In the name of Allah

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# New aspects in the pathogenesis and management of subacute thyroiditis

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# Introduction

- Subacute thyroiditis (SAT) is a rare inflammatory condition of the thyroid gland that can cause both high and low thyroid hormone levels.
- It is presumed to be caused by a viral infection, often following an upper respiratory infection.
- It can cause pain and swelling in the thyroid, as well as fever, malaise, and muscle aches.
- It is usually self-limited, but it can have permanent complications if untreated 2.
- The aim of this review is to summarize the most recent advances in SAT, with special attention given to the clinical application of the novel findings.

# Pathogenesis

- Susceptibility to SAT has been associated with certain types of human leukocyte antigens (HLA).
- Several HLA alleles were demonstrated not only to increase the risk of SAT, but also to correlate with SAT clinical course and determine the risk of recurrence.
- The most common viral triggers of SAT include Coxsackie viruses, Echo viruses, adenoviruses, influenza viruses, mumps and rubella viruses, parvovirus B19, orthomyxovirus, HIV, Epstein-Barr virus, hepatitis E and measles virus.
- The novel coronavirus disease 19 (COVID-19) has been shown to be a potent SAT-triggering factor, and that the clinical course of SAT in patients affected by COVID-19 is different from a typical one.
- Other potential triggers of SAT include tumor necrosis factor (TNF)-α inhibitors and interferon (IFN)-α inhibitors.

# Epidemiology

- The highest incidence of SAT regards middle aged women, and females account for 75–80% of all SAT patients.
- However, the symptoms of SAT were present in as many as 10–20% of patients hospitalized due to COVID-19 on intensive care units (ICU) and non-intensive care units, respectively.
- Moreover, recently young children affected by SAT have been reported.

# Clinical Manifestation and Factors Modifying Clinical Course

- The typical symptoms of SAT include anterior neck pain – usually radiating to the jaw, ear and upper mediastinum – as well as fever, rising especially at night. Fatigue, malaise and muscle pain can also occur. Many patients present clinical and/or biochemical manifestation of thyrotoxicosis, with usually low to moderate severity.
- The typical course includes three phases: thyrotoxicosis phase due to release of thyroid hormones from damaged follicles; hypothyroidism phase due to depletion of colloid and impaired hormone synthesis; and euthyroid phase due to follicular regeneration.

# Clinical Manifestation and Factors Modifying Clinical Course

- The most characteristic laboratory finding is a high erythrocyte sedimentation rate (ESR), sometimes reaching even three-digit value. C reactive protein (CRP) is elevated in many cases. White blood count (WBC) may also be increased. Anti-thyroid antibodies are usually normal. The ultrasound (US) pattern of SAT include hypoechoic and heterogeneous areas with blurred margins, poorly vascularized on color Doppler 2 .
- The clinical characteristics of the disease has been changing significantly for the recent years. More and more cases of painless SAT have been reported, with frequency reaching 6.25% in our studies published in 2019, but increasing instantly during the pandemic, including virtually the majority of patients with SAT hospitalized due to COVID-19.

# Clinical Manifestation and Factors Modifying Clinical Course

- Fever was also reported to occur less often than it was believed, and was frequently associated with microhaematuria.
- As it was previously mentioned, some cases of children with SAT have been reported. The most spectacular case regarded 5-year-old boy with airway compromise caused by SAT.
- Several years ago, the absence of thyroid antibodies was considered typical for SAT. However, elevated levels of anti-thyroid antibodies, including thyroid peroxidase antibodies (aTPO), thyroglobulin antibodies (aTg), and even thyrotropin receptor antibodies (TRAb) are more often present.

# Clinical Manifestation and Factors Modifying Clinical Course

- Despite the progress in availability of diagnostic tools, including laboratory markers and US examination, the diagnosis of SAT is still frequently delayed. The patient often visits many physicians before being finally diagnosed with SAT. The period of this delay was reported by our research team as ranging from two weeks even to six months. Due to misdiagnosis of infection, antibiotics were unnecessarily administered in nearly 50% of SAT patients. The ineffectiveness of one antibiotic resulted frequently in the use of another one, covering wider spectrum of bacteria.

**Table 1** Diagnostic criteria of subacute thyroiditis (based on [64], modified)

| Main criteria (all should be met) | Additional criteria (at least one should be met): |
|---|---|
| 1. Laboratory: elevation of ESR or at least CRP<br>2. Ultrasound: hypoechoic area/areas with blurred margin and decreased vascularization in US* | 1. Hard thyroid swelling<br>2. Pain and tenderness of the thyroid gland/lobe<br>3. Elevation of serum FT4 and suppression of TSH<br>4. Decreased radioiodine uptake<br>5. FNAB result typical for SAT |

*FNAB should be performed in all doubtful cases and in patients that show no improvement on a short term follow-up, in order to exclude malignancy

Remarks related to COVID-19 pandemic (should be taken into account during pandemic)

1. SAT diagnosis should be considered in patients with/after SARS-CoV-2 infections with:
   1.1 unexpected:
      1.1.1 *de novo* presence of tachycardia or arrhythmias
      1.1.2 deterioration of previously present tachycardia or arrhythmias
      1.1.3 deterioration of fatigue/malaise
   1.2 laboratory markers of thyrotoxicosis, including decreased TSH and increased FT4 – thyroid tests should be considered in all patients hospitalized due to COVID-19, especially in ICU patients
2. SAT is more frequently painless in COVID-19 patients and the presence of pain should not be treated as SAT criterion in this group, especially in hospitalized patients
3. As SAT may be the only manifestation of COVID-19, testing for SARS-CoV2 infection should be considered in all patients with SAT diagnosed during the pandemic