ROSACEA LYMPHOEDEMA RESPONDING TO PREDNISOLONE, METRONIDAZOLE AND KETOTIFEN THERAPY IN A PATIENT WITH ALOPECIA UNIVERSALIS

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SUMMARY : *A male patient with solid persistent facial lymphoedema following rosacea and associated with recalcitrant alopecia universalis is reported. While oral isotretinoin for a period of one year was unsuccesful in the therapy of rosacea lymphoedema, a considerable improvement was achieved with a combination of systemic prednisolone, metronidazole and ketotifen.*

Key Words: *Rosacea, Lymphoedema, Alopecia Universalis, Prednisolone, Metronidazole, Ketotifen.*

Rosaceous lymphoedema is the most severe and rare variant of rosacea afflicting patients psychologically and cosmetically (1). It occurs usually as a complication of long-standing chronic inflammation and responds poorly to therapy (2). Similarly, alopecia universalis is the most severe type of alopecia areata with unfavorable outcome. In this report, a male patient with facial lymphoedema following rosacea, which developed simultaneously with alopecia universalis is described.

CASE REPORT

A 35-year-old man referred with two year-history of chronic persistent oedema and erythema on the centrofacial region following rosacea of three years duration, which was responsible for transient episodes of flushing and swelling of the face. Periorbital oedema was more pronounced in the morning and impaired his sight. He was otherwise healthy apart from alopecia universalis that started five years ago and was refractory to various treatments including topical minoxidil, systemic corticosteroids and PUVA. For the treatment of facial erythema and oedema, he had taken isotretinoin (0.7 mg/kg/day) with little success for the last 12 months. On examination, there were a marked centrofacial non-pitting oedema, moderate erythema, some telangiectatic vessels, several small papules, keratotic spicules and a few pustules. Oedema was bilateral, symmetric and most prominent over the lower portion of the forehead, glabella, the upper lids and medial canti of the eyes and along the sidewalls of the root of the nose (Fig. 1). The patient was completely hairless and there were typical features of trachionychia in all nails. With skin surface biopsies, *Demodex folliculorum* mites were seen to be present in a large number at the forehead, cheeks and nose. Results of laboratory tests were all within normal limits. An interesting

Fig. 1: Rosacea lymphoedema associated with alopecia universalis.

Fig. 3 : Considerable improvement of lymphoedema after therapy with prednisolone, metronidazole and ketotifen.

observation was that when taking a punch biopsy from the forehead, a whitish and concentrated fluid had streamed out of the biopsy cut after which a tief pitting (approximately 1-1.5 cm in depth) had occurred at the biopsied area as a result of the strong and prolonged pressure with fingers. Histopathologic examination of the biopsy material revealed orthokeratosis, short and keratin-filled epidermal follicular invaginations, a microvesicle located in the subgranular layer and filled with an eosinophilic homogenous material, dermal oedema, lymphohistiocytic infiltrate around dilated vessels and hairless follicles, and few hypoplastic sebaceous glands (Fig. 2). Special stains for

Fig. 2: Photomicrograph of skin biopsy specimen showing follicular plugging, a subgranular microcyst, dilated vessels, perivascular and perifollicular lymphohistiocytic infiltrate and dermal oedema (Hematoxylin-eosin X 4).

infectious agents such as mycobacteria and leishmania gave negative results as well as those for amiloid and musin. With a diagnosis of lymphoedematous rosacea combined with alopecia universalis, prednisolone (30 mg/day), metronidazole (2X500 mg/day) and ketotifen (2 mg/day) were started. As a considerable improvement was achieved with this combination within six weeks in lymphoedema (Fig. 3), systemic metronidazole and prednizolone were stopped with tapering doses. However, any hair regrowth did not occur during systemic prednisolone therapy. He currently continues to use ketotifen and topical metronidazole.

DISCUSSION

Solid persistent facial oedema (SPFO) is an uncommon condition related to congenital, neoplastic, infectious, inflammatory and other miscellaneous disorders (3). Some authors had considered that Morbihan's disease (Degos, 1957), a disorder characterized chronic persistent oedema and erythema affecting upper portion of the face with unknown etiology, and rosaceous lymphoedema are the same entities (2,4,5).

Ethiopathogenesis of lymphoedema following rosacea is unclear as well as that of rosacea. Solar degeneration of dermal connective tissue, or local host responses to *Demodex* mites, hair and keratin debris, or immunologic, genetic,

traumatic factors may cause a chronic inflammation which probably induce lymphatic obstruction and mast cell-induced dermal fibrosis resulting in lymphoedema (1). A case of SPFO following rosacea in a patient with primary lymph vessel dysplasia was also reported (2). Similarly, the causal factor(s) of alopecia areata and its progression to alopecia universalis are not completely understood although there are evidences suggesting a T cell-mediated autoimmune reaction to an unknown hair-associated antigen (6). In this case, the simultaneous occurrence of alopecia universalis with rosaceous lympoedema may be completely coincidental but one may also speculate that the long-standing perifollicular inflammation caused by alopecia areata can be a facilitating factor for the development of lymphoedema in addition to rosaceous chronic inflammation, or less likely, a common ethiopatogenetic factor might cause the development of both rosacea and alopecia areata and to progress into their most severe forms.

SPFO is generally refractory to therapy (1,2). The combination of isotretinoin and ketotifen has provided a complete regression in some patients with SPFO following acne (7) and rosacea (5). A patient with rosacea lymphoedema who was successfuly treated with systemic prednisolone and metronidazole was reported (8). Ketotifen is a potent H_1 antagonist, and inhibits mast cell degranulation which is believed to be responsible for fibrosis that is one of possible causes of chronic lymphoedema (1,9). Metronidazole has antiinflammatory properties in addition to its antibacterial and antiprotozoal effects, and is effective in all types of rosacea (9). Since rosacea lymphoedema is thought to develop on the background of chronic inflammation of any cause including bacterial (e.g. *Helicobacter pylori*) or demodectic infections (1,2,7-9) it may be reasonable to combine ketotifen, a mast cell stabilizator, with metronidazole and prednisolone. Clofazimine, antibiotics, interferon-γ, lymphatic massage (Sobye), and in severe cases, irradiation and plastic surgery have been used with variable success (8). In the present case, prednisolone, metronidazole and ketotifen combination achieved a great regression of lymphoedema and complete resolution of erythema and inflammatory lesions.

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