Endocrinology, Diabetes & Metabolism CASE REPORTS

A Housin and others | Subacute thyroiditis

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Fever of unknown origin as the major manifestation of subacute thyroiditis

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Summary

Fever of unknown origin is a commonly encountered medical problem. Most common causes include infections, malignancy, and connective tissue diseases. Endocrine causes are rare but are well documented. While fever is common in some endocrine disorders, fever of unknown origin as the sole presenting feature is very rare. We describe a case report of a 63-year-old male who presents with fever of unknown origin. Imaging and biopsy results confirmed the diagnosis of subacute thyroiditis. He was started on prednisone with a good response. We conclude that subacute thyroiditis should be considered in the work up of fever of unknown origin even in the absence of classical signs and symptoms.

Learning points:

- Fever of unknown origin is a rare sole presentation of subacute thyroiditis.
- The classic signs and symptoms may not be manifest at the time of presentation.
- Normal thyroid function tests and elevated markers of inflammation often make infections, malignancy and autoinflammatory conditions the prime consideration.
- Imaging of the thyroid gland may point to a morphologic aberration and prompt a thyroid biopsy.
- After exclusion of infection, a rapid response to steroids may be both diagnostic and therapeutic.

Background

Fever of unknown origin is one of the most challenging medical problems. Most common causes include infections, malignancy, and autoimmune disorders. Subacute thyroiditis is a well-documented cause of fever of unknown origin but it usually presents with classical signs and symptoms. Thyroid function testing is almost always abnormal at the time of presentation which helps in making the diagnosis. We present a case of subacute thyroiditis presenting with fever of unknown origin. The patient did not exhibit any classic thyroid symptoms and his TSH was normal at the time of presentation. Therefore, a thyroid disorder was not suspected initially. This unusual presentation of a common medical problem highlights the importance of considering subacute thyroiditis in the differential diagnosis of fever of unknown origin.

Case presentation

A 63-year-old male presented to the emergency department (ED) with a 4-week history of low-grade fever, approximately 4 kg weight loss and generalized weakness. His past medical history included treated hypertension, dyslipidemia, and benign prostatic hyperplasia. He also had a 40 pack-year history of cigarette smoking. He immigrated to Canada from Bangladesh in 2008 and his last travel was to Bangladesh 5 months prior to his presentation where he spent 15 days. He denied any livestock exposure or sick contacts.

On arrival to the ED, his blood pressure was 124/95 mmHg, pulse was 106 bpm, temperature was 37.7°C, O_2 saturation was 98%, and respirations were 18/min. His respiratory, cardiovascular and neurological examinations were unremarkable. There was no hepatosplenomegaly

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and the oropharyngeal exam was normal. Notably, the thyroid examination was unremarkable. Given the patient's history, clinical presentation and travel history, an infectious cause was the main diagnostic consideration.

Investigation

Extensive investigations by the infectious disease service were unremarkable. Tuberculosis (TB) was strongly suspected but the Quantiferon TB test was negative. In the current COVID-19 pandemic, RT-PCR testing for SAR-COV-2 was negative on two occasions. Notable, were the elevations of C-reactive protein (CRP): 40.5 mg/L, erythrocyte sedimentation rate (ESR): 74 mm/h and liver enzymes – ALT: 42 U/L, ALP: 132 U/L. Normochromic normocytic anemia- Hgb: 110 g/L with a normal ferritin level of 258 µg/L were noted. Chest X-ray and ECG were both unremarkable.

Malignancy was another top consideration in the differential diagnosis, however, the CT of chest, abdomen and pelvis was negative for malignancy and was generally unremarkable except for an incidental abnormal thyroid gland finding. It revealed an asymmetric thyroid gland with diffuse hypoenhancement of the left side of the thyroid gland with surrounding haziness (Fig. 1). Sonography revealed an asymmetric goiter with patchy hypoechogenicity with irregular margins in the lower portions of both lobes; the color flow Doppler signal was low (Fig. 2). The serum thyrotropin (TSH) on initial presentation was within the normal range, that is, 0.41 mU/L. Serum thyroglobulin at 2 weeks after the first presentation was 58.4 µg/L, which dropped to 18.7 µg/L in 3 weeks. Targeted fine-needle aspiration biopsy (FNAB) of the thyroid aberration showed a mixture of benign-looking follicular cells and mixed inflammatory cells, including many multinucleated giant cells, histiocytes, and epithelioid cells, lymphocytes and neutrophils. The cytologic features were consistent with granulomatous (subacute) thyroiditis (Fig. 3).

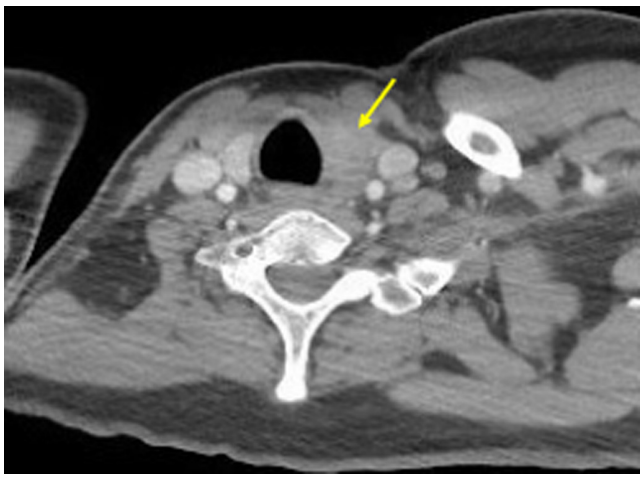

Figure 1
CT scan showing asymmetric thyroid gland with diffuse hypoenhancement of the left side (arrow).

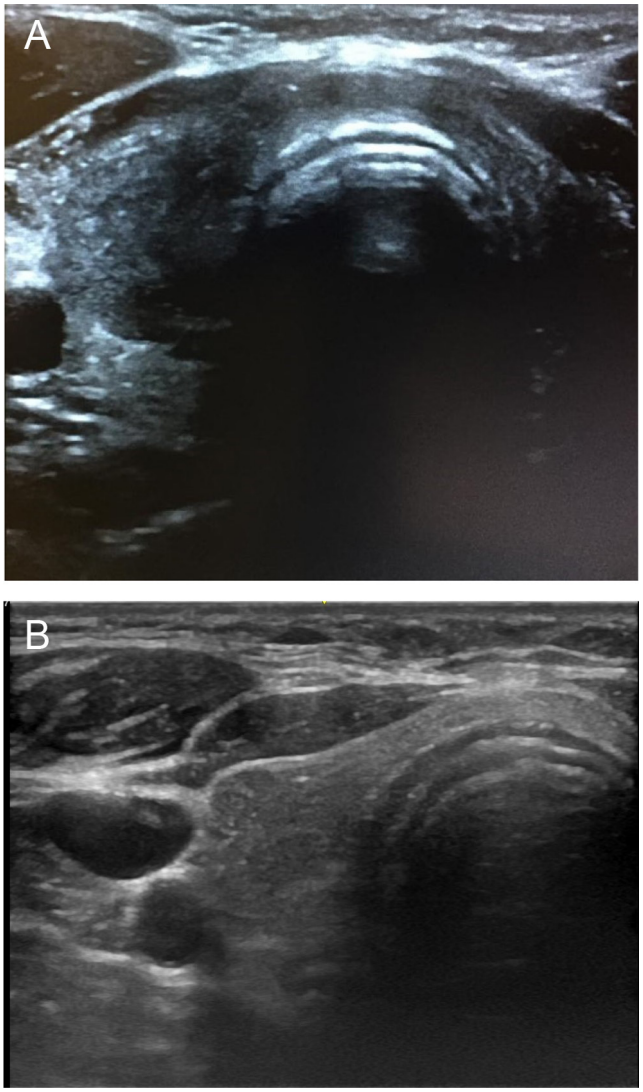

Figure 2
Ultrasonography of the thyroid. (A) US on presentation showing an asymmetric goiter with patchy hypoechogenicity and irregular margins in the infero-posterior portions of both lobes. (B) After 3 months of treatment: a decrease in the size of the goiter, improved echogenicity, however, there remained a haziness in the lower borders.

Treatment

The patient was started on prednisone 30 mg daily.

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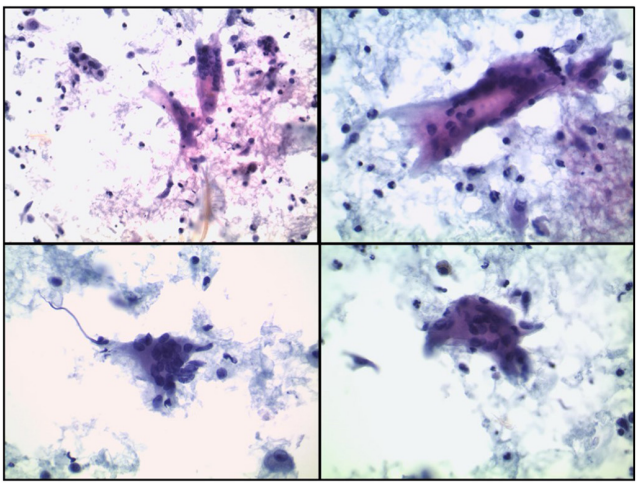

Figure 3
Cytologic features of subacute (granulomatous thyroiditis) showing many multinucleated giant cells admixed with different inflammatory cells, including epithelioid histiocytes, macrophages, lymphocytes and neutrophils (Cytospin preparations, Papanicolaou stain).

Outcome and follow-up

He noticed a significant improvement in his constitutional symptoms within 2 days. The prednisone was tapered by 5 mg every 2 weeks and he continued to do well. After 3 months of follow up, as expected, our patient's TSH increased to 12 mU/L but he remained clinically euthyroid and did not require replacement therapy. This classic evolution confirmed the diagnosis.

Discussion

Fever of unknown origin (FUO) is one of the most difficult medical problems encountered in medicine. Three criteria define this condition: (i) an illness lasting more than 3 weeks, (ii) fever >38.3°C on several occasions, and (iii) no diagnosis established after 1 week of investigations. Infections, malignancies and autoimmune disorders are the most common causes of FUO, although the etiology remains idiopathic in many cases (1, 2). Endocrine causes of FUO are rare. Fever is common in a few endocrine disorders (e.g. thyroid storm, adrenal crisis, and pheochromocytoma). However, FUO as the sole presenting feature is very rare with only a few reported cases in the literature (1, 3). The endocrine disorder most likely to present as an FUO is subacute thyroiditis (SAT); however, telltale findings in these reported cases often point to this disorder (4, 5). In a large retrospective analysis of 852 patients with SAT, a temperature greater than 38°C was found in 28% of patients (6).

Also termed granulomatous, giant cell, or de Quervain thyroiditis, SAT accounts for about 5% of thyroid disorders (2, 3). The annual incidence is 4.9 cases per 100,000/year, the peak incidence occurs at 30 to 50 years of age, and the female to male ratio is 3-5:1. It is a self-limiting, inflammatory thyroid disorder, probably of viral origin, that usually follows an upper respiratory tract infection and spontaneously regresses (2, 3, 7). Many viruses have been identified as the cause such as coxsackie, mumps, measles, and influenza viruses (4, 8). Several case reports and small case series have reported atypical SAT appearing during or up to several weeks after resolution of COVID-19. SARS COV-2 targets angiotensin type 2 receptors which are abundantly expressed in the thyroid (9). As such, this association should be considered in the management of these patients.

The main clinical presentation of SAT is a painful, tender anterior neck swelling which is found in approximately 70–90% of patients. The pain radiates to the ear, throat, jaw or occiput (2, 3, 4, 10). This is in contrast to another consideration in the differential diagnosis, namely painless thyroiditis. In this autoimmune disorder, the gland is small and non-tender, and patients usually do not complain of pain (11). Patients with SAT commonly present with fatigue and mild hyperthyroid symptoms in addition to weight loss (3, 10).

Thyroid function tests in SAT usually follow a triphasic pattern. Early in the course, the patient experiences transient hyperthyroidism due to massive follicular destruction which leads to a suppressed TSH and elevated thyroxine. Subsequently, following depletion of preformed thyroid hormone, around 30% of patients go through a hypothyroid phase. Patients usually experience a spontaneous recovery of thyroid function, but the hypothyroid phase can last for several months before the thyroid function returns to the euthyroid state (3, 4).

Our patient did not have the classical signs or symptoms of SAT. The absence of neck pain and tenderness and the fact that he only presented with persistent fever and constitutional symptoms, made SAT or silent thyroiditis unsuspected. In addition, our patient's TSH was within the reference range at the time of presentation (low normal). We can reconcile these findings by noting the early, localized involvement of the thyroid gland by the inflammatory process. In fact, both the CT scan and the ultrasound of the neck described the involvement of only the infero-posterior portion of the gland. The affected, albeit restricted area, was shielded from palpation and did not result in the release of massive amounts of preformed thyroid hormone. Unchecked over

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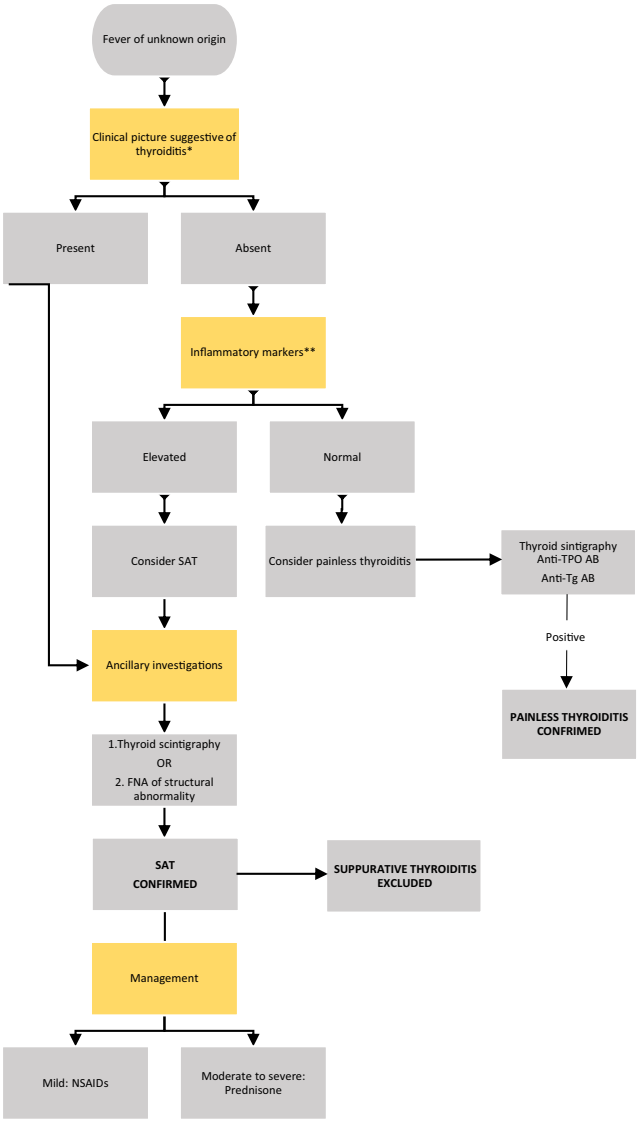

Figure 4
Suggested approach for thyroiditis as a suspected cause of fever of unknown origin. SAT, subacute thyroiditis; Anti-TPO AB, anti-thyroid peroxidase antibodies; Anti-Tg AB, Anti-thyroglobulin antibodies. *include: 1) upper respiratory tract infection prodrome, 2) thyroiditis (neck pain and swelling), 3) systemic symptoms (constitutional and/or thyrotoxic); ** ESR and CRP.

time, the inflammation would have progressed to other parts of the gland and would have become clinically apparent ('creeping thyroiditis').

Inflammatory markers, ESR and CRP, are usually high during the initial phase. Other findings may include mild anemia, leukocytosis, and elevated liver enzymes during the early hyperthyroid phase (3, 4, 8). Despite the localized nature of the thyroiditis on cross-sectional imaging in our patient, the acute phase reactants and elevated liver enzymes prompted further investigations for SAT. Most patients with SAT have negative antithyroglobulin antibodies and antithyroid peroxidase antibodies as opposed to painless thyroiditis in which 50% of patients have positive antibodies (3, 11). Both antibodies were negative in our case, making silent thyroiditis less likely. A low radioiodine uptake with high inflammatory markers confirm the diagnosis of SAT (4, 8). However, the contrast-enhanced CT scan precluded this investigation because of iodine interference with the tracer uptake by the gland. Ultrasound of the thyroid gland is not necessary for the diagnosis but, when performed, shows an enlarged patchy, hypoechoic thyroid with irregular margins and reduced vascularity (3, 4, 8). These same findings in our case prompted sonographic-guided FNAB which solidified the diagnosis by showing the typical cytologic features of SAT, including many multinucleated giant cells (Fig. 3).

There are no universal guidelines on the management of SAT. Usually, nonsteroidal anti-inflammatory agents (NSAIDS) are used as first-line agents for pain. If the symptoms persist despite the use of NSAIDs or if there are severe symptoms, corticosteroids are used. Acute suppurative thyroiditis should be excluded before starting steroids (2, 3, 7). Therapy with corticosteroids generally provides rapid relief of symptoms within 24–48 h (7) (Fig. 4).

Conclusions

FUO is a commonly encountered medical problem. Five to fifteen percent of cases go undiagnosed (10). In the absence of clinical and biochemical thyroid abnormalities, a thyroid problem can be overlooked. We presented a case of subacute thyroiditis presenting only with FUO and constitutional symptoms. In our case, a thyroid problem was brought to our attention only after an incidental thyroid abnormality was described on CT of the neck. Subacute thyroiditis is the most common endocrine disorder presenting as FUO. We have shown that it should be considered in the differential diagnosis once the common causes have been ruled out, even if localizing findings are absent and the initial TSH is within normal limits.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Author contribution statement

Ahmad Housin wrote the manuscript. Michael Tamilia was responsible for the supervision and editing of the manuscript. Marc Pusztaszeri reviewed the manuscript and provided the expertise on thyroid pathology. Ahmad Housin and Michael Tamilia take responsibility for the integrity of the data.

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