deviation. Categorical data were presented as percentage (%) values. Between-group comparisons of normally distributed continuous variables were made with Student's t-test, and non-normally distributed variables with the Mann-Whitney U test. For the categorical variables, Fisher's exact test was used. P values lower than 0.05 were considered statistically significant.

3. Results

The patient group consisted of 5 men (25%) and 15 women (75%), and the control group consisted of 8 men (25.8%) and 23 women (74.2%). The mean ages of the groups were 44.9±8.22 and 44.3±11.17, respectively. There were no differences between the groups in terms of age and gender distribution ($p>0.05$ for both). Serum TSH, fT4, fT3, ESR, and CRP values in the patient group were significantly different from the control group depending on the SAT diagnosis. In the comparison of thyroid autoantibodies, no difference was found between the groups in terms of TgAb and TPOAb positivity.

While there was no difference between the groups in terms of leukocyte count and leukocyte subgroups in the evaluation of hemogram parameters, the platelet count was found to be significantly higher in the patient group than in the control group. In biochemical tests, alanine aminotransferase (ALT) levels were similar between groups, while alkaline phosphatase (ALP) levels were found to be significantly higher in the patient group than in the control group. There was no difference between the groups in terms of 25-hydroxy vitamin D levels. The comparison of demographic characteristics and laboratory parameters of the patient and control groups is given in Table 1.

Table1. The demographic characteristics and laboratory parameters of the patient and control groups

	Patients (n:20)	Healthy Controls (n: 31)	p
Age (year)	44.9±8.22	44.3±11.17	>0.05
Gender (male/female)	5/15	8/23	>0.05
TSH (uIU/mL)	0.05±0.014	1.66±0.5	**<0.001**
fT3 (pg/mL)	6.77±3.86	3.24±0.14	**<0.001**
fT4 (ng/dL)	3.84±1.6	1.19±0.17	**<0.001**
ESR (mm/h)	70.1±20.3	12.5±5.4	**<0.05**
CRP (mg/L)	54.4±14.2	1.2±0.72	**<0.001**
TPOAb positivity	3/20	1/31	>0.05
TgAb positivity	6/20	5/31	>0.05
Leukocyte (10^3/uL)	7.95±2.99	7180±2200	>0.05
Thrombocyte (10^3/uL)	355±107	272±74	**<0.01**
ALT (U/L)	25±14	21±14	>0.05
ALP (U/L)	91.3±29.3	59±33.8	**<0.001**
25-hydroxy vitamin D (ng/ml)	23±17	16.4±6.6	>0.05

**TSH: thyrotropin, fT3: free triiodothyronine, fT4: free thyroxine, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, TPOAb: anti-thyroid peroxidase antibodies, TgAb: anti-thyroglobulin antibodies, ALT: alanine aminotransferase, ALP: alkaline phosphatase*

When we evaluated the treatments our patients had, remission was achieved in 12 patients with NSAID treatment. Six of our patients received steroid treatment. 5 of these patients were given steroid treatment in another center and applied to our clinic with SAT activation. NSAID treatment was administered to these patients, steroid treatment was discontinued, and no recurrence was observed in the follow-up after remission was achieved. In one of our patients, NSAID was given initially, but due to severe symptoms while using NSAIDs, it was necessary to switch to steroid therapy. No recurrence was observed in the follow-up of this patient after remission was achieved with steroids and treatment was discontinued. Moderate elevation of transaminases occurred in two of the patients treated with NSAIDs, and therefore remission was achieved by switching to ASA treatment.

One of our patients was in the 16th week of pregnancy at the time of admission. After diagnosing this patient with SAT, NSAID treatment was administered due to the appropriateness of the patient's trimester for safe use, and it was immediately discontinued after symptomatic improvement was achieved. No obstetric problems were encountered in the peripartum and postpartum follow-ups of the patient who gave birth at term. The patient is still being followed as euthyroid without recurrence.

The mean time from symptom onset to remission of the patients was 52 days.

4. Discussion

In this study, we compared the laboratory characteristics of our 20 SAT patients with the control group and evaluated the treatments and treatment responses of the patients. SAT is a rare thyroid disease, but it is the leading cause of painful thyrotoxicosis. The most important symptoms are pain in the thyroid lodge in the neck and tenderness on palpation. Since SAT is not a very common disease, the probability of misdiagnosis is high. In these cases, patients presenting with SAT findings can be treated with empirical antibiotics with a preliminary diagnosis of a bacterial infection or get treatment due to tachycardia (5,6). All of our patients had anterior neck pain. In 20% of our patients, there was a history of empirical antibiotic therapy before the diagnosis of SAT was clear. It was observed that these patients could not be relieved with the empirical treatment given and applied to our clinic which is a tertiary center. 15% of our patients were those treated with tachycardia and referred to us with newly diagnosed hyperthyroidism while being investigated. In summary, 35% of the patients had delays in the diagnoses and treatments because the diagnosis of SAT was not considered.

In the laboratory evaluation, thyroid function tests, ESR, and CRP levels of our patients were found to be consistent with SAT, and different compared to the control group. When thyroid autoantibodies were examined, TPOAb was positive in 15% of the patient group, and 3% in the control group; TgAb was positive in 30% of the patient group and 16% in the control group. Although there was no statistically significant difference between the groups in terms of autoantibody positivity, positivity rates were higher in the patient group. Transient positivity in thyroid autoantibodies can be seen in SAT, as there is antigenic stimulation with the destruction of thyroid follicles (7). In a recently published study, it was revealed that most of these antibodies are of the IgM type and increase the thyroglobulin clearance, and show a protective feature against the formation of a permanent autoimmune thyroid response (8). Based on this point, it can be predicted that the risk of developing permanent hypothyroidism may be lower in SAT patients who develop a transient autoantibody response.

While no difference was found between the patient and control groups in terms of leukocyte count and leukocyte subgroups in hemogram evaluations, the platelet count, another hemogram parameter indicating inflammation, was found to be significantly higher in the patient group than in the control group. In inflammation, platelet count increases probably secondary to the expansion of megakaryocyte number due to inflammatory cytokines (9). We evaluated the platelet elevation in our patients in favor of reactive thrombocytosis.

ALP levels of our patients were significantly higher than the control group. Thyroid hormone receptors are abundant on osteoblast-like cells and stimulate late expression of receptor activator of nuclear factor kappa-B ligand (RANKL) on cell surfaces. RANKL on osteoblasts binds to the RANK receptor expressed on osteoclast progenitor cells and induces their differentiation into multinucleated osteoclasts. This leads to increased bone resorption, followed by bone formation. ALP is an ectoenzyme that binds to the cell membrane and is released into the bloodstream in response to various stimuli (10). An in vitro study showed that T3 has a stimulating effect on membrane-bound ALP release by osteoblastic cells (11). Although more significant ALP elevation is expected in Graves' disease, we associated the elevation of the ALP levels of the patients with thyrotoxicosis in our study.

Vitamin D deficiency is quite common in endocrine diseases and its replacement is considered to have a beneficial effect (12). In a study conducted with patients with SAT, vitamin D levels were found to be low (13). In the current study, we could not find a statistically significant difference between vitamin D levels in the comparison of the patient and control groups.

Treatment of patients with SAT should be directed towards relieving the pain and the tenderness in the thyroid lodge; and improving symptoms of hyperthyroidism, if present. To date, there are no randomized controlled trials evaluating optimal treatment in SAT. Treatment strategies are based on observational data and clinical experience (3). While some patients do not require treatment, clinical relief can be achieved with NSAID or ASA treatment in mild cases (14). If initial treatment is not sufficient or severe symptoms occur, it may be necessary to switch to steroid therapy (15). With steroid treatment, symptoms are usually relieved within the first 24 hours, but the course of the disease does not change. The inflammatory response is suppressed, but the pathological event continues subclinically. There are different treatment protocols with high or low steroid doses (16). Re-exacerbation can be seen after discontinuation or dose-reduction of steroid treatment in 20% of patients (17). In the event of an exacerbation, it is recommended to increase the dose of steroid therapy to the initial dose or to the previous dose at which the patient's symptoms do not recur. Such situations result in the patient becoming dependent on steroids for a long time. In a study evaluating the recurrence rate with NSAID and steroid use, the total recurrence rate was found 19.8%, and recurrences were observed more frequently in patients receiving only steroid therapy than in patients treated

with NSAID only (23% vs. 10.5% p:0.04) (18). Five of our patients had been initiated steroid treatment in another center and they applied to us because of the exacerbation of the disease after the reduction of the steroid dose. Since their symptoms were not very severe, we tapered and discontinued steroid treatment and gave NSAIDs to these patients during the exacerbation period. Symptom control was achieved in approximately 2 weeks in these patients. Only one of our patients received steroid therapy because of severe symptoms and insufficient control with NSAID therapy. We did not detect exacerbation or recurrence in the 1-year period in any of our patients.

While receiving NSAID treatment two of our patients developed moderate transaminase elevation. They were switched to ASA therapy, and after that, both patients' transaminases returned to normal and did not rise again. Although it is not preferred in the first place in providing symptom control, ASA should also be kept in mind in the management of SAT. In the initial phase of thyrotoxicosis, beta-adrenergic blockers are useful in symptomatic treatment. Since three of our patients had adrenergic symptoms, we also gave propranolol treatment to these patients.

In the follow-up of SAT patients, thyroid function tests should be monitored every two to eight weeks to confirm resolution of hyperthyroidism and subsequent return of thyroid function to normal, and to detect possible development of hypothyroidism. The mean time to remission in our patients was 52 days. If the patients enter the hypothyroid phase after acute inflammation, administration of thyroid hormones may be necessary. Due to the high incidence of transient hypothyroidism, it should not be thought that levothyroxine replacement therapy should be continued for life. During the follow-ups, five of our patients developed hypothyroidism, and levothyroxine replacement was started. Two of these patients were those who switched to NSAID treatment by us after receiving steroid treatment from an external center, and three of them were those who only used NSAIDs in the treatment. In the follow-ups, the need for levothyroxine disappeared in two of these five patients. Statistical comparison was not made because the number of samples was small between the groups in terms of the frequency of development of permanent hypothyroidism in patients receiving NSAID or steroid treatment. In recent years, studies have been published showing that persistent hypothyroidism is more common in SAT patients receiving steroid therapy (18). In a retrospective study of 252 patients with SAT, it was concluded that 5.9% of them developed permanent hypothyroidism, and all of them had bilateral hypoechogenic areas on thyroid ultrasound at first admission, which may be a useful prognostic marker for the development of potential thyroid dysfunction after SAT (19). Bilateral involvement was present in 65% of our patients. On the other hand, 80% of the patients who developed permanent hypothyroidism had bilateral involvement. Since the number of patients was small, a statistical comparison could not be made.

We diagnosed one of our patients with SAT at the 16th week of pregnancy. The patient had anterior neck pain, hyperthyroidism, elevated acute phase response, and classical ultrasonographic findings. Thyroid scintigraphy was not performed because there was no hesitation in the diagnosis and it was contraindicated in pregnancy. In the literature, there are case reports stating that treatment-free follow-up, or treatment with paracetamol or steroids (20). We started NSAID treatment, which was safe for our patient during her current gestational week. After symptomatic relief, we terminated the treatment in the 3rd week. Thyroid functions returned to normal in the 5th week after the initiation of treatment, and the patient did not have a recurrence during her pregnancy. No obstetric problems were encountered in the peripartum and postpartum follow-ups of the patient who gave birth at term. She is still being followed as euthyroid without recurrence.

In conclusion, although SAT is not a very common disease, it may be encountered by clinicians from different specialties in daily practice. The correct interpretation of the symptoms and the referral of the patient to an internist or an endocrinologist by the clinicians are important in terms of timely diagnosis of the patient and not being exposed

to unnecessary treatments. We think that clinicians should not act in a rush in initiating steroid therapy in order to provide rapid symptomatic relief in patients after the diagnosis of SAT. Since SAT shows a self-limiting feature, this will be an important approach to protect the patient from steroid dependency and side effects due to long-term steroid use, as well as the risk of recurrence, which has been demonstrated by previous studies. Internal medicine and endocrinology specialists have important duties in this regard.

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