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Subacute Thyroiditis: An Unusual Presentation of Fever of Unknown Origin Following Upper Respiratory Tract Infection

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
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Patient: Male, 44-year-old
Final Diagnosis: Subacute thyroiditis
Symptoms: Fever
Medication: —
Clinical Procedure: None
Specialty: General and Internal Medicine

Objective: Rare disease

Background: Fever of unknown origin (FUO) is a diagnosis that requires a demanding workup from physicians before confirming a diagnosis. Thyroid diseases are a rare cause of FUO. Subacute thyroiditis is an inflammatory disease that can lead to a wide spectrum of presentations.

Case Report: We report a case of a previously healthy male who presented with persistent fever of 4 weeks following an upper respiratory tract infection associated with constitutional symptoms. His laboratory workup included complete blood counts (CBC), complete metabolic panel (blood urea and creatinine, liver function tests, and serum electrolytes), blood cultures, abdominal and pelvic ultrasound, and computed tomography abdomen and pelvis that were inconclusive. His thyroid function tests showed a hyperthyroid state and a thyroid scan confirmed a picture of thyroiditis. The patient was treated with Ibuprofen and then with prednisolone; he showed significant improvement over a few days and was discharged with treatment of tapering doses of prednisolone over 6 weeks. Two weeks after discharge the patient had a follow-up at an outpatient clinic and was found to be in good health with resolution of his symptoms.

Conclusions: Thyroid disorders are not a common cause of FUO, and even if the clinical assessment of the patient is not suggestive of thyroid disease, we should consider it a possible cause. and thyroid function test should be performed to exclude thyroid problems.

MeSH Keywords: Fever • Fever of Unknown Origin • Thyroiditis, Subacute

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Background

Thyroiditis is an inflammatory condition of the thyroid gland that consists of 3 main types. The first type is acute suppurative thyroiditis, which is a bacterial infection of the gland. The second type is subacute thyroiditis, which usually follows a viral infection. The third type is chronic thyroiditis, which is an autoimmune inflammation [1]. Subacute thyroiditis is an uncommon condition with an incidence of 4.9 cases per 100 000 population per year; it is a self-limiting disease that may last 2 to 7 months [2]. Thyroiditis usually has several phases: hyperthyroidism, which is the typical presentation, followed by an euthyroid state, followed by a hypothyroid state, and ultimately the restoration of normal thyroid function. Each phase lasts several weeks. Therefore, regular monitoring of the thyroid function is important to confirm the resolution of hyperthyroidism, to detect and follow the hypothyroid state and follow the subsequent normalization of thyroid function [2].

Thyroiditis has a wide spectrum of presentations. The most common clinical features are neck pain, thyroid tenderness on palpation, and a diffuse goiter (diffusely enlarged gland) [3–5]. Although fever and constitutional symptoms are common in this disease, persistent fever without neck pain or thyroid tenderness is a rare presentation. We report here a case of a patient with subacute thyroiditis who presented after a history of upper respiratory tract infection with fever of unknown origin (FUO), without neck pain, tenderness of the thyroid gland or goiter. We also reviewed the literature related to the patient's presentation.

FUO is defined as fever higher than 38.3°C on several occasions for a duration of more than 3 weeks with uncertain or provisional diagnosis after 1 week of hospital evaluation [6]. Classically, infections, malignancies, and connective tissue diseases constitute the major causes. However, many cases have no definite diagnosis. A prospective multicenter study in the Netherlands [7] showed interesting percentages for different etiologies of FUO. Infection-related causes were found in up to 16% of cases, while neoplastic causes were found in 7% of cases. Others causes, such as noninfectious inflammatory conditions, were found in 22% of the cases, while miscellaneous causes were found in 4% of cases, interestingly, in 51% of the cases, no obvious cause of fever was found.

Case Report

A 44-year-old male known to have hypertension, presented with fever for 4 weeks. The fever was daily, came in spikes, and was associated with chills, generalized fatigability, and odynophagia. He reported a weight loss of 3 kg for the same duration. Ten days before his presentation, he had a runny nose and sore throat which resolved with symptomatic treatment. He denied having a cough, chest pain, palpitation, heat intolerance, change in bowel habits, sick contact, or recent travel. There was no history of unprotected sexual contact. He did not smoke or consume alcohol. The patient had no history of intravenous drug use; he had no family history of thyroid diseases.

He had been treated at another hospital where his complete blood counts (CBC), serum electrolytes, kidney and liver function tests, blood cultures, abdominal and pelvic ultrasound and computed tomography of the abdomen and pelvis were inconclusive. He received 2 different consecutive courses of antibiotics for 7–10 days, each without clinical improvement.

He presented to our hospital with the persistence of his symptoms and more fatigue and persistent fever. On examination, he was in distress, fever of 38.5°C, heart rate of 100 beats per minute, and blood pressure of 130/80 mmHg. Neck examination showed no thyromegaly or lymphadenopathy. General and systemic examination was unremarkable. Laboratory investigations showed hemoglobin 12 g/dL, WBC 11 000, erythrocyte sedimentation rate (ESR) 57 mm/hour, C-reactive protein (CRP) 102 mg/L, thyroid stimulating hormone (TSH) 0.01 mIU/L

Table 1. Laboratory findings of the patient at presentation and after treatment.

	At presentation	Hospital course	4 weeks after discharge	12 weeks after discharge	Normal range
WBC count	11 000	12 000	8500	6000	4000–11 000
ESR	57	50	20	–	<30 mm/hr
CRP	102	176	85	7	0–5 mg/L
TSH	<0.01	<0.01	0.12	0.54	0.30–4.50 mIU/L
Free T4	46	37.7	21.2	–	11.6–21.9 pmol/L
Free T3	13	6.2	5.5	–	2.5–6.5 pmol/L

WBC – white blood cell; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; TSH – thyroid stimulating hormone.

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(Table 1) and negative anti-thyroid peroxidase. An autoimmune workup that includes antinuclear antibodies (ANA) was negative. The respiratory viral panel was done, and it was negative. Multiple sets of blood cultures, a urine culture, 2 malaria blood films (thin and thick), viral hepatitis serology (A, B, C, and E), brucella and human immunodeficiency virus (HIV) screening were negative. The patient's chest x-ray was normal, and a repeated ultrasound of the abdomen and pelvis was unremarkable. Thyroid scintigraphy showed decreases uptake in both lobes suggestive of thyroiditis.

Treatment was initiated with Ibuprofen 400 mg twice daily for 3 days but there was only minimal improvement in his symptoms. Consequently, prednisolone 40 mg daily was given and after 2 days he showed significant improvement of clinical condition with no fever reported. The patient was discharged on prednisolone tapering dose for 6 weeks with outpatient follow up. After 2 weeks, he was seen in the outpatient clinic and found to be in good health, with resolution of his symptoms. Repeated blood laboratory tests after 4 weeks showed gradual improvement in TSH levels, with a normal level after 12 weeks.

The ultrasound of the thyroid performed 1 month after discharge showed a heterogeneous thyroid, suggestive of a post-inflammatory period. The right lobe nodule, which was 0.8×0.7 cm, had minimal internal vascularity, no calcifications, and no evidence of regional infiltrations.

Discussion

Subacute thyroiditis is a granulomatous inflammation of the thyroid gland. Other names for it are sub-acute nonsuppurative thyroiditis, de Quervain's thyroiditis, painful thyroiditis, and giant cell thyroiditis. Subacute thyroiditis can be secondary to viral upper respiratory tract infection. Many viruses have been identified as the cause, such as coxsackie virus, mumps virus, measles virus, and adenovirus [8]. Some cases have shown a strong association with HLA-B35. Our patient had a history of sore throat 10 days before his presentation to our hospital which resolved with symptomatic treatment.

The main clinical presentation of subacute thyroiditis is neck pain [2]. The pain can be confined to the thyroid area or radiating through the neck to the jaw, throat, ears, or upper chest. An enlarged tender thyroid gland is usually found on palpation during the examination. Fever and constitutional symptoms are common as well. Symptoms of hyperthyroidism are found in 50% of cases [2]. Our patient did not exhibit neck pain or thyroid tenderness, but his main concerning complaints were persistent fever and fatigue, and on examination, he did not have a palpable thyroid gland or cervical lymphadenopathy.

Diagnosis is usually clinical and later confirmed with laboratory tests for hyperthyroidism which is seen in nearly all patients, and a high ESR, which can be >50 mm/hour and may exceed 100 mm/hour, or elevated CRP, and reduced radioiodine uptake in thyroid scan [4]. Ultrasound, if performed, may show enlarged and hypoechoic thyroid glands with reduced vascularity and irregular margin. In our patient both ESR and CRP were high, and both were helpful markers for monitoring treatment response, in addition to signs of clinical improvement. A study on the prevalence of elevated CRP in differentiating inflammatory from non-inflammatory thyroid disease found that elevated CRP is always found in subacute thyroiditis. Other findings may include mild anemia and leukocytosis. Liver function tests can be abnormal during the initial phase of the hyperthyroid state. Although our patient's liver function tests were normal, he had mild leukocytosis and mild anemia, which were resolved after treatment initiation.

A radioiodine imaging of the thyroid gland can show low uptake (usually less than 1% to 3%) or a minimal heterogeneous uptake of radionuclide uptake during the early stage.

On ultrasonography, the thyroid can be normal size or enlarged but will be diffusely or focally hypoechogenic. Ultrasound of the thyroid gland of our patient at 1 month after discharge showed features of post-inflammatory changes supporting previous inflammation.

Therapy, if needed, is usually directed toward relief of thyroid pain and tenderness, and alleviating symptoms of fever and myalgia as well as inflammation. It is usually practice to started with oral non-steroidal anti-inflammatory drugs (NSAID) and if there are no improvements in pain in 2 to 3 days, steroids therapy should be initiated. Our patient did not show signs of improvement on naproxen over 3 days; consequently, prednisolone was started, after which the patient showed significant improvement within a few days. Following recovery from the transient hyperthyroid state, a few patients may develop hypothyroidism which requires lifelong hormonal replacement therapy with levothyroxine [3]. Thyroid diseases are considered among the rare causes of FUO. After searching the literature, we found a number reported cases of subacute thyroiditis, mainly published after the year 2000, where patients presented with FUO [9–17]. Table 2 shows the main clinical and biochemical features and outcomes of the 8 cases. The age range was between 40 and 81 years, have male predominant. Almost all the cases had some associated symptoms with fever. Some of cases in the literature responded to NSAIDs or a short course of prednisolone (10 mg daily for 1 to 2 weeks), but due to persistence of symptoms despite the use of NSAID, or due to severe disease, a higher dose with prolonged duration of steroid might be needed to get better response and outcome, as was shown in 2 cases and the present case (see

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Table 2. Summary of reported subacute thyroiditis cases in presented the literature as pyrexia of unknown origin.

Case	Age	Gender	Main symptoms	Exam	Labs	Main Treatment	Outcome
Alexander et al. (2009) [9]	43	Male	Fever, neck pain for 1 month, no H/O if URTI	Goiter, tremors	ESR: 123 TSH: 0.0001 FT 4: 46	NSAIDs and beta-blocker at first but no response; prednisolone 60 mg for 2 weeks then tapper for 1 month	Hypothyroidism
Cunha et al. (2010) [10]	55	Female	Fever, night sweats for 1 month; H/O URTI		ESR: 98 CRP: 84 Ferritin: 611 TSH: 0.009 FT4: 2.1 ATG: pos.	Not mentioned	Not mentioned
Weiss et al. (2000) [11]	81	Male	Fever, confusion, and bilateral lower extremity weakness		ESR: 98 TSH: 0.02 FT4: 3.1 FT3: 6.0	Beta-blocker	Profound hypothyroidism at 3 months; euthyroidism at 14 months
Karachalios et al. (2010) [12]	72	Male	Fever, malaise for 1 month	No findings	ERS: 102 CRP: 52 TSH: 0.024 FT4: 185 ATG: neg.	Low dose steroid dose (prednisolone 10 mg), showed good response	Not mentioned
Kim et al. (2013) [13]	48/	Female	Fever, neck pain		ESR: 65 TSH 0. 065 CRP 2.07	Prednisone 10 mg per day (intravenous)	Hypothyroidism after 3 weeks
Burke et al. (2013) [14]	67	Female	Fever, myalgia, headache, and arthralgia		ESR: 79 TSH: 0.018 T4: normal, ATG: normal	A 2-week course of corticosteroid therapy	After 2 weeks, TSH level and ESR returned to normal. The patient was asymptomatic
Muqtadir et al. (2015) [15]	40	Male	Fever for 2 months	Unremarkable	ESR: 90 TSH: 0.02 FT4: 3.66 ATG: neg.	Prednisolone 10 mg for 10 days then stopped without tapering	Not mentioned
Raj et al. (2018) [16]	80	Male	Fever, headache, recurrent falls	Sinus tachycardia with a grade 2/6 systolic ejection murmur in the aortic area	ESR: 86 CRP 192 TSH: 0.01 Total T4: 13.4	Prednisone 40 mg daily	Not mentioned
Dalugama (2018) [17]	42	Male	Fever, malaise weight loss or 3 weeks	Bilateral cervical lymphadeno-pathy; anterior neck tenderness; no thyromegaly	ESR: 80 CRP: 112 TSH: 0.012 FT4: 42	Prednisolone 10 mg for one week then stopped	Euthyroidism
Present case	40	Male	Fever, chill, fatigability	Unremarkable	ESR: 57 CRP: 102 TSH: <0.01 Total T4: 49	Prednisolone 40 mg	Euthyroid

URTI – upper respiratory tract infection; H/O – history of; ESR – erythrocyte sedimentation rate (mm/hr); CRP – C-reactive protein (mg/L); TSH – thyroid stimulating hormone (μIU/mL); Total T4 (pmol/L); ATG – anti-thymocyte globulin (neg/pos/normal).

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Table 2). The current treatment of subacute thyroiditis in patients who present with the fever that is prolonged is usually guided by the assigned clinician. Treatment is mainly symptomatic with analgesics to control the inflammation and pain, and beta-blockers to control symptoms of hyperthyroidism.

Conclusions

In conclusion, although thyroid disorders are not a common cause of FUO, initial workup should include thyroid function tests even if the clinical picture is not suggestive of hyperthyroidism.

FUO has a wide spectrum of causes ranging from infectious causes to inflammatory and autoimmune conditions, which make the diagnosis sometimes challenging and subacute thyroiditis (a thyroid disorder) is one of the challenging conditions. Therefore, initial workup should include thyroid function tests even if the clinical picture is not suggestive of hyperthyroidism.

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