

Subacute Thyroiditis – literature overview and COVID-19

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 DOI: <https://doi.org/10.20883/medical.e472>

Keywords: subacute thyroiditis, de quervain thyroiditis, COVIS-19, SARS-CoV-2

Published: 2020-12-29

How to cite: Domin R, Szczepanek-Parulska E, Dadej D, Ruchała M. Subacute Thyroiditis – literature overview and COVID-19. JMS [Internet]. 2020 Dec 29;89(4):e472. doi:10.20883/medical.e472



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ABSTRACT

Subacute thyroiditis (SAT), also known as de Quervain's thyroiditis, is a rare thyroid gland disorder, although it is the most common type of painful thyroiditis. The incidence of this disorder is relatively low but likely to be underestimated. Epidemiological studies vary, estimating a prevalence of 12/100,000/year and patients with SAT constitute less than 5% of all patient consultations due to thyroid disease. For the reason, that SAT can present with a variety of symptoms to different specialists. This review summarises current knowledge of SAT with an emphasis on reports related to SARS-CoV-2.

Introduction

De Quervain's subacute thyroiditis (SAT) is a rare thyroid gland disorder first described in 1895 by *Mygind* and later characterised by *de Quervain* in 1904 [1]. Among thyroid disorders, it is the most common type of painful thyroiditis [2]. It should be highlighted that "de Quervain's thyroiditis" is not synonymous with "de Quervain's disease", a type of tenosynovitis affecting tendons in the first dorsal compartment of the wrist [3]. The

incidence of SAT is relatively low, however likely to be underestimated. Due to its diverse and non-specific symptoms, patients are often diagnosed by family doctors, otolaryngologists, oncologists and other specialists before they eventually consult an endocrinologist. This review summarises the current knowledge of SAT and potential etiological factors (including severe acute respiratory syndrome coronavirus 2, SARS-CoV-2), clinical presentation, along with present diagnostic and therapeutic options.

Materials and Methods

The PubMed search engine was searched for the phrases "subacute thyroiditis", "subacute thyroiditis differential diagnosis", "subacute thyroiditis case report", "thyroiditis differentiation" and "SARS-CoV-2" to identify articles focused on the clinical presentation (including atypical cases), data on etiological factors, novel diagnostic methods and treatment recommendations of SAT.

Subacute thyroiditis

Epidemiology

Results of epidemiological studies vary but most indicate that SAT occurs mostly in females, with a peak incidence between 40 and 50 years of age [4]. Its estimated prevalence is equal to 12/100000/year, while subjects with SAT constitute less than 5% of all patients consultations due to thyroid disease. It was also observed that it occurs more frequently among first-degree relatives and twins.

Aetiology

The aetiology of SAT is unknown but predisposing factors include previous viral infection (i.e. adenoviruses, EBV, Dengue, hepatitis, influenza), immunomodulating treatment or genetic predisposition related to human leukocyte antigens (HLA) (B*35, B*18:01, DRB1*01 and -C*04:01) [5–9]. HLA-B*35 is the first and the most studied SAT susceptibility gene but its precise role in SAT occurrence is unclear. However, as SAT is related to viral infection, there may be a direct link considering HLA-B*35-restricted viral antigen presentation. There are a few hypotheses on the mechanism. One is molecular mimicry resulting in the cross-reactive immune response – specific viral amino acids may be similar to autologous thyroid peptides, thereby generating autoreactive T-cells that promote an autoimmune response against the thyroid. The second hypothesis is that as a result of infection, changes in tissue components occur through the release of viral products or the presentation of virus antigens by host cells. Then, along with the HLA-B*35 antigen, the thyroid cells are recognised as foreign and destroyed by the immune system [10].

Immunisation-related induction

COVID-19

SARS-CoV-2 originated in the Chinese city, Wuhan, in December 2019 and has since become a global pandemic. In most cases, the symptoms are mild, mainly a fever, cough or fatigue but in some people, especially the elderly with comorbidities, it can lead to pneumonia, causing acute respiratory distress syndrome (ARDS) and multiorgan dysfunction (MODS) [11].

The literature search revealed a total of eight patients/cases descriptions (7 women and 1 man). Six women aged 18–46 y.o. developed SAT soon after (from a few days up to 6 weeks) recovery from SARS-CoV-2 infection, with typical clinical presentation (i.e. anterior neck pain, fever, cough) accompanied by markers of thyrotoxicosis. Only one patient had a previous medical history of thyroid disease (small diffuse non-toxic goitre). Response to treatment with prednisone in five and ibuprofen in one patient was good. On a follow-up visit, the parameters of thyroid function were back to reference ranges in four patients and two patients presented subclinical hypothyroidism [12–14].

Two patients were diagnosed with SAT in the course of SARS-CoV-2 infection. One report concerned a 69-year-old female with a previous history of non-toxic nodular goitre with a dominant benign nodule in the right lobe and repeatedly documented euthyroidism. During recovery after back surgery in hospital, she experienced cough, fever and dyspnoea. A swab confirmed SARS-CoV-2 infection and computed tomography of the chest revealed typical changes related to Coronavirus Disease 19 (COVID-19). On the fifth day of hydroxychloroquine and lopinavir treatment, the patient complained of palpitations, insomnia, and agitation. Thyroid laboratory findings revealed thyrotoxicosis. A thyroid scan using Tc-99 detected no uptake and bedside ultrasonography showed enlarged hypoechoic goitre with a previously documented nodule in the right lobe. Based on clinical presentation and examination, the patient was diagnosed with SAT, possibly triggered by SARS-CoV-2. Biochemical thyrotoxicosis decreased after treatment with methimazole, intravenous methylprednisolone and oral continuation with prednisolone. Non-steroid anti-inflammatory drugs (NSAIDs) were

not implemented because of patients' hypersensitivity. Interestingly, the patient was still positive for SARS-CoV-2 after two months, although the patient was completely asymptomatic [15].

The second report described a 34-year old male primarily diagnosed with COVID-19, who presented new symptoms on the 9th day of illness. He complained of anterior neck pain refractory to paracetamol and dequalinium lozenges and developed tachycardia ranging from 90 to 120 beats/min. No other symptoms were present. Laboratory and ultrasound investigations revealed typical SAT features. After prednisolone and propranolol treatment, his symptoms and thyroid function normalised [16].

Post-vaccine

The presence of SAT was also documented following vaccines. *Passah et al.* reported a case of a young female with symptomatic thyrotoxicosis and neck pain of about one-month duration, with no past medical history of infection or sore throat. Eight weeks before symptoms, she was vaccinated with a live influenza virus vaccine. Previously, a few other cases of SAT after vaccination were reported, including the hepatitis B vaccine [17].

Paraplegia, sensory loss, SAT and Dengue fever

A 65-year old man was admitted to the Hospital of Guangzhou Medical University (Guangzhou, China) because of acute paraplegia and sensory loss. Almost a week before, he experienced an episode of fever which resolved a few days before admission, with sequential development of neurological symptoms. After laboratory tests and imaging diagnostics, the patient was diagnosed with acute transverse myelitis complicated with SAT as a result of a Dengue viral infection [18].

Clostridium difficile

SAT is associated with common viral infections. However, a recently published report suggests its induction after bacterial infection. A 24-year-old male soldier admitted for clinical evaluation prior to the military programme, reported mild anterior neck pain, fatigue, night chills and sometimes palpitations persisting for one month. A few months earlier, he was initially treated for *Clostridium difficile* infection with vancomycin. However, in further investigation, his diarrhoeal

problems were still present. Biochemical tests revealed a decreased level of thyroid-stimulating hormone (TSH) and slightly increased T3 and C-reactive protein (CRP), with other thyroid parameters within their reference ranges. Ultrasound examination detected no abnormalities. After evaluation, he was treated with fidaxomicin for 10 days for *C. difficile* infection. He fully recovered and his thyroid parameters went back to reference ranges 8 weeks after the first evaluation [19]. However, in this particular case, in the differential diagnosis, we should consider autoimmune background, as bacterial induction of SAT seems controversial.

Immunomodulating drugs

The cases presented below document that drugs used as immunomodulatory agents in autoimmune diseases, such as anti-TNF- α inhibitors, can also play a role in the development of SAT [20].

Infliximab

A 56-year old male suffering from Leśniowski-Crohn Disease started treatment with infliximab to reduce diarrhoea. Four weeks later, he presented with neck pain and swelling with tenderness in the thyroid area. Laboratory tests revealed features of thyrotoxicosis, ultrasound examination demonstrated hypoechogenic goitre and a fine needle biopsy showed amyloid deposition. His symptoms resolved and thyroid function returned to normal after treatment with prednisolone, however, goitre did not. Previously, there were few cases of anti-TNF- α induced SAT but never with accompanying amyloid deposition [21].

Adalimumab

A 26-year old female suffering from psoriasis and psoriatic arthritis was prescribed adalimumab because of disease progression causing joint degeneration. Seven months later, she started to cough so treatment was discontinued for three weeks, then the patient developed symptoms like fever, sore throat, anterior neck tenderness, lymphadenopathy, hand tremors and palpitations. In laboratory tests, there were features of thyrotoxicosis and hypoechogenic heterogeneous lesions in ultrasound examination. The symptoms resolved, and thyroid function resumed after

treatment with prednisolone. Due to the increased risk of thyroid diseases in patients receiving anti-TNF- α therapy, the authors recommend regular thyroid gland examination before and during treatment with anti-TNF- α inhibitors [22].

Clinical presentation

Typical

Inflammation and thyreometabolic dysregulation underlying SAT result in various symptoms, including goitre, pain in the neck area, palpable thyroid nodule or lymphadenopathy. However, other local symptoms like migratory thyroiditis, hard goitre and pain radiation to jaw, ears or chest are also possible. Systemic symptoms are flu-like (fever, myalgia, weakness) with acute onset and related to the stage of the disease and thyroid hormones levels range from clinically overt hyper- to hypothyroidism [4, 23–26].

SAT usually comprises consecutive phases of hyper-, hypo- and euthyroid state independently of the initiating factor. The inflammatory process leads to thyroid gland destruction and thyroglobulin (Tg) proteolysis, which results in the release of thyroxine (T4) and triiodothyronine (T3) into the bloodstream. Secondary to that, pituitary-thyroid axis regulation is disrupted by the suppression of TSH. With decreasing inflammation, the thyroid regenerates and hormonal homeostasis is restored. Each phase lasts for two to eight weeks [27].

Laboratory findings

Standard biochemical parameters should be measured including TSH, free thyroid hormones (fT3, fT4), anti-thyroid peroxidase antibodies (aTPO), anti-thyroglobulin antibodies (aTG) and anti-TSH receptor antibodies (TRAb), CRP and erythrocyte sedimentation rate (ESR). In the first phase of SAT, when most diagnoses are made, we should expect biochemical thyrotoxicosis, elevated CRP, elevated ESR and negative thyroid antibodies [28]. However, in some cases, the presence of elevated antibodies (aTPO, aTG, TRAb) may also occur [29].

Hernik et al. investigated the possible use of hepcidin levels in SAT. Hepcidin is a reactive inflammatory protein regulating ferrum homeostasis and is increased during SAT. Promising

results show that with a cut-off value, diagnosis is more likely. Additionally, it could be used as a monitoring tool, due to its decreasing manner during effective treatment [28].

An important note is that the diagnosis of SAT cannot be excluded if biochemical parameters are normal. In the study by *Tachibana et al.*, the mean interval between symptoms and abnormal laboratory findings was 6.3 weeks and the longest interval was 11 weeks [30].

Imaging

Typical imaging diagnostics include ultrasound and scintigraphy, with the use of radioactive iodine and Tc99m. The most common features of ultrasound examination are heterogeneous hypoechoic areas of the affected tissue with a lack of flow on colour Doppler. Most changes are bilateral with characteristic features like "lava flow" [31], in turn, decreasing the uptake of radioactive iodine and Tc99m [32, 33]. Another valuable diagnostic parameter is strain ratio (SR) acquired during real-time sonoelastography of the thyroid gland, which is high in SAT compared to hyperthyroidism and Hashimoto's thyroiditis [34]. Recently, a novel diagnostic tool, a fusion scan of images from ultrasound and 124I-PET was reported, which might be useful when a scintigraphy scan does not match the ultrasound examination findings [35].

Fluorodeoxyglucose Whole-Body Positron Emission Tomography/CT (18F-FDG PET/CT) is another tool. During SAT, there is a possibility of increased FDG uptake, so this condition should be included in the differential diagnosis when assessing lesions with an increased maximum standardised uptake value (SUVmax) [36].

Fine needle aspiration cytology (FNAC)

The diagnosis of SAT does not require obligatory FNAC examination, though it might be helpful, especially in the exclusion of co-existing thyroid pathologies (i.e. thyroid nodules) and differential diagnosis in cases of uncertainty [37].

Thyroid puzzle - case reports

Fever of unknown origin

In 1961, *Petersdorf and Beeson* characterised fever of unknown origin (FUO) as a body tem-

perature equal or higher than 38.3°C with a duration of three weeks without a diagnosis after one-week intensive inpatient investigation [38]. Currently, due to diagnostic technology development, the one-week inpatient investigation is no longer required but experts suggest certain initial tests to establish the diagnosis of FUO [39]. As SAT can present by fever only, with no other typical clinical signs of thyrotoxicosis, it should be taken into consideration during the evaluation of FUO [2, 40–42].

Acute myocardial infarction and sustained ventricular tachycardia

The most common cause of acute myocardial infarction (AMI) is the rupture of atherosclerotic plaques leading to thrombosis in coronary arteries, which instantly decreases blood flow, that is, the oxygen demand of the myocardium is greater than the oxygen supply. More aetiologies of MI include trauma, vasculitis, drug use, coronary artery anomalies, coronary artery embolism or aortic dissection. Excess demand on the heart, which can be the result of hyperthyroidism, is also listed [43].

Hyperthyroidism/thyrotoxicosis is the first clinical stage of SAT. AMI seems an unlikely presentation of SAT, yet *Guerrero et al.* reported a case of a 32-year-old female presenting with chest pain and biochemical markers of MI and thyrotoxicosis with changes in their ECG. There were no disturbances in coronarography and echocardiography. Five days earlier, she was diagnosed with SAT based on neck pain, goitre and fever. The final diagnosis was a thyrotoxic crisis in the course of early relapse of SAT. After treatment with prednisolone and propranolol symptoms, biochemical and ECG changes resolved [44].

Another extremely rare presentation was the case of a 38-year-old woman with no previous medical history, complaining of fatigue and palpitations. Physical examination revealed tender goitre. The ECG showed bigeminy and premature ventricular contractions (PVCs) with a ventricular rate of about 140 bpm. During the examination, the monitor displayed an episode of sustained ventricular tachycardia, 278bpm, which was stopped by an infusion of landiolol. Cardiac biochemical parameters were within reference ranges and features of thyrotoxicosis [45].

Encephalopathy

Encephalopathy is a symptom of brain dysfunction, recognised by an altered mental state and other neurological dysfunctions. Hashimoto encephalitis is also known as “steroid-responsive encephalopathy associated with autoimmune thyroiditis” (SREAT) or “non-vasculitic autoimmune meningoencephalitis” (NAIM) [46]. *Chung et al.* presented a case of a 49-year-old female admitted to the hospital because of neurological symptoms. Physical examination revealed somnolence, memory impairment, dysarthria, right-hand weakness, gait disturbance and tender goitre. There were no major deviations in laboratory findings besides thyrotoxicosis and brain magnetic resonance imaging was normal. By contrast, imaging of the thyroid presented an acute phase of SAT. After initial treatment with steroids, her mental status improved significantly but two months later, she experienced a relapse in neurological deterioration accompanied by hypothyroidism. Her symptoms resolved after treatment with pulses of methylprednisolone and levothyroxine substitution [47].

Psychosis

According to the American Psychiatric Association and the World Health Organization, “psychosis” is defined as a state of impaired reality testing with the presence of hallucinations, delusions or both [48]. It can be induced by thyrotoxicosis or hyperthyroidism but generally, psychosis is not the main feature of these conditions. An 18-year-old male presented to the emergency department due to features of psychomotor arousal and paranoid mental state for three days. There was no medical history of previous drug use or psychiatric disorders in the family. Physical examination revealed tachycardia, moist skin, and elevated body temperature, and the thyroid gland was hard and tender on palpation. Laboratory tests revealed biochemical thyrotoxicosis. Due to his mental state, the patient was admitted to the psychiatric department and initially treated with prednisolone and antipsychotic drugs with good effect. On a follow-up visit, the patient remained asymptomatic and was attending school again [49].

Differential diagnosis

Before setting the diagnosis of the classic variant of SAT, we should take into consideration

a few differential diagnoses like suppurative thyroiditis [50], Riedel's thyroiditis or haemorrhage to the thyroid nodule. There is also the possibility of a painful variant of Hashimoto's thyroiditis, however, only a dozen cases have been described over the last few decades [51]. Other differential diagnoses should include disorders causing thyrotoxicoses like Graves's disease or intoxication with thyroid hormones medications.

Treatment

Once the diagnosis is established, treatment should be initiated, however, there is no consensus regarding the scheme of steroid administration. In our department, the following scheme is administered: 40 mg of prednisolone daily in a tapered manner with dose reduction every week for 6–8 weeks. In less severe cases or subjects with contraindications to steroid therapy, the use of NSAIDs like ibuprofen or naproxen can be beneficial, however, is not obligatory. Regarding the study by *Sato et al.*, the effect of stand-alone steroids treatment is superior to NSAIDs [52]. As an additive treatment, in the hyperthyroidism stage, we recommend propranolol and in hypothyroidism levothyroxine but only when the patient is symptomatic.

A novel therapeutic approach was investigated and reported in a study by *Shao-Gang et al.*, intra-thyroid injections of lidocaine and dexamethasone saline solution every other day for one week. The results were compared to typical treatment with oral prednisolone and the injection group was characterised by a more rapid reduction of pain and a shorter duration of treatment [53].

Unfortunately, some patients will need surgical treatment, especially when a malignancy is suspected by FNAC examination or when the patient is unresponsive to pharmacological treatment and symptoms (tender goitre, dysphagia) persist [54, 55].

Outcome and recurrence

Most patients will recover with no long-term complications, though some may experience a relapse or persistent/chronic hypothyroidism.

The recurrence rate is 20–30%, yet the reason for this is still unknown and factors determining the risk of recurrence are lacking. In a recent study by *Stasiak et al.* focused on haplotypes, the co-presence of HLA-B*18:01 and HLA-B*35 was associated with a higher risk of recurrence, suggesting that high-risk patients should be initially treated with higher doses of steroids with slower dose reduction [56]. Long-lasting hypothyroidism demanding substitution of levothyroxine will occur in 0.5–15% of patients but predictive factors are still unknown [4].

Final word

The diagnosis of SAT, also known as de Quervain's thyroiditis, can be challenging due to the diversity in severity and presentation of symptoms. The described inducing factors and various clinical presentations of SAT confirm that this condition is indeed a disease of "thousand faces". Even if recognised as a typical endocrine disorder, due to its insidious nature, ill patients can visit physicians of various specialities, so clinicians should be aware of its symptoms and potential triggering factors.

Acknowledgements

Conflict of interest statement

The authors declare no conflict of interest.

Contribution

R.D. overviewed the literature, prepared draft and did the final editing. E. S-P. is the originator of the paper, collected literature and made major corrections. D.D. proofread the manuscript. M.R. is the senior author. All authors of this paper have read and approved the final version.

Funding sources

There are no sources of funding to declare.

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