A Case of Rosacea Fulminans Responsive to Combination Treatment with Dapsone, Doxycycline and Topical Tacrolimus

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Rosacea fulminans is a rare variant of rosacea characterized by sudden onset of papules, pustules, and coalescing nodules on the face in postadolescent women. A combination regimen including systemic isotretinoin and oral plus topical potent corticosteroids is the recommended therapy. We report a case of rosacea fulminans in Taiwan in a 48-year-old woman who still had persistent facial erythema and continually active papulopustules after initiation of the conventional therapy for 3 months. Rapid clearing of the skin lesions was achieved in one month by introducing systemic doxycycline and dapsone plus topical tacrolimus. (Dermatol Sinica 27: 117-121, 2009)

Key words: Rosacea fulminans, Dapsone, Tacrolimus

INTRODUCTION

Rosacea fulminans is a rare disease of unknown etiology which occurs mainly in postadolescent women. It is characterized by an abrupt explosive outbreak without prodromes, consisting of papules, pustules, confluent nodules with draining sinuses on the face. A dull to blue-red, cyanotic erythema of all involved facial areas is typical, often accompanied by pronounced facial edema. It was initially described by O’Leary and Kierland in 1940 as pyoderma faciale, and was later reclassified by Plewig et al., who recommended the use of oral isotretinoin plus short-course systemic and topical potent corticosteroids. Some cases, however, did not respond to isotretinoin and could achieve complete healing by dapsone. The exact prevalence of rosacea fulminans is unknown and it is uncommonly reported in Asian people, especially in Taiwan. We present a rare case of rosacea fulminans in Taiwan, who was refractory to the conventional treatment but successfully treated with systemic dapsone plus doxycycline and topical tacrolimus.

CASE REPORT

A 48-year-old otherwise normal healthy woman presented to us with abrupt onset of numerous erythematous papulopustules and plaques over the face for 3 days (Fig. 1A). No obvious flushing or blushing was noticed previously. Shortly before the episode, she had taken a mixed herbal medicine comprising Bupleuri radix, Angelicae sinensis radix,
Moutan radicis cortex, Cimicifugae rhizome, Coptidis rhizome, Rehmanniae radix, Taraxacum mongolicum, Eriobotryae folium, Gardeniae fructus, Paeoniae radix rubra, Coicis semen, Menthae herba and Glycyrrhizae radix.

Physical examination showed facial telangiectasia and bilateral conjunctival injection. Histopathology of the confluent papular lesions showed focal parakeratosis, necrosis of the uppermost part of a mild acanthotic epidermis, and marked exocytosis of mononuclear cell and neutrophils. In the dermis, there were follicular disruption by dense inflammatory cell infiltrates consisting of lymphocytes, neutrophils and scattered histiocytes without obvious granulomatous formation (Fig. 1B). Bacterial culture of the pustular content showed only light colonies of coagulase negative Staphylococcus species. Laboratory study showed mild leukocytosis and slight elevation of C-reactive protein level.

Under the diagnosis of rosacea fulminans, systemic isotretinoin at 40 mg/day was initiated, together with prednisolone 20 mg/day, doxycycline 200 mg/day and 0.75% topical metronidazole gel. The papulopustular lesions began to remit and oral prednisolone was tapered in 1 month.

During the next 3 months, however, new active papulopustules continued to develop as the patient was kept on isotretinoin at 40 mg/day (Fig. 2A). Persistent marked erythema with telangiectasia remained a major concern. Because the patient expressed reluctance to continue the use of systemic isotretinoin, treatment was shifted to dapsone 100 mg/day and doxycycline 200 mg/day plus topical application of 0.03% tacrolimus ointment (the only available preparation in our hospital). The marked facial erythema faded significantly in only 3 weeks, and a maintenance dose of dapsone 100 mg/day and doxycycline 200 mg/day were continued for 2 months. No more active papulopustules have ever been observed in the subsequent 6-month follow-up (Fig. 2B).
DISCUSSION

Rosacea fulminans has proved controversial in its classification and was not included as a rosacea sub-type or variant by the National Rosacea Society (NRS) Expert Committee. It is characterized by the sudden onset of confluent papules, pustules, nodules, and draining sinuses on the chin, cheeks, and forehead within a background of diffuse facial erythema.

Our case is unusual in that (1) temporally close association with the intake of herbal medication, (2) coexistence of ophthalmic rosacea, (3) incomplete response to conventional treatment with oral isotretinoin and oral/topical steroids, but good response to systemic dapsone and doxycycline. It is not clear why rosacea fulminans occurs almost exclusively in women. The reported cases seem to focus in Caucasians and rarely in Asians, especially in Taiwanese. The etiology of rosacea fulminans still remains mysterious. Precipitating factors include emotional stress, such as intense, prolonged, psychological trauma, and in some cases, during pregnancy or the postpartum period. Drugs have not been demonstrated to be the underlying cause, although in some cases various medications such as thyroid hormones, iron supplements, antihypertensives, oral contraceptives, oral tetracyclines and erythromycin, topical benzoyl peroxide and many topical antibiotics were concomitantly used without causal relationship to the disease. Some reports suggest that certain medications, such as pegylated interferon alpha-2B and ribavirin or high-dose vitamin B₆ and B₁₂, may be associated with rosacea fulminans. Although a close temporal relationship exists between onset of rosacea fulminans and the intake of herbal drugs in our patient, their causal association remains to be determined.

Ophthalmic rosacea is not a rare complication of ordinary rosacea, but its concurrence with rosacea fulminans seems to be less addressed. In our patient, conjunctival injection was obvious from the beginning of disease presentation and seemed to aggravate by taking isotretinoin (Fig. 2A). This is why we took the risk of inducing pseudotumor cerebri to combine doxycycline with isotretinoin in the early stage of treatment. Although pseudotumor cerebri did not develop in our patient, it has been described in some cases and should be taken into consideration when planning to combine these two drugs.

The superb efficacy of isotretinoin in the treatment of rosacea fulminans has been well documented. The recommended dose ranges from 0.2-0.5 mg/kg to 1 mg/kg and duration lasts for 3-4 months. Combination with systemic prednisolone 1.0 mg/kg/d and topical potent corticosteroids for the initial 2 weeks was suggested by Plewig et al. to cool down the inflammation. However, similar to our case, Bormann et al. described a case of rosacea fulminans in whom the recommended therapy failed to achieve obvious improvement, while use of dapsone led to complete healing in 5 weeks. The mechanism of dapsone in treating rosacea fulminans is not clear but may be due to its suppressive effect on neutrophils. Dapsone could reduce the concentration of toxic O₂ intermediate and prevent the migration of neutrophils into the tissue by inhibition of integrin-mediated cellular adhesion on the vessel walls. The beneficial effect of dapsone in granulomatous rosacea has also been reported.

Recent reports showed the efficacy of topical tacrolimus in treating rosacea. Pabby et al. and Goldman found rapid improvement of steroid-induced rosacea within 1 to 3 weeks by either topical tacrolimus alone or in combination with tetracycline. A small open-label trial conducted by Bamford et al. showed that tacrolimus might be especially helpful for erythema but not for papulopustular manifestation of rosacea. In our case, the cessation of oral isotretinoin and the addition
of 0.03 % topical tacrolimus dramatically induced rapid improvement of persistent facial erythema within one month. As a calcineurin inhibitor, the effect of tacrolimus is not exactly defined but may be due to its down-regulation of local immune and inflammatory process. To date, no studies have been performed that compared 0.03% and 0.1% tacrolimus ointment on rosacea fulminans. A better result may be expected by using higher concentration (0.1%) of tacrolimus in our case, although the risk of skin irritation may also be increased.

In summary, the combination of systemic dapsone, doxycycline and topical tacrolimus is worthy of trial for rosacea fulminans poorly responsive to the conventional treatment with oral isotretinoin.

REFERENCES
猛暴性酒渣是酒渣的一個少見的變異型，特色是青春期後的女性，在臉上突發性的丘疹、膿泡及融合在一起的結節。一般建議治療的方式為合併使用口服isotretinoin及類固醇，再加上強效的局部類固醇塗抹。我們報告台灣地區一個猛暴性酒渣的案例，一位48歲的女性病人，在經過傳統的治療方式3個月後，仍然有持續性的臉部潮紅並且一直都有新的丘疹及膿泡出現。然而，臉上的病灶卻在使用口服doxycycline及dapsone加上局部塗抹tacrolimus一個月內，快速消除。（中華皮誌：27: 117-121, 2009）