Subacute, Silent, and Postpartum Thyroiditis

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KEYWORDS

• Thyroiditis • Subacute thyroiditis • Silent thyroiditis
• Postpartum thyroiditis

Thyroiditis is a broad term that indicates thyroid gland inflammation. There are many types of thyroiditis, which can generally be divided into painful or painless categories.[1] Painful types include subacute and suppurative thyroiditis, as well as unusual cases induced by radioactive iodine administration, trauma, or other rare causes. Painless types include Hashimoto thyroiditis, the most common type of chronic thyroid disease, as well as silent, postpartum, drug-induced, and Riedel thyroiditis.

Thyroid function in patients with thyroiditis depends on the type of thyroiditis and, in certain cases, evolves from thyrotoxicosis to hypothyroidism and eventually to restoration of normal thyroid function. This classic triphasic course of thyroid dysfunction is characteristic of the 3 entities considered in this article: subacute, silent, and postpartum thyroiditis. The other types of thyroiditis are not discussed further, except in the context of the differential diagnosis. **Table 1** provides a comprehensive summary of the text of this article and can be referenced throughout the discussion that follows.

SUBACUTE THYROIDITIS

Clinical Findings and Course

Subacute thyroiditis, also called subacute granulomatous or de Quervain thyroiditis, is the most common cause of thyroid pain.[1,2] This condition usually presents as a prodrome of low-grade fever, fatigue, and pharyngitis symptoms. The thyroid gland becomes extremely painful and tender to palpation, with pain often radiating up to the jaw or ear and associated dysphagia. The pain can be unilateral or bilateral. The thyroid gland can be enlarged up to 3 to 4 times its normal size, but an extremely large or grossly nodular goiter is not characteristic of subacute thyroiditis and should raise the possibility of alternate diagnoses.

About 50% of patients with subacute thyroiditis have an initial thyrotoxic phase because of unregulated release of preformed thyroid hormone from damaged thyroid

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Med Clin N Am 96 (2012) 223–233
doi:10.1016/j.mcna.2012.01.003 **medical.theclinics.com**
0025-7125/12/$ – see front matter

Table 1
An overview of pertinent findings in subacute, silent, and postpartum thyroiditis

	Subacute Thyroiditis	Silent Thyroiditis	Postpartum Thyroiditis
Clinical findings	Viral URI prodrome, small painful goiter, symptoms and signs of thyroid dysfunction (variable)	Small painless goiter, symptoms and signs of thyroid dysfunction (variable)	Small painless goiter, symptoms and signs of thyroid dysfunction (variable)
Clinical course	Classic triphasic course (thyrotoxic, hypothyroid, recovery) but variable	Classic triphasic course (thyrotoxic, hypothyroid, recovery) but variable	Classic triphasic course (thyrotoxic, hypothyroid, recovery) but variable
Demographics	Incidence: approximately 3/100,000/y ♀:♂, 4:1 Peak age, 40–50 y Seasonal	♀:♂, 4:1 Peak age, 30–40 y More common in areas of iodine sufficiency	♀ only Occurs within 12 mo of pregnancy 8%–11% of pregnancies
Etiology	Probably viral	Probably autoimmune	Autoimmune
Laboratory findings	Elevated WBC, ESR, CRP level; approximately 25% have antithyroid antibodies, usually low titer; thyroid function varies with phase	Approximately 50% have antithyroid antibodies, thyroid function varies with phase	>80% have antithyroid antibodies, thyroid function varies with phase
Imaging	Decreased RaIU in thyrotoxic phase US: variable heterogeneous texture, hypoechogenic	Decreased RaIU in thyrotoxic phase US: variable heterogeneous texture, hypoechogenic	Decreased RaIU in thyrotoxic phase US: variable heterogeneous texture, hypoechogenic
Pathology	Granulomatous infiltrate	Lymphocytic infiltrate	Lymphocytic infiltrate
Differential diagnosis	Painful thyroid gland: rarely Hashimoto disease, Graves disease, RaI, amiodarone, contrast dye, suppurative thyroiditis, amyloid	Thyrotoxic phase: Graves disease Hypothyroid phase: Hashimoto disease	Thyrotoxic phase: Graves disease Hypothyroid phase: Hashimoto disease
Treatment	For pain: NSAIDs, glucocorticoids Thyrotoxic phase: β-blockers Hypothyroid phase: L-T_4	Thyrotoxic phase: β-blockers Hypothyroid phase: L-T_4	Thyrotoxic phase: β-blockers Hypothyroid phase: L-T_4
Long-term outcomes	5%–15% hypothyroid beyond a year	10%–20% hypothyroid beyond a year	15%–50% hypothyroid beyond a year
Recurrence rates	1%–4% after a year	5%–10% (much higher in Japan)	70% in subsequent pregnancies

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RaI, radioactive iodine; URI, upper respiratory illness; US, ultrasonography; WBC, white blood cell count.

follicular cells.[2] Therefore, if patients present early in the course of the disease, they may have clinical findings of thyrotoxicosis, although this is often mild. This phase usually lasts about 3 to 6 weeks, ending when the thyroid stores of preformed hormone are depleted. About one-third of patients subsequently enter a hypothyroid phase that can last up to 6 months. Thyroid pain has usually resolved by this time, and the predominant clinical features are those of hypothyroidism with a continued small goiter. Most patients return to euthyroidism within 12 months of onset of disease.

Demographics

The most comprehensive study of subacute thyroiditis analyzed 94 cases seen over 27 years in Olmsted County, Minnesota. The incidence rate was 3 cases per 100,000 per year in the most recent years of the survey.[2] Women seem to be more affected than men, in a 4:1 ratio.[2–5] The peak age of incidence is 40 to 50 years. Some studies suggest that there is a seasonal peak of cases during spring, summer, or fall, but this finding has not always been confirmed. There is no geographic or familial clustering.

Etiology

Subacute thyroiditis is probably caused by a viral infection of the thyroid gland. Implicated conditions include infections caused by Coxsackie virus, Epstein-Barr virus, adenoviruses, and influenza viruses; mumps; measles; primary human immunodeficiency virus infection; and a recent well-documented case occurring during an H1N1 influenza infection.[6]

Laboratory Findings

Patients with subacute thyroiditis have elevated erythrocyte sedimentation rates (often >50 mm/h) and C-reactive protein levels, consistent with acute inflammation.[2,3,5] The white blood cell count can be mildly elevated, although marked elevations raise the question of suppurative thyroiditis. During the thyrotoxic phase, thyrotropin (TSH) levels are low and free thyroxine (T_4) levels may be elevated, depending on the degree of thyrotoxicosis. During the hypothyroid phase, TSH levels are high and free T_4 levels may be low. Up to 25% of patients have low titers of antithyroid antibodies, although very high titers raise the question of painful autoimmune thyroiditis.[2–4,7]

Imaging Findings

A hallmark of subacute thyroiditis is low radioactive iodine uptake (RaIU) during the thyrotoxic phase, because the inflamed thyroid gland does not trap iodine.[7] As the thyrotoxic phase ends, the RaIU returns to normal or even becomes elevated during the hypothyroid phase. It is not necessary to obtain an ultrasonography of the thyroid in subacute thyroiditis, but, if ultrasonography is performed, it often shows inhomogeneous hypoechogenic texture, sometimes with nodules, because of the inflammatory process.[2,4,5,7,8]

Pathology

A biopsy of the thyroid gland is not usually necessary in subacute thyroiditis. However, if biopsy is performed due to uncertainty of the diagnosis, its result shows granulomatous infiltrate, sometimes with giant cells, consistent with a viral infection.[2]

Differential Diagnosis

In a patient who presents with a painful tender thyroid gland, by far the most common cause is subacute thyroiditis. However, there are other unusual causes of thyroid pain that must be considered if the patient has a consistent history, unusual symptoms, or a markedly enlarged gland.[9,10] These causes include Hashimoto disease, Graves disease, radioactive iodine administration, amiodarone-induced thyroiditis, contrast dye–induced thyroiditis, acute suppurative thyroiditis, or amyloid goiter.

During the thyrotoxic phase, the main differential diagnosis is between subacute thyroiditis and Graves disease. A recent history of neck pain indicates subacute thyroiditis, whereas the presence of ophthalmopathy or a thyroid bruit indicates Graves disease. Serum triiodothyronine (T_3) levels and T_3:T_4 ratios tend to be lower in subacute thyroiditis than in Graves disease, but there is significant overlap in thyroid hormone levels.[11] A definitive diagnosis can be made by RaIU measurement, because uptake is low in subacute thyroiditis and elevated in Graves disease.[7] Care must be taken to perform the RaIU test while the patient is still thyrotoxic, because RaIU increases as the patient enters the hypothyroid phase.

During the hypothyroid phase, the main differential diagnosis is between subacute thyroiditis and Hashimoto disease. A history of neck pain can be helpful but is often forgotten by patients if there was no obvious intervening thyrotoxic phase brought to medical attention earlier. Measurement of antithyroid antibodies may be helpful, because they tend to be absent or in low titer in subacute thyroiditis. In the absence of a definitive diagnosis, the patient may need monitoring or temporary treatment to see if the thyroid dysfunction resolves over time.

Treatment

Nonsteroidal antiinflammatory agents (NSAIDs) are the first-line treatment of thyroid pain in subacute thyroiditis. With NSAIDs alone, the median time for complete resolution of pain is 5 weeks, with a range of 1 to 20 weeks.[2] Glucocorticoids are used for severe cases or if NSAIDs are not effective. Typical prednisone dosages are 30 to 40 mg per day for 1 to 4 weeks, followed by tapering doses. Pain resolution is faster with glucocorticoids than with NSAIDs.[2] If glucocorticoids are stopped too soon, pain can recur and require restarting the drug for a longer course.[2,12]

β-Blockers are used for control of symptoms during the thyrotoxic phase, although often no treatment is needed if symptoms are mild. Thionamides (methimazole and propylthiouracil) are ineffective, because thyrotoxicosis is caused by the release of preformed thyroid hormone, rather than synthesis of new thyroid hormones. Once the patient enters the hypothyroid phase, levothyroxine (L-T_4) can be used to treat symptoms if needed. L-T_4 should also be administered if the patient is considering pregnancy regardless of symptoms. L-T_4 should be continued until 12 months have elapsed since the onset of subacute thyroiditis and can then be discontinued, because most patients would have fully recovered by that time.

Recurrence Rates and Long-Term Outcomes

Almost all patients with subacute thyroiditis recover full thyroid function, but about 5% to 15% have persistent hypothyroidism after 12 months.[2,4,5] In addition, recurrence rates of 1% to 4% have been described.[2] Recurrences are managed in the same manner as the initial occurrence, but, rarely, thyroidectomy has been used for repeated relapses.[2]

SILENT THYROIDITIS

Clinical Findings and Clinical Course

Silent thyroiditis, also called subacute lymphocytic thyroiditis, classically presents with the same triphasic course described earlier for subacute thyroiditis: thyrotoxicosis, followed by hypothyroidism, and eventual restoration of normal thyroid function.[1,13] The thyrotoxic phase occurs in 5% to 20% of patients and typically lasts 3 to 4 months. The hypothyroid phase is more common or at least is recognized more often. This phase typically lasts up to 6 months, before return to normal thyroid function, for a total duration of illness of up to 12 months. A small goiter is common but, unlike subacute thyroiditis, not painful.

Demographics

The incidence of silent thyroiditis is not well delineated, with reports that it accounts for 0% to 23% of thyrotoxicosis cases.[14–16] Silent thyroiditis seems to be more prevalent in areas of higher dietary iodine intake, accounting for up to 30% of cases of thyrotoxicosis in Japan.[17] Women are affected more commonly than men, in a 4:1 ratio.[13] The peak age of incidence is 30 to 40 years.

Etiology

Silent thyroiditis is probably autoimmune in nature, given the frequent presence of antithyroid antibodies and the characteristic pathologic findings of lymphocytic infiltration of the thyroid gland.[18]

Laboratory Findings

During the thyrotoxic phase of silent thyroiditis, TSH levels are low and free T_4 levels may be elevated, depending on the degree of thyrotoxicosis. During the hypothyroid phase, TSH levels are high and free T_4 levels may be low. About 50% of patients have antithyroid peroxidase (anti-TPO) antibodies.[1]

Imaging Findings

As in subacute thyroiditis, patients with silent thyroiditis have a low RaIU during the thyrotoxic phase.[1] Similarly, because the thyrotoxic phase ends, the RaIU returns to normal or becomes elevated during the hypothyroid phase. Ultrasonography of the thyroid often shows inhomogeneous hypoechogenic texture.[19]

Pathology

A thyroid gland affected by silent thyroiditis has a diffuse lymphocytic infiltrate that resembles Hashimoto disease but lacks Hürthle cells, lymphoid germinal center formation, or fibrosis of Hashimoto disease.[18,20]

Differential Diagnosis

During the thyrotoxic phase, the main differential diagnosis is between silent thyroiditis and Graves disease. The presence of ophthalmopathy or a thyroid bruit indicates Graves disease. Serum T_3 levels and T_3:T_4 (or free T_3 to free T_4) ratios tend to be lower in silent thyroiditis than in Graves disease, but there is significant overlap in thyroid hormone levels.[11,21,22] Titers of thyroid receptor antibodies (TRAb) or thyroid-binding inhibitory immunoglobulins are usually much higher in Graves disease than in silent thyroiditis,[11,19,23,24] although there is no cutoff with 100% accuracy. Doppler ultrasonography tends to show higher blood flow in Graves disease.[19,24] A definitive diagnosis can be made by RaIU measurement, because uptake is low in silent thyroiditis and elevated in Graves disease. Care must be taken to perform the RaIU test while

the patient is still thyrotoxic, because RaIU increases as the patient enters the hypothyroid phase.

During the hypothyroid phase, the main differential diagnosis is between silent thyroiditis and Hashimoto disease. Measurement of antithyroid antibodies is often not helpful, because they may be present in either case. In the absence of a definitive diagnosis, the patient may need monitoring or temporary treatment to see if the thyroid dysfunction resolves over time.

Treatment

Treatment of silent thyroiditis is similar to that of subacute thyroiditis, except that NSAIDs or glucocorticoids are not used, because there is no neck pain. β-Blockers are used to control symptoms during the thyrotoxic phase, although often no treatment is needed if symptoms are mild. Thionamides are ineffective and not used. Once the patient enters the hypothyroid phase, L-T_4 can be used to treat symptoms if needed. L-T_4 should be administered if the patient is considering pregnancy regardless of symptoms. L-T_4 should be continued until 12 months have elapsed since the onset of silent thyroiditis and can then be discontinued.

Recurrence Rates and Long-Term Outcomes

Most patients with silent thyroiditis recover full thyroid function, but about 10% to 20% have persistent hypothyroidism after 12 months.[1] Recurrence rates are about 5% to 10% but may be much higher in Japan, with one study from Japan reporting a long-term recurrence rate of 65%.[20] Recurrences are managed in the same manner as in the initial occurrence, but some patients with multiple recurrences have opted for radioactive iodine ablation of the gland.[20]

POSTPARTUM THYROIDITIS

Clinical Findings and Clinical Course

Postpartum thyroiditis is defined as the development of thyroid dysfunction in a previously euthyroid woman within 12 months after pregnancy. Almost all cases occur after a term pregnancy, although there are reports of cases developing after a miscarriage. Like subacute and silent thyroiditis, the clinical course is classically triphasic, with an initial thyrotoxic phase followed by a hypothyroid phase and an eventual return to a euthyroid state, all within 12 months.[25] However, the pattern of thyroid dysfunction is quite variable; 25% to 40% of patients exhibit the classic triphasic course, whereas 20% to 30% develop only thyrotoxicosis and 40% develop only hypothyroidism.[25–27] The thyrotoxic phase occurs at 2 to 6 months post partum (median time of onset, 13 weeks) and is usually asymptomatic. However, irritability, heat intolerance, fatigue, and palpitations are more common in thyrotoxic women with postpartum thyroiditis.[28] This phase typically lasts 2 to 3 months. The hypothyroid phase occurs 3 to 12 months post partum (median time of onset, 19 weeks) and is often symptomatic, with cold intolerance, dry skin, loss of energy, and problems with concentration.[25,28] Most patients have a small painless goiter. Given the known effects of altered thyroid function on mood, investigators have questioned whether postpartum thyroiditis may play a role in the development of postpartum depression.[28] However, results from these studies have been mixed, and one randomized controlled trial of L-T_4 therapy in anti-TPO–positive postpartum women did not report a reduction in the incidence of postpartum depression.[29]

Demographics

Postpartum thyroiditis occurs in 8% to 11% of unselected pregnancies, with some variability owing to the population studied and the frequency of monitoring.[25,30–32]

There are several well-defined risk factors that greatly increase a woman's chance of developing postpartum thyroiditis. The best predictor is the presence of anti-TPO antibodies at the end of the first trimester of pregnancy, with 30% to 50% of these women progressing to postpartum thyroiditis.[25,28,30,33] Women with a past history of thyroid disease have a 40% risk of developing postpartum thyroiditis, whereas those with type 1 diabetes mellitus or a family history of thyroid disease have a 20% risk.[30]

Etiology

Postpartum thyroiditis is autoimmune in nature, with an HLA linkage, anti-TPO antibodies in most patients, laboratory findings of immune system activation, and dense lymphocytic infiltrates in affected thyroid glands.[28]

Laboratory Findings

Laboratory tests of thyroid function in postpartum thyroiditis are similar to those in subacute and silent thyroiditis. During the thyrotoxic phase, TSH levels are low and free T_4 levels may be elevated, depending on the degree of thyrotoxicosis. After the thyrotoxic phase, the American Thyroid Association recommends obtaining a serum TSH level test every 2 months in all women with postpartum thyroiditis until 1 year post partum, to monitor for the development of hypothyroidism.[28] During the hypothyroid phase, TSH levels are high and free T_4 levels may be low. More than 80% of patients have anti-TPO antibodies.[28]

Imaging Findings

As in subacute and silent thyroiditis, patients with postpartum thyroiditis have a low RaIU during the thyrotoxic phase.[1] Similarly, because the thyrotoxic phase ends, the RaIU returns to normal or becomes elevated during the hypothyroid phase. Ultrasonography of the thyroid almost always shows inhomogeneous hypoechogenic texture.[34]

Pathology

Pathology test results of the thyroid gland in postpartum thyroiditis show dense lymphocytic infiltration consistent with the autoimmune nature of the disease but without germinal centers or extensive Hürthle cell metaplasia that can be seen in Hashimoto disease.[1]

Differential Diagnosis

During the thyrotoxic phase, the main differential diagnosis is between postpartum thyroiditis and Graves disease. There may in fact be some overlap because both are autoimmune processes, and women with a history of 1 entity can eventually develop the other. The presence of ophthalmopathy, a thyroid bruit, or TRAb indicates Graves disease. T_3 levels and T_3:T_4 ratios are higher in Graves disease than in postpartum thyroiditis. A definitive diagnosis can be made by RaIU measurement because uptake is low in postpartum thyroiditis and elevated in Graves disease. However, it can be logistically difficult to perform an RaIU test on a postpartum woman because issues of breastfeeding and neonatal exposure to the radioactive iodine must be taken into account.

During the hypothyroid phase, the main differential diagnosis is between postpartum thyroiditis and Hashimoto disease. There is likely overlap, because a significant number of women with postpartum thyroiditis eventually develop permanent autoimmune hypothyroidism. Measurement of antithyroid antibodies is not helpful because these antibodies are usually present in either case. In the absence of a definitive

diagnosis, the patient may need monitoring or temporary treatment to check if the thyroid dysfunction resolves over time (see caveats later).

Treatment

Treatment of postpartum thyroiditis is similar to that of silent thyroiditis, with extra caution indicated for breastfeeding women. β-Blockers are used for control of symptoms during the thyrotoxic phase, although often no treatment is needed if symptoms are mild. Once the patient enters the hypothyroid phase, L-T_4 can be used to treat symptoms if needed. L-T_4 should be administered if the patient is considering another pregnancy regardless of symptoms. If treatment is not started for hypothyroidism, TSH levels should be rechecked every 1 to 2 months until the patient is 12 months post partum.[28]

The issue of whether to continue L-T_4 after 12 months have elapsed since the onset of postpartum thyroiditis is complicated. Permanent hypothyroidism is common in postpartum thyroiditis, especially in certain high-risk subgroups (see later). Many of these women are still breastfeeding, and L-T_4 should be continued. Other women may be considering another pregnancy within a year, and intercurrent hypothyroidism would be detrimental to the pregnancy and developing fetus. Therefore, the decision to discontinue L-T_4 in women with postpartum thyroiditis should be individualized, based on the patient's likelihood of permanent hypothyroidism and personal situation.[28]

There have been 3 randomized controlled trials that attempted to prevent postpartum thyroiditis in high-risk women. Two trials of iodine or L-T_4 supplementation performed during or after pregnancy in women with anti-TPO antibodies failed to reduce the risk of postpartum thyroiditis.[35,36] In contrast, selenium administered to anti-TPO–positive women during and after pregnancy decreased the rate of postpartum thyroiditis from 50% in placebo-treated women to 29% in selenium-treated women.[37] The rate of permanent hypothyroidism decreased from 20% to 12%. However, the recent American Thyroid Association guidelines do not recommend treating high-risk women with selenium until its safety and efficacy can be further evaluated.[28]

Recurrent Rates and Long-Term Outcomes

In anti-TPO–positive women who recover from postpartum thyroiditis, there is a 70% recurrence rate in subsequent pregnancies.[25,28] In the long-term, 15% to 50% of women with a history of postpartum thyroiditis develop permanent hypothyroidism.[26,31,33,37–42] The longest study to date reported on more than 700 women who had postpartum thyroiditis 12 years earlier; 38% had hypothyroid.[31] Risks of permanent hypothyroidism increase in women with a hypothyroid phase of postpartum thyroiditis, high titers of anti-TPO antibodies, a hypoechogenic ultrasonography, or higher TSH levels at 6 months post partum.[31,33] Given these risks, all women with a history of postpartum thyroiditis should have TSH levels checked every year indefinitely.[28]

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