Subacute thyroiditis: Clinical characteristics and treatment outcome in fifty-six consecutive patients diagnosed between 1999 and 2005

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ABSTRACT. ***Objective:*** **To identify predictive factors of clinical outcome of subacute thyroiditis.** ***Design:*** **Retrospective case series of 56 consecutive patients treated in 3 outpatient clinics between 1999 and 2005. Medical records were reviewed for demographic data, seasonal disease distribution, laboratory and clinical course, treatment, and short-term outcome.** ***Main outcome:*** **Mean age was 48.6±12 yr; 70% were females. Twenty-five percent had antithyroid antibodies and 9% had recurrent disease. Differences in occurrence by season were not significant (*p*=0.28). Ultrasound, performed in 35 patients, revealed thyroid nodules in 25 (median size, 17 mm). Ten patients received no treatment, and 43 received either non-steroidal anti-inflamatory drugs (NSAID) (no.=25) or glucocorticoids (no.=18); data for 3 patients were missing. Median disease duration was 77 days; mean peak free T_4 (FT_4) level was 43.7±25.3 pmol/l. A hypothyroid phase was documented in 31 patients, and remained permanent in 6. Peak FT_4 level, but not erythrocyte sedimentation rate or clinical score, was positively correlated with the highest TSH level and with disease duration. Untreated patients had less severe clinical disease than treated patients, but a similar outcome. Patients given glucocorticoids had a shorter overall disease duration (*p*=0.03), with no differences in duration of hyperthyroidism, peak FT_4 or highest TSH levels, compared with patients given NSAID.** ***Conclusion:*** **Subacute thyroiditis follows an unpredictable clinical course that is hardly affected by its clinical features or treatment.**

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INTRODUCTION

Subacute thyroiditis (also called de Quervain thyroiditis or granulomatous thyroiditis) is a self-limited, possibly viral, inflammatory thyroid disease, usually associated with thyroid pain and systemic symptoms (1-3). The incidence appears to be highly variable worldwide and higher in women between the ages of 40-50 yr (up to 80%) than in men (3-5). The hallmark for diagnosis is the triad of painful thyroid, elevated erythrocyte sedimentation rate (ESR) and low radioiodine uptake.

The natural history of subacute thyroiditis involves 3-4 phases that generally unfold over 4-6 months. The acute phase of thyroid pain may last 2-6 weeks, and up to 50% of patients have symptoms of thyrotoxicosis. The spilling of thyroid hormones into the circulation due to the acute inflammatory process is responsible for the hyperthyroidism seen in the first phase. Transient asymptomatic euthyroidism follows, and a short phase of mild hypothyroidism evolves in most patients (1-3). In the recovery phase, thyroid function tests normalize (1-5). Permanent hypothyroidism following subacute thyroiditis has been reported in up to 5-15% of patients by some authors (4, 6, 7).

Although the clinical features and outcome of subacute thyroiditis have been described, most of the studies focused on epidemiological analyses (4, 5, 8-10) or treatment modalities (11-13), and data on prognostic factors are lacking. Furthermore, some of these studies were conducted in the 1980s (5-7, 13-17), when sensitive TSH tests were not yet available and ultrasonography was not widely used; others were small studies including up to 36 patients only (6, 11-14).

In this study, we reviewed the medical records of 56 consecutive patients with subacute thyroiditis to identify clinical characteristics and predictors of outcome.

Key-words: Thyroid, subacute thyroiditis, hypothyroidism, thyroid nodule, antithyroid antibodies.

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MATERIALS AND METHODS

The medical records of 61 consecutive patients with subacute thyroiditis who were treated in 3 outpatient clinics in the central coastal area of Israel between 1999 and 2005 were reviewed for demographic data, seasonal disease distribution, laboratory and clinical course, treatment, and short-term (within 12 months) outcome. Five patients were excluded because lymphocytic (painless) thyroiditis or hashitoxicosis could not be ruled out. The diagnosis of subacute thyroiditis in the remaining 56 patients was based on clinical grounds, ESR (80%), and scintigraphy findings (62%), and/or radioiodine uptake (28.5%). Patients presenting with permanent or transient hypothyroidism in which subacute thyroiditis was suspected to be the underlying cause, were not included in this study because of lack of confirmatory tests. Thyroid ultrasound was performed in 35 patients. The disease was scored for severity as follows: fever: none [0], <38 C [1], >38 C [2]; tenderness: none [0], mild [1], severe [2]; goiter by ultrasonography or palpation: none [0], yes [1]; ESR: normal [0], 25-60 mm/h [1], >60 mm/h [2]. This score system has not been previously reported and was designed based on clinical features of the inflammatory process, independently of the degree of hyperthyroidism.

A commercial chemiluminescence immunoassay (Immulite 2000 DPC, CA) was used to measure serum TSH (normal reference values 0.50-5.0 mU/l), free T_4 (normal 10.3-20.0 pmol/l), and total T_3 (normal 1.29-3.1 nmol/l); and a commercial immunometric enzyme immunoassay (Organtec, Germany) was used to measure antithyroid antibodies [normal range for anti-thyroglobulin (Tg), <150 IU/ml; and for anti-thyroid peroxidase (TPO) <75 IU/ml].

For comparison between groups the Student's t-test was used for parametric variables and chi-square test for non-parametric variables. Pearson's coefficient was used for analysis of correlation. A *p*-value ≤0.05 was considered significant.

RESULTS

The clinical characteristics of the patients with subacute thyroiditis are shown in Table 1. Antithyroid antibodies were present in 10 (25%) of the 39 patients with available data, and the disease was recurrent in 5 (9%) of the patients, 3 of whom were antithyroid antibody positive. The seasonal distribution at diagnosis is shown in Figure 1. The incidence peaked in autumn and was lower in spring, but the differences were not statistically significant (p=0.28). Ultrasound performed in 35 patients revealed thyroid nodules >4 mm in 25 (multiple nodules in 19 and single nodules in 6). The median size of the largest nodules was 17 mm (range, 4-37). Another 2 patients had thyroid nodules diagnosed by palpation alone. Follow-up data on thyroid nodules were available for 12 patients: 10 showed spontaneous resolution on ultrasonography.

At diagnosis, TSH level was suppressed to <0.01 mU/l in all patients. Elevated ESR was documented in all except 2 patients; it was >60 mm/h in 80% and >100 mm/h in 25%. The hyperthyroid phase lasted a median of 43 days (range, 15-90). Peak FT_4 during this period was more than 2-fold of normal in 46% of patients, and it was positively correlated with overall disease duration (p<0.01) and peak TSH in the hypothyroid phase (p<0.01) (Table 2). No positive correlations were noted between clinical score or ESR and peak FT_4, or maximal TSH. There was an inverse correlation between clinical score and disease duration (Table 2).

Table 1 - *Clinical characteristics at diagnosis in all patients with subacute thyroiditis and subgoups with or without a second hypothyroid phase.*

	All patients* (no.=56)	Euthyroid (no.=21)	Hypothyroid (no.=31)	*p*
Age (yr)	48.6±12	47±12	49±13	0.559
Females (%)	70	66	74	0.801
Clinical score (mean±SD)	4.82±1.5	5.13±1.06	4.6±1.7	0.268
ESR (mm/h)	76.4±34.6	78.7±29.0	77.1±39.2	0.876
Thyroid nodules (%)	73 (27/37)	75	71.4	0.880
Recurrent disease (%)	9 (5/51)	9.5	6.5	0.354
Antithyroid antibodies (%)	25 (10/39)	0	35	<0.001
Maximal FT_4 (pmol/l) (mean±SD)	43.7±25.3	36.6±14.6	49.6±31.3	0.093
Maximal TT_3 (nmol/l) (mean±SD)	4.27±1.8	3.76±1.1	4.71±2.1	0.213
Duration of hyperthyroidsm (days)	44.9±17.6	45±17	43.2±17.6	0.716
Maximal TSH (mU/l) (median)	6.9 (0.9-126)	3.6 (0.9-4.9)	15.8 (6-126)	<0.001
Overall duration (days, median) **	77 (25-360)	50 (25-105)	112 (30-360)	<0.001
Treated (NSAID, Steroids) (%)	81 (53, 47)	86 (50, 50)	77 (58, 42)	0.222

*Follow-up data was incomplete for 4 patients; **After excluding 6 patients with permanent hypothyroidism. ESR: erythrocyte sedimentation rate; FT_4: free T_4; TT_3: total T_3; NSAID: non-steroidal anti-inflammatory drug.

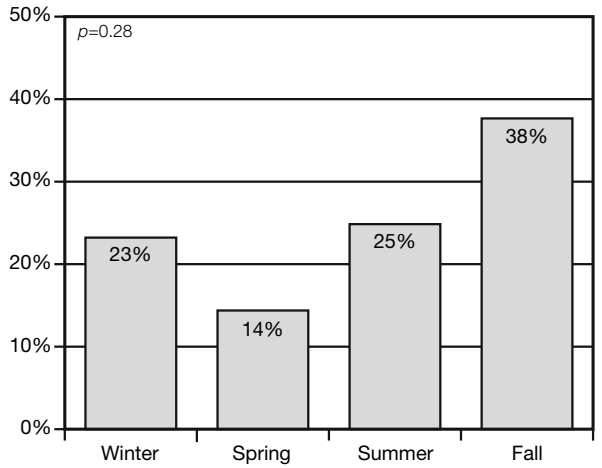

Fig. 1 - *Seasonal distribution of 56 patients with subacute thyroiditis showing no significant differences.*

A second phase of hypothyroidism was observed in 60% of patients, with a peak TSH >10 mU/l in 39% and >50 mU/l in 13%, and a lowest FT_4 of <10 pmol/l in 50% and <7 pmol/l in 22%. Compared to the euthyroid patients, patients with a hypothyroid phase had more antithyroid antibodies at baseline (p=0.01) and a tendency to higher maximal FT_4 (p=0.093) in the preceding phase; clinical score, ESR, and duration of hyperthyroidsm were similar in the two groups (Table 1). Permanent hypothyroidism developed in 6/56 (10%) patients, accounting for 20% of those going into a hypothyroid phase. Antithyroid antibodies were present in 2 of them, and no differences were observed in ESR, peak FT_4 or treatment modalities compared to patients with transient hypothyroidism. However, a higher maximal TSH level (median, 49.5 mIU/l *vs* 12.3 mIU/l, p=0.045) was noted in the permanent compared to the transient hypothyroid group.
Findings for the comparison of the treated (no.=43) and untreated (no.=10) groups are shown in Table 3. Untreated patients had a lower clinical score (p=0.007), lower ESR (p=0.001), and a tendency to a shorter hyperthyroid phase. There was no between-group difference in the occurrence of transient or permanent hypothyroidism. Within the treatment group, there were no significant differences between those given non-steroidal anti-inflammatory drugs (NSAID) (no.=25) or glucocorticoids (no.=18), except for a higher clinical score (p=0.02) and shorter disease duration (p=0.018) in the glucocorticoid subgroup (Table 3). Three patients in the NSAID subgroup and 2 in the glucocorticoid subgroup developed permanent hypothyroidism (p=ns).

DISCUSSION

The results of our study confirmed most of the clinical characteristics of patients with subacute thyroiditis previously reported by others (1-4). This study supports studies (4, 5, 10) in which no association was found between subacute thyroiditis and seasonality; contrary to others (8, 18), who noted a significant increase in summer.
In our series, there was a high prevalence of thyroid nodules already in the initial phase of subacute thyroiditis, detected mainly by ultrasonography; with no evidence of malignancy in the few patients who underwent fine needle aspiration. Most of the nodules disappeared spontaneously on the resolution of subacute thyroiditis. Similar findings were noted in an earlier, large series of 269 patients with subacute thyroiditis (5). In another study, 16 of 61 patients underwent unnecessary thyroidectomy (9). Furthermore, hypoechoic areas on ultrasound in subacute thyroiditis are not necessarily true nodules. Taken together, these data suggest that when the suspicion is low, fine needle aspiration can be postponed until resolution of the subacute thyroiditis.
In our study, thyrotoxicosis lasted about 6 weeks and was followed by a second phase of hypothyroidism in 31 patients, of whom 6 remained with permanent hypothyroidism. Since this was a retrospective study, a short hypothyroid phase could have been missed in some patients. Overall, the median disease dura-

Table 2 - *Correlation between clinical and biochemical variables in patients with subacute thyroiditis.*

	Max FT_4	ESR	Lowest FT_4	Clinical score	Disease duration
ESR	0.082				
Lowest FT_4	–0.177	0.104			
Clinical score	0.199	0.690**	0.150		
Disease duration	0.403*	–0.178	–0.183	–0.422*	
Max TSH	0.358*	–0.173	–0.474**	–0.240	0.636**

*p<0.01; **p<0.001; ESR: erythrocyte sedimentation rate; FT_4: free T_4.

Table 3 - *Short- and long-term outcome of subacute thyroiditis according to treatment modalities.*

				Treated		
	Untreated (no.=10)	Treated (no.=43)	*p*	NSAID (no.=25)	GCS* (no.=18)	*p*
Clinical score (mean±SD)	3.0±1.4	5.1±1.3	0.007	4.7±1.3	5.7±1.1	0.02
ESR (mean±SD)	43±25	82±33	0.001	77.6±35	88±30.6	0.325
Antithyroid antibodies (%)	44 (4/9)	13.5 (5/37)	0.086	16.6 (3/18)	22 (2/9)	1.000
FT_4 max (mean±SD)	46.3±26	43.1±26	0.590	47.4±32	36.1±11.5	0.419
Hyperthyroidism (days) (mean±SD)	36.4±16	46.8±6	0.109	44.3±13	50.5±20	0.248
TSH highest (median)	14.6 (1.4-61)	6.6 (0.9-126)	0.212	7.6 (0.9-126)	5.7 (1.4-16)	0.198
FT4 lowest (mean±SD)	8.7±1.9	10±3.9	0.313	9.5±4.1	10.8±3.7	0.365
Overall duration (median)	105 (30-180)	76 (25-360)	0.386	90 (25-360)	60 (35-90)	0.018
Hypothyroid phase (%)	70 (7/10)	56 (24/41)	0.724	65 (15/23)	50 (9/18)	0.772
Permanent hypothyroid (%)	10 (1/10)	9.5 (5/53)	1.000	12 (3/25)	11.1 (2/18)	1.000

*Seven patients were switched from non-steroidal anti-inflammatory drug (NSAID) to glucocorticoids (GCS); ESR: erythrocyte sedimentation rate; FT_4: free T_4; TT_3: total T_3.

tion was about 3 months and correlated positively with thyroid function tests but not with clinical score. An interesting finding in our study was the inverse correlation of the severity of the hypothyroidism with the preceding high FT_4 levels in the hyperthyroid phase, despite the absence of clear predictors of permanent hypothyroidism. Surprisingly, a severe clinical presentation (fever, pain, tenderness, goiter, ESR) was not associated with worse outcome.

Antithyroid antibodies have been observed in up to 50% of patients with subacute thyroiditis, and disappear during the recovery phase in most of them (6, 7, 9). They were found to be the only factor associated with permanent hypothyroidism (18-20). Antithyroid antibodies were observed in 25% of our patients, all of whom acquired transient hypothyroidism. However, the presence of antithyroid antibodies, did not predict the development of permanent hypothyroidism. The only distinguishing factor we identified was TSH level, which was significantly higher in the patients in whom permanent hypothyroidism developed afterwards.

Since painful thyroiditis is a self-limiting condition, treatment consists of symptomatic relief only. The 10 patients in our study who did not receive medical treatment had a less severe clinical form of the disease and a shorter hyperthyroid phase. However, their short-term outcome was not different from those who received medical treatment.

There are 2 types of medical treatment for patients with subacute thyroiditis, NSAID and glucocorticoids. Although some authors prefer prednisone because of the quick relief of symptoms it provides, it has been associated with an increased recurrence rate (up 20%) in a few studies (4, 12, 21). In small series of 12 patients, there were no differences in the duration of hyperthyroidsm between the two treatment groups (13). In a larger study, however, early-onset hypothyroidism was not affected by the treatment modality, whereas the rate of permanent hypothyroidism was higher in those treated with glucocorticoids (4). The authors did not address the role of disease aggressiveness in these findings. In our series, 25 patients were treated with NSAID and 18 with prednisone. Although the prednisone group had more severe clinical features, there were no between-group differences in the development of hypothyroidism. Indeed, the overall disease duration was significantly shorter in the prednisone group. At the end of our study, there were no new recurrences in either group.

Our study has several limitations. First, it was a retrospective analysis and diagnostic tests were not performed uniformly in all patients. Asymptomatic or mildly symptomatic patients first presenting during the hypothyroid phase were not included because their diagnosis would have been based on medical history only. In addition, the frequency of laboratory test and follow-up visits was widely variable, and did not include sequential measurements of anti-thyroid antibodies. Since anti-thyroid antibodies disappear during the recovery phase (6, 7, 9), their persistence may indicate the presence of autoimmune thyroid disease. Finally, the number of patients who developed permanent hypothyroidism in our study was relatively

small, as expected by the low incidence reported by others (4, 6, 7). A large multicenter study would be needed to reach significant conclusions in this regard. In summary, our study of a contemporary and relatively large series of patients with subacute thyroiditis confirmed some of the clinical characteristics previously reported by others and supports the use glucocorticoids to shorten disease duration. We also found that the degree of biochemical thyrotoxicosis, but not its clinical correlate, is associated with a prolonged disease duration and more profound hypothyroid phase. Permanent hypothyroidism was not uncommon. However neither the clinical features nor the presence of antithyroid antibodies nor the choice of treatment appeared to be predictive of the short-term outcome.

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