Histological, Clinical and Laboratory Findings of Acute Exacerbation of Hashimoto’s Thyroiditis—Comparison with those of Subacute Granulomatous Thyroiditis

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Abstract

As reported previously, acute exacerbation of Hashimoto’s thyroiditis shows quite unique histological findings, namely localized edematous inflammation. Similar histological characteristics and clinical manifestations were observed in 7 of 492 patients with Hashimoto’s thyroiditis (A group). Their clinical and laboratory findings were compared with those of 15 cases with subacute granulomatous thyroiditis (S group). Age and sex distribution and goiters in A group were 39±21 years old (mean±s.d.), 7/0 (F/M), and 6/1 (diffuse/nodular), respectively. These were somewhat different from those of S group (45±9, 12/3, and 3/12, respectively).

Thyroid functions in A group showed wide variation: 3 cases were euthyroid, 2 were mildly hypothyroid, and one was mildly thyrotoxic and one borderline thyrotoxic, and all of the S group patients were thyrotoxic. Their thyroid radiopertechnetate uptake, scintigraphy, duration from the onset till the first visit, and ESR and CRP values were also different from those of S group.

Clinical courses and outcomes of A group were generally favorable, but one of them finally underwent a total thyroidectomy. Per os and intrathyroidal administrations of steroid were effective, but there was observed a recurrence of symptoms in 3 cases. Finally, all 6 cases were left with diffuse goiters, 4 of them remaining euthyroid, and 2 falling into hypothyroidism.

The acute exacerbation of Hashimoto’s thyroiditis is a rare complication, which is found to be different from subacute thyroiditis on histological, clinical and laboratory findings and is generally subtle. Steroid medication is considered to be the therapeutic choice but careful observation is necessary to avoid a recurrence.

On rare occasions Hashimoto’s thyroiditis may be accompanied by pain or tenderness, and mimics subacute nonsuppurative (granulomatous) thyroiditis (Doniach et al., 1960, Suzuki et al., 1964, Ingbar 1985a). Recently we have encountered a patient with Hashi-
moto's thyroiditis who had been suffering from repeated episodes of acute exacerbation (Ishihara et al., 1986). Histological findings by needle biopsies and surgery revealed quite unique characteristics, namely reversible and localized edematous inflammatory changes.

A retrospective study surveyed 7 cases with known Hashimoto's thyroiditis in which patients had episodic bout(s) of spontaneous pain in the thyroid region, high fever, and quite similar histological findings.

This paper deals with histological characteristics, and the clinical and laboratory findings of these 7 cases in comparisons with those of 15 cases with subacute granulomatous thyroiditis.

Materials and Methods

By means of routine needle biopsy, a diagnosis of Hashimoto's thyroiditis was made in 492 cases over the past 5 years. Lymphocytic infiltrations, destructions and/or degenerative changes in the follicular epithelia, and fibrosis are the clues in diagnosing Hashimoto's thyroiditis (Torizuka et al., 1976).

Eight of the 492 cases had been suffering from spontaneous pain on the anterior neck and high fever exceeding 38°C. Seven of these 8 cases were found to share common and unique histological findings and were diagnosed as having acute exacerbation of Hashimoto's thyroiditis. A group consists of these 7 cases, and S group of 15 cases with histologically proven subacute granulomatous thyroiditis. One of the above 8 cases showed granulomatous changes together with findings of Hashimoto's thyroiditis (Ishihara et al., 1986), and was included in S group.

Total T4, T3, and antibodies to thyroglobulin (anti-Tg) and thyroid microsomes (anti-M) were assayed with commercially available kits. Serum TSH was measured by a highly sensitive double antibody RIA which could detect at least 0.156 µU/ml. The normal range was from 0.31 to 3.2 µU/ml (Mori et al., 1980).

Thyroid 99mTc pertechnetate uptake and scintigram were performed 30 min after 2mCi i.v. injection using a scintillation camera. The normal range of uptake was from 0.4 to 2.5%.

For the statistical analysis Student's t-test was used.

Results

1. Histological findings

Except for the previously reported case (Ishihara et al., 1986), Fig. 1 shows histological findings obtained from the painful region of 6 cases in A group. In all these cases, the low power extentions proved the existence of Hashimoto's thyroiditis. In addition, follicle structures of the involved region were destroyed to various degrees. The widened interstitial spaces were occupied mostly by fibrotic changes and by lymphocytic infiltrations. Unlike the dense fibrosis seen generally in the thyroid of Hashimoto's thyroiditis, the arrangement of collagen fibers was quite loose and these fibers were short. These findings were observed commonly in 6 cases presented in this study, and were considered to represent a localized edematous inflammation. These unique edematous features were confirmed to be the pathological characteristics of A group. None of the cases showed any granuloma or pseudogiant cell formations.

2. Clinical findings

Table 1 summarizes the clinical findings for A and S groups at the time of the first visit. The age distribution in A group showed a relatively wide range of 15 to 76, averaging 39±21 (s.d.), while S group had a higher age distribution and a narrower range (45±9). All of the A group patients were female while 3 of the 15 patients in S group were male. The duration from the onset till the first visit in A group ranged from 1 day to 4 weeks (11.9±9.3 days) which was longer than it was in S group (5.7±4.9 days).

The maximal body temperatures of these 2 groups were quite similar.

All but one in A group had diffuse or bilateral goiters even though the region of their spontaneous pain and tenderness was only partial. However, 12 of 15 patients
Fig. 1. Histological findings of 6 new cases with acute exacerbation of Hashimoto's thyroiditis
1-1: Case 1, H.E.×100, 1-2: Case 2, H.E.×400, 1-3: Case 3, H.E.×100, 1-4: Case 4, H.E.×100,
1-5: Case 5, H.E.×100, 1-6: Case 6, H.E.×400
Low power microscopy showed diffuse destructive and degenerative changes in follicles and epithelial cells, and usually dispersed arrangements of thyroid
follicles with remarkable fibrotic changes in interfollicular spaces and interstitium were observed. High power photomicrographs show that fibrotic changes were quite unique and accumulated collagen fibres were short and loosely arranged.
Table 1. Comparisons of clinical findings for patients with acute exacerbation of Hashimoto’s thyroiditis (A group) and patients with subacute nonsuppurative thyroiditis (S group)

<table>
<thead>
<tr>
<th></th>
<th>A group</th>
<th>S group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>7</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Age mean ± s. d.</td>
<td>39±21</td>
<td>45±9</td>
<td>n. s. †</td>
</tr>
<tr>
<td>range</td>
<td>15—76</td>
<td>29—63</td>
<td></td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>7/0</td>
<td>12/3</td>
<td>n. s.</td>
</tr>
<tr>
<td>Duration* mean ± s. d.</td>
<td>11.9±9.3</td>
<td>5.7±4.9</td>
<td>n. s.</td>
</tr>
<tr>
<td>(Days) range</td>
<td>1—28</td>
<td>1—14</td>
<td></td>
</tr>
<tr>
<td>Body temp. mean ± s. d.</td>
<td>39.0±0.5</td>
<td>38.6±0.5</td>
<td>n. s.</td>
</tr>
<tr>
<td>(°C) range</td>
<td>38.5—40.5</td>
<td>38.0—39.0</td>
<td></td>
</tr>
<tr>
<td>Goiter (diffuse/nodular)</td>
<td>6/1</td>
<td>3/12</td>
<td>0.025</td>
</tr>
</tbody>
</table>

* : Duration of disease from the onset
† : not significant

Table 2. Thyroid functions and laboratory findings for patients with acute exacerbation of Hashimoto’s thyroiditis (A group)—comparison with subacute nonsuppurative thyroiditis (S group)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>T4 μg/100ml</th>
<th>T3 ng/100ml</th>
<th>iT4 ng/100ml</th>
<th>TSH μU/ml</th>
<th>Anti-Tg</th>
<th>Anti-M</th>
<th>99mTcO4⁻ uptake %</th>
<th>WBC</th>
<th>ESR mg/100ml</th>
<th>CRP mg/100ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.8</td>
<td>123</td>
<td>1.12</td>
<td>0.7</td>
<td>(—)</td>
<td>(—)</td>
<td>0.13</td>
<td>6,700</td>
<td>37</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>8.9</td>
<td>94</td>
<td>1.16</td>
<td>4.1</td>
<td>(—)</td>
<td>(—)</td>
<td>2.1</td>
<td>10,200</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5.2</td>
<td>14.0</td>
<td>×10²</td>
<td>×10²</td>
<td>2.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>13.0</td>
<td>0.7</td>
<td>×10⁴ ×10² ×2⁵</td>
<td>0</td>
<td>12</td>
<td>(—)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6.8</td>
<td>83</td>
<td>1.19</td>
<td>8.0</td>
<td>(—)</td>
<td>(—)</td>
<td>2.5</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>15.0</td>
<td>187</td>
<td>2.3</td>
<td>0.16</td>
<td>(—)</td>
<td>(—)</td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>7.0</td>
<td>100</td>
<td>1.36</td>
<td>1.5</td>
<td>(—)</td>
<td>×10²</td>
<td>0.29</td>
<td>7.100</td>
<td>120</td>
<td>6.4</td>
</tr>
</tbody>
</table>

mean 9.1   117  1.40  4.2  2/7  3/7  1.1  41
s.d. 3.6   42   0.5   5.1

S group
mean 18.3  269  3.0  0.24  2/15  3/15  0.05  8,700  71  7.4
s.d. 4.6   73   1.3  0.09

P 0.001  0.001  0.05  0.05  n.s.  n.s.  0.02  n.s.  n.s.  n.s.
n.s.: not significant

in S group had nodular goiters, of which only 3 had diffuse goiters. The difference between the two groups was statistically significant (p<0.025).

3. Thyroid states and laboratory findings on the first examination

Table 2 compares thyroid function test results and WBC, erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) values for both groups. Most of the T4,
T3 and fT4 in A group were distributed close to their normal ranges, while those in S group showed thyrotoxic levels. TSH in A group showed a wide variety but in S group it was mostly suppressed. Thyroid 99mTc pertechnetate uptake in S group was extremely low, but in A group not as low in 4 cases. All of these thyroid function test results showed statistically significant differences between the two groups. A significant negative correlation was observed between TSH and T4 (A+S: r=-0.67, p<0.01, A only: r=-0.83, p<0.01), and TSH correlated significantly with thyroid 99mTc pertechnetate uptake (A+S: r=0.91, p<0.01, A only: r=0.91, p<0.01).

Individually, 3 of them (Cases 1, 2 and 7) were euthyroid, 2 (Cases 3 and 5) were mildly hypothyroid and 2 (Cases 4 and 6) were thyrotoxic.

Detectability and the titers of anti-Tg and anti-M in A group were rather low, and no significant differences from those in S group were observed.

ESR and CRP in A group were not as elevated as in S group, though the data obtained at the time of the bout were insufficient.

Fig. 2. Thyroid 99mTc pertechnetate scintigrams of 6 patients with acute exacerbation of Hashimoto's thyroiditis

2-1: Case 1, 2-2: Case 2, 2-3: Case 3, 2-5: Case 5, 2-6: Case 6, 2-7: Case 7. the data for case 4 are not shown because of extremely low RI trapping and no apparent visualization of the thyroid gland.
Fig. 2 shows thyroid scintigrams for 99mTc pertechnetate in A group. Except for cases 4 (no visualization) and 5 (diffuse homogeneous RI trapping Fig. 2-5), relatively heterogeneous RI trappings and trapping defects were observed in the remaining patients. The left lobe in case 1 (Fig. 2-1), the middle portion of the left lobe in case 2 (Fig. 2-2), the entire right lobe and the apical portion of the left lobe in case 3 (Fig. 2-3), the upper half of the right lobe in case 6 (Fig. 2-6), and the upper part of the right lobe in case 7 (Fig. 2-7: the photo failed to show the defect clearly because of low RI trapping) showed trapping defects, and all of these coincided with the painful regions. Case 4 had pain and tenderness in the upper to middle portion of the right lobe, and case 5 felt severe pain in the bilateral apical portions.

4. Clinical course and outcome

Table 3 shows the clinical course and outcome of patients in A group. Initially, 15 to 20 mg of per os prednisolone was prescribed in 4 cases (Cases 1, 2, 5, and 6), and 2 cases (Cases 3 and 7) were treated by intrathyroidal injection of 40 mg triamcinolone acetate, while case 4 was given 1 g of aspirin per day.

After per os or intrathyroidal steroid administration, most of the clinical manifestations reduced rapidly or disappeared within 1 to 4 days. However, intrathyroidal injection or rapid reduction of the steroid dose resulted in the reappearances of pain and/or tenderness in 3 cases after all (Case 1, 3 and 7). Case 1 was first treated with a daily dose of 20 mg prednisolone for only 2 days. Fever and pain disappeared, the thyroid nodule was reduced, and the patient decided to stop taking steroid. After 4 days the inflammatory signs reappeared and she again took steroid for 3 days. After following a similar course for a week, the last bout was experienced, and steroid medication for 7 days was prescribed. This gave her complete relief from the bout. Case 3 was first treated with a daily dose of 100 µg of L-thyroxine. Triamcinolone was injected at the time of her 2nd bout, 2 months from the onset. After the injection, she suffered from 3 other bouts within 4 months, but these were tolerable and only thyroid medication was given regularly. Twenty-four months from the onset, she experienced one more mild episode and this also was not followed by any special

<table>
<thead>
<tr>
<th>Case</th>
<th>Initial</th>
<th>Treatment</th>
<th>No. of Episode</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>PD 20</td>
<td></td>
<td>4</td>
<td>2 m</td>
<td>D. E.</td>
</tr>
<tr>
<td>2</td>
<td>PD 20</td>
<td></td>
<td>1</td>
<td>1 m</td>
<td>D. E.</td>
</tr>
<tr>
<td>3</td>
<td>TA 40</td>
<td>T4 100</td>
<td>6</td>
<td>24 m</td>
<td>D. H.</td>
</tr>
<tr>
<td>4</td>
<td>As 1.0</td>
<td>T4 100</td>
<td>1</td>
<td>3 m</td>
<td>D. H.</td>
</tr>
<tr>
<td>5</td>
<td>PD 15</td>
<td></td>
<td>1</td>
<td>1 m</td>
<td>D. E.</td>
</tr>
<tr>
<td>6</td>
<td>PD 15</td>
<td>TA 40</td>
<td>1</td>
<td>2 W</td>
<td>D. E.</td>
</tr>
<tr>
<td>7</td>
<td>TA 40</td>
<td>various</td>
<td>12</td>
<td>4 m</td>
<td>Thyrex.</td>
</tr>
</tbody>
</table>

PD: prednisolone (mg/day), TA: triamcinolone acetate (mg), As: aspirin (g/day), T4: synthetic L-thyroxine (µg/day), various: see Ref. (Ishihara et al., 1986) for the details.

D. E.: diffuse goiter and euthyroid
D. H.: diffuse goiter and hypothyroid
Thyrex: total thyroidectomy
medication. Since then she has remained quite well. Case 7 has already been described in detail (Ishihara et al., 1986). While all but one in S group showed no worsening. Only one case was found to have typical histological granulomatous changes even after 8 months from the onset.

Most of the A group patients responded favorably but case 7 finally had to have a total thyroidectomy. All 6 cases were found to have a diffuse firm goiter even after remission from the acute exacerbation(s). Four of them remained euthyroid, but 2 of them (Cases 3 and 4) fell into hypothyroidism and were treated with L-thyroxine. On the other hand, none of the 15 patients in S group fell into hypothyroidism nor left a diffuse goiter.

As for antibody titers of patients in A group, recent follow-up studies have revealed that only 2 of 6 cases studied have positive titers (Case 3: anti-Tg × 10² × 2², anti-M × 10² × 2²; Case 4: anti-Tg negative, anti-M × 10² × 2², respectively, Case 7 was not tested.)

Discussion

Recently we have reported serial changes in thyroid histology in a patient with repeated episodes of acute exacerbation of Hashimoto's thyroiditis (Ishihara et al., 1986).

In all 7 cases with acute exacerbation of Hashimoto's thyroiditis, quite similar histological findings characterized by localized edematous inflammatory changes were observed. These findings might be concluded as pathological characteristics of this condition. Doniach et al. (1960) and Suzuki et al. (1964) have reported several patients showing acute inflammatory changes. However they did not describe these histological characteristics but nevertheless clearly showed the existence of Hashimoto's thyroiditis. As reported, the inflammatory changes subside quickly with treatment and are reversible (Ishihara et al., 1986). They might have not studied the histology at the time of acute inflammation. Moreover, we have shown that the association of subacute thyroiditis with Hashimoto's thyroiditis may occur but can be well differentiated by histological examination (Ishihara et al. 1986).

The major clinical manifestations of these patients (A group) were quite similar to those of subacute nonsuppurative thyroiditis, but their clinical and laboratory findings were found to be different from those of the latter (S group) from various points of view. Patients in A group showed wide age distribution, prevalency in the female and all but one of them had diffuse goiters. These findings in A group were quite compatible with those generally seen in Hashimoto's thyroiditis in Japan (Torizuka et al., 1986), and different from those in subacute nonsuppurative thyroiditis as shown in the text (Ingbar 1985) and in the present study. Histological findings for A group also proved the coexistence of Hashimoto's thyroiditis. However, the detectability and titers of anti-Tg and anti-M were rather low. Balfour et al. (1961) reported that the detectability or titer of circulating antibodies to thyroglobulin and the thyroid particulate component did not always reflect the degree of tissue destruction. Further, we observed an apparent reduction in antibody titer and increase in the serum Tg concentration in the first bout in one patient (Ishihara et al., 1986). The leakage of antigenic substances due to tissue destruction may be considered to be related to low or negative antibody through the absorption of circulating antibodies, but follow up studies of antibody titers in these patients did not show any apparent increases afterwards.

Patients with subacute nonsuppurative thyroiditis usually show thyrotoxic hormone levels and extremely low radioiodine uptake
Thyrotoxicosis and extremely low radioiodine uptake are also seen commonly in patients with painless thyroiditis and post-partum tissue destruction (Woolf 1980; Amino et al., 1982). These conditions are considered to be induced by certain immunological impacts (Woolf 1980; Nikolai et al., 1980; Inada et al., 1981; Farid et al., 1983) and to involve the entire gland. At the same time, 5 of 7 patients in A group were euthyroid or even mildly hypothyroid and showed visible scintigrams with defect(s). Doniach et al. (1960) reported that patients with subacute auto-immune thyroiditis could have high, normal or low iodine uptake. Though not all of their cases were identical to the acute exacerbation described here, they had already pointed out some important clinical features almost 30 years ago. Suzuki et al. (1964) also reported 5 similar cases and discussed the differential diagnosis from subacute thyroiditis in detail. The limited involvement of the thyroid and primarily low T4 and T3 content in the gland (Chopra et al., 1973) may be related to the lack of thyrotoxicosis or to an extremely low thyroid uptake. Through both A and S groups or even A group alone, serum TSH was found to correlate negatively with T4 and positively with 99mTc pertechnetate uptake. T4 with Tg may have leaked from the thyroid due to tissue destruction, and in the case where the leakage was not sufficient enough to elevate serum T4 to the thyrotoxic level, TSH would not be fully suppressed and stimulated the uninvolved region of the thyroid to trap radiopertechnetate. The relatively longer duration of the first consultation from the onset and less lower values for ESR and CRP in A group may also reflect the local nature of the involvement.

The clinical course and outcome in A group were also found to be somewhat different from those in S group. In 3 of 7 cases, multiple bouts were observed in the same region as the first bout, diffuse goiters were observed in all cases after remission from the bouts, and 2 cases lapsed into hypothyroidism. Doniach et al. (1960) also reported that some of their cases lapsed into hypothyroidism afterwards. While all but one of S group experienced only one episode, and they usually showed migration or creeping of the painful portion, none of the patients were left with palpable goiters or hypothyroidism after recovery.

As for the treatment of acute exacerbation of Hashimoto’s thyroiditis, initially, a daily dose of 15 to 20 mg of per os prednisolone and a gradual tapering off for more than 1 month seem to be optimal. Suzuki et al. (1964) reported the effectiveness of per os steroid medication, but they also experienced difficulty in getting rid of the drug. Intrathyroidal injection of triamcinolone acetate, which has been known to be quite effective in reducing goiter size in Hashimoto’s thyroiditis and in ameliorating acute inflammatory changes (Yoshizumi 1972; Nagata et al., 1974), induced very rapid improvement but was found to be effective for only a short period of time. Moreover, repeated bouts were encountered in both of the treated cases. Although intrathyroidal injections were given in severe cases, in one of the cases the bouts were not ameliorated by a daily dose of 1.5 mg of betamethasone (Ishihara et al., 1986). Therefore, this rather unique method of treatment cannot yet be regarded as unsuitable for the acute exacerbation. This will be clarified when the effectiveness of a larger per os dose steroid in severe cases is acknowledged.

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References


