Exophthalmus–Myxoedema Circumscriptum Praetibiale–Osteoarthropathia Hypertrophicans (E.M.O.) Syndrome in Graves’ Disease: A Review of Eight Cases Reported in Japan

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Saito, S., Sakurada, T., Yamamoto, M., Yamaguchi, T., Yoshida, K., Sasai, Y., and Yoshinaga, K. Exophthalmus–Myxoedema Circumscriptum Praetibiale–Osteoarthropathia Hypertrophicans (E.M.O.) Syndrome in Graves’ Disease: A Review of Eight Cases Reported in Japan. Tohoku J. exp. Med., 1975, 115 (2), 155–165 — Case 1 showed recurrence of hyperthyroidism accompanied by pretibial myxedema and digital clubbing 14 years after thyroidectomy for Graves’ disease. Case 2 had had pretibial myxedema for the past 20 years and myxedema tuberosum at the right shoulder for the past 10 years, and on admission showed exophthalmos and digital clubbing with thyroid gland demonstrating histological picture of chronic thyroiditis. This case was in slight hypothyroidism and serum LATS was highly positive. Eight cases of E.M.O. syndrome have so far been reported in Japan, including our own. Six cases of these were males. Two cases did not show any sign of hyperthyroidism throughout their entire courses, including our Case 2 described here. Three cases had never received treatment for Graves’ disease prior to the occurrence of this syndrome. The serum LATS was positive in all 5 cases thus far reported. —— E.M.O. syndrome; pretibial myxedema; thyroid acropathy; Graves’ disease

Exophthalmos, pretibial myxedema, and digital clubbing occasionally developing in the course of Graves’ disease have been attracting much interest in the field of studies on the thyroid gland and its diseases. Such symptoms complicated by Graves’ disease were first reported by Thomas in 1933, and later collectively named “exophthalmus-myxoedema circumscriptum praetibiale-osteoarthropathia hypertrophicans (E.M.O.) syndrome” by Braun-Falco and Petzoldt in 1967, or “Exophthalmus-pratibiales Myxödem-Akropachy (E.M.A.) Syndrom” by Richter in 1971. The occurrence of these symptoms, however, have been encountered rather infrequently. Even in Richter’s (1971) worldwide survey, only 31 cases have been collected, except Levitt’s (1953) 8 cases with no detailed descriptions. This report is to provide the findings we have obtained in a review of a total of 8 cases of E.M.O. syndrome so far reported in Japan including 2 cases
experienced in our own clinic, with some comments on the features of this syndrome.

**CASE REPORTS**

Described in detail are 2 patients of E.M.O. syndrome seen at the Second Clinic of the Department of Internal Medicine in the Tohoku University Hospital.

*Case 1.* A 47-year-old male, clerk. In 1944, with complaints of weight loss, palpitation, and exophthalmos, he underwent a subtotal thyroidectomy in another hospital on a diagnosis of Graves' disease. In 1957, symptoms of hyperthyroidism recurred and simultaneously left pulmonary tuberculosis was found; he visited our clinic to be admitted in January 1958. After the hospital treatments with methyl-mercaptopimidazole for hyperthyroidism and with streptomycine, PAS, and INAH for tuberculosis, the patient was discharged in March of the same year. About 17 months later (September 1959), however, weight loss, sweating, palpitation, and tremor of the fingers gradually became apparent, accompanied by a bilateral pretibial swelling, and he was readmitted in June, 1960.

His height was 161 cm and body weight was 60 kg, pulse rate was 80 and irregular. There was lid lag bilaterally, Graefe's sign was positive, exophthalmometry (Hertel) was 17.5 mm in the right and 16.5 mm in the left (Fig. 1). The skin was moist, and tremors were evident in the eyelids, tongue and fingers. The thyroid gland was markedly enlarged, with an estimated weight of 60 g. No cardiac murmur was audible.

The skin over lower two-thirds of pretibial area was distinctly edematous bilaterally and almost elliptically swollen. Evident in coarse hair growth, these parts had a tangerine-peel appearance, yellowish purple, and were elastic at palpitation, leaving no pitting (Fig. 2). The finger-tips in both hands were enlarged showing a feature of digital clubbing (Fig. 3).

![Fig. 1. Case 1. 47-year-old male.](image-url)
The blood pressure was 135/75 mmHg, and blood counts and liver function tests were normal. Serum total protein was 7.8 g/100 ml, γ-globulin being 28.4%. The electrocardiogram showed evidence of atrial fibrillation. Vital capacity was 4.5 liter, and FEV 67.2%. Fasting blood sugar (FBS) was 114 mg/100 ml, serum total cholesterol 142 mg/100 ml, BMR +54%, PBI 15.4 μg/100 ml, and thyroidal 24 hour 131I uptake (131I uptake) was 47%.

After admission, treatment of hyperthyroidism with radio-iodine (131I) followed by methylthiouracil led BMR to revert to normal and atrial fibrillation to disappear 6 months later. At this stage, however, both exophthalmos and digital clubbing remained unimproved. For pretibial myxedema, locally injected hyaluronidase helped to relieve edema appreciably.

Case 2. A 58-year-old male, farmer. About 20 years previously, he had
noticed pretibial swelling bilaterally, from where oily material had occasionally exsudated. Some 10 years before, a cherry-sized soft mass appeared on the right shoulder, which progressively enlarged up to a fist-size; he visited our hospital in August 1972, to have it treated surgically. After admission to the surgical clinic, he was scheduled to undergo an operation for the mass suspected as sarcoma of the right shoulder. However, histological examinations disclosed myxedema convincingly responsible for the right shoulder and pretibial swelling, and the patient was referred to our clinic in September. Although he complained of a sensation of cold and constipation at that time, he had no previous experience whatever of any signs suggestive of hyperthyroidism or goiter.

With 163 cm in height and 52 kg in weight, he had a regular pulse rate of 52. The thyroid gland was impalpable, the eyebrows scanty, and voice was slightly hoarse. Exophthalmometry indicated 21 mm bilaterally. Digital clubbing was typical in both hands (Fig. 4). There were no abnormalities in either the heart, lungs or abdomen. In the dermatological findings, a pretibial swelling was bilaterally similar to that of Case 1. A fist-sized mass on the right shoulder was dark-red, smooth on the surface and freely movable (Fig. 5).

![Fig. 4. Digital clubbing in Case 2.](image)

The blood red cell count was $350 \times 10^4$, hemoglobin 70%; while the white cell count was 5,000. FBS was 90 mg/100 ml, and serum total protein 6.6 g/100 ml of these $\gamma$-globulin was 12.6%, and serum cholesterol was 240 mg/100 ml. The liver and kidney were functionally normal. Vital capacity was 3.7 liter, and FEV 68%. Sinus bradycardia was confirmed by ECG.

On admission in our clinic, the patient's thyroid function tests were: BMR, -10%; $^{131}$I-triiodothyronine resin sponge uptake (Triosorb test), 25%; serum thyroxine ($T_4$) and triiodothyronine ($T_3$), 4.8 $\mu$g/100 ml and 85 ng/100 ml, respectively; and $^{131}$I uptake, 4.4%. Thus, the relevant indications showed the
patients' thyroid function was low or low-normal. However, the application of double antibody radioimmunoassay revealed a normal level of 2.5 μU/ml for serum thyroid stimulating hormone (TSH). On the other hand, serum long-acting thyroid stimulator (LATS) was excessively high at 1261±598%. Antithyroglobulin autoantibody (tanned red cell hemoagglutination test) was 1:5, and antimicrosome autoantibody 1:25,600.

Three months after admission, the relevant levels for thyroid function were: BMR, -16%; serum T₄ and T₃, 3.3 μg/100 ml and 15 ng/100 ml, respectively; ¹³¹I
uptake, 4%; serum cholesterol, 310 mg/100 ml; and serum TSH, 125 μU/ml. Thus, the indicated levels for thyroid function were compatible with those in primary hypothyroidism. Histological appearance of the thyroid gland (Fig. 6) obtained by open biopsy revealed considerable variation in size and shape of the follicles, and the enlarged epithelia. There were variation in the size of the nuclei, marked increase of chromatins and giant nuclei. These findings suggested chronic thyroiditis.

Hyaluronidase frequently injected to a total of 100,000 units had effected in reducing to some extent the size of the mass on the right shoulder. The bilateral pretibial myxedema was almost relieved with the application of steroid occlusive dressing leaving only a slight coloration locally. The administration of T₃ also helped to alleviate the symptoms of hypothyroidism.

Biopsy skin specimens were taken from the lesions on the pretibial areas of both cases and on the right shoulder of the second case. They were fixed for 48 hr in 10% neutral formalin, then embedded in paraffin and sectioned at 6 μm. Staining was done with hematoxylin-eosin, van Gieson’s picrofuchsin, Masson’s trichrome, Weigert’s resorcin fuchsin, Wilder’s reticulum, periodic acid Schiff (PAS), azure A, and alcian blue. PAS, azure A, and alcian blue stains were controlled by being treated with diastase, streptomyces or testicular hyaluronidase, chondroitinase ABC,
Fig. 9. The mucinous material shows a strong affinity for alcian blue in the presence of MgCl₂ at 0.05 M. Alcian blue stain, ×100.

Fig. 10. Treatment with streptomyces hyaluronidase abolishes the azurophilia of the mucinous material. Azure A stain at pH 3.0, ×100.

All specimens from the two patients showed essentially the same histological and histochemical findings. The epidermis was slightly atrophic, the rete ridges being absent in many places. In the middle to the deep dermis there was clearly delineated area in which separation and replacement of the collagen fibers by a faintly basophilic staining, amorphous, or finely fibrillar material and an increase in the number of small spindle-shaped fibroblasts occurred (Fig. 7). In that mucinous area, the reticular fibers appeared diminished or absent. Elastic fibers fragmented and thinned. The mucinous material was PAS-negative and showed an azurophilia at pH 2.5 or higher (Fig. 8). At pH 3.0 or higher, the material was metachromatic. On the other hand, the material showed a strong affinity for alcian blue at pH 5.8, which was not altered by the addition of 0.025 to 0.05 M concentrations of magnesium chloride (Fig. 9). The affinity was slightly reduced in the presence of magnesium chloride at 0.1 M and completely disappeared at 0.2 M. Digestion in diastase, or sialidase failed to alter the affinity for azure A or alcian blue. Treatment with streptomyces or testicular hyaluronidase, or chondroitinase ABC completely abolished the azurophilia and the affinity for alcian blue in the presence of 0.05 M or higher magnesium chloride (Fig. 10).
TABLE 1. 8 cases of E.M.O.

<table>
<thead>
<tr>
<th>Case</th>
<th>Reporter</th>
<th>Age</th>
<th>Sex</th>
<th>Thyroid function in E.M.O. syndrome</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Present authors</td>
<td>47</td>
<td>Male</td>
<td>Hyperthyroid</td>
</tr>
<tr>
<td>2</td>
<td>Present authors</td>
<td>58</td>
<td>Male</td>
<td>Slightly hypothyroid</td>
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<td>3</td>
<td>Kurosawa, S. (1957)</td>
<td>29</td>
<td>Female</td>
<td>Euthyroid</td>
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<td>Tagami, H. et al. (1966)</td>
<td>64</td>
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</tr>
<tr>
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<td>Tatsumo, I. (1969)</td>
<td>47</td>
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<td>Momotani, N. et al. (1972)</td>
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<td>8</td>
<td>Matsuura, K. et al. (1974)</td>
<td>71</td>
<td>Female</td>
<td>Hyperthyroid</td>
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</table>

**Review of E.M.O. Syndrome in Japan**

Table 1 summarized the clinical features of 8 patients with E.M.O. syndrome ever reported in Japan including our present 2 cases. The table shows the predominance of male over female, and no instance of age under 20. The intervals between the initial occurrence of Graves' disease and the onset of pretibial myxedema or digital clubbing were uncertain in Case 2, and in Case 5 the onset was almost simultaneous. In the remaining 6 cases, the intervals ranged between 1 and 37 years. In all cases except Case 5, pretibial myxedema preceded digital clubbing. The 5 cases received surgical or medical treatment for Graves' disease, pretibial myxedema developed 9 months to 14 years after initial treatment. The status of thyroid function identified at the onset of E.M.O. syndrome was hyperthyroid in 4 cases, euthyroid in 3, and slightly hypothyroid in the remaining 1 case. It is remarkable that any signs of hyperthyroid had not found throughout the entire course in Cases 2 and 5.

**DISCUSSION**

In association with Graves' disease, the incidence of about 5% was noted for pretibial myxedema and some 0.6% for thyroid acropathy (Gimlette 1964). But as to the incidence of E.M.O. syndrome, no reliable description is available in previous reports. This may suggest that the syndrome is a rare complication of Graves' disease. The incidence of pretibial myxedema in Graves' disease in our own experience was 0.5% and that of acropathy was only 0.1%. The paucity of descriptions about the incidence of either pretibial myxedema or thyroid acropathy, let alone E.M.O. syndrome, may probably be attributed to overlook of such syndromes or more probably, it may be that incidence of such complications in Japan is fewer than in the Western countries.

The sex distribution of E.M.O. syndrome cases in a worldwide survey of Richter, shows the male-to-female ratio of 12:19, contrary to the Japanese cases where the males outnumbered the females. No cases under the age of 20 are listed in Richter's tabulation, 4 cases showed no digital clubbing, but X-ray films of the extremities disclosed without exception periosteal new bone formation, which
is one of the signs indicating thyroid acropathy (Thomas 1933). Kinsella and Back (1968) also considered the possibility of overlook of thyroid acropathy that could only be identified roentgenographically in patients showing no apparent digital clubbing.

Pretibial myxedema or acropathy is believed to occur following few months to some 30 years after the onset of symptoms suggestive of Graves' disease (Kriss et al. 1967). Most reports agree that in usual cases exophthalmos occurs first, then pretibial myxedema, followed by acropathy (Gimlette 1964). This tendency was also observed in the Japanese cases; as many as 7 of the 8 patients developed pretibial myxedema ahead of acropathy.

E.M.O. syndrome is reported to occur in most cases following the treatment of Graves' disease (Richter 1971). However, in the Japanese instances of E.M.O. syndrome, Graves' disease was treated in 5 of 8 cases, the remaining 3 developed the syndrome independent of the therapy for Graves' disease. It seems still premature to approve or disapprove the relationship of the treatment of Graves' disease to the onset of E.M.O. syndrome.

The histochemical results of the skin mentioned above indicate the presence of hyaluronic acid in greater amount in the dermis (Sasai 1971). It is well known that the cutaneous change in pretibial myxedema consists of the deposition of mucinous material throughout the dermis. Watson and Pearce (1949), in chemical analysis of whole skin from pretibial myxedema found an increased amount of hyaluronic acid, and to a lesser extent, chondroitin sulfate. On the contrary, Schiller et al. (1962), in chemical analysis of skin in hypothyroid rats, found that the myxedematous tissue had an increased concentration of hyaluronic acid and a decreased amount of chondroitin sulfate B. In the case of chemical analysis of whole skin, the substances obtained are not limited to the interfibrillar ground substance but are mixture of substances from the connective tissue fibers, cells, sweat glands, pilosebaceous follicles, blood vessels, and epidermis, unless it is separated. Our preliminary study indicated that the condroitin sulfate B was intimately associated with the connective tissue fibers and other specialized structures rather than with the interfibrillar ground substance. Thus, it is
likely that the mucinous material is mainly composed of hyaluronic acid.

In our Case 2, no symptoms suggestive of hyperthyroid were observed and the thyroid function was low or low-normal throughout the entire course. Nevertheless, the patient showed ophthalmopathy and dermopathy with acropathy, particularly with strongly positive LATS. Also in Case 5 no symptoms of hyperthyroidism could be observed other than goiter. Recently, the term "Graves' disease" has come to imply some combination of hyperthyroidism and goiter with infiltrative ophthalmopathy or pretibial myxedema and the frequent presence in the serum of LATS (Burke 1968). Furthermore, it does not necessarily require the presence of hyperthyroidism (Michaelson and Young 1970). We agree this view from the findings of our Case 2.

On the other hand, Greene (1951) and Haydar (1963) reported instances of E.M.O. syndrome developed in cases of apparent hypothyroidism with histological evidence of chronic thyroiditis (lymphocytic thyroiditis). In our Case 2 with a histological diagnosis of chronic thyroiditis, hypothyroidism developed 3 months after admission. The case is of interest for the study of the intriguing pathogenic relation between Graves' disease and lymphocytic thyroiditis. The case also represents a very rare instance in which myxedema tuberosum has developed on the right shoulder beside pretibial myxedema.

Lipman et al. (1967) investigated the relationship of Graves' disease associated hyperthyroidism, ophthalmopathy and dermopathy to LATS. According to his report, the rate of detection of LATS was progressively higher with the combination of the three symptoms and was detected most frequently with dermopathy. Instances of LATS detected in cases of thyroid acropathy were also reported elsewhere (Kinsella and Back 1968). These findings suggest that the E.M.O. syndrome would have a comparatively high incidence of LATS detection. In the present Japanese cases of E.M.O. syndrome, those having LATS determined all responded positively. From the above review, it is apparent that E.M.O. syndrome and LATS are closely related pathogenically, though any plausible explanations have not yet been given as to its genesis.

References