Ofuji’s Disease: A Review of 34 Patients in 10 Years

Jia-Jen Wu  Chia-Yu Chu

Ofuji’s disease is clinically characterized by chronic and recurrent annular clusters of sterile follicular papules and pustules superimposed on plaques with central clearing and peripheral extension. Indomethacin is considered to be a first choice of treatment, but the pathogenesis of this disease is still obscure. Although most cases of Ofuji’s disease have been reported in Japanese people, it is not rare in Taiwan according to our clinical experience. In this study, we reviewed 34 patients with biopsy-proven Ofuji’s disease who came to our clinic over the past decade. Extra-facial involvement was noted in 15 of 34 patients (44%), and 7 had palmoplantar lesions. We emphasize on the features of extra-facial involvement, especially the palmoplantar lesions, because it may lead to clinical and pathological confusion in diagnosing the disease. We also found indomethacin seemed to have a higher effective rate (89%) as compared to other treatments in our cases. (Dermatol Sinica 26: 65-74, 2008)

Key words: Eosinophilic folliculitis, Extra-facial involvement, Ofuji’s disease

INTRODUCTION

Eosinophilic pustular folliculitis (EPF) is a noninfectious disease characterized by the histologic features of a predominant infiltration by eosinophils in and around hair follicles. There are 3 variants: classic, HIV-associated and infantile EPF. The first case of EPF was described by Ise and Ofuji1 in 1965 in a Japanese woman who had recurrent follicular pustules on her face and trunk with peripheral eosinophilia. The condition was later termed classic EPF, also known as Ofuji’s disease (OD).2,3 The other 2 variants, HIV-associated and infantile EPF shared the same histologic findings but were distinguishable based on clinical features and laboratory data.4,5

OD is clinically characterized by chronic and recurrent annular clusters of sterile follicular papules and pustules superimposed on plaques with central clearing and peripheral extension. The histology of such lesions was distinctive.2 There were epidermal spongiosis and vesiculation of the follicular infundibula with an infiltrate of eosinophils in early lesions, and perifollicular vesicles containing numerous eosinophils and mononuclear cells extending to the entrance of the sebaceous duct in later lesions. OD was mostly reported in Japanese people, and its clinical information in Taiwanese people was relatively scarce.6-9 Tsai et al.9 reviewed 23 cases of EPF in 2003. However, they included not only non-HIV EPF, but also 7 HIV-EPF cases. In their case series, the percentage of extra-facial involvement was only 19% in the non-HIV group, and none of them had lesions over palms and soles.

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To further characterize the clinical features, laboratory data, and treatment response of OD in Taiwanese, we retrospectively collected 34 cases who came to our clinic over the past decade.

MATERIAL AND METHOD

Thirty-four patients with OD who came to our clinic from January 1998 to July 2007 were collected. The diagnosis of OD was based on clinical features and was confirmed histologically in all of the patients. Their clinical course, laboratory data and treatment response were analyzed by reviewing the medical records. Duration of the disease was defined by the time interval between the age of onset and undergoing the biopsy. Leukocytosis was defined by white blood cell count over 10,000/μL. Eosinophilia was defined by eosinophils over 6% and an absolute eosinophilic count over 350/mm³. The effect of treatment was evaluated based on the records documented by the dermatologists. The treatment was considered effective if skin lesions disappeared, improved, or if there was a decrease in new lesions or in the frequency of disease flare-up. The treatment was considered ineffective if there was no obvious improvement or if no further information could be obtained due to loss to follow-up. Previous treatments were also taken into account, if the medication and response were precisely reported.

Those who were better diagnosed with HIV-associated or infantile EPF and those who had skin lesions responsive to antifungal agents were excluded in this study, even though the histologic findings might not be able to distinguish these conditions.

RESULTS

The general background information of the patients is shown in Table 1; mean age of onset was 32.3 years (range, 15-53 years). Sixteen men and 18 women were included in this study. Disease duration ranged between 3 weeks to more than 10 years.

Clinical findings

All patients but 1 had typical lesions of OD on their faces: indurated, erythematous plaques studded with papules and pustules that often formed annular configurations with a tendency of peripheral extension and central clearing (Fig. 1A). The only patient without facial involvement had OD presenting as scattered discrete erythematous papulopustules over the back (Fig. 1B) and pompholyx-like lesions over the fingers. Itching was complained in 24 patients, while no subjective symptoms were mentioned by the remaining 10 patients. Initial clinical diagnoses for facial lesions other than OD included follicular mucinosis, granulomatous disorder, autoimmune disease (subacute cutaneous lupus erythematosus or lupus profunda), lymphocytic infiltration, rosacea, polymorphic light eruption, and figurate erythema such as erythema chronicum migrans and erythema annulare centrifugum. OD was correctly diagnosed or at least among the differential diagnoses in 26 of the 34 patients (76%). Extra-facial involvement was noted in 15 of 34 patients (44%) (Table 1, 2). The trunk was involved in 11, the extremities in 7 (upper limbs only in 3, lower limbs only in 1, and both in 3), and palms and soles in 7. The extra-facial lesions could occur at any stage of the disease: preceding, concurrent with, or following the facial lesions. They could be transient and then spontaneously resolve, or could persist along with the facial lesions. When located on the trunk or extremities, the lesions of OD tended to have similar morphology to the facial ones (Fig. 1C), while the lesions on the palms and soles resembled pompholyx, dyshidrotic eczema or pustulosis palmoplantaris (Fig. 1D, E). Nail dystrophy was documented in 1 patient with palm-and-sole involvement (Fig. 1F).

There were no concurrent constitutional symptoms such as fever, malaise, or muscle weakness.
Laboratory data

There was no routine laboratory investigation for patients with suspected Ofuji’s disease at our hospital. In 17 patients whose complete blood...

Fig. 1

(A) Typical lesions of Ofuji’s disease on the face of a 29-year-old male patient: indurated, erythematous plaques studded with papules and pustules that formed annular configurations with a tendency of peripheral extension and central clearing.

(B) Scattered discrete erythematous papulopustules on the back of a patient without facial involvement.

(C) Typical lesions of extrafacial Ofuji’s disease on the trunk.

(D, E) Plantar lesions of Ofuji’s disease resembling pompholyx and pustulosis palmarplantaris.

(F) Palmar lesions and nail dystrophy in Ofuji’s disease.
count and differential count were checked, 2 (12%) had leukocytosis (12,800 and 11,210/µL, respectively) and 12 (71%) had eosinophilia (6.3-31.3%, 357-3509/mm³). The degree of eosinophilia seemed to correlate to the disease activity, as the eosinophil count returned to normal in several patients after their skin lesions improved. Serum total IgE was checked in 3 patients, and the values were 101.0, 64.5, and 32.9 IU/ml. Autoimmune profiles including autoantibodies, C3, C4, and/or rheumatoid factor, were examined in 10 patients whose lesions were once suspected to be due to an autoimmune process. Positive anti-nuclear antibody (1:320 homogeneous) was found in 1 patient, while the results of the rest were all within normal limits. KOH examinations for lesions from 3 patients all failed to reveal any spores or hyphae. Two patients had their pustular content sent for bacterial culture; one grew Propionibacterium acnes (1+), and the other was sterile.

**Histopathology**

Totally 36 tissue specimens were obtained. Two patients had biopsies on 2 different sites, one on the face and the other on the extra-facial lesions. Samples were all adequate for histologic examination and diagnosis. The 29 specimens obtained from facial skin all fulfilled the features of OD, with a predominant infiltration by eosinophils in and around hair follicles with some degree of spongiosis and destruction of follicle (Fig. 2A, B). Follicular mucinosis was noted in 1 specimen. Biopsy of extrafacial lesions was performed in 7 patients:

**Table. 1 Background Information**

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age at onset (years)</td>
<td>15–53 (32.3)</td>
</tr>
<tr>
<td>Men/women</td>
<td>16 : 18</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>12/17 (71%)</td>
</tr>
<tr>
<td>Affected site</td>
<td></td>
</tr>
<tr>
<td>Facial</td>
<td>33/34 (97%)</td>
</tr>
<tr>
<td>Extra-facial</td>
<td>15/34 (44%)</td>
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</table>

**Table. 2 Clinical Details of The 15 Cases with Extra-Facial Involvement**

<table>
<thead>
<tr>
<th>Locations</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Trunk</td>
<td>11/15 (73%)</td>
</tr>
<tr>
<td>Extremities</td>
<td>7/15 (47%)</td>
</tr>
<tr>
<td>Palms and soles</td>
<td>7/15 (47%)</td>
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**Chronological relationship**

<table>
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<tr>
<th>Description</th>
<th>Value</th>
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<tr>
<td>Preceding the facial lesions</td>
<td>2/15 (13%)</td>
</tr>
<tr>
<td>Concurrent with the facial lesions or not specified</td>
<td>12/15 (80%)</td>
</tr>
<tr>
<td>Following the facial lesions</td>
<td>1/15 (7%)</td>
</tr>
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The diagnostic findings of EPF were identical to the facial lesions. However, the lesions on palms and soles presented as subcorneal pustules containing neutrophils and eosinophils histopathologically as there was no hair follicle in the region (Fig. 2C, D). Direct immunofluorescence study was done in 11 of the 36 specimens; granular IgM and C3 deposits over the basement membrane zone were detected in one specimen.

For those with both facial and extra-facial involvement who only had biopsy on the face or on the extra-facial regions, the diagnosis of OD was still established according to the typical clinical presentation and to the parallel treatment effects on various sites.

### Table. 3 Comparison of The Data in This Study with Another Case Series From Southern Taiwan

<table>
<thead>
<tr>
<th></th>
<th>Tsai et al.</th>
<th>Our series</th>
</tr>
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<tbody>
<tr>
<td>Case number</td>
<td>16</td>
<td>34</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>13-50 (31.2)</td>
<td>15-53 (32.3)</td>
</tr>
<tr>
<td>Male-to-female ratio</td>
<td>1: 2.2 (5 males and 11 females)</td>
<td>1: 1.1 (16 males and 18 females)</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>8/13 (62%)</td>
<td>12/17 (71%)</td>
</tr>
<tr>
<td>Facial lesions</td>
<td>16/16 (100%)</td>
<td>33/34 (97%)</td>
</tr>
<tr>
<td>Extra-facial lesions</td>
<td>3/16 (19%)</td>
<td>15/34 (44%)</td>
</tr>
<tr>
<td>Involvement of palms and soles</td>
<td>0/16 (0%)</td>
<td>7/34 (21%)</td>
</tr>
<tr>
<td>Treatment and effective ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>11/11 (100%)</td>
<td>0/3 (0%)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>3/6 (50%)</td>
<td>24/27 (89%)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>0/2 (0%)</td>
<td>4/7 (57%)</td>
</tr>
<tr>
<td>Dapsone</td>
<td>0/3 (0%)</td>
<td>1/5 (20%)*</td>
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* In combination with topical clobetasol propionate

### Treatment and response

Approximately half of the patients had been treated elsewhere before came to our hospital. Previous diagnoses included acne or eczema most frequently, and they had been treated with topical and/or systemic antibiotics or steroids. Therapies which had been tried—in our clinic or before the patients came to our hospital—but showed minimal effect included topical fusidic acid, topical steroids (betamethasone valerate, fluticasone propionate, betamethasone dipropionate, and clobetasol propionate), oral prednisolone, oral antibiotics (doxycycline, minocycline, and tetracycline), oral antifungal agents (itraconazole), oral dapsone, and oral colchicine. However, the combination of oral dapsone and topical clobetasol propionate was found to be effective in 1 patient. Tacrolimus ointment (0.1%) exacerbated
the symptoms of erythema and itchiness in another patient. Oral antihistamines might have a role in symptom relief only.

Once the diagnosis was made, non-steroidal anti-inflammatory drugs would usually be prescribed as the first choice of treatment. Apparent clinical improvement was observed in most of the cases. Naproxen was effective in 4 of the 7 patients (57%), but clearance of the lesions was never achieved with this agent as monotherapy. The therapeutic effect of indomethacin seemed to be superior not only because the effective rate was higher (24/27, 89%), but also due to the finding that those who were partially responsive or even unresponsive to naproxen could have definite control of their skin lesions when indomethacin was taken instead. Apparent clinical improvement was observed within 1 week, with the dosage ordinarily starting at 75-mg per day and then tapered gradually based on the disease activity. The longest follow-up duration was 6 years in a patient who needed indomethacin 150-mg per day for long term control. In those with recalcitrant disease, discontinuation of the therapy was pursued by flare-up of skin lesions, as soon as within 2 days. No definite case of spontaneous resolution could be identified, due to lack of information for those who did not return to our clinic for further treatment.

DISCUSSION

Most cases of OD have been reported in Japan. In Europe and the United States, the majority of EPF patients were recognized in association with HIV infection. The male-to-female ratio for OD approximates 5:1 in

Fig. 2
Histopathology of skin biopsies on the facial (A,B) and plantar (C,D) lesions from patients with Ofuji’s disease. (A,B) A predominant infiltration by eosinophils in and around hair follicles with some degree of spongiosis and destruction of follicle. (H&E, original magnification Ax40, Bx400) (C,D) Epidermal acanthosis with confluent parakeratosis and occasional neutrophilic microabscess, accompanied with spongiotic pustule formation also containing neutrophils and eosinophils. (H&E, original magnification Cx40, Dx400)
On the contrary, when the face was affected simultaneously. Another study from Singapore also reported a ratio of 1:1.6. Whether the difference in sex distribution stands for a racial variation and on the finding of peripheral eosinophilia was an uncommon finding in our patient group (12%), but it was observed in at least 31 out of 92 cases (34%) in a review and was frequent in severe stages.

The extra-facial involvement of OD has been well recognized in the literature. The distribution is on the face (85% of cases), back and trunk (59%), but also can include the extremities, palms and soles despite the fact that follicles are not found in either palms or soles. One fifth of patients display palmoplantar lesions. Saruta and Nakamizo found that palmar lesions had been present in as many as 27.5% of cases reported in 1980. We emphasize on the features of extra-facial involvement, especially the palmoplantar lesions, not only because the extra-facial distribution is found not infrequently in our patients, but also due to its contribution to clinical and pathological confusion. One of the major differences between our patient group and the cases collected by Tsai et al. is the percentage of extra-facial involvement (44% vs. 19%). Although OD with palmoplantar lesions had been reported more than 2 decades ago in Taiwan, none was observed in Tsai’s series.

Most of our patients with extra-facial involvement had typical EPF lesions on their trunk and extremities, and such lesions were hardly mistaken as other condition especially when the face was affected simultaneously. On the contrary, palmoplantar purpuric or vesicular lesions of OD seldom yielded a correct diagnosis due to their clinical resemblance to pompholyx, dyshidrotic eczema or pustulosis palmoplantaris (PPP). We assume that extra-facial OD would be probably under-reported. While the face is most commonly affected and most noticeable site, clinicians should be more alert to recognize possible extra-facial lesions, which may facilitate a prompt diagnosis and treatment. OD started as pustulosis palmoplantaris-like lesions in 7% of Japanese cases and the mean time interval between the onset of palmoplantar lesions and the development of the typical EPF lesions in other regions was 26 months. Although it is suggested that the histologic pattern, absolute peripheral eosinophilia, negative bacterial culture and the rapid response to indomethacin are indicative of EPF, histopathological study may not be absolutely helpful in distinguishing PPP and palmoplantar lesions of OD, since acanthosis and hyperkeratosis are regarded as normal histologic variations in the region, and there could also be large numbers of eosinophils in the pustules of PPP.

In addition to the viral infection and decreased CD4 cell count, the clinical manifestations distinguish HIV-associated EPF from OD. Rather than coalescing papulo-pustular plaques, discrete erythematous urticarial follicular papules are seen in the HIV variant with exquisite pruritus. Similar presentations have been reported in non-HIV patients treated for hematological malignancy and in non-HIV patients who were immunocompetent. In our series, there was 1 case whose lesions presenting as discrete and itching folliculitis on the back, with exceptional spare of the face. There was no signs of immunodeficiency, and HIV screening was negative in this patient. His disease was well-controlled by oral indomethacin 150-mg per day, a 2-folds dose with comparison to other patients, but discontinuation or tapering the drug had been unattainable due to consequent flare-up. Whether this type of EPF should be attributed to a subtype of OD or to
another variant of EPF is disputed, and more subjects are required to explore the clinical characteristics of this entity.

The pathophysiology of OD is unclear. Although an association between immune deficiency and EPF is strongly indicated in HIV-associated EPF, it is clinically distinct from most cases of OD. The diversity of clinical presentation and affected populations indicate that EPF seems to be a reaction pattern as much as a disease, i.e. a single histopathologic picture encompassing a number of diseases of immune dysregulation. Our data did not provide additional information in terms of the etiology. Incidental positive findings in autoimmune profiles and the direct immunofluorescent study were more likely due to variations in normal population. Ferrandiz et al. hypothesized that EPF in their patients was caused by an overgrowth of Pityrosporum species in the follicle. However, bacterial culture was done in 2 patients, and only 1 of them was weakly positive for Propionibacterium acnes in our series. There was no enough evidence supporting Pityrosporum species in provoking follicular inflammation in OD.

While various treatments have been tried with no established definitely effective therapy for other types of EPF, indomethacin is proposed as the first line treatment for OD, and the rapid response to the medication may even be of great diagnostic value, especially when a biopsy is unfeasible. The effectiveness of indomethacin for the treatment of OD was first reported in 1984, and its mode of action was through inhibition of cyclooxygenase which reduced the synthesis of an eosinophil chemotactic factor isolated from seborrheic skin in EPF. In our patients, oral indomethacin possessed an overwhelmingly superior therapeutic effect when compared with other treatments including oral steroids, dapsone, and naproxen. Nonetheless, long-term indomethacin should be prescribed with caution regarding its complications in the gastrointestinal tract. In this study, discontinuance of the therapy was necessitated in 1 patient who developed gastric ulcer. The importance of preventive measures, such as a thorough risk and benefit assessment, usage of gastroprotective agents, and early detection of symptoms are stressed, particularly in whom long-term treatment might be needed.

In conclusion, our study confirms that OD is not rare in Taiwan. Furthermore, extrafacial or palmoplantar distribution of the lesion is not infrequent, with a percentage much higher than previously reported but close to that in the Japanese literature. Although complications in the gastrointestinal tract might limit its usage, indomethacin is recommended as the first choice of treatment OD, based on its clinical effectiveness in the majority of patients.

REFERENCES
太藤氏病：十年內三十四位病人之回顧

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太藤氏病，臨床上為慢性、反覆發作之環狀板塊，伴有毛孔一致性的丘疹及膿疱散佈其上，且有中央消散及向外擴張的情形。此病之致病機轉目前尚不明，但indomethacin被認為是首選治療藥物。雖然文獻上所報告的太藤氏病病例大多為日本人，依我們的經驗，此病在台灣也並不罕見。在此回溯過去十年間，來本科求診，經切片確診之34例太藤氏病患者。我們發現，34例病患中有高達15例 (44%) 出現臉部以外之病灶，其中有7例出現手掌腳掌病灶。由於極易造成臨床上與病理上之混淆而延誤診斷，我們在此特別強調此臉部外病灶之臨床表現。我們也發現在本研究的病例中，使用indomethacin治療似有較佳之療效，其治療之有效率為89%。（中華皮誌：26:65-74, 2008）