

ORIGINAL ARTICLE

Eosinophilic pustular folliculitis: A proposal of diagnostic and therapeutic algorithms

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ABSTRACT

Eosinophilic pustular folliculitis (EPF) is a sterile inflammatory dermatosis of unknown etiology. In addition to classic EPF, which affects otherwise healthy individuals, an immunocompromised state can cause immunosuppression-associated EPF (IS-EPF), which may be referred to dermatologists in inpatient services for assessments. Infancy-associated EPF (I-EPF) is the least characterized subtype, being observed mainly in non-Japanese infants. Diagnosis of EPF is challenging because its lesions mimic those of other common diseases, such as acne and dermatomycosis. Furthermore, there is no consensus regarding the treatment for each subtype of EPF. Here, we created procedure algorithms that facilitate the diagnosis and selection of therapeutic options on the basis of published work available in the public domain. Our diagnostic algorithm comprised a simple flowchart to direct physicians toward proper diagnosis. Recommended regimens were summarized in an easy-to-comprehend therapeutic algorithm for each subtype of EPF. These algorithms would facilitate the diagnostic and therapeutic procedure of EPF.

Key words: algorithms, diagnosis, eosinophilic pustular folliculitis, Ofuji's disease, therapy.

INTRODUCTION

Eosinophilic pustular folliculitis (EPF) is a sterile inflammatory dermatosis of unknown etiology that was first described in a case report by Ise and Ofuji as “a variant of superficial pustular dermatosis” in 1965.¹ The eruption of EPF consists of papulopustules that tend to form annular plaques. Histologically, EPF is characterized by an eosinophil-dominated infiltrate within and around the pilosebaceous units, often accompanied by eosinophilic microabscess formation.^{2,3} This type of EPF is currently called Ofuji's disease or classic EPF.⁴ It was once thought that classic EPF affects males predominantly.⁴ However, an exhaustive published work-based study showed no sex difference in classic EPF between 2003 and 2013.⁵ This tendency was further confirmed by a nationwide epidemiological survey conducted in Japan during the period from 2010 to 2011.⁶

Immunosuppression-associated EPF (IS-EPF) and infancy-associated EPF (I-EPF) are variants of EPF, both of which have been constantly reported since 1980s.⁴ IS-EPF comprises HIV-associated eosinophilic folliculitis (HIV-EF) and a similar EF observed in immunodeficient patients without HIV infection. In this study, we divided IS-EPF into “IS/HIV” and “IS/non-HIV” according to the presence or absence of seropositivity for HIV. IS-EPF is often associated with persistent and intense pruritus. I-EPF affects the scalp whereas classic EPF rarely does. Histological findings of I-EPF are indistinguishable from those of classic EPF whereas the entity of I-EPF remains controversial.⁷

Recently, an additional variation on classic EPF was proposed as episodic eosinophilic dermatosis of the face (EEDF).⁸ EEDF lacks the typical features of classic EPF, such as pustule formation and peripheral extension of the lesions, but responds well to oral indomethacin.

Diagnosis of EPF can be difficult and require careful differential diagnosis.⁹ Eruptions of classic EPF resemble those of common diseases, such as acne vulgaris, dermatomycosis or eczema. IS-EPF presenting with itchy eczematous papules may be overlooked because it can spontaneously disappear when the underlying immunocompromised state resolves.

Treatment of EPF can be difficult. A chronic course of EPF requires long-term application of regimens. Thus, topical or systemic steroids must be used with care. Furthermore, steroids do not always successfully ameliorate eruptions of EPF. Although systemic indomethacin is effective for 88% of classic EPF cases (Table S2a), indomethacin-resistant cases exist (Table S4).

In this study, we created algorithms for procedures to facilitate the diagnosis and selection of therapeutic options on the basis of descriptions available in public domain databases.

METHODS

Subjects

We collected publications released between 1965 and 2013 and available on PubMed and Igaku Chuo Zasshi (Ichushi or Japana Centra Revuo Medicina), including the first case described as

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Table 1. Cases in which the lesions mimicked those of EPF

Diagnosis	<i>n</i>	Notes
Dermatomycosis	5	Presence of fungi; good response to antifungal agents
Bacterial folliculitis	4	<i>Pseudomonas</i> and <i>Staphylococcus</i> ; good response to antibiotics
Infestation	4	Scabies, toxocariasis, cutaneous larva migrans, strongyloidiasis
Drug-induced	6	Allopurinol, timepidium bromide, carbamazepine, indeloxazine hydrochloride, minocycline, paroxetine, etizolam, maprotiline
L-tryptophan-induced	1	Eosinophilic-myalgia syndrome concurrent with EPF involving the torso and palms
Cutaneous T-cell lymphoma	2	Initial lesions resembling those of EPF
Mycosis fungoides	1	Lesion of follicular type resembling those of EPF
Follicular mucinosis	3	Absence of eosinophilic infiltrate in the upper outer sheath of the hair follicle (follicular mucinosis can be associated with EPF)
Foreign body reaction	1	Caused by subcutaneous silicone injections to augment the nose and chin

n indicates the number of cases found in the published work. For full information, see Table S1. EPF, eosinophilic pustular folliculitis.

“a variant of superficial pustular dermatosis” by Ise and Ofuji.¹ The query key words were “eosinophilic pustular folliculitis”, “eosinophilic pustular dermatosis”, “eosinophilic folliculitis”, “Ofuji’s disease” and “eosinophilic pustulosis”, as described previously.⁵

There were 421 citations that contained 583 cases of bona fide EPF. We identified descriptions of a total of 1175 regimens including 878 in classic EPF and EEDF, 137 in IS/HIV, 45 in IS/non-HIV and 115 in I-EPF (Table S2).

A full list of citations is provided as Supporting Information Data S1. Note that this data set is constantly updated for the content and thus may be different from the version uploaded in the past.

Classification of EPF

Regarding classification of EPF, we followed the proposal by Nervi *et al.*: classic, IS-EPF and I-EPF.⁴

Classic EPF presents with recurrent annular clusters of sterile follicular papulopustules superimposed on plaques with a tendency toward central clearing and peripheral expansion. EEDF, a variation of classic EPF, was classified as classic in this study.⁸ EEDF lacks typical features of classic EPF such as pustule formation and peripheral extension of the lesion, whereas responds well to oral indomethacin.

Immunosuppression-associated EPF involves an underlying disease causing immunosuppression. IS-EPF was further divided into “IS/HIV” and “IS/non-HIV” in this study, according to the presence or absence of seropositivity for HIV.

We defined I-EPF as EPF causing sterile papulopustules in individuals under the age of 10 years or as any case diagnosed as I-EPF by the reporting authors. I-EPF is a variant of EPF with the least characterization.⁷

Efficacy of treatment

Unless indicated, efficacy of treatment is based on a published work-based study conducted by us and provided as Supporting Information (Table S2).

Limitations

Limitations of this study include publication bias, lack of adequately controlled trials and lack of validated measures of the outcome.

RESULTS

Differential diagnosis of EPF

The diagnosis of EPF is occasionally difficult and problematic as EPF may share clinical appearance of histological findings with other diseases.⁹ Therefore, we reviewed publications in advance and collected cases in which lesions showed close resemblance to those of EPF (Table 1, S1). There were 27 such cases, in which the final diagnoses were dermatomycosis (*n* = 5), bacterial folliculitis (*n* = 4), infestation (*n* = 4), drug-induced eruption (*n* = 6), L-tryptophan-induced eruption (*n* = 1), cutaneous T-cell lymphoma (*n* = 2), mycosis fungoides (*n* = 1), follicular mucinosis (*n* = 3) and foreign body reaction to injected silicon (*n* = 1). Dermatomycosis was diagnosed by skin biopsy and periodic acid-Schiff-staining. Bacterial folliculitis was diagnosed through isolation of the infectious agents, such as *Pseudomonas* or *Staphylococcus*, and was confirmed by responsiveness to antimicrobial agents. Infestation was diagnosed by the appearance of typical lesions of cutaneous larva migrans, identification of scabies mites, presence of antibodies to *Toxocara* or fecal examination. Drug-induced or L-tryptophan-induced eruptions were diagnosed based on the disease course. Cutaneous T-cell lymphoma, mycosis fungoides and follicular mucinosis were diagnosed by skin biopsy.

Diagnostic algorithm

Based on a published work-based comprehensive analysis, we created a diagnostic algorithm for EPF (Fig. 1).

The first step toward a diagnosis of EPF is to suspect when pruritic erythematous papulopustules show resistance to topical steroids. The eruptions may or may not show peripheral extension with central clearance with pigmentation. Here, we propose 10 representative diseases that should be considered, namely, acne vulgaris, rosacea, lupus miliaris disseminatus faciei (LMDF), bacterial folliculitis, dermatomycosis, scabies, arthropod bites, palmoplantar pustulosis (PPP), seborrheic dermatitis and mycosis fungoides.

Microscopy of a potassium hydroxide preparation (KOH test) can rule out dermatomycosis and scabies. Complete blood counts and screening for antibody to HIV are useful to test for any underlying patient conditions, such as AIDS or hematological abnormalities.

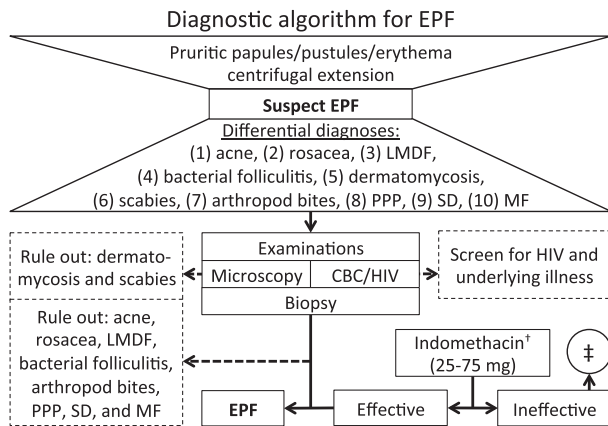


Figure 1. Diagnostic algorithm for eosinophilic pustular folliculitis (EPF) is shown. The first step is to suspect EPF for pruritic papules, pustules or erythema with centrifugal extension. Exclude dermatoses such as acne vulgaris, rosacea, lupus miliaris disseminatus faciei (LMDF), bacterial folliculitis, dermatomycosis, scabies, arthropod bites, palmoplantar pustulosis (PPP), seborrheic dermatitis (SD) or mycosis fungoides (MF). Microscopy of a potassium hydroxide preparation (KOH test) can rule out dermatomycosis and scabies. Complete blood count (CBC) and screening for antibody to HIV are useful to screen underlying conditions such as AIDS or hematological abnormalities. Biopsy is the most important examination. Follicles must be included and studied carefully through serial sectioning. If biopsy is unfeasible, application of indomethacin topically or systemically (25–75 mg/day) can be used as a diagnostic therapy. If indomethacin is ineffective, consider biopsy. †Beware of contraindications of indomethacin. ‡Return to differential diagnoses; consider biopsy.

Biopsy is the most important examination. Follicles must be included and studied carefully through serial sectioning. Presence of microabscesses containing eosinophil-dominant granulocytes in the upper portion of the outer root sheath is the hallmark of EPF.⁹

Although biopsy is the best way for definitive diagnosis, obtaining the patient's consent for biopsy is often difficult. In such cases, therapeutic diagnosis with oral indomethacin at 25–75 mg/day is helpful. In case the patient cannot take oral indomethacin due to gastric symptoms, topical application of indomethacin is an alternative option. Contraindications of indomethacin must be considered as discussed later (Fig. 2e).

Therapeutic algorithms

Next, we developed a set of therapeutic algorithms for EPF (Fig. 2). An algorithm is basically composed of a short description of therapeutic goal and first- and second-line drugs (Fig. 2a–d). An algorithm for classic EPF is strengthened with regimens for maintenance, combination therapy, a list of alternative drugs (tentatively effective options with limited number of reported cases) and options for indomethacin-resistant cases (Fig. 2a). An excerpt of important information on practice is included in the set (Fig. 2e).

Topical tacrolimus and pimecrolimus must be used with care: (i) continuous long-term use must be avoided due to adverse effects including a risk for rosacea; (ii) concurrent ultraviolet (UV) therapy must be avoided; and (iii) children younger than 2 years of age should not be applied (see <https://astellas.us/docs/protopic.pdf>; http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021302s011lbl.pdf).

Classic EPF

The goal in treating classic EPF is to resolve the lesion and control recurrence of EPF (Fig. 2a).

First-line drugs for classic EPF include systemic indomethacin (25–75 mg/day) and its prodrugs such as acemetacin (90–180 mg/day) and indomethacin farnesil (200–400 mg/day). The efficacy of indomethacin is quite high, although that of indomethacin farnesil and proglumetacin (dose not provided in the published work) is somewhat controversial (Table S2a). We included topical indomethacin as first-line, because it showed a high efficacy (complete response/partial response, 21%/76% in 33 cases as shown in Table S2a).

Second-line drugs include ultraviolet (UV), *Sairei-to* (6.0–9.0 g/day, see Table S5b for detail), systemic cyclosporin (100–150 mg or 3–5 mg/kg per day), transdermal nicotine patch (6.25–12.5 mg),¹⁰ systemic tetracyclines (minocycline 100–200 mg/day or doxycycline 100 mg/day) and systemic diaminodiphenyl sulfone (DDS; 50–100 mg/day). Any form of UV can be expected with good response for classic EPF (Table S5d). Dose of ultraviolet is not established yet for EPF. In general, UV-B (UVB) or narrowband UV-B (NB-UVB) was applied 2–3 times a week with an initial dose of 40 mJ/cm² or 1/2 of minimal erythema dose, which was increased by 10–50%. UV-A (UVA) was applied twice a week with initial dose of 1/2 minimal phototoxic dose without psoralen until the lesion subsided. Protocol for psoralen plus UVA therapy (PUVA) was followed to European protocol for psoriasis.

Recalcitrant cases can be coped with combination therapy, in which either systemic indomethacin (either indomethacin 25–75 mg/day, acemetacin 90–180 mg/day) or DDS (50–100 mg/day) together with either topical indomethacin or tacrolimus. One or a few of the second-line drugs can be combined further (Fig. 2a). However, cyclosporin should not be combined with systemic indomethacin to avoid synergistic nephrotoxicity (Fig. 2e).

Most of the alternative drugs are uncommon regimens, which appeared in published works (Table S5a,c). Topical tacrolimus is effective in combination or in single use. Naproxen (300–1000 mg/day) and loxoprofen (60–120 mg/day) are other non-steroidal anti-inflammatory drugs (NSAIDs), which can work well on EPF. Tranilast (300 mg/day) successfully treated a patient with EEDF, who could not continue indomethacin due to a gastrointestinal symptom.⁸ EPA (1800 mg/day), suplatast tosilate (300 mg/day), nicotinamide (900 mg/day), metronidazole (500 mg/day), etretinate (25–50 mg/day) and acitretin (0.5 mg/kg per day) were reported to be effective. Topical injection of triamcinolone (5 mg/mL) was reported to achieve complete response in a case.

There were 19 cases of classic EPF, in which systemic indomethacin (50–100 mg/day) did not ameliorate lesions

(a) Classic EPF

Goal: to resolve the lesion and control recurrence	
First-line drugs	Maintenance
- Indomethacin ^{†,‡}	- Tapering of drugs
- Topical indomethacin	- Topical indomethacin
	- Ultraviolet [§]
	- Screen for underlying disease
Second-line drugs	
- Ultraviolet [§]	
- Sairei-To (6.0-9.0 g) [¶]	
- Cs (100-150 mg or 3-5 mg/kg)	
- Nicotine patch (6.25-12.5 mg)	
- Tetracyclines ^{††}	
- DDS (50-100 mg)	
Combination therapy	Indomethacin-resistant cases
Main (#1 or #2):	- Topical tacrolimus ^{††}
#1 Indomethacin ^{†,‡}	- Sairei-To (6.0-9.0 g) [¶]
#2 DDS (50-100 mg)	- Naproxen (300-1000 mg) [‡]
Attendant (any of the below):	- Cs (3-5 mg/kg)
- Topical indomethacin	- DDS (50-100 mg)
- Topical tacrolimus ^{††}	- Metronidazole (500 mg)
- Second-line drug(s)	- Acitretin (0.5 mg/kg)
	- PUVA [§]
	- Prednisolone (5-10 mg)
	- with topical tacrolimus
	- Combination therapy
	- Other alternatives
Alternative drugs (single usage or in combination)	
- Topical tacrolimus ^{††}	- Triamcinolone ^{§§}
- Naproxen (300-1000 mg) [‡]	- Metronidazole (500 mg)
- Loxoprofen (60-120 mg) [‡]	- Etrinate (25-50 mg)
- Tranilast (300 mg)	- Acitretin (0.5 mg/kg)
- EPA (1800 mg)	- Biologics ^{¶¶}
- Suplatast tosilate (300 mg)	- Oral care ^{†††}
- Nicotinamide (900 mg)	

(b) IS/HIV

Goal: to alleviate pruritus until CD4 T cell-number recovers
First-line drugs
- HAART
- Topical tacrolimus ^{††}
- UVB/NB-UVB [§]
Second-line drugs
- Topical antifungal ^{§§§}
- Indomethacin ^{†,‡}
- Tetracyclines ^{††}
- DDS (50-100 mg)
- Metronidazole (500-750 mg)
- Itraconazole (200-400 mg)
- Isotretinoin (0.3-1.2 mg/kg)
- Ivermectin (if infested)

(c) IS/non-HIV

Goal: to alleviate symptoms until IRIS dissolves
First-line drugs
(Rule out GVHD)
- Topical steroid ^{†††}
- UVB/NB-UVB [§]
Second-line drugs
- Topical tacrolimus ^{††}
- Indomethacin ^{†,‡}
- Systemic prednisolone ^{†††}
(0.1-1.0 mg/kg/)
- Tetracyclines ^{††}
- DDS (50-100 mg)

(d) Infancy

Goal: to wait for spontaneous resolution
First-line drugs
- Topical steroid ^{†††}
- Erythromycin (25-50 mg/kg)
Second-line drugs
- Systemic antibacterial ^{¶¶¶}
- Topical tacrolimus
(0.03%, > 2-year-old) ^{††}
- UVA [§]

(e) Contraindications/notes

(1) Some contraindications of NSAIDs
- ≤ 14-year-old
- Pregnant or breastfeeding
- With nephrotoxic agents (e.g. systemic Cs, tacrolimus, or triamterene)
(2) Contraindicated combination
- Ultraviolet and topical tacrolimus
(3) Adverse drug reactions
- Beware of DIHS/DRESS syndrome for DDS and minocycline

Figure 2. Therapeutic algorithms for (a) classic, (b) IS/HIV, (c) IS/non-HIV and (d) infancy-associated eosinophilic pustular folliculitis (EPF) and (e) an excerpt of contraindications and notes are shown. Dose/day for systemic use is put in the parenthesis. [†]Systemic indomethacin (25–75 mg), acetaminophen (90–180 mg), indomethacin farnesil (200–400 mg). [‡]Non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated or cautioned in the following patients: allergic to aspirin or other NSAIDs, under 14 years of age (safety and efficacy not established), pregnant or breastfeeding women, on anticoagulant treatment, with active peptic ulcer, with application of nephrotoxic agents (such as systemic cyclosporin [Cs], tacrolimus or triamterene), with failure of kidneys/liver/heart/pancreas. [§]Avoid concurrent application of topical tacrolimus; ultraviolet (UV)-B (UVB)/narrowband UVB (NB-UVB), 2–3 times/week with 40 mJ/cm² or 1/2 minimal erythema dose with increment by 10–50%; UV-A (UVA), twice/week of 1/2 minimal phototoxic dose without psoralen; psoralen plus UVA therapy (PUVA), to follow European protocol for psoriasis. [¶]Beware of pseudoaldosteronism by glycyrrhizin. ^{††}Oral minocycline (100–200 mg) or doxycycline (100 mg). ^{†††}Avoid long-term use and beware of rosacea or rosacea-like dermatitis; contraindicated for patients aged 2 years or less; use 0.03% for children of under 2 years of age; avoid concurrent UV therapy. ^{§§}Injection of 5 mg/mL, s.c., ad libitum. ^{¶¶}Interferon (IFN)-α-2b, 3–9 × 10⁶ units 2–3-times/week; IFN-γ, 2 × 10⁶ Japan Reference Unit 5-times/week; infliximab, 5 mg/kg per 2 weeks. ^{††††}Care of dental caries, gingivitis, dentures or metal allergy to dental prostheses. ^{†††††}Steroidal treatment is a convenient option for self-limiting IS/non-HIV and infancy-associated EPF; avoid long-term use and beware of rosacea-like dermatitis. ^{§§§}Includes metronidazole and permethrin. ^{¶¶¶}Dicloxacillin, Neosporin (bacitracin-neomycin-polymyxin B), penicillin, cefaclor or cephalexin. Cs, cyclosporin; DDS, diamindiphenyl sulfone; DIHS/DRESS, drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms; EPA, eicosapentaenoic acid; GVHD, graft-versus-host disease; HAART, highly active antiretroviral therapy; wk, week.

(Table S4). Such cases can be managed with topical tacrolimus, *Sairei-to* (6.0–9.0 g/day), naproxen (300–1000 mg/day), cyclosporin (3–5 mg/kg per day), DDS (50–100 mg/day), metronidazole (500 mg/day), acitretin (0.5 mg/kg per day), PUVA (a regimen followed to European protocol for psoriasis) and prednisolone (5–10 mg/day) together with topical tacrolimus. Combination therapy described above or use of alternative drugs may be effective.

Maintenance of lesion or control of recurrence is important for classic EPF. It can be managed by topical indomethacin and UV (Table S5d). Tapering of medications is recommended. UV is effective for controlling pruritus. Irrespective

of the subtype of EPF, we recommend NB-UVB because there are few risks, including a small risk of increased skin cancer, a sunburn reaction, itching, burning sensation and folliculitis.¹¹ However, patients must attend phototherapy constantly.¹²

IS/HIV

The goal in treating IS/HIV is to alleviate pruritus and to treat AIDS (Fig. 2b).

First-line drugs include highly active antiretroviral treatment (HAART), topical tacrolimus, UVB and NB-UVB. IS/HIV is typically seen when CD4⁺ count drops below 300/μL.¹³ In

addition, there is an association between low nadir (66.28/ μ L) and low CD4⁺ cell count (115.54/ μ L) and the development of IS/HIV.¹⁴ Therefore, HAART to treat AIDS is an effective option. Lesions and pruritus of IS/HIV can be manageable with topical tacrolimus. However, long-term use of topical tacrolimus should be avoided not to induce rosacea or rosacea-like dermatitis. UVB or NB-UVB 2–3 times a week, starting at 1/2 minimal erythral dose with increments of 10–50%, for approximately 2 months effectively reduce pruritus and resolve the lesion (Table S5d).

The second-line drugs include topical antifungals (including topical ketoconazole, topical metronidazole and topical permethrin), systemic indomethacin (25–75 mg/day), tetracyclines (minocycline 100–200 mg/day or doxycycline 100 mg/day), DDS (50–100 mg), metronidazole (500–750 mg/day) and itraconazole (200–400 mg/day). Oral ivermectin may be effective, although the dose of which is not established. It was reported that a single dose of 12 mg of oral ivermectin resolved a case of IS/HIV of a 38-year-old Japanese man infested with *Demodex folliculorum* after 2 weeks.¹⁵

As IS/HIV is often accompanied by AIDS, it is important to rule out infestations, bacterial or fungal infections. Indeed, bacterial folliculitis can mimic lesions of EPF.¹⁶

IS/non-HIV

The goal in treating IS/non-HIV is to alleviate symptoms, of which spontaneous remission can occur (Fig. 2c). Most patients with IS/non-HIV suffer from immune reconstitution inflammatory syndrome (IRIS) due to bone marrow transplantation or peripheral blood stem cell transplantation (Data S1). The goal of treatment is, therefore, to alleviate symptoms such as pruritus until the patient recovers from IRIS.

First-line drugs include topical steroid, which is effective. However, long-term use of topical steroid should be avoided so as not to induce rosacea or rosacea-like dermatitis. UVB with accumulated dose of 0.74 J/cm² (details not provided) achieved complete response in a case of a 60-year-old man with IS/non-HIV, which developed during the course of B-cell lymphoma.¹⁷ We speculate NB-UVB is also effective for IS/non-HIV and included it as a first-line drug.

Second-line drugs include topical tacrolimus, indomethacin (25–75 mg/day), systemic prednisolone (0.1–1.0 mg/kg per day), tetracyclines (minocycline 100–200 mg/day or doxycycline 100 mg/day) and DDS (50–100 mg/day).

When the eruption is difficult to differentiate from that of graft-versus-host disease (GVHD), treatment for GVHD should be prioritized.

I-EPF

As lesions of I-EPF often resolve spontaneously, symptomatic treatment usually suffices (Fig. 2d). Use of indomethacin or other NSAIDs should be avoided for infants.

First-line drugs include topical steroid and systemic erythromycin (25–50 mg/kg per day). Topical steroid was used in 50 cases with an efficacy of 82% (Table S2d). Systemic macrolides (dose not provided in the published work) were used in 16 cases with an efficacy of 56% (Table S2d).

Second-line drugs include systemic antibacterial agents (including dicloxacillin, Neosporin® [Johnson & Johnson, New Brunswick, NJ, USA] or a mixture of bacitracin-neomycin-polymyxin B, penicillin, cefaclor and cephalexin; dose not provided in the published work), topical tacrolimus and UVA (dose not provided in the published work). For children, the dose of tacrolimus should be 0.03%. Tacrolimus is contraindicated for those aged 2 years or less.

Contraindications and notes for regimens

In the set of algorithms, we included excerpts of: (i) contraindications of NSAIDs; (ii) contraindicated combination of UV and topical tacrolimus; and (iii) a risk of drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms syndrome for minocycline and DDS (Fig. 2e).

DISCUSSION

Diagnosis of EPF is difficult if the physician does not consider EPF as a differential diagnosis. Patients may be improperly treated for recalcitrant exanthema under wrong diagnoses. Lesions of EPF closely mimic those of acne vulgaris, rosacea, LMDF, bacterial folliculitis, dermatomycosis, scabies, arthropod bites, PPP, seborrheic dermatitis or mycosis fungoides. These dermatoses can be excluded by microscopic examination of scales by KOH test and skin biopsy. Alternatively, trial treatment with oral indomethacin (25–75 mg/day) or topical indomethacin can help diagnosis. The diagnostic algorithm for EPF that we present here will assist diagnostic procedure (Fig. 1).

The paucity of effective regimens for EPF had challenged dermatologists for years. Most of the fundamental regimens, such as oral steroids, sulfonamides, DDS and tetracyclines, were tried by Ofuji *et al.* and had been reported by 1970.^{1,2} Nevertheless, the achievement of complete clearance of lesion was far from assured at that time. A breakthrough came when indomethacin was serendipitously recognized as an efficacious medicine for classic EPF.^{18,19} The discoveries of the beneficial effects of topical tacrolimus, oral *Sairei-to*, and oral cyclosporin, all of which were effective against indomethacin-resistant EPF as well, followed and enriched the therapeutic options.^{20–23}

The multiplicity of options, however, may be confusing for those attempting to chart treatment. To ease this difficulty, we developed a therapeutic algorithm by reviewing published therapies and their efficacies. A separate algorithm was made for each subtype of EPF because the goal of therapy differs in each subtype.

Currently, no treatment ensures cure of EPF. However, lines of evidence indicate that a key for cure is normalization of T-helper (Th)2-type immune dysregulation. Candidate targets for this purpose are interleukin (IL)-4, IL-13, CCL26 (eotaxin-3), prostaglandin D2, peroxisome proliferator-activated receptor- γ , CRTH2 (chemoattractant receptor-homologous molecule on Th2 cells or CD294), or basophils and mast cells.^{24–29} Further investigation of these targets is required.

In summary, the algorithms described here should facilitate the diagnostic and therapeutic procedures of EPF.

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CONFLICT OF INTEREST: None declared.

REFERENCES

- Ise S, Ofuji S. Subcorneal pustular dermatosis; a follicular variant? *Arch Dermatol* 1965; **92**: 169–171.
- Ofuji S, Ogino A, Horio T, Oseko T, Uehara M. Eosinophilic pustular folliculitis. *Acta Derm Venereol* 1970; **50**: 195–203.
- Ofuji S. Eosinophilic pustular folliculitis. *Dermatology* 1987; **174**: 53–56.
- Nervi SJ, Schwartz RA, Dmochowski M. Eosinophilic pustular folliculitis: a 40 year retrospect. *J Am Acad Dermatol* 2006; **55**: 285–289.
- Nomura T, Katoh M, Yamamoto Y, Kabashima K, Miyachi Y. Eosinophilic pustular folliculitis: the transition in sex differences and interracial characteristics between 1965 and 2013. *J Dermatol* 2015; **42**: 343–352.
- Yamamoto Y, Nomura T, Kabashima K, Miyachi Y. Clinical epidemiology of eosinophilic pustular folliculitis: results from a nationwide survey in Japan. *Dermatology* 2015; **230**: 87–92.
- Ziemer M, Boer A. Eosinophilic pustular folliculitis in infancy: not a distinctive inflammatory disease of the skin. *Am J Dermatopathol* 2005; **27**: 443–455.
- Matsumura Y, Miyachi Y. Atypical clinical appearance of eosinophilic pustular folliculitis of seborrheic areas of the face. *Eur J Dermatol* 2012; **22**: 658–662.
- Fujiyama T, Tokura Y. Clinical and histopathological differential diagnosis of eosinophilic pustular folliculitis. *J Dermatol* 2013; **40**: 419–423.
- Yoshifuku A, Higashi Y, Matsushita S, Kawai K, Kanekura T. Transdermal nicotine patches for eosinophilic pustular folliculitis. *J Dermatol* 2013; **40**: 711–714.
- Laube S, George SA. Adverse effects with PUVA and UVB phototherapy. *J Dermatolog Treat* 2001; **12**: 101–105.
- Ellis E, Scheinfeld N. Eosinophilic pustular folliculitis: a comprehensive review of treatment options. *Am J Clin Dermatol* 2004; **5**: 189–197.
- Cedeno-Laurent F, Gomez-Flores M, Mendez N *et al.* New insights into HIV-1-primary skin disorders. *J Int AIDS Soc* 2011; **14**: 5.
- Rajendran PM, Dolev JC, Heaphy MR Jr, Maurer T. Eosinophilic folliculitis: before and after the introduction of antiretroviral therapy. *Arch Dermatol* 2005; **141**: 1227–1231.
- Nara T, Katoh N, Inoue K, Yamada M, Arizono N, Kishimoto S. Eosinophilic folliculitis with a Demodex folliculorum infestation successfully treated with ivermectin in a man infected with human immunodeficiency virus. *Clin Exp Dermatol* 2009; **34**: e981–e983.
- Hayakawa J, Fukuda M, Shiohara T. A case of human immunodeficiency virus infection that showed eosinophilic pustular folliculitis-like eruption. *Jpn J Clin Dermatol* 1997; **51**: 693–696.
- Ishiguro M, Kamakura T, Nakajima K, Ikeda M, Kodama H. Eosinophilic folliculitis developed in B cell lymphoma (translated). *Pract Dermatol* 2006; **28**: 683–686.
- Tanaka A, Tada J, Takaiwa T. Two cases of eosinophilic pustular folliculitis (translated). *Rinsho Derma (Tokyo)* 1978; **20**: 523–528.
- Inada S, Kohno T, Matsubayashi Y *et al.* Three Cases of Eosinophilic Pustular Folliculitis with Basophil Infiltration. *Nishinihon J Dermatol* 1983; **45**: 149–160.
- Kabashima K, Sakurai T, Miyachi Y. Treatment of eosinophilic pustular folliculitis (Ofuji's disease) with tacrolimus ointment. *Br J Dermatol* 2004; **151**: 949–950.
- Sugita K, Kabashima K, Koga C, Tokura Y. Eosinophilic pustular folliculitis successfully treated with sequential therapy of interferon-gamma and ciclosporin. *Clin Exp Dermatol* 2006; **31**: 709–710.
- Fukamachi S, Kabashima K, Sugita K, Kobayashi M, Tokura Y. Therapeutic effectiveness of various treatments for eosinophilic pustular folliculitis. *Acta Derm Venereol* 2009; **89**: 155–159.
- Katoh M, Nomura T, Miyachi Y, Kabashima K. Eosinophilic pustular folliculitis: a review of the Japanese published works. *J Dermatol* 2013; **40**: 15–20.
- Satoh T, Shimura C, Miyagishi C, Yokozeki H. Indomethacin-induced reduction in CRTH2 in eosinophilic pustular folliculitis (Ofuji's disease): a proposed mechanism of action. *Acta Derm Venereol* 2010; **90**: 18–22.
- Otsuka A, Doi H, Miyachi Y, Kabashima K. Treatment of eosinophilic pustular folliculitis with ciclosporin: suppression of mRNA expression of IL-4 and IL-13. *J Eur Acad Dermatol Venereol* 2010; **24**: 1489–1491.
- Satoh T, Ito Y, Miyagishi C, Yokozeki H. Basophils infiltrate skin lesions of eosinophilic pustular folliculitis (Ofuji's disease). *Acta Derm Venereol* 2011; **91**: 371–372.
- Otsuka A, Miyagawa-Hayashino A, Walls AF, Miyachi Y, Kabashima K. Comparison of basophil infiltration into the skin between eosinophilic pustular folliculitis and neutrophilic folliculitis. *J Eur Acad Dermatol Venereol* 2012; **26**: 527–529.
- Nakahigashi K, Doi H, Otsuka A *et al.* PGD2 induces eotaxin-3 via PPARgamma from sebocytes: a possible pathogenesis of eosinophilic pustular folliculitis. *J Allergy Clin Immunol* 2012; **129**: 536–543.
- Kataoka N, Satoh T, Hirai A, Saeki K, Yokozeki H. Indomethacin inhibits eosinophil migration to prostaglandin D2: therapeutic potential of CRTH2 desensitization for eosinophilic pustular folliculitis. *Immunology* 2013; **140**: 78–86.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. SI_Tx_Pubmed_Ichushi_ver151216: Full set of published work information used in this study.

Table S1. Summary of cases in which lesions mimicked those of eosinophilic pustular folliculitis, a supplement for Table 1

Table S2a. Regimens applied to classic EPF

Table S2b. Regimens applied to IS/HIV

Table S2c. Regimens applied to IS/non-HIV

Table S2d. Regimens applied to I-EPF

Table S3a. Summary of combination therapies

Table S3b. Summary of combination therapies in detail

Table S4. Summary of indomethacin-resistant cases

Table S5a. Summary of uncommon regimens

Table S5b. Summary of treatment by Sairei-to

Table S5c. Summary of treatment by interferon

Table S5d. Summary of treatment by ultraviolet