SUBACUTE THYROIDITIS – AN UNDERESTIMATED DIAGNOSIS: DESCRIPTION OF A CASE SERIES

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Abstract. *Subacute thyroiditis is a relatively rare thyroid disease that develops after acute viral upper respiratory tract infection and manifests with neck pain, fever and transient hyperthyroidism. The diagnosis is often delayed due to the non-specific presentation and laboratory findings. It is misdiagnosed with upper respiratory tract infections, cervical lymphadenitis, even with acute pyelonephritis. The authors present a series of 12 patients with subacute thyroiditis and discuss the main steps in the diagnosis, differential diagnosis and treatment of this disease.*

Key words: *subacute thyroiditis, diagnosis, differential diagnosis, treatment*

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INTRODUCTION

Subacute thyroiditis (ST) is a rare immune-mediated inflammatory thyroid disorder that develops as non-suppurative painful thyroiditis, manifesting with tender and diffuse enlargement of the thyroid gland and non-specific constitutional symptoms (fever, fatigue loss of appetite), usually after upper respiratory tract infection [1]. Nodular and painless forms also have been described [1]. ST can present as fever of unknown origin with painless thyroid gland and subtle functional abnormalities [2]. The histological examination of the thyroid gland reveals granulomatous inflammation with giant cells. Thyroid function usually changes in time with a predictable course: thyrotoxicosis due to cell destruction, followed by euthyroid and short hypothyroid states and ultimately – normalization of thyroid function.

ST is also known as de Quervain's thyroiditis. It usually affects middle-aged and young adults, more often women (female : male ratio = 3-5 : 1) [3]. The incidence of ST is not well-understood because the

disease is frequently misdiagnosed for other conditions, such as upper respiratory tract infections, cervical lymphadenitis, bronchitis, etc. According to the Rochester Epidemiology Project in Olmsted county, Minnesota [3], the average annual incidence is 12.1 cases per 100 000 per year, with a higher incidence in females than in males (females : males = 19.1 : 4.1 per 100 000 per year), and in middle aged persons, with the incidence decreasing in elderly.

The pathogenesis of ST is not well understood. It is presumed to be caused by pathological immune response against the thyroid gland after viral infections (antigen mimicry, cross-reactivity, implantation of viral antigens within the thyroid, etc.). The incidence shows seasonal changes – higher in summer, and increase in epidemical areas with viral infections – Cocksackie, mumps, measles, adenovirus, etc. [4 ,5]. Yet, other studies reveal relatively steady incidence throughout the year [3, 6].

ST shows strong association with HLA-B35 molecule, expressed by human macrophages. It has been speculated that the thyroid damage is due to activation of

cytotoxic T-cells by the complex (viral) antigen-B35 and subsequent thyroid cell destruction by T-cells and by antibodies both directed against the antigen-B35 complex that has structural similarity to thyroid follicular cell antigens (i.e., antigen mimicry and cross-reactivity) [7, 8]. Viral inclusion bodies have not been described in ST [7]. Due to the transient character of the viral infections and the elimination of the viral antigens from the human body by the immune system, ST has a self-limiting course, unlike the chronic and progressive or relapsing-remittent course of immune thyroid diseases, such as Hashimoto's thyroiditis and Graves-Basedow's disease.

Independent of the triggering factor, ST usually leads to predictable changes in thyroid function, divided in four major stages, each lasting from 2 to 8 weeks (Table 1) [8].

After immune-mediated destruction of the follicular cells has begun, the thyroid gland becomes swollen and painful, constitutional symptoms develop (fever, fatigue, loss of appetite, etc.). The cellular destruction is associated with liberation of thyroid hormones and transient increase in their blood levels with clinical and biochemical signs of thyrotoxicosis (stage 1) without increase of thyroid function (increased FT4 and FT3 levels, suppressed TSH), along with increased leukocyte count, ESR and CRP levels. After the viral infection subsides, the immune-mediated destruction of the follicular cells ceases and restoration to euthyroid state (stage 2, it could be shorter than 2 weeks) is usually observed, with decrease in leukocyte count, ESR and CRP, and decrease in edema, tenderness and thyroid pain. This stage is followed by transient hypothyroid state (stage 3), explained by the restoration of the normal thyroid tissue and hormonal secretion, and restoration of normal thyroid function (stage 4). This cyclic course is explained by the changes in immune-mediated destruction of the gland and the natural restoration abilities of the thy-

roid. Recovery to euthyroid state is observed in the majority of cases, rarely permanent hypothyroidism requiring LT4 supplementation is observed [3,8]. The disease can recur in the same patient [3, 8].

Pathohistological examination of the thyroid reveals enlarged gland on gross examination, with widespread neutrophil, lymphocyte and histiocyte infiltration, giant-cell-containing granulomatous inflammation, follicle destruction and follicular cell necrosis on microscopic examination [8]. As it was mentioned above, no viral inclusion bodies within the thyroid tissue have been described [8]. Fine-needle aspiration biopsy shows the presence of inflammatory cells, clusters of follicular cells and colloid masses [8] and rarely demonstrates giant cells.

The clinical manifestations of ST are non-specific: edema and pain in the thyroid region, often irradiating towards the upper neck, ears, jaw or even upper chest, constitutional symptoms (fever, fatigue, loss of appetite, myalgia, arthralgia, etc.), symptomatic thyrotoxicosis [8]. As it was mentioned above, the thyroid can be painless and ST can manifest as fever or thyrotoxicosis of unknown origin. The symptoms can develop gradually or appear abruptly, with or without preceding respiratory tract infection. Due to the non-specific clinical symptoms, ST is often misdiagnosed for other inflammatory condition, affecting the neck or the respiratory tract. The course of the disease is usually self-limiting, even without treatment, but ST may recur.

The diagnosis is based on the typical pain and edema of the thyroid plus fever, increased acute-phase markers (ESR, CRP, leukocyte count), changes in thyroid hormone and TSH levels (depending on the stage of ST, as described above), and imaging studies [8]. Positive antithyroid antibodies (antithyroid peroxidase or antithyroglobulin antibodies) have been described in ST patients, probably as a result of immune response against the liberated thyroid antigens from the destructed follicular cells, as a process

Table 1. Clinical and laboratory stages of subacute thyroiditis

Parameter	Stages			
	Stage 1	Stage 2	Stage 3	Stage 4
Thyroid function	Thyrotoxicosis	Euthyroid	Transient hypothyroidism	Euthyroid (reconvalescence)
Neck pain, constitutional symptoms (fever, fatigue, etc.)	Marked	Subsiding	Subsiding	Absent
FT3, FT4	↑	Normal	↓	Normal
TSH	↓	Normal	↑	Normal
ESR, CRP	Marked increase	Start to decrease	(almost) Normal	Normal

of natural cleansing of the intracellular constituents from the necrotic cells [9].

The imaging studies are one of the pillars of ST diagnosis. Ultrasound examination reveals normal or enlarged thyroid gland with diffuse or local hypoechogenicity with low flow on Color-Doppler during thyrotoxicosis stage, as opposed to Graves-Basedow's disease where the flow is increased during thyrotoxicosis [10, 11]. After recovery thyroid ultrasound returns to normal [11]. Radionuclide assays demonstrate low uptake during thyrotoxicosis stage ($< 1-3\%$) or heterogeneous and faint radionuclide uptake [8].

The differential diagnosis should be made with acute suppurative thyroiditis, autoimmune thyroid disease (Hashimoto's thyroiditis and Graves-Basedow's disease), thyroid cancer, especially in nodular forms, neck lymphadenitis and lymphadenopathy of other origin, infectious diseases, especially in the cases of fever of unknown origin, acute inflammatory conditions of the upper respiratory tract, dental problems, temporal (giant-cell) arteriitis, other inflammatory diseases, including bronchitis, pneumonia, pyelonephritis, endocarditis, etc.

The treatment strategies in ST have several goals: a) decreasing the pain, fever and general symptoms with non-steroid anti-inflammatory drugs (NSAIDs) and/or corticosteroids, the latter being the primary treatment option in most cases; b) maintaining euthyroid state – beta-blockers in the thyrotoxic phase and LT4 in the hypothyroid phase, where clinically indicated; c) general supportive measures, including proper hydration, bed rest, gastroprotection, etc.

Up to date, there are no trials on the treatment of ST. Therefore, all treatment recommendations are based upon observational data and clinical experience. The pain and thyrotoxicosis may require temporary administration of non-steroidal anti-inflammatory drugs and/or corticosteroids plus beta-blocker treatment, respectively. Corticosteroids are generally more effective than NSAIDs, and gastroprotection is needed in both cases. Different NSAIDs have been administered in ST patients and all have shown clinical effect in therapeutic doses. When the symptoms are severe and when NSAIDs are ineffective or partially effective, corticosteroids are indicated – prednisolone 40 mg (8 tablets a day, or equivalent) with rapid reduction of the dose (decrease with 1 tablet every 5-7 to 14 days) to a maintenance dose of 5-10 mg (1-2 tablets) a day. If pain and edema re-occur, the dose should be increased by 1 or 2 tablets to the previous dose where the patient was asymptomatic. Usually within 2-8 weeks the symptoms and the thyroid dysfunction resolve. One should not forget that cortico-

steroid treatment offers rapid alleviation of symptoms and decrease in acute-phase markers of inflammation but it does not prevent the development of early- or late-onset thyroid dysfunction, nor the relapse of ST after subsequent upper respiratory tract or other infections. When overt thyrotoxicosis is observed, beta-blockers are indicated. When transient hypothyroidism is observed, LT4 may be needed for a short period of time. In patients with frequent relapses surgical treatment may be needed.

DESCRIPTION OF THE CASE SERIES

For the period October 1, 2015 – June 1, 2018 we observed overall 12 patients with subacute thyroiditis (ST), 3 male and 9 female, mean age 42.2 ± 11.1 years (18-56 years). The diagnosis ST was based on the typical clinical presentation and physical signs (neck pain, enlarged and painful thyroid gland with or without tachycardia and fever), laboratory signs (elevated ESR and/or CRP, hyperthyroid state) and ultrasound characteristics (enlarged hypoechogenic thyroid gland with decreased flow) [2, 3, 6, 10, 11]. Two male patients had metabolic syndrome with type 2 diabetes mellitus on oral anti-diabetic medications, one female and one male patient had Hashimoto's thyroiditis. Overall 8 patients were initially referred to otorhinolaryngologist or internal medicine specialist for suspected year-nose-throat, respiratory or other infection, and only 4 were referred directly to endocrinologist for suspected subacute thyroiditis.

All patients presented with neck pain and subfebrile fever, enlarged and tender thyroid gland, increased ESR (67.7 ± 30.7 mm/h., 25-106 mm/h.), 7 had mild anemia (hemoglobin levels of 106-122 g/l), CRP was investigated in 5 patients and was found increased in all of them ($16.7 - 318$ mg/l, normal range < 5 mg/l). All patients presented in hyperthyroid state – thyrotoxicosis in 10 and subclinical hyperthyroidism in 2. Anti-thyroid peroxidase antibodies were investigated in 10 and were found positive in 2, anti-thyroglobulin antibodies were investigated in 4 and were found positive in 1. The comparative analysis of female and male patients revealed no differences concerning the levels of ESR, TSH, FT4. The only borderline statistical difference (trend) between male and female patients was in the age – 50.7 ± 9.2 in male compared to 36.7 ± 9.6 years in female subgroup ($p = 0.052$).

Two patients underwent fine-needle aspiration biopsy and non-specific changes were found in all of them – inflammatory cells, follicular cells and colloid in the aspirate. No giant cells were detected in our series.

Overall 11 patients were started on corticosteroid treatment with prednisolone 0.5 mg/kg/day (30 to 40 mg prednisolone a day) with excellent therapeutic results. Only one male patient was started on NSAID treatment due to underlying diabetes mellitus and laboratory data for subclinical hypothyroidism with borderline increased ESR interpreted as reconvalescent ST, but due to insufficient effect was switched to prednisolone 0.5 mg/kg/day.

Overall 2 patients required temporary beta-blocker treatment for tachycardia.

lent effect in all our patients. Until now, we observed no relapses of ST.

Our case series brings forward several interesting problems. First, one female and one male patient had history of Hashimoto's thyroiditis, but presented with typical clinical course of ST with negative thyroid antibodies in the female patient and positive anti-thyroid peroxidase antibodies in the male. The clinician should not forget that the presence of one thyroid disease does not preclude the possibility of another. Second, ST can develop in diabetic

patients and this association underlines the importance of diabetes for the corticosteroid treatment of immune-mediated diseases. Two patients had concomitant type 2 diabetes mellitus at the background of metabolic syndrome. The presence of diabetes should not preclude the use of corticosteroid treatment if needed, but close blood glucose monitoring is mandatory in such cases and appropriate changes in antidiabetic treatment should be made if required. Moreover, in patients with ST and metabolic syndrome without overt diabetes, close monitoring of blood glucose is needed because of the risk of full-blown diabetes after the initiation of corticosteroids. And third, subacute thyroiditis may be misdiagnosed for other inflammatory diseases and should not be forgotten as a cause of fever of unknown origin, especially when neck pain is present.

In conclusion, we present a series of 12 patients with ST, the majority are female, middle-aged and otherwise healthy, only 2 patients had an established thyroid disease (Hashimoto's thyroiditis), and 2 patients were diabetic (one of them with Hashimoto's thyroiditis). The diagnosis ST was based on the typical clinical picture, laboratory findings of acute inflammation and hyperthyroid state, and ultrasound changes. Fine-needle aspiration biopsy is usually not needed in ST patients and the results are non-specific. The treatment consisted in anti-inflammatory agents (corticosteroids in 11 and NSAID in 1, followed by corticosteroids due to insufficient effect), short course with beta-blockers in 2. In all patients we observed subsiding of inflammation and restoration of thyroid function.

Fig. 1. Thyroid ultrasound examination of the thyroid gland – enlarged gland with decreased parenchymal echogenicity

DISCUSSION

Subacute thyroiditis is a relatively rare immune-mediated inflammatory thyroid disease presumed to be caused by a post-viral inflammatory process [8]. It is characterized by pain in the neck and the presence of swollen and tender thyroid gland, fever, fatigue, anorexia, with or without symptoms of dysthyroid condition. The clinical course of ST follows well-defined and predictable changes in thyroid function: usually initial hyperthyroid phase at presentation, followed by transient euthyroidism, hypothyroidism and returning to euthyroid state. For a period of 29 months we observed overall 12 cases of ST, diagnosed with neck pain, the presence of painful goiter, laboratory signs of acute inflammation and dysthyroid state. The majority of patients were female (female : male ration = 3:1), middle-aged and otherwise healthy. The majority of patients were initially misdiagnosed for other inflammatory conditions (8 of 12 were misdiagnosed for having ear-nose-throat, respiratory or other infection) but eventually were referred to endocrinologist with suspected subacute thyroiditis. Corticosteroid treatment was initiated in 11/12 and the last patient was first started on NSAID and subsequently switched to corticosteroids. Corticosteroid treatment had excel-

The results of our study show that ST should be considered as a cause of neck pain and fever of unknown origin. In patients with diabetes mellitus corticosteroid treatment is not contraindicated but it requires close monitoring of blood glucose levels.

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