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Subacute Thyroiditis and Painless Thyroiditis: Clinical Characteristics of 221 Patients Diagnosed between 2009 and 2015

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Background and Objectives: In the past, subacute thyroiditis causing thyrotoxicosis included both painful and painless subgroup, but it is representative for the painful subacute thyroiditis these days. So we evaluated the clinical and laboratory characteristics of subacute thyroiditis and compared with the painless (silent) thyroiditis, and identified predictive factors of permanent hypothyroidism and recurrence. **Materials and Methods:** This was a retrospective case series study analyzing clinical data of 221 consecutive patients diagnosed between 2009 and 2015. Medical records were reviewed for diagnostic route, age distribution, laboratory data, clinical course and long-term follow up outcome. **Results:** The mean age was 48 years; female v/s male ratio 3.4:1. Median disease duration was 110 days; mean peak free T4 level was 2.9 ng/dL. 56.7% of painless thyroiditis patients were diagnosed on health checkup or routine thyroid function test with symptoms not typically associated with thyrotoxicosis. Permanent hypothyroidism was not uncommon (11/221; 5.0%). Higher peak thyroid-stimulating hormone (TSH) was associated with permanent hypothyroidism in painless thyroiditis. Lower peak TSH was associated with recurrence rate in both subacute and painless thyroiditis. In painless thyroiditis, short duration of thyrotoxicosis phase was also associated with recurrence rate. **Conclusion:** Considerable numbers of painless thyroiditis without symptoms were diagnosed on health checkup. Higher peak TSH was associated with permanent hypothyroidism in painless thyroiditis. Recurrence rate was related with lower peak TSH in both groups.

Key Words: Subacute thyroiditis, Painless thyroiditis, Postpartum thyroiditis, Permanent hypothyroidism, Recurrence

Introduction

Thyrotoxicosis can be associated with the early phase of subacute thyroiditis in both painful and painless variants. Painful subacute thyroiditis has been termed granulomatous or de Quervain's thyroiditis and commonly representative of subacute thyroiditis nowadays. So in our study, all subacute thyroiditis patients were divided into subacute thyroiditis and painless (silent) thyroiditis group, including painless postpartum thyroiditis. Here we collected and compared clinical characteristics and laboratory data of subacute thyroiditis and painless thyroiditis. We also accumulated data about how painless thyroiditis was diagnosed. Painless thyroiditis is a common disease that can be seen in inpatient and outpatient clinic. There is a certain portion of painless thyroiditis without symptom diagnosed

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on health checkup or thyroid function test screening on admission. But there is a few data on percentage of eventual prevalence of painless thyroiditis without symptoms of thyrotoxicosis. So we analyzed diagnostic route of painless thyroiditis.

Subacute thyroiditis is typically diagnosed by pain or tenderness of neck and/or symptoms of thyrotoxicosis.[1,2] It is a self-limited, possibly viral, inflammatory thyroid disease. The natural history of subacute thyroiditis involves 3-4 phases that generally last over 4-6 months. The initial phase of thyrotoxic state may last 2-6 weeks. The spilling of thyroid hormones into the circulation due to the acute inflammatory process is responsible for the thyrotoxicosis seen in the first phase. After transient asymptomatic euthyroidism, a short phase of mild hypothyroidism follows in most patients.[3-6] Permanent hypothyroidism caused by subacute thyroiditis has been reported in up to 5-15% of patients.[7-9]

Although the clinical features and outcome of subacute thyroiditis have been described, data on predictive factors of permanent hypothyroidism and recurrence are lacking.[10,11] Furthermore, some studies lack data on radioiodine scan or image.[12-15] No study has examined clinical characteristics or predictive factors of recurrence or permanent hypothyroidism of subacute and painless thyroiditis in Republic of Korea. In this study, we reviewed the medical records of 221 consecutive patients with subacute thyroiditis and painless thyroiditis to identify clinical characteristics and predictors of permanent hypothyroidism and recurrence.

Materials and Methods

The medical records of 221 consecutive patients with subacute thyroiditis and painless thyroiditis who were diagnosed in our medical center between 2009 and 2015 were reviewed for age distribution, laboratory data and outcome.

We defined subacute thyroiditis as a disease with neck tenderness or pain and typical clinical courses of thyrotoxicosis with sequential transient or permanent hypothyroidism and radioiodine scan. Painless thyroiditis was defined as a disease with same clinical courses and radioiodine scan finding of subacute thyroiditis without neck tenderness or pain. We excluded Hashimoto's thyroiditis by analyzing initial thyroid hormone test and presence of goiter. Patients with Graves' disease were excluded on the basis of radioiodine scan and clinical course. All patients were divided into subacute thyroiditis and painless thyroiditis, including painless postpartum thyroiditis group associated with pregnancy. Patient with permanent hypothyroidism developed after thyroiditis was defined as patients who remained hypothyroidism state even after 4-6 months and needed levothyroxine supplementation.

A commercial chemiluminescence immunoassay (ECLIA, Roshu [Kobas 2601]) was used to measure serum thyroid-stimulating hormone (TSH) (normal reference values, 0.27-4.2 μIU/mL), free T4 (FT4) (normal, 0.93-1.70 ng/dL), total T3 (normal, 0.8-2.0 ng/mL) and antithyroid antibodies (normal range for thyroid stimulating receptor [TSH-R] <1.74 IU/L, and for anti-thyroid peroxidase [TPO] <34 IU/mL). Erythrocyte sedimentation rate (ESR) was examined by capillary photometry kinetic method. Categorical variables were compared using the chi-square tests. Continuous variables, reported as mean with standard deviation (SD), were compared using a Mann Whitney U-test. Pearson's correlation analysis was used to describe the correlation between quantitative variables. All statistical analysis was performed using the SPSS version 18.0 statistical software program (SPSS, Chicago, IL, USA). The results were considered to be statistically significant when the p value was less than 0.05.

Results

Patient Characteristics

Total 221 patients were involved in this study. 171 patients were female, 50 patients were male. The sex ratio was 3.4:1. There were 64 subacute thyroiditis patients and 157 painless thyroiditis patients, including 15 painless postpartum thyroiditis patients.

Clinical Characteristics and Laboratory Data

Weight loss was presented in 52 patients. Fatigue was observed in 39 patients, goiter in 34 patients, febrile sense or chilling in 29 patients, palpitation in 28 patients, and tremor in 24 patients. The clinical characteristics and laboratory data of the 221 patients included in the study are summarized in Table 1. Age distribution ranged from 23 to 88 years (mean age, 48). It shows both subacute thyroiditis and painless thyroiditis patients were distributed especially in age 30–69. Age distribution of postpartum thyroiditis was higher in 30–39 due to the age of women in their childbearing years (Fig. 1).

The mean ESR was 59.2±37.0 mm/h in subacute thyroiditis patients. Median peak free T4 was 2.9 ng/dL in total subacute and painless thyroiditis patients. Peak free T4, peak TSH, duration, and incidence of permanent hypothyroidism showed no significant difference between subacute thyroiditis and painless thyroiditis, except that ESR was higher in subacute thyroiditis, duration of thyrotoxicosis was longer in painless thyroiditis.

Anti-TPO antibodies were positive in 7 of 29 patients (24%) in painless thyroiditis. Painless thyroiditis recurred in 22 of 157 patients (14%), 2 of whom had positive anti-TPO antibody. Recurrence rate was not higher in the group with positive anti-TPO antibody.

Diagnostic Route of Painless Thyroiditis

The routes that painless thyroiditis was diagnosed were classified under four entry. First, Patients diagnosed on health checkup (including patients diagnosed on health checkup in other local clinics): 36 patients, 22.9%. Second, inpatients or outpatients who were evaluated with thyroid function test because of nonspecific other symptoms (ex. dizziness, heart failure, etc.) in clinics include out endocrinology: 53 patients, 33.8%. Third, patients who were evaluated with thyroid function test because of thyrotoxicosis symptoms (fatigue, palpitation, tremor, etc.): 53 patients,

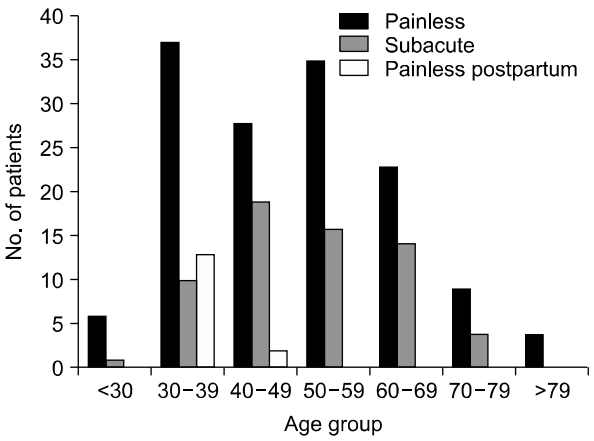

Fig. 1. Age distribution of subacute and painless thyroiditis, including postpartum painless thyroiditis patients (postpartum thyroiditis is not included in painless thyroiditis in this figure).

Table 1. Laboratory findings of subacute thyroiditis and painless thyroiditis

	All patients (n=221)	Subacute thyroiditis (n=64)	Painless thyroiditis (n=157)	p value
Age (years) (median, range)	48 (23–88)	50.5 (26–76)	47.0 (23–88)	0.078§
Female gender (%)	77 (171/221)	88 (56/64)	73 (115/157)	0.032†
ESR (mm/h) (mean±SD)	36.5±33.2	59.2±37.0	27.0±26.7	<0.001§
Anti-TPO antibody (%)	21 (9/43)	14 (2/14)	24 (7/29)	0.693‡
Anti-TSH receptor antibody (%)	6 (8/133)	3 (1/27)	6 (7/106)	>0.999‡
Peak FT4 (ng/dL) (mean±SD)	2.93±3.3	4.0±5.8	2.5±1.3	0.738§
Duration of thyrotoxicosis (days)	52.9	39.5	59.1	0.038§
Peak TSH (mU/L) (median)	22	21	22	0.057§
Overall duration (days) (median)	110	120	106	0.800§
Permanent hypothyroid (%)	5 (11/221)	8 (5/64)	4 (6/157)	0.304‡
Recurrence (%)	12 (28/221)	9 (6/64)	14 (22/157)	0.994‡

§Mann-Whitney U-test
†Chi-squared test by two-sided Pearson's exact test
‡Chi-squared test by two-sided Fisher's exact test
FT4: free thyroxine, TPO: thyroid peroxidase, TSH: thyroid stimulating hormone

33.8%. Fourth, patients diagnosed after delivery, postpartum thyroiditis: 15 patients, 9.6%. Thus, 89 cases (56.7%) of painless thyroiditis were diagnosed on health checkup or routine thyroid function test with symptoms not typically associated with thyrotoxicosis.

Clinical Characteristics and Laboratory Data with Extremely High Free T4

Peak free T4 during thyrotoxicosis phase was more than 2-fold of normal in 38 patients and there were some patients with extremely high free T4 in our study. We found four cases of extremely high peak free T4 more than or equal to 20 ng/dL. All these four patients had neck pain. Three patients were women, one patient was man, with age distribution 34 to 60. These patients tend to go through longer duration of thyrotoxicosis. ESR elevation was not significantly higher than the other patients and existence of antibody was not in consideration because antibody was not checked in half of the patients. One patient experienced one recurrence, the other one patient showed permanent hypothyroidism. In textbook, extremely high free T4 is assumed to be Graves' disease, but there was patient with subacute thyroiditis that free T4 exceeded 30 ng/dL.

Correlation of Clinical Characteristics and Laboratory Data with Permanent Hypothyroidism

Permanent hypothyroidism developed in 11 patients (5.0%) of all subacute and painless thyroiditis patients. Table 2 shows arranged laboratory data of subacute and painless thyroiditis to distinguish predictive factors of permanent hypothyroidism after thyroiditis. In subacute thyroiditis group, there was no statistically significant predictive factor of permanent hypothyroidism. When compared with the other patients, patients with permanent hypothyroidism showed no difference in ESR, antibodies, free T4 and TSH. Longer overall duration was the result of long-term follow up period of permanent hypothyroidism. On the other hand, laboratory data of painless thyroiditis shows that higher peak TSH seems to be related with permanent hypothyroidism ($p<0.001$).

Correlation of Clinical Characteristics and Laboratory Data with Recurrence

There were 28 patients (12.7%) who experienced recurrence in both groups. The recurrence rate (9% vs. 14%) showed no statistically significant difference between subacute thyroiditis and painless thyroiditis. Among 28 patients, 18 patients were female and 10 patients were male. Among the patients who experienced recurrence, three patients experienced 3 times of recurrence, two patients experienced 2 times of recurrence.

We analyzed laboratory data to find predictive factors of recurrence of subacute thyroiditis and painless thyroiditis on Table 3. In subacute thyroiditis, low peak TSH measured in the clinical course of subacute thyroiditis was associated with recurrence rate ($p\leq 0.007$). Even at painless thyroiditis, low peak TSH was associated with recurrence rate ($p\leq 0.018$). One more predictive factor of recurrence in painless thyroiditis was short duration of thyrotoxicosis phase ($p\leq 0.001$).

Table 2. Laboratory findings of subacute and painless thyroiditis according to permanent hypothyroidism

	Subacute patients (n=64)	Permanent hypothyroidism in subacute thyroiditis (n=5)	p value	Painless thyroiditis (n=157)	Permanent hypothyroidism in painless thyroiditis (n=6)	p value
Anti-TPO antibody (%)	14 (2/14)	0 (0/2)	>0.999†	24 (7/29)	66 (2/3)	0.136†
Anti-TSH receptor antibody (%)	3 (1/27)	0 (0/1)	>0.999†	6 (7/106)	33 (1/3)	0.178†
Peak TSH (mU/L) (median)	21	35	0.127*	22	53	<0.001*
Overall duration (days) (median)	120	430	<0.001*	106	868	<0.001*

*Mann-Whitney U-test
†Chi-squared test by two-sided Pearson's exact test
TPO: thyroid peroxidase, TSH: thyroid stimulating hormone

Table 3. Laboratory findings of subacute and painless thyroiditis according to recurrence

	Subacute thyroiditis patients (n=64)	Recurrence in subacute thyroiditis (n=6) (9%)	p value	Painless thyroiditis (n=157)	Recurrence in painless thyroiditis (n=22) (14%)	p value
Peak TSH (mU/L)	21	12.72	0.007*	22	6.38	0.018*
Peak FT4 (ng/dL) (mean±SD)	4.0±5.8	2.5±1.3	0.991*	2.5±1.3	2.9±1.3	0.086*
Duration of thyrotoxicosis (days) (mean)	39.5	56.3	0.325*	59.1	48.6	0.001*
Overall duration (days) (median)	120	100	0.566*	106	112	<0.001*

*Mann-Whitney U-test
FT4: free thyroxine, SD: standard deviation, TSH: thyroid stimulating hormone

Table 4. Clinical characteristics of painless thyroiditis patients according to postpartum history

	Postpartum thyroiditis (n=15)	Non-postpartum painless thyroiditis (n=142)	p value
Age (years) (median, range)	35 (32-41)	49.5 (23-88)	<0.001§
Female gender (%)	100 (15/15)	70 (100/142)	0.012†
Anti-TPO antibody>60 (%)	60 (3/5)	17 (4/24)	0.075†
Anti-TSH receptor antibody>10 (%)	15 (2/13)	5 (5/93)	0.187†
Peak FT4 (ng/dL) (mean±SD)	2.2±1.2	2.7±1.6	0.135§
Peak TSH (mU/L)	36.87	19.93	0.071§
Liver function test abnormality (%)	30 (3/10)	17 (21/124)	0.384†
Hypothyroid phase (%)	53 (8/15)	31 (44/142)	0.091†
Permanent hypothyroid (%)	20 (3/15)	2 (3/142)	0.012†
Recurrent disease (%)	13 (2/15)	14 (20/142)	>0.999†

§Mann-Whitney U-test
†Chi-squared test by two-sided Pearson's exact test
‡Chi-squared test by two-sided Fisher's exact test
FT4: free thyroxine, SD: standard deviation, TPO: thyroid peroxidase, TSH: thyroid stimulating hormone

Recurrence rate was not higher in the group with positive anti-TPO antibody.

Postpartum Thyroiditis

Postpartum thyroiditis is believed to be the consequence of over reactivation in immune system after delivery. In postpartum thyroiditis, ages of the patients were lower, because of childbearing age (Table 4). Permanent hypothyroidism developed more in postpartum thyroiditis patients than non-postpartum painless thyroiditis patients group (20% vs. 2%, p≤0.012). But it should be considered that the number of postpartum thyroiditis patients was only 15. There was no difference in the incidence of liver function test abnormality, incidence of hypothyroid phase, recurrence rate and presence of thyroid antibodies between postpartum thyroiditis patients and non-postpartum painless thyroiditis patients.

Discussion

Subacute thyroiditis (de Quervain's thyroiditis) is a transient, inflammatory thyroid disease associated with neck pain as well as thyrotoxicosis symptoms. The results of our study reconfirmed clinical characteristics of patients with subacute thyroiditis previously reported by others.[4-7]

The mean age was 40 years in the study of 1127 subacute thyroiditis patients.[16] Iitaka et al.[17] reported mean age of 38.4 years in 3344 subacute thyroiditis patients. The mean age of our patients with subacute thyroiditis was 50.5. Similar to previous studies, the majority of our patients were between 30-69 year of age.[18,19]

The mean age of painless thyroiditis in our study was 47.0. Painless thyroiditis was also more prevalent

in females, with female:male ratio of 2.7:1. 56.7% of our patients with painless thyroiditis were diagnosed on health checkup or routine thyroid function test with symptoms not typically associated with thyrotoxicosis. So there may be more cases of painless thyroiditis that can be ignored undiagnosed and many patients with heterogeneous parenchymal echogenicity on sonographic finding without history of thyroid disease may have experienced undiagnosed thyroiditis without symptom.

Permanent hypothyroidism is a known complication that can occur in 5–15% of subacute thyroiditis.[7–9] The rate of permanent hypothyroidism in all patients involved in our study was 5.0% (11/221) and it was not different between subacute thyroiditis and painless thyroiditis group. There may be different pathogenesis of transient or permanent hypothyroidism. Transient hypothyroidism is caused by temporary destruction of thyroid cells by inflammation. In permanent hypothyroidism, subacute thyroiditis may trigger auto reactive B cells to produce TSH-receptor antibodies, resulting in TSH receptor antibody-associated thyroid dysfunction in some patients.[8,20–22] Antithyroid antibodies were detected in 20–50% of patients with subacute thyroiditis or painless thyroiditis and disappeared during the recovery phase in most of them.[8,9,12] Some studies suggest that antithyroid antibodies were the only factor associated with permanent hypothyroidism in subacute thyroiditis.[11,23] In our study, antithyroid antibodies were not associated with permanent hypothyroidism. Instead, higher peak TSH showed statistically significant association with permanent hypothyroidism only in painless thyroiditis. But further study with large number of subacute and painless thyroiditis patients will be needed to confirm the difference.

Recurrence of subacute thyroiditis is reported to be rare in many studies. One study reported 4 recurrent episodes of subacute thyroiditis occurred in 3 of 222 patients (1.4%).[24] In a larger study that evaluated data for 3344 patients with subacute thyroiditis between 1970 and 1993, subacute thyroiditis recurred in 48 of 3344 patients (1.4%) (mean, 14.5±4.5 years after the first episode). Five patients experienced a third episode (mean, 7.6±2.4 years after the second episode).[17] Nishihara et al.[25] reported recurrent episodes of subacute thyroiditis at intervals of 13.6±5.6 years which were accounted for 1.6% of all cases. But other studies show higher recurrence rate of approximately 9–20% in subacute thyroiditis patients.[10,14,15] The recurrence rate of 12.7% (28 patients) in our study was also relatively high. Of whom, three patients experienced 3 times of recurrence, two patients experienced 2 times of recurrence. Theoretically, late recurrence after several years possibly occurs after the disappearance of immunity to the previous viral infection. But there is no definite evidence supporting this theory, because the titers of various viral antibodies were not increased during the clinical course of recurrence.[24] Of course, our study has limitation that exact level of peak free T4 and TSH would be underestimated because thyroid function test was not done frequently in the course of disease. But we analyzed predictive factors of recurrence and found low peak TSH was associated with recurrence of subacute thyroiditis and painless thyroiditis ($p \leq 0.05$). Low peak TSH could probably mean recurrence of thyroiditis at recovering phase of hypothyroidism and the interval of recurrence was very short in some patients. Still, there should be more studies with large number of patients about predictive factors of permanent hypothyroidism and recurrent thyroiditis.

In summary, our study of contemporary and relatively large series of patients with subacute or painless thyroiditis confirmed some of the clinical characteristics previously reported by others. More than half of painless thyroiditis were diagnosed on health checkup or routine thyroid function test without symptoms of thyrotoxicosis. Permanent hypothyroidism was not uncommon (5.0%) and higher peak TSH was associated with permanent hypothyroidism in painless thyroiditis. Recurrence was relatively common (12.7%) and recurrence rate was higher in both subacute thyroiditis and painless thyroiditis with low peak TSH.

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