

Pyrexia of unknown origin: it can be de Quervain's thyroiditis!

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Abstract

Singer classified inflammatory diseases of the thyroid into three broad categories: acute, subacute, and chronic thyroiditis. Subacute disease includes granulomatous or de Quervain's thyroiditis and lymphocytic thyroiditis (silent); whereas the chronic group includes chronic lymphocytic (Hashimoto's thyroiditis) and fibrous (Riedel's) thyroiditis. Subacute thyroiditis (de Quervain's thyroiditis) is an uncommon, painful thyroid inflammatory disorder. This condition can manifest in various clinical forms. Physicians must be aware of its clinical features to make the correct diagnosis and initiate treatment appropriately. We report two cases that went from pillar to post without proper diagnosis for 4 weeks undergoing a battery of unnecessary investigations, causing emotional trauma, and increasing cost of the treatment. Although it is a self-limiting disease without mortality, it can be incapacitating due to its smoldering symptoms. A high index of suspicion is hence required for timely diagnosis and initiating appropriate therapy.

KEY WORDS: Thyroiditis, odynophagia, neck pain, technetium-99 pertechnetate

Introduction

Subacute thyroiditis (SAT) (de Quervain's or granulomatous thyroiditis) is a self-limiting, inflammatory thyroid disorder, which is usually associated with pain in the neck in the region of the thyroid in addition to other varied systemic symptoms.^[1] It is characterized by inflammatory destruction of the thyroid parenchyma with leakage of the colloid and its constituents into the circulation. The insult to the thyroid is followed by an inflammatory response, which is initially composed of polymorphonuclear leukocytes and later lymphocytes, plasma cells, and histiocytes. In most cases, it is caused by a viral infection and is generally preceded by an upper respiratory tract infection. It is a disease of the adults, predominantly

women.^[2] The true incidence of the disease is not known, due to the uncommon nature of the disease and as many of the cases go unnoticed due to the atypical clinical manifestations. Although this is a self-limiting disorder, the disease tends to smolder with time if it is not treated early. Physicians must hence be aware of the clinical features of this disorder to make the correct diagnosis and treat appropriately. We report here two cases that presented as pyrexia of unknown origin.

Case Reports

Case 1

A 50-year old woman, previously healthy, was admitted with fever of 25 days duration associated with body aches. She also developed severe pain on the right side of the neck 1 week prior to hospital admission with difficulty in swallowing due to throat pain. She had no history of joint pains, change of voice, hemoptysis, and foreign body ingestion. She was seen by various physicians for fever and treated for malaria and enteric fever with antibiotics. On examination in our hospital, she was coherent, febrile with temperature 105°F, pulse 124/min, and regular blood pressure of 120/70 mmHg. There were no enlarged lymph nodes, pallor, icterus, clubbing, or pedal edema.

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Examination of neck showed slightly enlarged thyroid gland with excruciating, diffuse tenderness in the right side of the neck. Examination of all major systems was normal. Her initial blood investigation reports are as in the Table 1. Her blood picture showed neutrophilic, leukocytosis, elevated erythrocyte sedimentation rate (ESR) 1st hour (Westergren), and C-reactive protein (CRP). Considering the possibility of acute tonsillar abscess and pharyngeal wall abscess, she was started on injection piperacillin–tazobactam and clindamycin. She was also referred to ENT surgeon. Her throat examination and indirect laryngoscopy were normal. Her chest radiograph and ultrasound of abdomen were within normal limits. Her blood and urine cultures did not grow any organism. Contrast-enhanced computed tomography of the neck was carried out in view of severe localized pain, was also normal except for a few subcenteric cervical and submandibular lymph nodes. High-resolution ultrasound (HRUSG) of the neck revealed diffuse hypoechogenicity of thyroid gland with a small 0.5 × 0.5 cm nodule on the right upper pole of the thyroid (Figure 3). Vascular Doppler showed reduced vascularity of the gland. A provisional diagnosis of de Quervain's thyroiditis was made and pertechnetate $^{99m}\text{TcO}_4^-$ scintigraphy of thyroid gland before ($^{99m}\text{TcO}_4^-$) scintigraphy. It showed very low (<1%) tracer uptake by the thyroid gland suggestive of thyroiditis (Figures 1 & 2). There was no cold area. Her thyroid-stimulating hormone (TSH), free T3, and free T4 levels were 0.1 $\mu\text{IU/mL}$ (normal range: 0.3–6.5 $\mu\text{IU/mL}$), 0.8 ng/mL (normal range: 0.8–2 ng/mL), and 11.6 mg/dL (normal range: 5.5–13.5 mg/dL), respectively. Fine needle aspiration cytology of thyroid was planned but the patient refused for the same. She was treated with oral prednisolone 20 mg once a day and nonsteroidal anti-inflammatory drug (NSAID) (brufen) to which she responded. Her antibiotics were stopped and she became pain free on day four of starting prednisolone. As her clinical history, investigations and response to steroids were typical of painful thyroiditis, thyroid antibody profile was not carried out. She was discharged on day seven of starting prednisolone with an advice to stop prednisolone after 14 days. Two weeks at follow-up, she was asymptomatic and was advised to undergo a repeat $^{99m}\text{TcO}_4^-$ thyroid scan and thyroid profile after 3 months.

Case 2

A 52-year-old woman was admitted for intermittent fever of 1 month duration. There were symptoms of upper respiratory infection for 3–4 days, 1 week prior to the onset of fever. She developed throat pain while swallowing both solid and liquid food for 15 days prior to hospital admission. There was no history of joint pains, hemoptysis, and any foreign body getting stuck in the throat in the recent past. She was treated by doctors outside with antimalarials for 7 days and antibiotics for 14 days. Her fever, however, persisted. On admission to our hospital, she was coherent, febrile with a temperature of 102°F. She did not have pallor, icterus, clubbing, and lymphadenopathy. She had enlarged, painful, tender thyroid swelling in the neck. She was hemodynamically stable and systemic examination was normal. Her initial blood investigation reports

are as in the Table 1. Her ESR at first hour (by Westergren) and CRP were elevated. Rest of the blood reports were within normal limits. Considering a probable diagnosis of de Quervain's thyroiditis, she treated with oral prednisolone 20 mg once a day for 2 weeks. HRUSG of the thyroid revealed heterogeneous echogenicity with areas of hypoechogenicity. Her TSH, free T3, and free T4 levels were 0.5 $\mu\text{IU/mL}$, 1.8 ng/mL, and 14.6 mg/dL, respectively. $^{99m}\text{TcO}_4^-$ scintigraphy of the thyroid was subnormal (0.1%). She responded dramatically to oral prednisolone, with resolution of pain and fever. She, however, complained of palpitation and lack of sleep. Her sleeping pulse rate was 104/min. She was started on oral propranolol 20 mg thrice a day to which she responded and was advised to continue it for 4 weeks. She was asymptomatic when last seen at follow-up in the outpatient department. Repeat TSH, T3 and T4 at four weeks were normal.

Discussion

Subacute granulomatous thyroiditis (de Quervain's thyroiditis) is an uncommon disease that represents 0.16%–3.6% of all thyroid disorders.^[1] It was first described in 1904. The eponym de Quervain refers to the pathologist who described the typical histological findings (giant cell, pseudotubercular, granulomatous thyroiditis). Viral thyroiditis refers to the etiological diagnosis, whereas SAT refers to the clinical course of the disease.^[2]

It is the most common cause of a painful thyroid gland. It is probably caused by a viral infection with mumps virus, echovirus, coxsackievirus, Epstein–Barr virus, influenza and adenovirus.^[3,4] It is not immunologically mediated. Women are three to five times more likely to be affected than men.^[1] The average age of onset is from 30 to 50 years with significant clustering of cases in summer and early autumn.^[5] Individuals with HLABW35 have an increased propensity for developing SAT.^[6]

It presents clinically with acute onset of pain in the neck over the thyroid region. The pain may be exacerbated by turning the head or swallowing, and may radiate to the jaw, ear, or chest.^[1–3] Neck pain may be unilateral to begin with as in our first case. Pain may be associated with constitutional symptoms such as fever, malaise, night sweats, joint pains, and sore throat. There is generally unilateral or generalized thyroid tenderness with firm enlargement of the gland. This is because of the stretching of the thyroid capsule by the underlying inflammatory disease process.^[1] Symptoms of hyperthyroidism may be present, because of the release of the preformed thyroid hormones (T3 and T4) in the circulation due to the damage to the follicular epithelium.^[2]

Pathologically, early in the disease process, there is disruption of the thyroid follicles with release of the colloid into the stroma. This elicits an inflammatory response dominated initially by the neutrophils and later by lymphocytes, histiocytes, and giant cells with resultant granuloma formation.^[7] Colloidophagy and multinucleate giant cells surrounding the

Table 1: Laboratory investigations on admission

Parameters	Patient 1	Patient 2	Normal range
Hemoglobin (g/dL)	11.2	12.6	11.5–16.5
WBC count (cells/mm ³)	13,200	8,600	4,000–11,000
Platelets (cells/mm ³)	1.5	2.4	1.3–4
Sr. creatinine (mg/dL)	0.9	0.8	0.5–1.5
Sr. bilirubin (mg/dL)	0.6	0.8	0.5–1
ALT (U/L)	36	34	5–50
AST (U/L)	42	40	5–45
ALP (KA)	105	112	56–125
Sr. Na ⁺ (mmol/L)	139	141	135–145
Sr. K ⁺ (mmol/L)	4.2	3.6	3.5–5
FBS (mg/dL)	98	96	70–90
ESR (Westergren) (mm)	110	100	<30
CRP (mg/dL)	4.1	14	0.5–1.5
Sr. albumin (g/dL)	3.9	3.4	3.5–5.5
Urine (routine)	Normal	Normal	Normal

WBC, white blood cell; Sr, serum; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; Na⁺, sodium; K⁺, potassium; ESR, erythrocyte sedimentation rate (1st hour); FBS, fasting blood sugar, CRP, C-reactive protein.

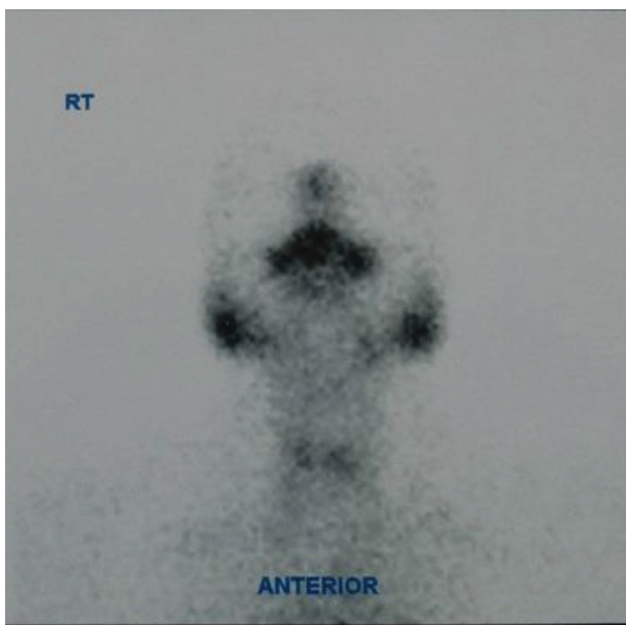


Figure 1: Thyroid scan of the first patient showing reduced uptake of tracer pertechnetate (99mTcO₄⁻).

colloid are characteristic features. In most cases, there is regeneration of the follicular epithelium and return of the thyroid function. Rarely fibrosis sets in the areas of destruction.^[6] Cytokine interleukin-6 has been implicated in thyroid destruction.^[7]

ESR usually is markedly elevated. A normal ESR essentially rules out the diagnosis of subacute granulomatous thyroiditis.^[9] The leukocyte count is normal or slightly elevated. Serum

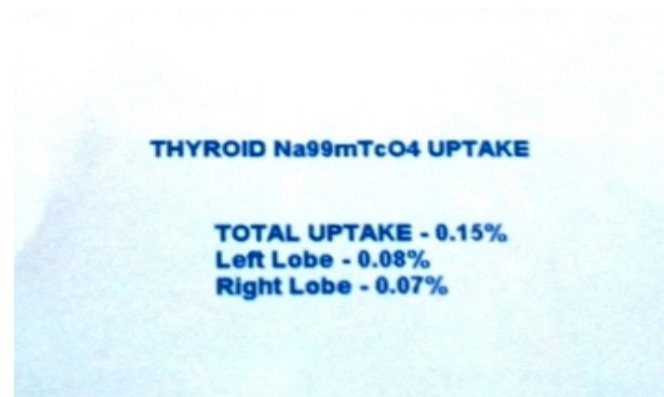


Figure 2: Thyroid scan of first patient showing reduced uptake of tracer pertechnetate (99mTcO₄⁻).

TSH concentrations are low to undetectable. Thyroid hormone levels may be elevated depending upon the stage of the disease. Ultrasound of the thyroid shows enlarged gland with a diffusely hypoechoic pattern in most of the patients. Radioactive iodine uptake (RAIU) is suppressed due to inability of the nonfunctioning follicular epithelium to concentrate iodine.^[6]

Therapy with antithyroid drugs is not indicated in these patients because this disorder is caused by the release of preformed thyroid hormone rather than synthesis of new T₃ and T₄.^[6] Therapy with beta-blockers may be indicated for the symptomatic treatment of thyrotoxicosis. Patients are reassured and NSAIDs are generally effective in reducing thyroid pain in mild cases. Patients with more severe disease require a tapering dosage of prednisone (20–40 mg/day) given



Figure 3: High-resolution ultrasound of neck of the first patient showing enlarged right lobe of thyroid with hypoechoic areas.

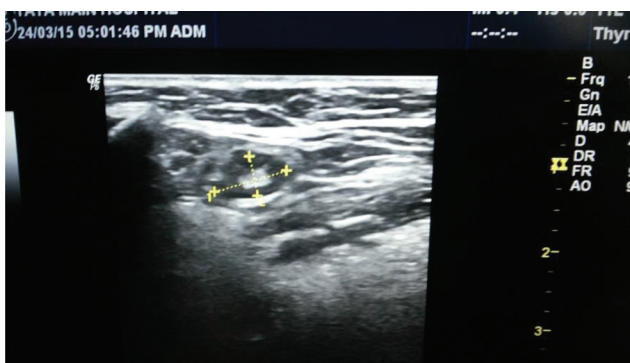


Figure 4: High-resolution ultrasound of neck of the first patient showing enlarged right cervical lymph node.

more than 2–4 weeks.^[8] Up to 20% of patients experience the recurrence of thyroid pain on discontinuation of prednisone.^[9]

Both the patients presented initially only with fever without any localizing symptoms and were treated outside as pyrexia of unknown origin by different doctors for infectious diseases, with antimalarials and antibiotics for variable duration. Thus, the disease can escape early recognition due to unusual presentation. Thyroid enlargement was too small to be noticed by the patients or their relatives. The clinical picture thus, simulated an acute to subacute infection. Even in our hospital, the first patient was seen by otolaryngologist to rule out acute tonsillitis, acute pharyngeal abscess in view of exquisite localized pain in the right side of the neck, and fever of 105°F on admission. A computed tomography scan of the neck was carried out, which was not necessary and added to the cost of the treatment. The diagnosis was suspected only after HRUSG of the neck was carried out. The second patient was rightly diagnosed in our hospital to have de Quervain's thyroiditis.

Several authors have reported a high incidence of diagnostic errors in this disease. In a review of 56 cases of SAT from Toronto General Hospital by Volpe and Johnston,^[9] there was wide variation in the onset and severity of the disease. In a study of clinical presentations of SAT in 23 patients from Western Saudi Arabia by Qari and Maimani,^[1] two patients had fever of unknown origin.^[4]

It is frequently mistaken for acute pharyngitis.^[10] Other mistaken diagnosis include acute tonsillitis, hyperthyroidism, hemorrhage into the cyst, nodular goiter, thyroid abscess, and rarely thyroid carcinoma, as rapidly growing thyroid cancer may be painful and tender.

The disease in its classic form is not difficult to diagnose. The combination of a painful, tender thyroid with an elevated ESR, low RAIU, and low TSH is virtually diagnostic. However, lack of awareness of this disorder has caused many errors in diagnosis.

Thus, awareness of the clinical manifestations of this disease is most important in preventing diagnostic errors. Early recognition and diagnosis are necessary for appropriate management of affected patients.

Conclusion

To conclude, de Quervain's thyroiditis is an uncommon disease that should be considered in the differential diagnosis of acute anterior neck pain, sore throat, painful deglutition, and fever especially if the patients do not respond to the treatment.^[1] In the clinical setting, technetium pertechnetate thyroid scan can help exclude other diseases, confirm the diagnosis, and expedite the initiation of appropriate therapy to prevent symptoms from smoldering for weeks.

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