Review Article

Subacute thyroditis — a review

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Subacute thyroiditis (SAT), also known as de Quervain's thyroiditis, is an important self-limiting cause of thyrotoxicosis. It is possibly a sequel of viral infection and histologically characterized by multinucleated giant cells around a colloid core along with neutrophil and lymphocyte infiltration. It affects both female and male (F:M 5:1) in their 3rd and 4th decade and clinically presents as fever, painful thyroid enlargement with other features of thyrotoxicosis such as weight loss, tremors, excessive perspiration and hyper-defecation. The course of disease is usually predictable, initial thyrotoxic phase (6-8 weeks) followed by short euthyroid phase (1-2 weeks) and hypothyroid phase (6-8 weeks) to complete recovery and restoration of euthyroidism. It is important to differentiate SAT from other causes of thyrotoxicosis as management strategy and prognosis differs significantly. Management in thyrotoxicsis phase includes pain management (NSAIDS or steroids) and ameliorating symptoms of thyrotoxicosis (beta blocker). There is no role of thionamides (Carbimazole or Methimazole) in management of Thyrotoxicosis due to SAT. Cautious short term levothyroxine supplement can be given in hypothyroid stage only if TSH >10 mIU/L and/or presence of symptoms. Usually long term prognosis is excellent.

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Subacute thyroiditis (SAT), also called de Quervain's thyroiditis is an important cause of Thyrotoxicosis. The classical presentation is presence of painful thyroid enlargement with other features of thyrotoxicosis such as weight loss, tremors, excessive perspiration and hyper-defecation. The clinical course is tri-phasic in form of initial thyrotoxicosis phase followed by euthyroid and then hypothyroid phase.

In this review we have detailed the epidemiology, pathophysiology, clinical features, diagnosis, differential diagnosis and treatment of SAT.

Epidemiology :

SAT Is considered an uncommon cause of Thyrotoxicosis in the West. SAT is suspected to have an infective etiology and hence it is not uncommon in India. However, it often remains undiagnosed and may present as Fever of Unknown origin[1]. Many of these cases are misdiagnosed as Graves disease and treated with Anti-thyroid drugs[2].

Subacute thyroiditis is more common in females as compared to males. According to an Indian series by Kalra et al, it is more common in the third decade. It has a seasonal predisposition with more cases reported from June to August in India. This seasonal trend observed in Indian patients often gives further endorsement to its infective origin[3].

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- **Subacute thyroiditis (SAT) or de Quervain's thyroiditis is an important cause of thyrotoxicosis with infective etiology.**
- **SAT should be differentiated from other causes of thyrotoxicosis as management strategy and prognosis differs significantly.**
- **NSAIDs, glucocorticoid are used for management of pain. Anti-thyroid drugs are not recommended in thyrotoxic phase.**
- **SAT is self-limiting with excellent long term prognosis.**

Pathogenesis and Pathophysiology :

As mentioned earlier, SAT is suspected to have an infective etiology and is thought to be caused directly or indirectly by a viral infection of the thyroid gland. This often follows an upper respiratory illness. Exact etiologic agent is not known, however mumps virus has been implicated in some cases. Other viruses affecting upper respiratory tract like coxsackievirus, influenza virus, echovirus, and adenoviruses may be other possible pathogens[4]. Thyroid autoimmunity does not appear to play a primary role in the disorder, but it is strongly associated with HLA-B35 in many ethnic groups. Molecular mimicry may play a role in pathogenesis as thyroid follicular cells have partial structural similarity with infection related antigen. However this process is self-limiting because unlike autoimmune thyroid disease, the immune reaction is not self-perpetuating[5].

In early phase (Thyrotoxic phase), viral attack and host mediated cytotoxicity or postviral inflammatory process leads to apoptosis of follicular epithelium and loss of follicular integrity. As a result, Thyroglobulin (Tg), preformed

Thyroxine (T4) and leothyronine (T3) are released into the circulation. Elevated T4 and T3 leads to clinical manifestations of thyrotoxicosis and suppress Thyrotropin (TSH) secretion. Biochemically, T3:T4 ratio remains normal as only stored hormones are released and Tg remains elevated which is often useful to differentiate with factitious thyrotoxicosis where Tg is usually suppressed.

This thyrotoxic phase undergoes spontaneous remission in 4-8 weeks, because most of the viruses causing SAT are self-limiting. At this time, the pool of stored thyroid hormone is mostly depleted and follicles are mostly destroyed. So thyroid gland is incapable of producing thyroid hormone, resulting in hypothyroidism which may last up to 2 months. As the inflammation subsides, the thyroid follicles regenerate and thyroid hormone synthesis and secretion resume, leading to euthyroidism. The rebound increase of TSH during this phase helps in follicular regeneration. Recovery is almost always complete.

Histopathologically, lesions are patchy in distribution and vary in their stage of development from area to area. Usually there is widespread infiltration with neutrophils and lymphocytes, disruption and collapse of thyroid follicles, and necrosis of thyroid follicular cells. One characteristic feature is presence of multinucleated giant cells around a colloid core, and that is why this is also known as giant cell thyroiditis[6]. During recovery phase, interfollicular fibrosis and an interstitial inflammatory reaction are present to varying degrees. However, an essentially normal histologic appearance is restored when the disease subsides.

Clinical Features, Diagnosis and Differential Diagnosis :

Subacute thyroiditis typically presents in three phases. The first phase is the thyrotoxicosis phase. This is followed by euthyroid and then hypothyroid phase. The patients in the hypothyroid phase often recover completely. Each of these phase may last for 2 to 8 weeks[7].

Subacute Thyroiditis Presentation As Thyrotoxicosis :

The thyrotoxicosis phase is often the most striking clinically and patients are often diagnosed during this phase of illness. Patients often present during this phase with hyperthermia, weight loss, tremors, tachycardia and pain in the neck region. A thyroid function test would suggest a typical biochemical identity of thyrotoxicosis in form of increased T3 and T4 with reduced TSH[8].

Often these patients are misdiagnosed as Graves disease and treated with anti-thyroid drugs. It is important to understand that all cases of thyrotoxicosis are not due to Graves' disease and hence donot merit treatment with Anti-thyroid drugs like Carbimazole, methimazole and PTU[9].

On clinical examination patients with Subacute thyroiditis lack the specific clinical features of Graves disease like Thyroid associated orbitopathy, thyroid dermopathy and thyroid acropachy. Thyroid associated orbitopathy (TAO) is often the most specific feature of Graves disease which is absent in Subacute thyroiditis. However, upper eyelid retraction may be often present in patients with SAT. Upper eyelid retraction is a result of sympathetic overactivity leading to persistent contraction of the Muller muscle of the eyelid. This is common to all causes of thyrotoxicosis and not limited to Graves disease. Exophthalmos however is specific Graves disease. Upper eyelid retraction can often simulate appearance of exophthalmos. Hence it is often important to measure the exact eyeball protrusion by exopthalmometry to differentiate a true exophthalmos seen in Graves disease from 'pseudoproptosis' seen in other causes of thyrotoxicosis[10].

Painful enlargement of the thyroid gland is often characteristic of SAT which is missing in Graves disease. Patients with SAT have pain in the thyroid region of the neck and may radiate to upper neck, jaw and upper chest. There is tenderness on palpation[8]. Patients with Graves disease on the other hand often has a diffuse, highly vascular goiter with absence of tenderness on palpation. Auscultation of the upper poles of the thyroid gland in case of a Graves disease reveals a thyroid bruit which is hallmark of the increased vascularity seen in Graves disease. The thyroid bruit is characteristically absent in case of SAT[11].

The pain and tenderness of the thyroid gland may also be seen in case of thyroid malignancy, acute suppurative thyroiditis and hemorrhage in a thyroid nodule. It is important to differentiate these conditions from SAT. Imaging of the thyroid gland, often combined with FNAC is useful to differentiate these conditions[12].

Ideally all patients presenting with thyrotoxicosis should undergo Tc99 Pertechnetate thyroid scan or Radioactive iodine uptake scan to differentiate the cases of thyrotoxicosis due to increase radioactive iodine uptake (also called Hyperthyroidism) from cases with reduced uptake. Reduced radioactive iodine uptake or Tc99 Pertechnetate tracer uptake is one of the characteristic features of SAT[3]. Patients with Graves diseases have an increased uptake. Toxic adenoma and toxic multinodular goiter have increased uptake in the specific region corresponding to the 'hot' nodule[11]. Fig 1 summarizes an approach to a patient presenting with thyrotoxicosis.

Another useful test to differentiate SAT from Graves disease is calculating the ratio of Total T3 and Total T4. In Graves disease there is a preferential production of T3 over T4 by the thyroid gland hence there is increase in Total T3/Total T4 ratio[13]. Increase of inflammatory mark-

ers like CRP and ESR are characteristically seen in SAT which are absent in case of Graves disease[14]. Table 1 summarize the differences between SAT and Graves disease.

Factitious thyrotoxicosis and painless thyroiditis are other common causes of reduced tracer uptake. Painless thyroiditis is differentiated from SAT on clinical ground. Painless thyroiditis, as the name suggests, if painless while SAT as described above is characteristically painful. Serum thyroglobulin (Tg) level is a useful test to differentiate factitious thyrotoxicosis due to excess intake of thyroxine from SAT. Serum Tg levels are reduced in case of factitious thyrotoxicosis while they are increased in case of SAT[15].

Table 1 — *Difference between Subacute thyroiditis and Graves' disease*

	Subacute Thyroiditis	Graves' Disease
History of recent Upper respiratory tract infection	Present	Absent
Pain in the neck region	Absent	Present
Thyroid associated orbitopathy	Absent (may have isolated upper eyelid retraction in some cases)	Present
Thyroid dermopathy	Absent	Present
Goiter	Tenderness present	No tenderness Diffuse enlargement
Thyroid bruit	Absent	Present
T3/T4 ratio	Normal	Raised
Radioactive iodine uptake scan / Tc99 Pertechnetate thyroid scan	Reduced uptake	Diffuse increase uptake
TSH receptor antibody	Negative	Positive
Treatment with Anti Thyroid drugs	Not required	Required
Follow-up	Tri-phasic – Thyrotoxicosis followed by Euthyroidism and then hypothyroidism	Persistent hyperthyroidism

Subacute Thyroiditis Presenting as Fever of Unknown Origin (FUO) :

Fever is defined as increased in body temperature with increase in hypothalamic set point, while hyperthermia is defined as increased in body temperature with normal hypothalamic set point. Thyrotoxicosis is an important cause of Hyperthermia[16].

A large number of cases have been reported in literature where patients with SAT have presented as differentials diagnosis of FUO. In a published case series by Das, more than 80% of the patients with SAT presented as FUO. Fever itself can cause excessive perspiration, tachycardia and sometimes weight loss because of anorexia. However, presence of characteristic pain in the thyroid region should merit an evaluation to rule out subacute thyroiditis[8]. Temperature more than 102°F are rarely in case of SAT and presence of relative bradycardia virtually rules out SAT[14].

Other Presentations of Subacute Thyroiditis:

Patients with subacute thyroiditis are often referred to endocrinologists with perplexing thyroid function tests. As described above, patients with SAT pass through three phase of their illness. Thyroid function test is often variable based on the phase of illness during which the thyroid function test was ordered. Additionally, the thyroid function test results may not concur with the observed clinical features. Hence in such cases in which subacute thyroiditis is suspected clinically, it is often advisable to repeat the thyroid function test after few weeks before any further investigation or treatment is is recommended.

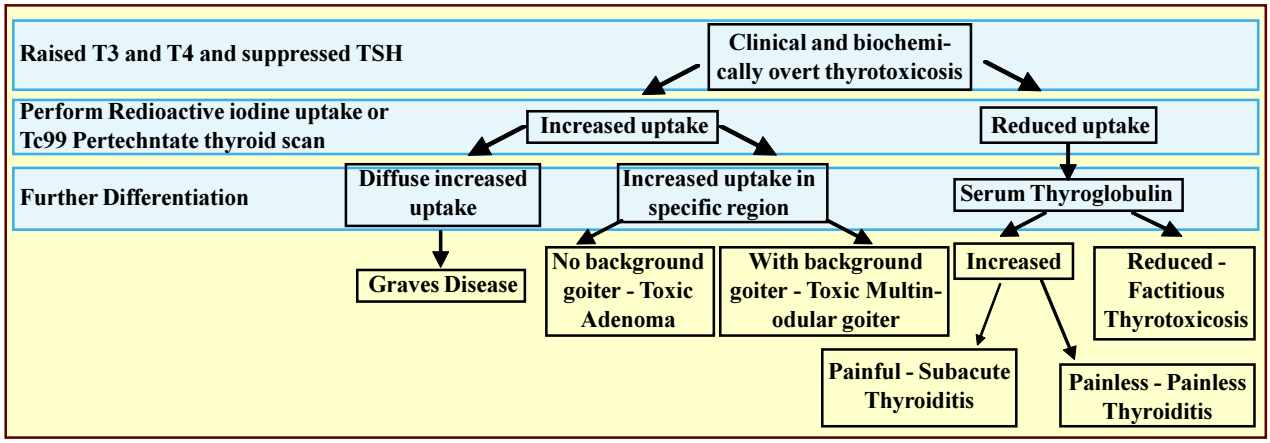
SAT often presents during the hypothyroid phase of the illness with biochemically subclinical or overt hypothyroidism. Thyroid peroxidase (TPO) antibody is useful in such a scenario. Patients with SAT have a negative TPO antibody, while those with Hashimoto's thyroiditis or postpartum thyroiditis (a form of painless thyroiditis) have high titers of TPO antibody. This differentiation is important because treatment with levothyroxine is indicated in patients with subclinical hypothyroidism with positive TPO antibody, while levothyroxine treatment may not be required in all patients with subclinical hypothyroidism due to SAT[17].

'Malignant pseudothyroiditis' is a term used for tender thyroid gland due to presence of underlying malignancy which may mimic SAT[18]. Temporal arteritis is another condition which produces pain, raised ESR and CRP and FUO. Hence temporal arteritis should also be considered an important differential diagnosis of SAT[19].

Treatment :

Treatment of SAT depends on the stage of the disease and mostly symptomatic. There are no trials assessing optimal treatment of subacute thyroiditis. However, in general, thyroid function should be repeated every two to eight week to confirm resolution of hyperthyroidism, detect transient hypothyroidism, and subsequent normalization of thyroid function.

Treatment target during thyrotoxic phase includes pain management and ameliorating symptoms of thyrotoxicosis. Most of the patients do not need any drug for pain management or need small doses of Nonsteroidal anti-inflammatory drugs (NSAIDS). Usually, those who need drug therapy for pain management, it is wise to start with acetylsalicylic acid (aspirin, 2600 mg daily) or an NSAID (eg, naproxen [500 to 1000 mg daily in two divided doses] or ibuprofen [1200 to 3200 mg daily in three or four divided doses]). Those not having any improvement in two to three days with NSAIDS or having severe pain at onset, should be offered prednisolone 40 mg daily. Prednisone therapy is highly effective for management of pain and should re-



sult in pain relief in one to two days; if not, the diagnosis should be questioned[20]. Once pain subsides, prednisolone should be tapered 5-10 mg every week to lowest possible dose as soon as possible. For recurrence of pain, restart prednisolone in full dose and continue atleast for 2 weeks and then attempt to taper again. Typically, a two to eight-week course of prednisone is required, and occasionally the course may be even more prolonged. Corticosteroid therapy may be associated with shorter overall disease duration[7].

If symptoms of thyrotoxicosis are mild and short lasting, no therapy is needed. However, those few patients who have bothersome symptoms of hyperthyroidism, such as palpitations, tremor or anxiety, may benefit from treatment with a beta blocker (for example, Propranolol 40 to 120 mg or atenolol 25 to 50 mg) daily for a few weeks while they are thyrotoxic. Thionamides should not be used because thyrotoxicosis in SAT is not caused by excess thyroid hormone synthesis[21].

Therapy for hypothyroidism is controversial. As most of the times symptoms are mild and short lived, treatment is not warranted. However, if TSH >10 mU/L and/or associated with more than mild symptoms, the patient should be given a short course of levothyroxine (50 to 100 mcg) and TSH should be kept in mid normal range. The T4 should then be discontinued, and the patient re-evaluated in four to six weeks to look whether euthyroidism is restored. TSH is needed for thyroid cell regeneration, so such therapy should be decreased as the symptoms subside[12].

Few patients suffer from recurrent attacks of SAT and needs mention. Studies are lacking for the best management strategy in this scenario. Prolonged steroid for pain management and radioiodine ablation during hypothyroid stage have been tried. Total thyroidectomy may be undertaken as a last resort[22].

Conclusion :

Subacute thyroiditis is an important cause of thyrotoxicosis and has an infective etiology. It typically presents as a painful thyroid enlargement, however it may present as FUO. NSAIDs are first line therapy for management of the pain associated with SAT. Glucocorticoids are used for patients who do not respond to NSAIDS and the response to glucocorticoids is generally dramatic. Anti-thyroid drugs are not recommended during the thyrotoxic phase of the illness. SAT Is a self-resolving illness with excellent long term prognosis. Primary care physicians need to be aware about SAT for timely diagnosis and treatment.

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(Continued on page 46)

(Continued from page 43)

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