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Diagnosis and treatment of subacute thyroiditis - a review of the literature

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Abstract

Introduction:

Subacute thyroiditis (SAT) is an inflammatory condition of the thyroid with characteristic presentations and clinical courses. The pathogenesis and determinants of the clinical course were unclear for many decades. The last few years have brought many clinically significant new data on the epidemiology, pathogenesis and management of subacute thyroiditis. The diagnosis is based on clinical presentation, laboratory tests (ESR, TSH, antithyroid antibodies), imaging tests (thyroid ultrasound, thyroid scintigraphy) and cytological tests. Taking into account all the new aspects of subacute thyroiditis pathogenesis and of its clinical course, the new - modified - criteria of subacute thyroiditis diagnosis have been proposed.

Aim of the study:

In this review, we provide a comprehensive overview of the current knowledge regarding subacute thyroiditis, including its epidemiology, pathophysiology, diagnostic methods, and the existing treatment options.

Brief description of the state of knowledge:

Many cases of subacute thyroiditis follow an upper respiratory viral illness, which is thought to trigger an inflammatory destruction of thyroid follicles. In most cases, the thyroid gland spontaneously resumes normal thyroid hormone production after several months. The most characteristic laboratory finding is a high erythrocyte sedimentation rate (ESR). C-reactive protein and white blood count (WBC) are also elevated in many cases. Anti-thyroid antibodies are believed to be usually normal. The ultrasound (US) pattern of subacute thyroiditis includes hypoechoic and heterogeneous areas with blurred margins, poorly vascularized on color Doppler. Treatment with high-dose acetylsalicylic acid or nonsteroidal anti-inflammatory drugs is directed toward relief of thyroid pain. It has been noticed that patients with a diagnosis of subacute thyroiditis visit more other clinics and receive antibiotics unnecessarily.

Conclusions:

Due to the high risk of incorrect diagnosis of subacute thyroiditis current subacute thyroiditis diagnostic criteria should be used. The diagnosis of subacute thyroiditis is frequently delayed, and misdiagnosis can result in unnecessary antibiotic use. Physicians should increase their awareness of subacute thyroiditis recognition by constantly updating their knowledge.

Keywords: thyroiditis; De Quervain’s thyroiditis; subacute thyroiditis; SAT; inflammation

Introduction

Thyroiditis is defined as an inflammation of the thyroid gland. There are several kinds of thyroiditis, and they can be associated with either increased, decreased, or normal thyroid function. Furthermore, they can be classified as painful or painless, depending on the etiology. Differentiating between the different kinds is dependent on the clinical setting, medical and family history, how fast the symptoms progressed, and most importantly, the presence or absence of neck pain. Typically, painful thyroiditis is caused by radiation, trauma, or infection, while painless thyroiditis is caused by autoimmune diseases or medications. Painful thyroiditis can be further divided into subacute granulomatous (de Quervain) thyroiditis, suppurative thyroiditis, and thyroiditis caused by radiation/trauma. Painless thyroiditis can be subdivided into Hashimoto thyroiditis, postpartum thyroiditis, subacute lymphocytic thyroiditis, drug-induced (amiodarone, interferon-alpha, interleukin 2, lithium) thyroiditis, and Riedel (fibrosis) thyroiditis. [1-6]

Subacute thyroiditis (SAT), which we would like to focus on, is also known as giant cell, granulomatous, painful, or de Quervain's thyroiditis. It is a self-limiting, non-suppurative, inflammatory process of the thyroid gland. It usually develops two to eight weeks after viral upper respiratory tract infections, accompanied by pain and fever. The thyroid is large, painful, and tender. It presents with fever, myalgia, arthralgia, weakness, and sore throat. [7-10]

Material and methods

We used the PubMed platform to find the most up-to-date knowledge on the pathogenesis, diagnosis and treatment of subacute thyroiditis. Upon entering the search term 'subacute thyroiditis' we gained access to 554 studies written between 1950 and 2023. We focused our attention on works published after the year 2000 that present knowledge in accordance with the principles of Evidence-Based Medicine. Based on the above studies, we have summarized the latest information on the diagnosis and treatment of subacute thyroiditis.

State of knowledge

Etiopathogenesis

Possible causes of de Quervain thyroiditis include viruses like mumps, measles, influenza, Epstein Barr virus, Dengue, human immunodeficiency virus, and adenoviruses, hepatitis B, cytomegalovirus, enterovirus, Coxsackie viruses A and B and now also severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Predisposing factors may also include immunomodulating treatment and genetic predisposition related to human leukocyte antigens (HLA). HLA-B*35 is the most extensively researched susceptibility gene for subacute thyroiditis. However, its precise role in the occurrence of subacute thyroiditis remains uncertain. In genetically predisposed patients, a previous viral infection occurring approximately 2-6 weeks earlier is considered a triggering factor for subacute thyroiditis. [1,3,5,11] A limited number of studies have suggested a possible link between subacute thyroiditis and vaccinations, including the COVID-19 vaccine. [12-15] However, further research is required to establish a definitive connection.

Epidemiology

Subacute thyroiditis affects females more frequently than males, with a female to male ratio of 4:1. The peak age of incidence is between 40 and 50 years. [1,3,8] According to a study conducted in 2023, the median age at which initial symptoms appear is 50.7 years, with a range of 28.0 to 71.6 years. [16] Additionally, during the COVID-19 pandemic, subacute thyroiditis symptoms were found in as many as 10-20% of COVID-19 patients who were hospitalized. [8]

Clinical presentation

Common initial clinical presentation of the subacute thyroiditis includes anterior neck pain that can spread up to the jaw or ear and/or down to the sternum, mild to moderate fever, fatigue, malaise, and mild to moderate thyrotoxic symptoms. The affected side of the thyroid gland (unilateral or bilateral) becomes hot and tender to palpation. The patient is unable to extend the neck and often sits with the neck flexed in order to avoid pressure on the thyroid gland. Swallowing is painful. There are usually signs of infection in structures adjacent to the thyroid, local lymphadenopathy as well as temperature elevation and, if bacteremia occurs, chills. Transient vocal cord paresis may also occur. Atypical cases of subacute thyroiditis without neck pain or tenderness have occasionally been reported in the literature. At times, the pain begins and may be confined to the one lobe, but usually spreads rapidly to involve the rest of the gland ("creeping thyroiditis"). In the acute period, due to the destruction of thyroid gland tissue, a large amount of thyroid hormone is released into the blood. An initial thyrotoxicosis phase lasts 3-6 weeks. As a result, features of hyperthyroidism such as tachycardia and increased metabolism may be seen. In a minority of cases, signs and symptoms of thyrotoxicosis may dominate the clinical picture, with weight loss, tremor and palpitations. The symptoms described above are considered typical for the first phase of subacute thyroiditis. Thyrotoxicosis phase results from the destruction of thyroid follicles and release of thyroid hormones. A typical course of the condition includes three phases. The first phase is characterized by pain and fever, followed by a second phase when these symptoms resolve. The third phase is marked by subsequent hypothyroidism. Persistent hypothyroidism is a rare condition. Following this, there is an intermediate hypothyroid phase that can last up to six months. This is due to the depletion of thyroid hormone stores. Within 12 months, 85%–95% of patients with the condition return to their baseline thyroid functioning. [2,3,5,7,8,10,17]

Diagnosis

The diagnosis of subacute thyroiditis is primarily clinical. Patients typically present with anterior neck pain, tenderness to palpation of the thyroid, and signs and symptoms of thyrotoxicosis during the initial thyrotoxic phase. Inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein, are elevated. TSH is usually suppressed with elevated or normal T4 and T3 levels during the thyrotoxic phase.

Due to the high risk of misdiagnosis of subacute thyroiditis, the following criteria have been proposed for its diagnosis.

It is important to note that pain and accelerated ESR may also be present in patients with thyroid cancer with a poor prognosis or with malignant tumor metastases to the thyroid gland. In addition, the painless form of subacute thyroiditis is becoming more common.

Main criteria (all must be met):

(a) significant increase in ESR (or CRP)
(b) typical ultrasound image of the thyroid gland, showing hypoechoic areas with blurred borders and reduced vascularisation
(c) cytological confirmation of subacute thyroiditis or at least the exclusion of malignant tumour on BAC in any case of diagnostic doubt.
Additional criteria must be met, with at least one of the following:
(a) firm and/or painful enlargement of a thyroid lobe or the entire thyroid gland,
(b) an increase in serum FT4 and a decrease in serum TSH, or
(c) low iodine uptake on scintigraphic examination, or
(d) hard thyroid swelling
(e) FNAB result typical for subacute thyroiditis, FNAB should be performed in all doubtful cases and in patients that show no improvement on a short term. [8,17-19]

Laboratory findings

Laboratory results usually include elevated levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), as well as suppressed thyroid-stimulating hormone (TSH), elevated free thyroxin (fT4) levels (tab. 1) and negative thyroid antibodies (aTPO, aTG, TRAb). [19] It is important to note that a diagnosis of subacute thyroiditis cannot be ruled out even if biochemical parameters are normal.
Subacute thyroiditis typically presents with thyrotoxicosis followed by transient hypothyroidism. Full recovery within a few weeks to a few months is typical. Some patients may experience only one phase, either thyrotoxic or hypothyroid, while others may experience both. [21]

Parameters	Stage 1	Stage 2	Stage 3	Stage 4
Symptoms	Thyrotoxicosis	Euthyroid	Hypothyroid	Euthyroid (recovery)
T4, T3	↑	N	↓	N
TSH	↓	N	↑	N

Table 1. Changes in the levels of hormones in the different stages of subacute thyroiditis
T4 - thyroxine; T3 - triiodothyronine; TSH - thyroid-stimulating hormone
↑ - elevated; ↓ - decreased; N – normal

Ultrasonography

Thyroid ultrasonography is a useful tool for diagnosing and monitoring patients with subacute granulomatous thyroiditis. The disease is characterized by a heterogenous hypoechoic area in the affected tissue, and no vascular flow on color Doppler ultrasonography. At the time of diagnosis, the lesions observed during the ultrasonographic scan can usually be described as either unilateral or bilateral.
Other useful diagnostic tool is the strain ratio (SR) obtained on real-time sonoelastography of the thyroid gland. The SR is higher in subacute thyroiditis compared to hyperthyroidism and Hashimoto's thyroiditis. [8,11,20]

Fine-Needle Aspiration Biopsy

Fine-needle aspiration cytology (FNAC) is not mandatory for the diagnosis of subacute thyroiditis, although it may be helpful, particularly in ruling out coexisting thyroid conditions such as thyroid nodules and in cases of diagnostic uncertainty. [11]

Despite recent advances in diagnostic methods, the diagnosis of subacute thyroiditis is still often delayed, and patients are unable to continue normal daily activities for weeks or even months. It has been realized that primary care physicians and some specialists do not consider the possibility of subacute thyroiditis in the differential diagnosis of neck pain. Therefore, physicians frequently prescribe antibiotics unnecessarily as the symptoms and laboratory results of the patients can be easily confused with different infective processes. [2,10,19]

Differential diagnosis

When diagnosing subacute thyroiditis (de Quervain's disease), it is important to differentiate it from other rare granulomatous thyroiditis, such as tuberculous thyroiditis and fungal infections (e.g. *Aspergillus spp.*, *Candida spp.*, *Cryptococcus spp.*, and *Pneumocystis jiroveci* infection in immunocompromised patients). If pain is not the primary symptom, the condition should be differentiated from a silent thyroiditis. A markedly accelerated ESR and association with previous viral disease are indicative of de Quervain's disease. Fine-needle aspiration biopsy (FNAB) is the decisive diagnostic tool.

Thyroid tumours that are malignant and have a poor prognosis, whether primary or metastatic, can cause neck pain. This is due to the tumour infiltrating neck tissues or stretching the thyroid capsule. As the tumour progresses, the ESR may increase. A clinical picture that strongly suggests subacute thyroiditis without a thorough evaluation of the thyroid gland by ultrasound and liquid-needle aspiration biopsy can delay oncological treatment and drastically worsen the prognosis.

Additionally, subacute thyroiditis shares symptoms with painless thyroiditis, postpartum thyroiditis, and amiodarone-induced thyroiditis, checkpoint inhibitor-induced thyroiditis, radiation thyroiditis, and palpable thyroiditis. In subacute thyroiditis, urine iodine levels are typically less than 500 mcg/l, which can help differentiate it from amiodarone-induced thyroiditis. It is worth noting that some patients may present with a fever of unknown origin, and further investigation may reveal subacute thyroiditis. To differentiate from non-thyroid disease, it is important to consider general symptoms such as fever and increased ESR. [1,7,8,10,17,19]

Treatment

Subacute thyroiditis is typically self-limited, and in most cases, the thyroid gland will spontaneously resume normal thyroid hormone production without the need for treatment. However, some patients may require treatment to relieve pain and control symptoms. Non-steroidal anti-inflammatory agents or aspirin may provide relief of symptoms, but if they are severe, corticosteroids administration should be considered.

No randomized controlled trials have been conducted to compare the doses or agents used in the treatment of subacute thyroiditis.

The typical first-line therapy for patients with mild to moderate symptoms is the administration of salicylic acid at a dose of 600 mg orally every six hours, naproxen at a dose of 500-1000 mg twice a day, or ibuprofen at a dose of 400-800 mg orally every eight hours. [1] If patients experience severe neck pain or have a minimal response to acetylsalicylic acid or nonsteroidal anti-inflammatory drugs after four days, oral corticosteroids (prednisone) should be initiated at a dose of 40 mg daily. [22] The usual duration of corticosteroid treatment is two months. After five to seven days, the dose should be gradually reduced by 5-10 mg per week until the lowest possible dose is reached. A 2013 study demonstrated that a dose as low as 15 mg of prednisolone was effective in treating subacute thyroiditis. [22] However, further studies are necessary to determine the lowest effective dose. Recent studies have compared the administration of corticosteroids to the use of non-steroidal anti-inflammatory agents and have shown that corticosteroids can reduce the time it takes for symptoms to resolve. [23,24] A study has shown that low initial doses of corticosteroids, along with an extended tapering period, may help to reduce recurrence rates of subacute thyroiditis. The study also suggested that intrathyroidal corticosteroid injections may be a safer and faster alternative to oral corticosteroids. [25] Three other studies have also reached similar conclusions, stating that ultrasound-guided intrathyroidal injection of corticosteroid and lidocaine can quickly relieve pain, shorten the duration of treatment, and lower the risk of adverse reactions. [9,26,27] Additionally, the procedure is associated with less injury to local tissue, a higher drug concentration in the lesion than oral administration of corticosteroids, and is generally better tolerated by patients. Local injection of lidocaine and corticosteroid through an insulin syringe has been reported as a potentially effective therapeutic approach for symptom relief. Further evaluation in larger studies is needed to confirm its efficacy compared to standard treatment with systemically administered corticosteroids. [28,29] In most cases of subacute thyroiditis, thyroid hormone supplementation (levothyroxine) is not required during the transient hypothyroid phase, unless patients are symptomatic or show clear signs of hypothyroidism. However, up to 15% of patients with subacute thyroiditis may develop permanent hypothyroidism, which can occur even more than a year after presentation. [30] Treatment with antibiotics is unnecessary for subacute thyroiditis. Referral for thyroidectomy is not recommended in the treatment of subacute thyroiditis. However, if necessary, the procedure is safe and associated with low morbidity. This is due to the possibility of associated papillary cancer based on cytological examination. [31]

Conclusions

Subacute thyroiditis, despite presenting with a typical clinical picture, is frequently misdiagnosed. Patients often seek consultation with doctors from various specialties before being referred to an endocrinologist. Due to the diverse clinical presentation and the growing prevalence of the painless form of subacute thyroiditis, proper diagnosis can be even more difficult. Therefore, it is more important for clinicians to be aware of the symptoms and factors that can trigger subacute thyroiditis in order to consider them in the differential diagnosis.

Disclosure
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Author's contribution
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As a review paper, our work does not present new data or analyses. Therefore, there are no specific datasets or data availability to report. The information and findings presented in this review are based on previously published studies, which can be accessed through their respective sources as cited in the reference section.

Conflict of Interest Statement
The authors declare that there are no significant conflicts of interest associated with this research work.

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