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SHORT COMMUNICATION

Successful Treatment of Morbihan Disease with Long-term Minocycline and its Association with Mast Cell Infiltration

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Morbihan disease is characterised by persistent lymphoedema on the upper half of the face, which is also referred to as rosaceous lymphoedema and solid persistent facial oedema (1). The term Morbihan disease was derived from the French region where the first patient was observed (2, 3). Clinical features include non-pitting oedema and erythema particularly on the forehead, glabella, eyelids, nose, and cheeks (4). Subjective symptoms are usually not so severe, but eyelid involvement may cause facial disfigurement, visual field narrowing, and severe lymphoedema similar to an elephantoid condition (4, 5). We present the first case in the English literature of Morbihan disease successfully treated with long-term minocycline monotherapy. Moreover, we examined the association of treatment response and mast cell infiltration in Morbihan disease.

CASE REPORT

A 74-year-old man noticed a progressive swelling on his right cheek in 2010. A similar lesion appeared on his left upper eyelid in July 2012. Topical steroids were ineffective and he was then referred to our hospital. He was not taking any medications. Physical examination showed asymptomatic, non-pitting oedematous erythema on the upper portion of his right cheek and left upper eyelid. Telangiectasia, flushing and erythematous papules were not noted on the face, and no cutaneous lesion was observed at other sites. He had no previous history of rosacea. The anti-nuclear antibody showed low titre positivity (1:80), however, circulating autoantibodies against Jo-1, SS-A/Ro, and SS-B/La were not detected using the enzyme-linked immunosorbent assay. Laboratory investigations showed no other abnormalities including serum angiotensin converting enzyme and creatine kinase levels and thyroid function tests. Histopathological findings of a cutaneous biopsy specimen from the oedematous erythema on the left upper eyelid revealed marked dermal oedema, perivascular and perisebaceous mononuclear cell infiltration, granulomatous reaction in the deep dermis, deep reaching fibrosis, and numerous mast cells throughout the dermis (Fig. 1A). Mast cell infiltration was confirmed with mast cell tryptase staining (Fig. 1B), and colloidal iron staining showed faint mucin deposition. Immunohistochemical analysis showed no remarkable deviation for CD3, CD4, CD8, and CD20 staining, and granulomatous reaction was not observed around lymphatic vessels with D2-40 staining. Chest computed tomography and cranial magnetic resonance imaging revealed no abnormalities.

We administered oral betamethasone at 1.5 mg/day for one week. No improvement was observed and the patient denied further use of systemic corticosteroid. The eruption gradually aggravated (Fig. 1C). We initiated oral minocycline at 50 mg/day in June 2013. Since significant improvement was not observed after 4 weeks of treatment, we increased the dosage of minocycline to 100 mg/day. The facial oedema and erythema then gradually improved (Fig. 1D) and minocycline was ceased after 4 months. Although pitting oedema on the left upper eyelid persisted, no recurrence has been observed for 8 months.

DISCUSSION

The pathogenesis of Morbihan disease is still unclear; it is either considered as a rare late-stage complication of rosacea/acne or as a distinct entity (2, 4). There was no previous history of rosacea in our case. Characteristic histological findings of Morbihan disease include dermal oedema, perivascular and periadnexal lymph-histiocytic

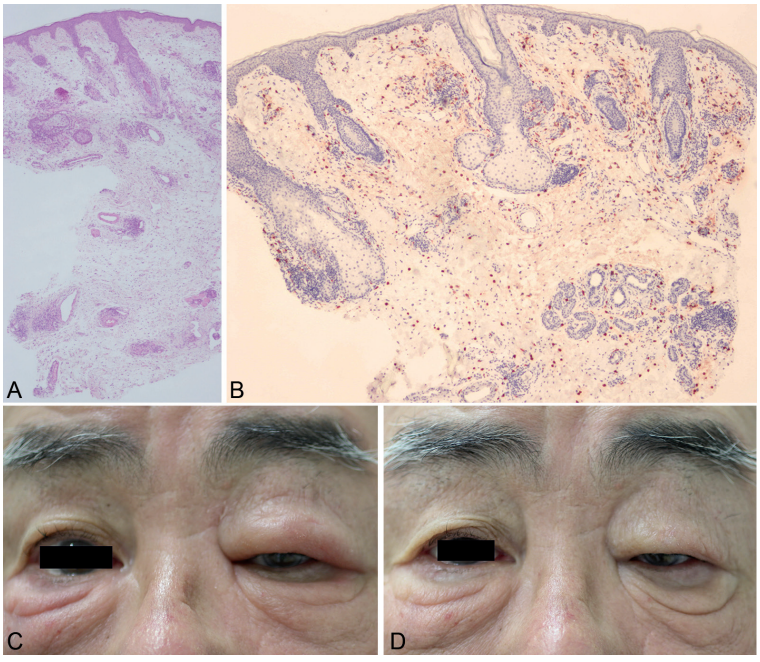

Fig. 1. (A) Histolopathogical examination of a biopsy specimen from left upper eyelid revealed dermal oedema, perivascular and perisebaceous mononuclear cell infiltration and granulomatous reaction at deep dermis (H&E staining, original magnification × 40). (B) Massive mast cell infiltration throughout the dermis was observed with mast cell tryptase staining (original magnification × 100). (C) Clinical presentation before the treatment of minocycline. Severe oedematous erythema was observed on his right cheek and left upper eyelid. (D) Clinical presentation after 4 months treatment of minocycline. Oedematous erythema improved despite the persistent pitting oedema on the left upper eyelid.

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infiltration, and granulomatous reaction. It was speculated that epithelioid cell granuloma around lymphatic vessels could induce continuous lymphoedema and subsequent lymphatic damage (1), however, granulomatous reaction around lymphatic vessels was not observed in our case.

There is no guideline for the treatment of Morbihan disease. Reported therapy includes systemic corticosteroids, oral antibiotics and isotretinoin (4). There are several reports regarding systemic corticosteroid: prednisolone 50 mg/day for one month was ineffective (1), prednisolone 20 mg/day (duration not available) showed only transient effect (6, 7), and a short course of corticosteroid (duration and dosage not available) provided no improvement (8). Thus, although systemic corticosteroid was reported to be effective for acute phase penile lymphoedema (9), its application in Morbihan disease seems difficult (10). In our case, a short-term administration of oral betamethasone was ineffective.

In one case, the combination of prednisolone of 20 mg/day for 2 weeks and doxycycline of 200 mg/day for 12 weeks improved the oedema and erythema (11). In contrast, minocycline monotherapy for 6 to 7 months did not show apparent improvement (dosage not available) (8). As for isotretinoin, it has been reported that the combination treatment of isotretinoin (0.7 mg/kg/day) and ketotifen (2 mg/day) for 4 months was effective (12). Recently, it was reported that long-term use of oral isotretinoin (40–80 mg/day for 10–24 months) successfully treated the disease (4). Since isotretinoin is not available in Japan, we used oral minocycline, and remarkable improvement, except for leaving a partial oedema in the left upper eyelid, was obtained within 4 months.

Mast cell infiltration was reported to be another histological feature of Morbihan disease (13), also reported in solid persistent facial oedema of acne (14). Marked infiltration of mast cells was observed in our case and in some previously reported cases (7, 13), but not in other cases (1, 2). The difference may depend on the stage of the disease and the way skin biopsies were taken. To our knowledge, there is no previous report on the evaluation of histopathological findings according to the disease stage in Morbihan disease. In our case, 2 cutaneous specimens obtained one year apart showed similar histopathological findings, including mast cell infiltration. The description about the infiltration of mast cells is not mentioned in most reported cases in the English literature, including a case series report (4).

We hypothesise that the response to treatment is associated with the degree of mast cell infiltration. There are 2 reported cases without mast cell infiltration in which long-term use of isotretinoin (60 mg/day for 26 weeks) or minocycline (200 mg/day for 2 months) was ineffective (1, 2). There are 2 reported cases with numerous mast cells, one of which was successfully treated with long-term use of both isotretinoin (0.7 mg/kg/day) and ketotifen (2 mg/day), and the other of which showed poor response to short duration tetracycline (7, 12). Minocycline was effective in our case, which showed massive infiltration of mast cells, and tetracycline has been shown to inhibit cytokine production of mast cells *in vitro* (15). Based on these observations, we speculate that the long-term use of isotretinoin or tetracycline is effective only in Morbihan disease with abundant mast cell infiltration.

The authors declare no conflict of interest.

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