Treatment of Pretibial Myxedema (PTM) with Topical Steroid Ointment Application with Sealing Cover (Steroid Occlusive Dressing Technique: Steroid ODT) in Graves’ Patients

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Abstract

Localized pretibial myxedema (PTM) is a sign of Graves’ disease. A 53-year-old man with Graves’ disease was admitted with the development of PTM following radioisotope $^{131}$I treatment for Graves’ hyperthyroidism. TSH receptor antibody (TRAb) titer was also increased after $^{131}$I treatment. TRAb was measured as thyroid stimulating antibody (TSAb) or TSH-binding inhibitory immunoglobulin (TBII). PTM was noted several months after $^{131}$I treatment. The PTM-development seems to be associated with the increased TRAb-activities. The localized pretibial myxedema was effectively treated with topical steroid (triamcinolone acetonide) ointment application with sealing cover (steroid occlusive dressing technique: steroid ODT).

We also report our experience of PTM-treatment with steroid ODT in 5 other PTM patients with positive TRAb. PTM was successfully treated with steroid ODT in two patients. In these two patients, the treatment was started within several months of the appearance of PTM. In the other 4 patients, the treatment was started 5-10 years after the appearance of PTM without any beneficial effects. Early detection and early treatment are necessary for the remission of PTM.

Key words: pretibial myxedema (PTM), Graves’ disease, TSH receptor Ab (TRAb), TSAb, TBII, topical steroid, ODT


Introduction

Localized myxedema is an infrequent manifestation of Graves’ disease. It is characterized by localized thickening of the skin (1-3). Myxedema is commonly localized in the pretibial area. Therefore, it is often referred to as pretibial myxedema (PTM). PTM is a sign of Graves’ disease. TSH receptor antibodies (TRAb) cause Graves’ hyperthyroidism (4). TRAb has been reported to be associated with PTM (5-8), and may play some role in the development of PTM. TRAb has been measured as thyroid stimulating antibody (TSAb) or TSH-binding inhibitory immunoglobulin (TBII) (9). In the present report, we describe a patient, in whom PTM developed after radioisotope $^{131}$I treatment for Graves’ hyperthyroidism. TRAb also increased after $^{131}$I treatment in this patient.

Various treatment modalities have been employed, including topical and systemic corticosteroids, compression dressings, and local injections (2, 3, 10-12). Kriss et al (10) and Fatourechi et al (2, 3) have reported moderate benefits of topical corticosteroid therapy. A long-term experience with thyroid dermopathy has been reported by only one group (2, 3, 13). We still do not know the clinical course and long-term outcome of patients with PTM.

We successfully treated PTM with topical steroid ointment application with sealing cover (steroid occlusive dressing technique: steroid ODT) in a patient, in whom PTM developed after $^{131}$I treatment for Graves’ hyperthyroidism. We reviewed 5 other patients with PTM and summarize our experience of PTM-treatment with steroid ODT.
Case Report

A patient with newly developed localized pretibial myxedema (PTM) after radioisotope $^{131}$I treatment for Graves' hyperthyroidism

A 53-year-old Japanese man visited our department with rapidly developing localized pretibial myxedema (PTM) and was admitted to our hospital (Fig. 1A, Fig. 3, Case 1 in Table 1). He had a history of Graves’ disease. He had visited a doctor with palpitation, excessive sweating, and body weight loss at the age of 48 years old (five years prior to admission). A diagnosis of Graves’ disease was made on the basis of history and signs of hyperthyroidism with diffuse goiter and the laboratory findings, including elevated serum T4 and T3 concentrations, undetectable serum TSH, and positive TSH receptor antibodies (TRAb). He had diffuse goiter but did not have exophthalmos. TRAb was measured as thyroid stimulating antibodies (TSAb) and TSH-binding inhibitory immunoglobulins (TBII) (4, 9). Antithyroid drug treatment was started with methimazole. After four years treatment with methimazole, he was found to have hepatic damage. This hepatic damage was thought to be induced by methimazole. Thus methimazole was changed to propylthiouracil (PTU). However, PTU again caused hepatic damage. PTU was discontinued. He was treated with radioactive iodine ($^{131}$I) four months prior to admission. He received 3 mCi $^{131}$I. Before $^{131}$I treatment, TSAb titers were 120-210% and TBII titers were 4-11%. He became euthyroid with $^{131}$I treatment. Four months after $^{131}$I treatment for Graves’ hyperthyroidism, the TSAb increased to 2,500% and TBII increased to 85%. PTM developed on the left pretibia (Fig.1A, B). Skin biopsy of PTM was performed on the day of admission. Histological examination revealed fraying of connective tissue fibers, and deposits of colloidal iron- and Alcian blue-stained mucinous materials (Fig. 2), demonstrating histopathologic features of PTM. The features consisted of normal collagen in the papillary dermis and separation of the collagen bundles by mucin. Mucin staining demonstrated abundant diffuse mucin within the dermal fenestrations as large amounts of glycosaminoglycans (GAG) diffusely dispersed in the reticular part of the dermis. PTM was successfully treated with topical steroid ointment application with sealing cover (steroid occlusive dressing technique: steroid ODT) (Fig. 1C, Fig. 3). PTM subsided without sequelae. During the course, exophthalmos had not been observed.

Figure 3 shows the clinical course of Case 1. Before $^{131}$I treatment, TSAb titers ranged from 120-210% (TBII 4-11%). Four months after $^{131}$I treatment, TSAb increased to 2,500% (TBII 85%). PTM developed on the left pretibia. PTM appeared with the increases of TSAb and TBII, and disappeared with steroid ODT, even in the presence of positive TSAb and positive TBII. Then TSAb and TBII decreased to normal levels.

PTM was successfully treated with steroid ODT.

Review of our 6 patients with PTM

We have seen 6 patients with PTM during the past 20 years (Table 1). Case 1 was described as this case report. The other 5 patients (Cases 2-6) are summarized in Table 1. All 6 patients had positive TSAb (1,560-3,562%) and positive TBII (4-11%).
Figure 2. Histology of pretibial myxedema (PTM) (Case 1). Histological examination revealed fraying of connective tissue fibers, and deposits of colloidal iron (A)- and Alcian blue (B)-stained mucinous materials, demonstrating histopathologic features of PTM. A. Blue staining of mucin with colloidal iron staining (×100). B. Mucinous materials with Alcian blue staining (×40). Mucin staining demonstrated abundant diffuse mucin within the dermal fenestrations as large amounts of glycosaminoglycans (GAG) diffusely dispersed in the reticular part of the dermis.

Figure 3. Clinical course of Case 1. A 53-year-old Japanese man visited our clinic with rapidly developing localized pretibial myxedema (PTM) and was admitted (Admission → 0). He had been treated with 131I for Graves’ hyperthyroidism four months prior to admission (131I → ). Before 131I treatment, TSAb (thyroid stimulating antibody) titers were 120-210%, and TBII (TSH-binding inhibitory immunoglobulins) titers were 4-11%. Four months after 131I treatment for Graves’ hyperthyroidism, the TSAb increased to 2,500% and TBII increased to 85%. PTM was successfully treated with topical steroid (triamcinolone acetonide) ointment application with sealing cover (steroid occlusive dressing technique: steroid ODT). With steroid ODT, PTM subsided. PTM appeared with the increases of TRAb (TSH receptor antibody) (TSAb and TBII), and disappeared with steroid ODT, even in the presence of positive TRAb.

Discussion

We successfully treated PTM with topical steroid ointment with sealing cover (steroid ODT) in a patient, in whom PTM developed following radioisotope 131I-treatment for Graves’ hyperthyroidism. TRAb increased after 131I treatment. We also reviewed 5 other patients with PTM. We reported our experience of PTM-treatment with steroid ODT. PTM was successfully treated with steroid ODT in two patients (Cases 1 and 2). In these two patients, the appearance of PTM. However, no improvements of PTM were observed in Cases 3-6 with steroid ODT. In these four patients, the treatment was started 5-10 years after the appearance of PTM. The time intervals between the PTM appearance and the start of steroid ODT were estimated to be several months in Cases 1 and 2, and 5-10 years in Cases 3-6. Cases 3, 4, 5, and 6 continued to have positive TSAb and TBII. Their TSAb- and TBII-titers continued to be high. Cases 3-6 continued to have PTM. TSAb- and TBII-activities decreased in Cases 1 and 2.

All 6 patients had PTM. Cases 1 and 2 did not have exophthalmos, but Cases 3-6 did have it. Graves’ hyperthyroidism preceded PTM in all of the 6 patients from 6 to 14 years. PTM was treated with steroid ODT in all of the 6 patients. Remission of PTM was observed in only 2 patients (33%). Written informed consent was obtained from the 6 patients for publication of this report.

Topical steroid ointment application with sealing cover (steroid occlusive dressing technique: steroid ODT) was done two times daily. A thin film of the 0.1% triamcinolone acetonide ointment (Kenalog Ointment, 0.1%, Bristol-Myers Squibb Co., Princeton, NJ, USA) was applied to the PTM areas. Then, the areas were covered with plastic film (Saran Wrap, Dow Chemical Co., USA). The edges of the covered areas were sealed with tape.

Sixty-eight to 92% at the time of initial diagnosis of PTM. These TSAb- and TBII-titers were high. PTM was successfully treated with steroid ODT in Cases 1 and 2. In these two patients, the treatment was started within several months
Table 1. Six Patients with Localized Pretibial Myxedema (PTM) and Graves’ Hyperthyroidism (GD); PTM Treatment with Topical Steroid Ointment Application with Sealing Cover (steroid Occlusive Dressing Technique: Steroid ODT)

<table>
<thead>
<tr>
<th>Case</th>
<th>M/W</th>
<th>Age at diagnosis, yr*</th>
<th>Localized pretibial myxedema (PTM)</th>
<th>Interval between PTM-appearance and treatment***</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>47</td>
<td>53</td>
<td>2500/85</td>
<td>Steroid ODT</td>
<td>Remission</td>
</tr>
<tr>
<td>2</td>
<td>W</td>
<td>34</td>
<td>42</td>
<td>3562/92</td>
<td>Steroid ODT</td>
<td>Remission</td>
</tr>
<tr>
<td>3</td>
<td>W</td>
<td>38</td>
<td>51</td>
<td>1578/76</td>
<td>Steroid ODT</td>
<td>No change</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>32</td>
<td>42</td>
<td>2180/82</td>
<td>Steroid ODT</td>
<td>No change</td>
</tr>
<tr>
<td>5</td>
<td>W</td>
<td>41</td>
<td>53</td>
<td>1892/73</td>
<td>Steroid ODT</td>
<td>No change</td>
</tr>
<tr>
<td>6</td>
<td>W</td>
<td>42</td>
<td>56</td>
<td>1560/68</td>
<td>Steroid ODT</td>
<td>No change</td>
</tr>
</tbody>
</table>

M/W: man/woman. Age at diagnosis, yr*: age (years old), when the diagnosis of Graves’ hyperthyroidism (GD) or localized pretibial myxedema (PTM) was made. TSAb: thyroid stimulating antibody. TBII: TSH-binding inhibitory immunoglobulin. TSAb/TBII (%)**: TSAb/TBII-titer (%) at the time when PTM was diagnosed. Interval between PTM-appearance and treatment***: the estimated time intervals between the PTM appearance and the start of topical steroid (triamcinolone acetonide) ointment application with sealing cover (steroid occlusive dressing technique: steroid ODT). In all of the 6 patients, PTM was treated with steroid ODT.

PTM treatment was started within several months after the appearance of PTM. In the other four patients (Cases 3-6), the treatment was started 5-10 years after the appearances of PTM without any beneficial effects. Early detection and early treatment are required for the remission of PTM.

Case 1 had $^{131}$I treatment for Graves’ hyperthyroidism. After $^{131}$I treatment, TRAb (TSAb and TBII) increased, and then PTM developed. The development of PTM seems to be associated with the increases of TRAb-activities. PTM was effectively treated with steroid ODT. With steroid ODT, PTM disappeared even in the presence of positive TRAb.

PTM is a sign of Graves’ disease (GD). PTM, characterized by the accumulation of glycosaminoglycans in the dermis and subcutaneous tissue, is an extrathyroidal manifestation of GD. The TSH receptor has been proposed as the common target antigen in GD and PTM. The presence of TSH receptor has been described in the dermis of Graves’ patients with PTM (7, 8). Daumerie et al (8) reported that TSH receptor was present in the pretibial area in the Graves’ patients with PTM, but absent in controls without thyroid diseases. Heufelder et al (14) proposed the TSH-receptor as the common target auto-antigen in GD and PTM. Daumerie et al (8) demonstrated the presence of TSH-receptor immunoreactivity in pretibial tissue of two patients with PTM. They reported that PTM developed after $^{131}$I treatment for GD. In Case 1, after $^{131}$I treatment for GD, TRAb increased and PTM developed. TRAb may play some role in the PTM development. All 6 of our patients with PTM had high TRAb titer at the time when PTM was diagnosed. However, in Case 1, PTM disappeared with steroid ODT in the presence of positive TRAb. This disappearance of PTM with topical steroid ODT in the presence of positive TRAb could be explained by the direct effects of topical steroid on PTM. Further study is clearly required.

PTM is an uncommon manifestation of GD. PTM is a late manifestation of GD, and usually follows Graves’ hyperthyroidism. Graves’ hyperthyroidism preceded PTM in all 6 of our patients. Remission of PTM with steroid ODT was observed in only 2 patients (33%).

In conclusion, we successfully treated PTM with steroid ODT in a patient, in whom PTM developed after $^{131}$I treatment for Graves’ hyperthyroidism. TRAb increased after $^{131}$I treatment. The PTM-development seems to be associated with the increase of TRAb activities. We also reviewed 5 other patients with PTM. We reported our experience of PTM-treatment with steroid ODT. PTM was successfully treated with steroid ODT in two patients. In these two patients, PTM was seen within several months after the appearance, and successfully treated with steroid ODT. In the other four patients, the treatment with steroid ODT was started 5-10 years after the appearance of PTM without any beneficial effects. Early detection and early treatment are required for the remission of PTM.
References