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Eosinophilic Pustular Folliculitis (Ofuji Disease): Clinical Spectrum, Pathogenesis, and Current Therapeutic Approaches

Sonya Marina[1]*, Valentina Broshtilova[2], Ivan Vasilevski[3], Yoanna Velevska[4] and Yoanna Petkova[2]

1Research and Education Sector, Medical Institute of the Ministry of Interior, Sofia, Bulgaria.

[2]Department of Internal Medicine, Pharmacology and Clinical Pharmacology, Pediatrics, Epidemiology, Infectious and Skin Diseases, Faculty of Medicine, Sofia University "St. Kliment Ohridski", Sofia, Bulgaria.

[3]Clinic of Pediatric Surgery, University Multiprofile Hospital for Active Treatment and Emergency Medicine "N. I. Pirogov", Sofia, Bulgaria.

[4]Department of Otorhinolaryngology, Ophthalmology and Dermatovenereology, Faculty of Medicine, Prof. Asen Zlatarov University, Burgas, Bulgaria.

***Correspondence:**
Sonya Marina, Research and Education Sector, Medical Institute of the Ministry of Interior, Sofia, Bulgaria.

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ABSTRACT

Introduction: *Eosinophilic pustular folliculitis (EPF; Ofuji disease) is a rare, usually chronic relapsing inflammatory skin disorder characterized by pruritic follicular papules and pustules and an eosinophil-rich inflammatory infiltrate. The main clinical variants are classic EPF, immunosuppression-associated EPF (including HIV-associated disease), and infantile EPF.*

Aim: *To summarize the clinical spectrum, proposed pathogenetic mechanisms, diagnostic features, and current therapeutic approaches to EPF.*

Materials and Methods: *A literature search was conducted in PubMed/MEDLINE, Scopus, and Web of Science for publications indexed between July 2000 and July 2026. Original research articles, systematic reviews, retrospective studies, and relevant clinical case reports were considered. Particular emphasis was placed on recent advances in understanding disease pathogenesis, diagnostic approaches, therapeutic strategies, and emerging treatment options. The identified literature was critically evaluated and synthesized to provide an updated overview of current knowledge and EPF management.*

Results: *Diagnosis requires correlation of clinical and histopathological findings and exclusion of infectious and other follicular dermatoses. The pathogenesis is multifactorial, with the type 2 immune response, eosinophil recruitment, and the PGD_2–PPARγ–CCL26 and IL-36 signaling pathways among the mechanisms under investigation. Treatment depends on the clinical variant, disease severity, age, and immune status. Indomethacin has the strongest supporting evidence among systemic treatments for classic EPF, whereas topical corticosteroids and management of the underlying condition are important in other variants. Alternative anti-inflammatory and targeted therapies have been reported for refractory cases; however, the available evidence is based predominantly on small case series and individual case reports.*

Conclusion: *Given the clinical and pathogenetic heterogeneity of EPF, an individualized diagnostic and therapeutic approach, careful clinicopathological correlation, and appropriate follow-up are essential. Further studies are needed to establish the efficacy and safety of emerging targeted therapies.*

Keywords
Eosinophilic pustular folliculitis, Ofuji's disease, Eosinophils, Folliculitis, Immunosuppression, Indomethacin.

Abbreviations
EPF: classic adult eosinophilic pustular folliculitis (Ofuji disease), IS-EPF: immunosuppression-associated eosinophilic pustular folliculitis, I-EPF: infantile eosinophilic pustular folliculitis, ART: antiretroviral therapy, Th2 immune response: type 2 immune response, PGD_2: prostaglandin D_2, PPARγ: peroxisome proliferator-activated receptor gamma, CCL26: chemokine (C-C motif) ligand 26 (eotaxin-3), IL-36Ra: interleukin-36 receptor antagonist, HSCT: hematopoietic stem cell transplantation, DRESS/DIHS: drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome, CTCL: cutaneous T-cell lymphoma, ESR: erythrocyte sedimentation rate, HLA: human leukocyte antigen, PAS: periodic acid–Schiff stain, GMS: Grocott–Gomori methenamine silver stain, NSAIDs: nonsteroidal anti-inflammatory drugs, NB-UVB: narrowband ultraviolet B, PUVA: psoralen–ultraviolet A, GVHD: graft-versus-host disease, JAK inhibitors: Janus kinase inhibitors, PDE4: selective phosphodiesterase 4 inhibitor.

Introduction
Eosinophilic pustular folliculitis (EPF), also known as Ofuji disease, is a rare, chronic relapsing inflammatory dermatosis first described in Japan by S. Ise and S. Ofuji between 1965 and 1970. The disease was initially characterized as a sterile follicular dermatitis presenting with recurrent papulopustular lesions and a prominent eosinophilic infiltrate involving the hair follicles [1,2].

Various terms have been used in the literature, including *eosinophilic pustular folliculitis*, *Ofuji disease*, and *eosinophilic folliculitis*. These terminological differences largely reflect the historical evolution of knowledge about the disease and the fact that a similar clinical and histopathological phenotype may occur in different immunological contexts. Currently, EPF is generally regarded as a heterogeneous group of clinical variants, including classic adult EPF (Morbus Ofuji), immunosuppression-associated EPF (IS-EPF), and infantile EPF (I-EPF). Historically, the immunosuppression-associated form has been described predominantly in association with HIV infection; however, EPF may also develop in other settings of immune dysregulation or immunosuppression, including in transplant recipients and patients with other immunocompromising conditions [3].

Despite its low prevalence, EPF is of considerable clinical importance because it poses significant diagnostic challenges. Its clinical presentation often resembles that of other dermatoses, including acneiform disorders, bacterial or fungal folliculitis, prurigo, and various eosinophilic dermatoses, necessitating a careful differential diagnostic approach. In many cases, a definitive diagnosis requires histopathological confirmation demonstrating eosinophilic infiltration around and within the follicular structures [4,5].

Epidemiology
EPF is a rare dermatosis that has been reported in various geographic regions, with the largest number of publications originating from Japan. Reliable population-based registries and standardized diagnostic criteria are lacking; therefore, published case series do not allow a reliable assessment of disease frequency or geographic variation [3,6].

Classic adult EPF is usually diagnosed during the third and fourth decades of life, although the disease may also occur at an older age. In a Japanese series of 91 patients with the classic form, the mean age at presentation was 39.7 years, with males accounting for 73% of patients and females for 27%. However, a broader analysis of published cases through 2013 demonstrated changes in the sex distribution over time. Among cases of classic EPF published between 2003 and 2013, no substantial sex difference was observed. These findings challenge the traditionally cited male-to-female ratio of approximately 5:1 as a universal characteristic of classic EPF. The marked male predominance reported in earlier series is more likely to reflect characteristics of specific populations and observation periods. Further support for this interpretation comes from data from Singapore, where a series of 23 adults with classic EPF included 8 males and 15 females, yielding a male-to-female ratio of 1:1.6 [3,7].

Historically, IS-EPF has been reported most frequently in association with HIV infection, particularly in patients with advanced immunosuppression and lower CD4+ T-lymphocyte counts. Reported frequencies vary considerably across clinical cohorts and should not be interpreted as population-level estimates [8,9].

Following the introduction of effective antiretroviral therapy (ART), the epidemiology and clinical course of HIV-associated EPF have changed. Historical data from the pre-ART era cannot be directly extrapolated to contemporary populations [9].

In addition to HIV infection, IS-EPF has been described in recipients of solid organ or hematopoietic stem cell transplants, in patients with hematological disorders, and in other settings requiring prolonged immunosuppressive therapy. Both individual case reports and case series of EPF following hematopoietic transplantation have been published. In a series of 11 patients who had undergone hematopoietic stem cell transplantation, EPF was considered in the context of a complex differential diagnosis that included drug reactions, infections, and other inflammatory dermatoses. Cases have also been reported in solid organ transplant recipients in whom the disease developed against a background of prolonged immunosuppression. These observations support an association between EPF and impaired immune regulation but do not establish a uniform etiological or epidemiological profile for immunosuppression-associated cases [10-12].

I-EPF occurs predominantly during the first months of life. In a systematic review of 61 cases, 95% of children developed symptoms before 14 months of age, the scalp was affected in all

cases, and more than 80% achieved spontaneous remission by the age of three years. The reported male predominance and favorable natural course are characteristic of this variant [13].

A meta-analysis by Mendes et al. (2026), which included 52 studies and 136 children, reported a mean age of 11.16 months, a male predominance of 80.58%, and scalp involvement in 92.10% of patients. These estimates were derived predominantly from individual case reports and small case series rather than population-based cohorts [14].

Overall, the epidemiological characteristics of EPF should be interpreted cautiously because of the small number of patients, the predominance of retrospective case series, individual case reports, and clinically selected cohorts, as well as the lack of standardized population-based studies. Differences in diagnostic criteria and terminology pose an additional challenge, particularly for the immunosuppression-associated and infantile variants. Historical publications frequently use different definitions of "eosinophilic folliculitis" and "eosinophilic pustular folliculitis", limiting direct comparisons between studies. Accordingly, contemporary epidemiological assessments of EPF should consider not only age and sex but also the clinical variant, immune status, geographic region, and diagnostic criteria applied [3,14].

Etiology and Pathogenesis

The etiology of EPF remains unclear. Current evidence suggests a multifactorial, folliculocentric inflammatory process involving interactions between the local pilosebaceous microenvironment and systemic immune status. The relative contribution of individual pathways likely varies among the classic, immunosuppression-associated, and infantile variants [3,15].

Histologically, EPF is characterized by a folliculocentric inflammatory infiltrate rich in eosinophils, with eosinophilic microabscesses and infiltration both around and within the pilosebaceous unit. These findings support the concept that eosinophils are not merely a diagnostic feature but also an important effector component of the inflammatory process [4].

Immunological Mechanisms and the Role of Eosinophils

Eosinophils are a characteristic effector component of the inflammatory infiltrate, but they do not act in isolation. T lymphocytes, macrophages, and other immunocompetent cells are also found in the lesions, supporting a model involving interactions among different cell populations [15].

In some patients, a type 2 (Th2) immune response is thought to be involved, in which IL-4, IL-5, and eotaxins may promote eosinophil activation, survival, and recruitment. This mechanism has been particularly well studied in IS-EPF, in which alterations in the expression of Th2-related cytokines and eotaxins have been described [15,16].

Activated eosinophils can release granule proteins and other pro-inflammatory mediators that contribute to follicular epithelial damage and the persistence of local inflammation. At the same time, current evidence indicates that interactions between eosinophils and other immune cells are likely important in sustaining the inflammatory process. Therefore, EPF should not be regarded as an isolated "eosinophilic reaction" [15].

The PGD_2–PPARγ–CCL26 Axis

One of the best-studied mechanisms in EPF involves prostaglandin D_2 (PGD_2), peroxisome proliferator-activated receptor gamma (PPARγ), and the chemokine eotaxin-3 (CCL26) [17].

Nakahigashi et al. demonstrated that PGD_2 and its metabolite 15-deoxy-$\Delta^{12,14}$-PGJ_2 stimulate CCL26 production by sebocytes through PPARγ. Increased CCL26 expression in the sebaceous glands of affected skin provides a mechanistic explanation for the local recruitment of eosinophils [17].

This axis links lipid signaling within the pilosebaceous unit to eosinophilic inflammation and may help explain the preferential involvement of seborrheic areas. However, it has not been established as a universal mechanism across all clinical variants [17].

The Pilosebaceous Unit and the Local Cutaneous Microenvironment

The predilection for the face and scalp suggests an active role for sebocytes. In addition to their structural function, sebocytes participate in local immune responses through the production of chemokines, including CCL26 [17].

IL-36 Signaling and Innate Immunity

IL-36α, IL-36β, and IL-36γ are members of the interleukin-1 (IL-1) cytokine family involved in cutaneous inflammation, whereas the IL-36 receptor antagonist (IL-36Ra) limits their signaling. The involvement of the IL-36 system in EPF remains a hypothesis under investigation [18].

Sato et al. reported increased expression of IL-36β, IL-36γ, and IL-36Ra in EPF lesions. These findings support the possible involvement of the IL-36 system in follicular inflammation [18].

Increased IL-36 expression may reflect either a direct contribution to inflammation or a secondary response to established lesions. At present, these molecules have not been established as specific diagnostic biomarkers [18].

Adhesion Molecules and Cell Migration

The selective accumulation of eosinophils within and around hair follicles suggests the involvement of mechanisms regulating cellular recruitment, adhesion, and transendothelial migration. Earlier immunohistochemical observations support a role for adhesion molecules in the local accumulation of inflammatory cells [4].

T Cells and Other Immunocompetent Cells

T lymphocytes and macrophages participate in follicular

inflammation alongside eosinophils. The composition and functional characteristics of this cellular network likely depend on the clinical subtype and the patient's immune status [15].

In classic EPF, type 2 immune mechanisms are thought to play a more prominent role, whereas in IS-EPF, the immunological profile may be modified by the underlying disease and the degree of immune dysregulation [15].

HIV-Associated EPF

One of the best-established associations of EPF is with HIV infection. IS-EPF occurs predominantly in patients with marked immune dysregulation and low CD4+ T-lymphocyte counts [9].

The study by Rajendran et al. demonstrated a close association between HIV-associated eosinophilic folliculitis and severe immunosuppression. The authors also examined changes in disease frequency and clinical course following the introduction of antiretroviral therapy [9].

A contemporary clinical example was reported by Kanaki et al., who described EPF in a patient with HIV infection. Their report confirms that, despite the availability of modern ART, EPF remains a relevant diagnostic consideration in patients with HIV who present with characteristic pruritic follicular papulopustules [19].

EPF Following Hematopoietic Stem Cell Transplantation and in Other Immunosuppressed Settings

Sasaki et al. described 11 biopsy-confirmed cases of EPF following hematopoietic stem cell transplantation (HSCT). All patients experienced severe pruritus and showed histological evidence of eosinophilic follicular infiltration; peripheral eosinophilia was identified in seven patients. These observations extend the clinical spectrum of immunosuppression-associated EPF beyond HIV infection [10].

These findings support the hypothesis that post-transplant immune alterations may create conditions conducive to eosinophilic follicular inflammation. In this population, the pathogenesis is likely complex and may involve both immunosuppression and immune reconstitution [10].

EPF has also been described in solid organ transplant recipients receiving long-term immunosuppressive therapy. Kim et al. reported a case of EPF in a solid organ transplant recipient in whom the disease was associated with prolonged immunosuppressive treatment [11].

Furthermore, Chen et al. described EPF in a patient following solid organ transplantation in the setting of chronic immunosuppression. The authors discussed the case in the context of immunosuppression-associated EPF and considered the possible roles of immune reconstitution and changes in immunosuppressive therapy [12].

In transplant recipients, EPF must be distinguished from infections, drug reactions, and other post-transplant dermatoses. The temporal relationship with medications and careful clinicopathological correlation are particularly important [10,20].

Potential Infectious, Allergic, and Other Factors

Various infectious and noninfectious factors have been discussed as potential triggers of EPF, including microorganisms, medications, and antigen exposures. However, the available evidence does not support identifying these factors as universal etiological agents. It is therefore more appropriate to consider them potential modulators of the inflammatory response in predisposed individuals [21].

Similar caution is warranted when considering hypotheses involving IgE-mediated hypersensitivity, autoimmune mechanisms, and specific microbial etiologies. Eosinophilia and elevated IgE levels have been reported in some patients, but EPF cannot be classified as a classical IgE-mediated allergic dermatosis [22].

Likewise, no specific autoantigen has been identified that would explain the disease as an organ-specific autoimmune condition. Consequently, the roles of microbial, allergic, and autoimmune factors remain insufficiently understood, and none should be presented as an established primary cause of EPF [22].

An Integrated Model of Etiology and Pathogenesis

An integrated pathogenetic model encompasses follicular chemokine signaling, eosinophil migration and activation, and the modifying effects of overall immune status. The PGD_2–PPARγ–CCL26 axis and IL-36 signaling represent important but non-universal mechanisms whose relative contributions to the different clinical variants remain to be established [15,17,18].

Clinical Forms and Associated Conditions of Eosinophilic Pustular Folliculitis

Three main clinical variants are distinguished: classic EPF, IS-EPF, and I-EPF. Hematologic and drug-associated manifestations should be discussed in the context of the underlying form or as a differential diagnostic consideration [3].

Classic Eosinophilic Pustular Folliculitis

Classic EPF is the originally described form of the disease and occurs predominantly in adults, without necessarily being associated with an underlying immunodeficiency. Clinically, it is characterized by recurrent, intensely pruritic follicular papules and pustules, most commonly localized to the face, trunk, and proximal extremities. A characteristic feature is the peripheral expansion of lesions, with a tendency to form annular or serpiginous configurations [3,5].

Histopathologically, a follicular and perifollicular infiltrate rich in eosinophils is observed, often with the formation of eosinophilic spongiotic pustules. The presence of eosinophils within the infiltrate and their follicular localization are important diagnostic features; however, they are not entirely specific and should be interpreted in the context of the clinical presentation and differential diagnosis [4].

Classic EPF generally follows a chronic, relapsing course.

The therapeutic approach is determined by the severity of the disease and the frequency of recurrences and includes various anti-inflammatory and immunomodulatory agents. Responses to individual treatment options vary among patients; therefore, treatment selection should be individualized [3].

Immunosuppression-Associated Eosinophilic Pustular Folliculitis

IS-EPF develops in the setting of immunosuppression or impaired immune regulation. Its distinction from the classic variant is primarily contextual, as the cutaneous morphology and histopathological findings overlap [9,10].

Depending on the underlying cause of immunosuppression, IS-EPF can be classified into HIV-associated and non-HIV-associated forms.

HIV-Associated Eosinophilic Pustular Folliculitis

HIV-associated eosinophilic folliculitis occurs predominantly in patients with advanced HIV infection and substantial impairment of cellular immunity. Clinically, it is characterized by intensely pruritic follicular papules and pustules, most commonly affecting the face, upper trunk, and upper extremities [8].

The development of the disease is associated with impaired immune regulation and an imbalance in the T-cell immune response. Histologically, a follicular and perifollicular infiltrate predominantly composed of eosinophils is observed, and the morphological findings may resemble those of classic EPF [9,19].

The introduction of ART has substantially altered the natural course of HIV-associated eosinophilic folliculitis. Effective control of HIV infection and restoration of immune function are often accompanied by improvement or regression of the cutaneous manifestations [9,19].

Non-HIV-Associated Eosinophilic Pustular Folliculitis

Non-HIV-associated IS-EPF occurs in various settings associated with immunosuppression, including following HSCT and in patients receiving long-term immunosuppressive therapy after solid organ transplantation [10].

Case series of EPF following HSCT have described the disease in the context of impaired immune regulation. In solid organ transplant recipients, the development of EPF has been associated with both the underlying immunosuppressed state and prolonged exposure to immunosuppressive medications [11,12].

These observations support the concept that EPF can develop in association with various forms of immunosuppression and is not restricted to HIV infection.

Infantile Eosinophilic Pustular Folliculitis

I-EPF occurs predominantly in infants and presents with recurrent papules and pustules, most commonly affecting the scalp and face. Unlike the classic form, annular plaques are not a typical finding [13,23]. Pruritus may disrupt sleep and cause irritability. Differentiating I-EPF from other pustular dermatoses of infancy requires careful clinicopathological assessment [13,23].

I-EPF generally follows a benign, self-limiting course. Nevertheless, differential diagnosis may be challenging because of its resemblance to other pustular dermatoses occurring in early childhood. Clinical and histopathological findings should therefore be assessed together [13,23].

Eosinophilic Pustular Folliculitis Associated with Hematological Neoplasms

EPF may also occur in association with hematological disorders. This association does not constitute a separate major clinical variant of EPF but rather represents a specific clinical context in which the disease develops in the presence of an underlying hematological condition [10].

Cases of EPF have been reported in association with various hematological disorders, including chronic lymphocytic leukemia. In these patients, the cutaneous manifestation may be the initial clinical sign or may develop during the course of an already diagnosed hematological disease [10].

Accordingly, an underlying hematological disorder should be considered in adults presenting with new-onset EPF, particularly in cases with an atypical course, recurrent or treatment-resistant lesions, or other clinical or laboratory abnormalities [10].

Drug-Associated Conditions and Differential Diagnosis

In patients exposed to medications, pustular and eosinophilic cutaneous reactions may occur that resemble EPF clinically and histopathologically. Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug-induced hypersensitivity syndrome (DIHS), is of particular importance because facial pustules may histologically mimic eosinophilic pustular folliculitis [20].

Therefore, in patients presenting with a new-onset pustular eruption following the initiation of a medication, assessment should extend beyond the morphology of the skin lesions to include systemic manifestations, eosinophilia, internal organ involvement, and the temporal relationship with drug exposure. These features help distinguish drug-induced reactions from EPF [20].

A comparative overview of the main clinical variants is presented in Table 1.

Clinical Presentation

The clinical presentation is determined by the morphology, distribution, and course of the lesions. The classic variant often presents with annular or polycyclic plaques with peripheral activity, whereas IS-EPF may manifest as disseminated, excoriated papules without clearly defined annularity [5].

Table 1: Comparative characteristics of the main clinical variants of eosinophilic pustular folliculitis.

Characteristic	Classic EPF	IS-EPF	I-EPF
Typical age	Adults	Predominantly adults	Infants and young children
Immune status	Usually no established immunosuppression	Immunosuppression present	Usually no established systemic immunosuppression
Main associations	Classic or idiopathic EPF	HIV infection, transplantation, immunosuppressive therapy	Early childhood
Clinical presentation	Pruritic follicular papules and pustules	Pruritic follicular papules and pustules	Papules and pustules, often affecting the scalp and face
Histopathology	Eosinophilic follicular and perifollicular infiltrate	Similar to classic EPF	Eosinophilic follicular inflammation
Clinical course	Chronic and relapsing	Associated with the underlying immunosuppressive condition	Usually benign and self-limiting

Note: HIV-associated and non-HIV-associated EPF are subvariants of immunosuppression-associated EPF. Hematological neoplasms represent an additional clinical association, whereas drug reactions, including DIHS/DRESS, are primarily important in the differential diagnosis [3,10,13].

Main Morphological Characteristics

The predominant primary lesions are erythematous follicular papules and papulopustules, often measuring approximately 1–3 mm in diameter. The pustules are usually folliculocentric and may arise on an erythematous base. In classic EPF, individual lesions gradually cluster and coalesce, forming well-demarcated annular, serpiginous, or polycyclic plaques. The characteristic morphological pattern involves peripheral inflammatory expansion, central clearing, and subsequent hyperpigmentation [5].

Annular plaques are a suggestive, but not obligatory, feature. In atypical facial and immunosuppression-associated forms, discrete papules may predominate, even in the absence of visible pustules [5,24].

Pruritus

Pruritus is often intense and may lead to excoriations, sleep disturbances, and reduced quality of life. Its severity varies among patients and across subtypes [8,25].

In IS-EPF, particularly in the setting of HIV infection, pruritus may be especially pronounced and may precede or accompany the onset of cutaneous lesions. Chronic pruritus is an important contributor to the functional and psychosocial burden of the disease, although EPF generally does not affect the patient's overall general condition [8,25].

Distribution

Classic EPF predominantly affects the face, neck, scalp, upper trunk, and proximal extremities. The main sites of involvement are [3,5]:

- The face, particularly the cheeks, forehead, perioral, and periorbital regions;
- The neck;
- The anterior and posterior trunk;
- The upper back and chest;
- The proximal extremities.

In IS-EPF, the distribution is often more disseminated, involving the scalp, face, neck, and trunk [3,5].

Palmar and plantar involvement is uncommon but has been reported. Although these areas have few or lack typical hair follicles, palmoplantar pustular lesions may form part of the clinical presentation of EPF. In such cases, particularly careful differential diagnosis is required to distinguish EPF from palmoplantar pustulosis and other pustular dermatoses. The mucous membranes and nails are usually spared [26].

Clinical Course

Classic EPF follows a relapsing course, with recurrent episodes of papulopustules alternating with periods of remission. The duration of active episodes and the intervals between successive relapses vary considerably [3,5].

New lesions may develop at the periphery of existing plaques or on previously unaffected skin. They generally resolve without scarring, although transient post-inflammatory pigmentary changes may occur [3,5].

Atypical Clinical Forms

Atypical EPF may present with solitary or large plaques, discrete papules, vesiculopustules, or facial involvement without typical annularity [5,24].

Of particular interest are atypical forms in which one or more classic features are absent, such as peripheral expansion, pustules, or clearly defined annularity. A case series of patients with facial EPF described presentations characterized by pruritic papules and erythema in seborrheic areas, without typical peripheral pustules or centrifugal spread; however, histopathological examination revealed the characteristic eosinophilic follicular infiltrate [5,24].

The absence of visible pustules does not exclude EPF in patients with a persistent pruritic eruption, provided that the histopathological findings and other clinical features are consistent with the diagnosis [5,24].

Associated Diseases and Clinical Context

Cases have also been reported in patients with other eosinophilic or immune-mediated disorders, including eosinophilic gastritis,

eosinophilic cellulitis (Wells syndrome), pyoderma gangrenosum, and Kimura disease. However, these associations are based predominantly on individual case reports or small case series and do not establish a shared pathogenetic mechanism [27].

Concomitant EPF has also been described in patients with seborrheic dermatitis, acne, lymphoproliferative disorders, or other neoplasms. In some cases, the association may reflect underlying immune dysregulation or treatment-related effects, whereas in others it may be coincidental. Given the limited evidence, a causal relationship cannot be considered established [27].

Biological, Immunological, and Histopathological Features

Laboratory and immunological investigations support the assessment of the disease and its associated conditions; however, the principal means of diagnostic confirmation remains clinicopathological correlation [27].

Laboratory Findings

Laboratory abnormalities in EPF are variable and nonspecific. The most characteristic peripheral blood finding is eosinophilia, which is observed in a substantial proportion of patients but is not obligatory; its absence does not exclude the diagnosis. The degree of eosinophilia may vary with disease activity, but the correlation between the absolute eosinophil count and the severity of cutaneous manifestations is insufficiently reliable to confer independent diagnostic or prognostic value [27].

Leukocytosis may be observed in some patients, usually in the context of peripheral eosinophilia. Mild elevations in inflammatory markers may also occur, but the erythrocyte sedimentation rate (ESR) and other nonspecific markers have no specific diagnostic value for EPF [27].

Serum immunological parameters may also be altered. Elevated total serum IgE levels have been reported in some patients, supporting the involvement of a type 2 immune response; however, this finding is nonspecific and is not present in all patients [27].

Given the association of IS-EPF with HIV infection, hematological disorders, and transplantation, laboratory investigations should be tailored to the clinical context. When clinically indicated, testing may include HIV screening, a complete blood count with differential, peripheral blood smear examination, and further evaluation for hematological or systemic disease [9,10].

Routine bone marrow examination is not part of the diagnostic workup for typical EPF. It may be considered in cases of marked, persistent, or unexplained eosinophilia or when other findings suggest an underlying hematological disorder [9,10].

Immunological Features

No universal systemic immunological defect has been established in classic EPF. Reported alterations in T-cell parameters and other immunological tests have been inconsistent and are not used as diagnostic criteria [27].

Putative associations with human leukocyte antigen (HLA) antigens have also been reported, but the evidence for a genetic predisposition is limited; HLA typing has no established role in routine clinical practice [27].

Microbiological Investigations

EPF is considered a noninfectious inflammatory disorder; therefore, routine bacteriological and mycological investigations generally do not identify a causative infectious agent. Nevertheless, a negative culture alone is not a diagnostic criterion [4,21].

Small numbers of bacteria, yeasts, or *Demodex* organisms have been described in histological specimens from patients with EPF. However, in a larger histopathological series, these microorganisms were generally located outside the area of active inflammation and were interpreted as nonpathogenic flora [4,21].

Accordingly, appropriate microbiological investigations are necessary when infectious folliculitis is suspected clinically. In patients with atypical presentations or immunosuppression, these may include bacterial culture, mycological examination, direct microscopy, or other targeted tests. This is particularly important because infectious diseases may mimic EPF both clinically and histologically [4,21].

Histopathology

A characteristic histological finding is a folliculocentric infiltrate of eosinophils and lymphocytes, predominantly involving the infundibulo-isthmic region and the level of the sebaceous duct [4,5].

The inflammatory process preferentially affects the infundibulo-isthmic region of the follicle and the level of the sebaceous duct. Follicular epithelial spongiosis and exocytosis of eosinophils and lymphocytes are observed in this area [4,5].

The histological spectrum includes follicular spongiosis and eosinophilic exocytosis and, in some biopsy specimens, intra- or perifollicular eosinophilic pustules. The absence of well-formed pustules or follicular rupture does not exclude EPF [4,5].

The eosinophilic infiltrate may extend from the follicular epithelium into the adjacent dermis. Eosinophils and lymphocytes generally predominate, whereas substantial numbers of intrafollicular neutrophils are less characteristic. This finding helps distinguish EPF from bacterial suppurative folliculitis, in which neutrophils and microorganisms typically predominate in the area of active inflammation [4,5].

Inflammation involving the sebaceous glands supports the role of the pilosebaceous unit but is not consistently present. Diagnostic significance lies in the overall eosinophilic follicular pattern rather than in any single microscopic finding [4,5].

Follicular rupture may be observed in more severe or advanced lesions, but it is likewise not an obligatory diagnostic criterion. When present, it may be followed by secondary mixed inflammation

in the dermis [4,5].

The histological appearance may vary according to the clinical variant. In IS-EPF, there is substantial overlap with other forms of eosinophilic follicular inflammation; therefore, histology alone is insufficient to distinguish EPF from all its clinical and pathological mimics [4].

Among the most important histopathological differential diagnoses are follicular mucinosis, *mycosis fungoides* and other cutaneous T-cell lymphomas, eosinophilic drug reactions, and certain infectious forms of folliculitis [28,29].

When follicular mucinosis is present, it is necessary to distinguish EPF from alopecia mucinosa and other mucinous follicular dermatoses. In EPF, mucin may be identified in the sebaceous lobules or follicular isthmus, but the clinical and histological context is decisive for correct interpretation [28,29].

In I-EPF, the histological appearance may also be variable. Published case series indicate that not all cases historically designated as "infantile EPF" fully meet the histological criteria for classic eosinophilic folliculitis. Accordingly, in infants, the diagnosis should be based on an integrated clinicopathological assessment [23,30].

Immunohistochemical, Immunofluorescence, and Ultrastructural Investigations

Immunohistochemical studies indicate that the inflammatory infiltrate in EPF contains substantial numbers of T lymphocytes and eosinophils, as well as macrophages and other immune cells. Studies of cell adhesion molecules have demonstrated the expression of ICAM-1, VCAM-1, and other mediators involved in leukocyte migration toward the inflamed pilosebaceous unit [15].

Immunohistochemical detection of IL-36β, IL-36γ, and IL-36Ra further supports the current model of local immune dysregulation in EPF. Increased expression of these molecules has been demonstrated in both EPF and nonspecific folliculitis; consequently, they cannot be used as specific diagnostic markers [18].

Direct immunofluorescence is not a routine diagnostic method for EPF and is negative or reveals nonspecific findings in most cases. Individual cases involving deposits of immunoglobulins or fibrinogen have been described in the literature, but these observations have not been consistently reproduced and have no established diagnostic value [22].

Cases involving circulating antibodies against components of basal keratinocytes or the hair follicle outer root sheath have also been reported. For example, one case demonstrated high titers of IgG and IgM antibodies against cytoplasmic components of basal cells and the outer root sheath. However, these findings are isolated or historical observations and neither establish an autoimmune etiology of EPF nor have routine diagnostic value [22].

Ultrastructural studies have demonstrated changes in the outer root sheath, including widening of intercellular spaces and reduced desmosomal adhesion, as well as degenerative changes in infiltrating eosinophils and neutrophils. Close interactions among T lymphocytes, Langerhans cells, and keratinocytes have also been observed. Some studies have found no viral particles or other evident pathogenic agents [31].

Diagnostic Significance of Biological and Histopathological Findings

Clinicopathological correlation is essential because the eosinophilic follicular infiltrate is not specific. Interpretation should take into account lesion morphology, patient age, immune status, and the results of targeted microbiological investigations [4].

Diagnosis

The diagnosis of EPF is based on clinicopathological correlation. No single laboratory or morphological criterion has absolute specificity; differential diagnosis is required to distinguish EPF from infectious, drug-induced, lymphoproliferative, and other eosinophilic dermatoses [4,27].

Clinical and Historical Diagnostic Criteria

The clinical criteria originally described by Ofuji and subsequently adopted are most useful for the classic form, but they have not been universally validated for all variants. Table 2 summarizes the main clinical and histopathological features relevant to diagnosis [2,3].

Table 2: Clinical Features and Diagnostic Criteria for Eosinophilic Pustular Folliculitis.

Category	Feature / criterion
Major clinical features	Recurrent, intensely pruritic follicular papules and papulopustules, usually sterile
Major clinical features	Annular, circinate, or polycyclic grouping of lesions
Major clinical features	Peripheral, centrifugal expansion of lesions with relative central clearing
Major clinical features	Predominant involvement of the face and trunk, including seborrheic areas
Major clinical features	Development of new lesions at the periphery of existing plaques
Major clinical features	Post-inflammatory hyperpigmentation
Major diagnostic criteria	Characteristic histopathological findings
Major diagnostic criteria	Sparing of the palms and soles
Additional criteria	Chronic relapsing course
Additional criteria	Absence of comedones
Additional criteria	Usually sparing of the mucous membranes
Additional criteria	Absence of systemic symptoms in the classic variant
Additional criteria	Development of new lesions on hyperpigmented areas
Additional criteria	Unpredictable therapeutic response
Additional laboratory and microbiological findings	Peripheral eosinophilia, a supportive but nonspecific finding
Additional laboratory and microbiological findings	No convincing evidence of an infectious causative agent

Histopathological Diagnosis

Skin biopsy is particularly important in diagnostically uncertain, atypical, persistent, or recurrent cases, as well as when the clinical presentation does not allow reliable differentiation of EPF from other eosinophilic or inflammatory follicular disorders. In such circumstances, the specimen should preferably be obtained from an active lesion, such as a fresh papule or papulopustule, or from the active peripheral margin of a plaque [4].

The typical histological pattern includes a folliculocentric and perifollicular infiltrate rich in eosinophils, often concentrated around the follicular isthmus and sebaceous duct. Follicular spongiosis, eosinophilic exocytosis, and accumulation of eosinophils within the outer root sheath epithelium may be observed. Intra- or intrafollicular eosinophilic microabscesses and pustules may also be present but are not obligatory [4].

In the series reported by McCalmont et al., which included 52 biopsies from 50 patients, perifollicular infiltrates of lymphocytes and eosinophils, as well as follicular spongiosis, were identified in all biopsies examined. The inflammation was concentrated predominantly at the level of the follicular isthmus and sebaceous duct, whereas eosinophilic pustules, sebaceous gland inflammation, and follicular rupture were observed less frequently. Therefore, the absence of well-formed eosinophilic pustules or follicular rupture does not exclude EPF [4].

The key diagnostic feature is the overall pattern of eosinophil-rich folliculocentric inflammation in an appropriate clinical context. If the clinical findings and biopsy results are discordant, the diagnosis should be reassessed; a repeat biopsy from an active lesion may be warranted [4].

Histopathological interpretation in I-EPF requires particular care. The series of 43 cases reported by Fertitta et al. demonstrated considerable variation in histological features, while Ziemer and Böer emphasized the heterogeneity of published cases and questioned whether all cases described as "infantile EPF" represent the same disease entity. Accordingly, diagnosis in infants should be based on a comprehensive assessment of age, clinical morphology, distribution, course, and histological findings [23,30].

Laboratory Investigations

Laboratory investigations are primarily supportive and etiological rather than confirmatory. Peripheral eosinophilia, leukocytosis, or elevated serum IgE levels may be observed in some patients, but these findings are nonspecific and not obligatory. In the absence of a specific laboratory biomarker, diagnosis should not be based on the degree of eosinophilia or the serum IgE level; these results must be interpreted alongside the clinical and histopathological findings [27].

In patients with immunosuppression or evidence of systemic disease, laboratory evaluation should be individualized and may include a complete blood count with differential, peripheral blood smear, and investigations directed toward identifying the underlying disease or immune status. In an adult with newly diagnosed EPF, particularly when risk factors or clinical evidence of immunodeficiency are present, HIV testing is reasonable. Persistent, marked, or unexplained eosinophilia warrants consideration of further hematological and systemic evaluation [8,10].

Microbiological Diagnosis and Differential Diagnosis

Microbiological testing is not necessary in every typical case. It is indicated when infectious folliculitis is suspected clinically or histologically, or in cases with an atypical course, immunosuppression, systemic manifestations, or an unexpected lack of therapeutic response. Microorganisms are not considered the primary causative factor in EPF. In the histological study by McCalmont et al., bacteria, yeasts, or *Demodex* organisms were identified in some biopsies; however, when located outside the inflammatory zone, they were interpreted as nonpathogenic colonizing flora. Therefore, the significance of microorganisms should be assessed according to their location and the overall clinicopathological findings [4].

Dermoscopy

Dermoscopy may complement clinical assessment, but no specific, validated dermoscopic pattern has been established for EPF. The absence of comedones and the presence of follicular papulopustules are insufficient to confirm the diagnosis [27].

Diagnostic Algorithm

The practical diagnostic algorithm combines clinical examination, assessment of age and immune status, targeted investigations, and biopsy when indicated. The sequential diagnostic steps are outlined below [3,4].

Step 1: Clinical suspicion

The diagnostic process begins when pruritic follicular papules and/or papulopustules are identified. The following features are particularly characteristic of classic EPF [2]:

- Annular, circinate, or polycyclic grouping of lesions;
- Peripheral expansion with relative central clearing;
- Predominant involvement of the face and trunk;
- Chronic relapsing course;
- Absence of comedones.

In immunosuppressed patients, including those with HIV infection, the possibility of disseminated or persistent papules and papulopustules without typical annular plaques should be considered [8].

Step 2: Assessment of the clinical context

Assessment should include the patient's age and immune status, the presence of HIV infection or other forms of immunosuppression, transplant or hematological status, medication exposure, and the duration and relapsing nature of the disease [10].

In infants, the frequent involvement of the scalp should be taken into account, while recognizing the heterogeneity of reported I-EPF cases [13].

Step 3: Supportive laboratory and microbiological investigations and dermoscopy

Depending on the clinical indications, the following investigations may be performed:

- Complete blood count with differential to assess for peripheral eosinophilia;
- Measurement of serum immunoglobulin E (IgE);
- HIV testing when clinically appropriate;
- Peripheral blood smear and additional hematological investigations in cases of persistent or marked eosinophilia;
- Bacteriological and/or mycological investigations when an infectious etiology is suspected;
- Periodic acid–Schiff (PAS) staining and other special stains when indicated by the clinical or histological findings.

Step 4: Skin biopsy and histopathological examination

In cases with an atypical or unclear clinical presentation, biopsy should be obtained from an active papule or papulopustule, preferably before the initiation of intensive anti-inflammatory treatment [4].

Histopathological examination should assess for the following features [4]:

- Folliculocentric and perifollicular inflammatory infiltrate rich in eosinophils;
- Follicular spongiosis;
- Eosinophilic exocytosis;
- Eosinophilic follicular microabscesses or pustules;
- Predominant involvement of the follicular isthmus and sebaceous duct region.

Eosinophilic pustules and follicular rupture are not obligatory histopathological findings. The results must be interpreted in conjunction with the clinical findings [4].

Step 5: Clinicopathological confirmation

Discordance between the clinical and histological findings necessitates reassessment of the diagnosis. Depending on the case, repeat biopsy and/or additional laboratory, microbiological, or other investigations may be undertaken to exclude alternative diagnoses [4].

Step 6: Determination of the clinical subtype and assessment for associated conditions

Following clinicopathological confirmation of EPF, the relevant clinical subtype should be determined:

- Classic EPF (Ofuji disease);
- IS-EPF, including HIV-associated EPF;
- I-EPF.

Drug-associated and neoplasm-associated cases are more appropriately considered secondary or associated contexts of eosinophilic folliculitis rather than necessarily constituting distinct major clinical subtypes [20].

Depending on the clinical indications, patients should also be assessed for associated diseases and secondary factors, including immunodeficiency, immunosuppression, and systemic or hematological disorders [10].

Differential Diagnosis

EPF frequently presents a diagnostic challenge because its clinical and histopathological features overlap with those of other dermatoses. Differential diagnosis is essential for appropriate therapeutic management (Table 3) [4,20].

Treatment

The therapeutic goals are to suppress cutaneous inflammation, control pruritus, reduce recurrences, and preserve quality of life. Given the limited number of high-quality comparative studies, treatment selection is based primarily on retrospective case series and clinical reports and should take into account the specific subtype and individual risk profile [27,32].

Topical Therapy

Topical corticosteroids are an appropriate first-line treatment for localized or moderately severe disease. They may reduce erythema, papulopustular lesions, and pruritus and are particularly useful in children and in patients for whom systemic therapy is undesirable or contraindicated. In published analyses, topical corticosteroids are among the most frequently used treatments for IS-EPF and I-EPF. However, the reported outcomes should be interpreted cautiously because of the heterogeneity of clinical cases and the lack of controlled comparative studies [27].

The potency, frequency, and duration of application should be tailored to the location of the lesions, the patient's age, and the risk of local adverse effects. Prolonged use of high-potency corticosteroids, particularly on the face and in intertriginous areas, should be avoided [27].

Topical calcineurin inhibitors, particularly tacrolimus, may be used as a steroid-sparing alternative for localized, recurrent, or corticosteroid-sensitive areas. Successful treatment of recurrent classic EPF with tacrolimus 0.1% has been reported in a patient resistant to topical corticosteroids. However, the evidence is limited to individual case reports and does not establish efficacy equivalent to that of indomethacin [27,33].

Systemic Therapy

Indomethacin

Oral indomethacin is the best-documented systemic treatment for classic EPF. In the analysis by Nomura et al., which included 1,171 published treatment regimens, efficacy in the classic variant was reported in approximately 84% of regimens involving oral indomethacin. This figure represents a summary of heterogeneous published cases rather than the results of a randomized comparative trial [32].

Daily doses of approximately 50–75 mg are frequently reported in the literature, with individualized dose titration. This information

Table 3: Key differential diagnostic features of eosinophilic pustular folliculitis.

Diagnosis	Clinical presentation	Histopathology and dermoscopy	Distinguishing features and investigations
Acne vulgaris	Comedones, papules, pustules, and nodules, predominantly affecting the face and trunk; mild or absent pruritus	Follicular occlusion, comedones, and a mixed inflammatory infiltrate, often containing neutrophils; dermoscopy: open and closed comedones and follicular openings	Presence of comedones and absence of characteristic eosinophilic follicular infiltration. Diagnostic pitfall: classifying every papulopustular lesion as acne without assessing pruritus and morphology.
Bacterial folliculitis	Follicular papules and pustules, erythema, and occasional tenderness	Neutrophilic follicular infiltration and suppuration; possible bacterial colonization; dermoscopy: yellowish pustules with an erythematous halo	Neutrophil predominance; pain may be more prominent than pruritus. Investigations: microbiological examination. Diagnostic pitfall: lack of microbiological confirmation and confusion with EPF because of the follicular pustules.
Dermatophytic folliculitis / Tinea	Follicular papules and pustules, erythema, and scaling; possible alopecia	Fungal elements in the stratum corneum and/or follicle; inflammation with a variable degree of eosinophilia	Mycological confirmation; PAS/GMS staining may reveal fungal structures. Investigations: mycological examination. Diagnostic pitfall: incorrectly interpreting the eosinophilic infiltrate as evidence of EPF.
Malassezia folliculitis	Monomorphic, pruritic follicular papules and pustules, most commonly affecting the trunk	Follicular inflammation with yeast elements; dermoscopy: uniform follicular papules without comedones	Demonstration of *Malassezia*; absence of the typical eosinophilic folliculocentric reaction. Investigations: mycological examination, depending on the clinical context. Diagnostic pitfall: confusing the condition with EPF in the presence of pruritus without evaluating lesion morphology and mycological findings.
Rosacea / Papulopustular rosacea	Persistent centrofacial erythema, telangiectasia, papules, and pustules	Perivascular and perifollicular inflammatory infiltrate; dermoscopy: linear and branching vessels	Predominant erythema, characteristic facial distribution, and prominent vascular changes. Diagnostic pitfall: overlooking the vascular component and misinterpreting papulopustular lesions.
Prurigo	Pruritic nodules, excoriations, and lichenification	Chronic dermatitis; dermoscopy: crusts and excoriations	Absence of the typical folliculocentric pustular reaction. Diagnostic pitfall: overestimating the diagnostic significance of pruritus alone.
Eosinophilic dermatoses	Polymorphic skin lesions	Eosinophilic infiltrate with variable distribution	A nonfollicular pattern in some eosinophilic dermatoses. Diagnostic pitfall: grouping different conditions under the nonspecific term “eosinophilic dermatitis” without further specification.
Eosinophilic dermatosis of hematologic malignancy (EDHM)	Pruritic papules, plaques, vesicles, or bullous lesions in patients with hematologic disease	Superficial and deep perivascular and/or interstitial infiltrate containing numerous eosinophils	Usually not strictly folliculocentric; underlying hematologic disease is present. Diagnostic pitfall: equating every eosinophilic dermatosis with EPF.
Pustular psoriasis	Sterile pustules on an erythematous background; possible generalized or palmoplantar involvement	Subcorneal neutrophilic pustules, including spongiform pustules of Kogoj; acanthosis; dermoscopy: homogeneous erythema and white scales	Sterile pustules, psoriatic morphology, and possible systemic symptoms. Diagnostic pitfall: confusion with infectious folliculitis or EPF.
Subcorneal pustular dermatosis (Sneddon–Wilkinson disease)	Flaccid pustules, annular configurations, and a chronic course	Subcorneal neutrophilic pustules; dermoscopy: superficial pustules	Chronic course, superficial pustules, and usually an absence of systemic symptoms. Diagnostic pitfall: confusion with pustular psoriasis or other pustular dermatoses.
Eczematous dermatitis	Erythema, pruritus, infiltration, vesicles, and crusts	Spongiosis with a lymphocytic and sometimes eosinophilic infiltrate; dermoscopy: variable inflammatory changes	Inflammation is not strictly folliculocentric. Diagnostic pitfall: incorrectly interpreting eosinophils in the infiltrate as a specific feature of EPF.
Atopic dermatitis	Pruritus and chronic relapsing dermatitis	Spongiosis, with possible eosinophils; dermoscopy: excoriations and lichenification	History of atopy and typical lesion distribution. Diagnostic pitfall: underrecognition of the diagnosis in adults.
Contact eczema	Erythema, vesicles, and pruritus at the site of contact	Spongiosis; dermoscopy: vesicles and erythema	Clear exposure to an irritant or allergen. Diagnostic pitfall: failure to investigate contact allergy.
Nummular eczema	Round, coin-shaped, pruritic plaques, often affecting the extremities	Spongiosis; dermoscopy: homogeneous erythema and crusts	Characteristic coin-shaped lesions. Diagnostic pitfall: confusion with tinea.
Seborrheic dermatitis	Erythematous plaques with greasy scales in seborrheic areas	Spongiosis and parakeratosis; dermoscopy: yellowish scales and diffuse erythema	Typical distribution on the scalp and face. Diagnostic pitfall: confusion with rosacea or psoriasis.
Arthropod bite reaction / Papular urticaria	Intensely pruritic papules, sometimes with a central punctum; commonly affecting exposed areas	Dermal eosinophilic infiltrate, edema, and variable epidermal changes	Nonfolliculocentric eosinophilic reaction and a history of exposure. Diagnostic pitfall: confusion with EPF because of intense pruritus and eosinophilia.

Scabies	Intense, particularly nocturnal, pruritus; characteristic distribution	Eosinophilic and lymphocytic infiltrate; mites, eggs, or fecal pellets may be identified in the stratum corneum	Identification of *Sarcoptes scabiei* and characteristic clinical distribution. Investigations: microscopic examination or another appropriate diagnostic test. Diagnostic pitfall: overlooking scabies because of nonspecific inflammatory changes.
Follicular mucinosis	Follicular papules and plaques; possible alopecia	Mucin in the infundibulum and outer root sheath, with follicular dilation; dermoscopy: altered follicular openings	Prominent follicular mucinosis; differentiation from EPF with secondary mucinosis and cutaneous T-cell lymphoma is necessary. Investigations: histopathological examination. Diagnostic pitfall: failure to perform histopathological examination or underestimation of alopecia.
Alopecia mucinosa	Follicular papules and plaques associated with alopecia	Prominent follicular mucinosis, usually with a lymphocytic infiltrate	More pronounced mucinosis and alopecia; possible association with cutaneous T-cell lymphoma (CTCL). Investigations: histopathological examination and evaluation for an underlying lymphoproliferative disorder when indicated. Diagnostic pitfall: assuming a benign follicular process without appropriate evaluation.
Folliculotropic mycosis fungoides / Cutaneous T-cell lymphoma	Persistent plaques, papules, or tumoral lesions; the face and scalp are frequently affected in the folliculotropic form	Atypical lymphocytic infiltrate, folliculotropism, and occasional mucinosis and eosinophils	Atypical lymphocytes, persistence, clinical evolution, and/or evidence of clonality. Investigations: histopathological and immunohistochemical examination, with additional tests as indicated. Diagnostic pitfall: delayed diagnosis in persistent or atypical lesions.
Eosinophilic drug eruption	Polymorphic rash; possible papules, plaques, and pustules	Eosinophilic dermal infiltrate with variable spongiosis and/or interface changes	Temporal association with medication exposure and absence of the characteristic follicular architecture of EPF. Diagnostic pitfall: overlooking drug causality or misdiagnosing the eruption as EPF.
Graft-versus-host disease	Maculopapular, erythrodermic, or bullous eruption following transplantation	Interface dermatitis with keratinocyte apoptosis	Transplantation history and interface histology. Diagnostic pitfall: disregarding the transplantation history.
Eosinophilic cellulitis (Wells syndrome)	Erythematous, infiltrated, pruritic, or burning plaques	Eosinophilic infiltrate and so-called flame figures	Nonfolliculocentric inflammation; absence of typical follicular papulopustules. Diagnostic pitfall: confusion with bacterial cellulitis or another eosinophilic dermatosis.
Granuloma faciale	Well-demarcated reddish-brown to violaceous plaques on the face	Mixed dermal infiltrate and characteristic Grenz zone	Absence of the typical folliculocentric eosinophilic pustular reaction. Diagnostic pitfall: misdiagnosis as rosacea or another inflammatory facial dermatosis.
Secondary syphilis	Polymorphic papular or pustular eruption; possible involvement of the palms and soles	Plasmacytic infiltrate; possible endovasculitis	Serological confirmation and characteristic clinical context. Investigations: serological testing. Diagnostic pitfall: failure to perform serological testing.
Pemphigus	Flaccid bullae and erosions, sometimes with pustules	Acantholysis; dermoscopy: erosions and absence of a typical follicular pattern	Positive Nikolsky sign; bullous and erosive morphology. Investigations: histopathology, direct immunofluorescence, and specific tests as indicated. Diagnostic pitfall: misclassification as an infectious or follicular process.
Langerhans cell histiocytosis	Particularly important in the differential diagnosis in infants; papules and erythematous or crusted lesions	Infiltrate of Langerhans cells, often accompanied by eosinophils	CD1a and langerin positivity; absence of typical eosinophilic folliculitis. Diagnostic pitfall: misdiagnosis as a benign neonatal pustular disorder.
Erythema toxicum neonatorum	Papules and pustules arising during the first days after birth; self-limiting condition	Eosinophilic-neutrophilic inflammation	Typical neonatal onset and rapid spontaneous resolution. Diagnostic pitfall: unnecessary treatment or confusion with infection.
Transient neonatal pustular melanosis	Superficial pustules present at birth, followed by hyperpigmented macules; usually without erythema	Subcorneal pustules, usually containing neutrophils; dermoscopy: superficial pustules	Absence of erythema and characteristic postpustular hyperpigmentation. Diagnostic pitfall: confusion with infectious pustulosis.
Infantile acropustulosis	Recurrent, pruritic pustules on the palms and soles	Subcorneal neutrophilic pustules; dermoscopy: pustules in acral areas	Characteristic acral distribution. Diagnostic pitfall: confusion with scabies.
Miliaria pustulosa	Pustules associated with heat, occlusion, and sweating	Eccrine duct obstruction or rupture with inflammation	Eccrine rather than follicular localization. Diagnostic pitfall: misclassification as folliculitis.
Neonatal acne	Papules, pustules, and comedones, predominantly affecting the face of the newborn	Acneiform follicular changes	Presence of comedones and the typical neonatal context. Diagnostic pitfall: confusion with neonatal pustular disorders or EPF.
Pigmentary incontinence / Incontinentia pigmenti	Sequential vesicular, verrucous, and pigmentary stages	Eosinophils and melanophages; dermoscopy: variable findings	Linear distribution along the lines of Blaschko. Diagnostic pitfall: confusion with infection or another vesicular dermatosis.

Note: CTCL, cutaneous T-cell lymphoma; PAS, periodic acid–Schiff; GMS, Grocott–Gomori methenamine silver stain [4,20,28].

should not be interpreted as a universal dosing regimen. The risks of gastrointestinal, renal, and cardiovascular adverse effects necessitate assessment of contraindications and appropriate monitoring [27,34].

The therapeutic effect may be partly explained by suppression of prostaglandin signaling and alterations in PGD_2–CRTH2-mediated eosinophil migration, as described in experimental and clinical studies [35,36].

A rapid clinical response to indomethacin may support the diagnosis in a patient with typical clinical and histopathological findings, but it is not a specific diagnostic test. Before treatment is initiated, contraindications and
individual risks associated with nonsteroidal anti-inflammatory drugs (NSAIDs) should be assessed, including a history of peptic ulcer disease or gastrointestinal bleeding, renal disease, significant cardiovascular risk, and concomitant treatment with anticoagulants or antiplatelet agents [27].

Other Systemic Anti-inflammatory Agents

In cases of inadequate response or intolerance to indomethacin, contraindications to NSAIDs, or chronic relapsing disease, alternative systemic agents may be considered. The evidence base for most of these agents is considerably more limited [37].

Dapsone has been used in classic and refractory EPF and may produce clinical improvement in some patients. Its presumed effect is associated with anti-inflammatory activity against neutrophils and other granulocytes. The available evidence derives primarily from individual case reports and small case series and does not support its use as an equivalent first-line alternative to indomethacin. Before treatment is initiated, the risk of hemolytic anemia and methemoglobinemia should be assessed, including testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency when indicated, together with appropriate laboratory monitoring [32,37].

Systemic corticosteroids may rapidly suppress inflammation, but relapses are common when the dose is reduced or treatment is discontinued. Consequently, they are not considered the preferred long-term treatment for classic EPF. They may be considered as a short-term option for severe, extensive, or highly symptomatic disease when rapid suppression of inflammation is required and other approaches are unsuitable [27].

Systemic retinoids, including isotretinoin and acitretin, have been used in refractory EPF, with variable therapeutic success. Their potential anti-inflammatory and sebostatic effects provide a biological rationale for their use; however, the available clinical evidence is insufficient to establish them as standard treatments. Monitoring of the lipid profile and liver function is required, together with strict consideration of teratogenic risk [27].

Other NSAIDs, including ketoprofen, have been used in individual patients and small case series. Maintenance treatment with indomethacin or ketoprofen has been beneficial in some patients with recurrent disease, but insufficient evidence is available to establish the equivalent efficacy of other NSAIDs compared with indomethacin [37].

Cyclosporine may be considered in selected patients with severe, refractory EPF, but its use is limited by nephrotoxicity, arterial hypertension, infections, and drug interactions. The available evidence is insufficient to support a routine recommendation [32,37].

Colchicine, clofazimine, and other anti-inflammatory agents have also been described in a limited number of cases. Evidence of their efficacy remains insufficient, and therapeutic responses are inconsistent; therefore, they cannot be considered standard treatment options [27].

Antibiotics and antifungal agents are generally ineffective as specific treatments for EPF unless a concomitant infection or an infectious factor requiring separate treatment has been identified [27].

Control of Pruritus

Pruritus is one of the predominant symptoms of EPF and may significantly impair sleep, daily functioning, and quality of life. Antihistamines may be used for symptomatic relief, particularly in patients with severe pruritus and sleep disturbances [27].

Antihistamines, including cetirizine, may reduce pruritus in some patients but do not replace anti-inflammatory treatment. Evidence of a specific antieosinophilic therapeutic effect in EPF remains limited [27].

Phototherapy

Phototherapy may be considered for extensive, recurrent, or refractory EPF when standard systemic agents are ineffective or contraindicated. Narrowband ultraviolet B (NB-UVB) phototherapy has been described in individual clinical reports and small case series. In a patient with refractory EPF associated with palmoplantar pustulosis, NB-UVB resulted in sustained clinical clearance and enabled gradual discontinuation of indomethacin [27].

Psoralen plus ultraviolet A (PUVA) has also been described as a treatment option. However, given its long-term phototoxicity and carcinogenic risk, NB-UVB may be preferred when phototherapy is appropriate. Evidence supporting the efficacy of phototherapy in EPF remains limited and does not justify its classification as a first-line treatment [27].

Treatment According to Clinical Subtype

Classic EPF

For localized disease, topical corticosteroids may be used, with the addition or subsequent use of a topical calcineurin inhibitor when

necessary. For more severe, extensive, or recurrent disease, oral indomethacin is the systemic treatment option with the strongest supporting evidence, provided there are no contraindications. In cases of inadequate response or intolerance, dapsone, systemic retinoids, an alternative NSAID, NB-UVB, or cyclosporine in severe refractory cases may be considered [27,32].

HIV-associated EPF

In HIV-associated EPF, initiation or optimization of ART is a central component of treatment. Restoration of immune function may be followed by a reduction in cutaneous disease activity. Historically, this form has been observed predominantly in advanced HIV infection and in patients with low CD4 cell counts, whereas the introduction of effective ART has been associated with a reduced incidence of the disease and improvement in cutaneous manifestations [9,38].

When necessary, topical corticosteroids and other anti-inflammatory agents may be added to ART. The selection of systemic treatment should take into account drug interactions, renal and hepatic function, and the overall risk of infection [9,38].

EPF Associated with Other Forms of Immunosuppression

In patients who have undergone HSCT or solid organ transplantation, the therapeutic approach should be individualized. Before escalating anti-inflammatory or immunosuppressive treatment, infection, drug reactions, and graft-versus-host disease (GVHD) should be actively excluded when clinically relevant [10,11].

Where feasible, the safety and justification of modifying the immunosuppressive regimen should be considered. The standard approach to classic EPF cannot always be applied directly, particularly when indomethacin is contraindicated because of renal dysfunction, gastrointestinal risk, or drug interactions [10,11].

Infantile EPF

In I-EPF, a conservative approach is generally preferred because of the tendency toward spontaneous remission. Clinical observation is appropriate in mild cases, whereas topical corticosteroids may be used for symptomatic or more pronounced lesions. Systemic agents are usually unnecessary [13,14].

A systematic review and single-arm meta-analysis by Mendes et al., including 52 studies and a total of 136 pediatric patients, confirmed that corticosteroids were the most frequently used therapeutic strategy. The authors emphasized the substantial heterogeneity and limited quality of the available evidence [13,14].

Refractory EPF and Emerging Therapeutic Options

In cases of inadequate or absent therapeutic response, the first step should not be an automatic escalation to more intensive immunosuppression. The accuracy of the diagnosis, clinical subtype, histopathological findings, presence of bacterial, fungal, viral, or parasitic infection, possible drug reactions, HIV infection and other conditions associated with immune dysregulation, underlying hematologic disease, treatment adherence, dose, duration and tolerability of previous therapy, as well as contraindications and drug interactions, should be reassessed [27,37].

In confirmed refractory EPF, NB-UVB, dapsone, systemic retinoids, an alternative NSAID, or cyclosporine may be considered. Treatment selection should be individualized because sufficient high-quality comparative studies of these approaches are lacking [27,37].

Emerging targeted approaches focus on type 2 inflammation, eosinophilic signaling, and the JAK/STAT pathways. Published findings remain preliminary and do not yet support the standardization of biologic or small-molecule therapies for EPF [39-41].

Successful responses to dupilumab, which blocks IL-4Rα and IL-4/IL-13 signaling, have been reported in refractory cases. However, the evidence is based on individual case reports, with no controlled studies available [39].

Case reports and small case series involving JAK inhibitors, including tofacitinib and baricitinib, as well as other isolated observations, have been published. Sufficient data on long-term efficacy, optimal dosing, and safety for this indication are lacking [40-42].

Apremilast, a selective PDE4 inhibitor, has been reported as a successful treatment in an individual case involving facial and palmoplantar disease. This isolated clinical observation does not, however, justify its inclusion in a standard treatment algorithm [43].

Mepolizumab, which targets IL-5, has been described as a pathogenetically plausible treatment option in individual patients. Routine use in EPF is not supported by the currently limited evidence [44].

Practical Therapeutic Approach

1. **Confirm the diagnosis and determine the clinical subtype.** The classic, HIV-associated, IS-EPF, and I-EPF forms should be distinguished [32].
2. **Assess disease severity and extent.** Topical anti-inflammatory treatment is preferred for localized disease, whereas oral indomethacin may be used for more severe or recurrent classic disease in the absence of contraindications [32].
3. **Treat the underlying condition.** ART is of primary importance in HIV-associated EPF. In other forms of immunosuppression, potential infectious, drug-related, and transplant-associated factors should be assessed [38].
4. **Reassess cases with an inadequate response.** Before switching to alternative or more intensive treatment, the diagnosis, treatment adherence, duration of therapy, contraindications, and possible comorbidities should be reviewed [37].
5. **Individualize treatment for refractory disease.** Depending

on the clinical situation, dapsone, systemic retinoids, alternative NSAIDs, NB-UVB, or cyclosporine may be considered [37].

6. **Consider experimental options.** In carefully selected patients with refractory EPF, targeted therapies such as dupilumab, JAK inhibitors, apremilast, or anti-IL-5 agents may be discussed, taking into account the limited evidence base [39,41].

Prognosis

The prognosis of EPF depends on the clinical variant and the underlying immunological context. The classic variant often follows a chronic, relapsing course; in IS-EPF, the clinical course is modified by the underlying disease, whereas the infantile form is usually self-limiting [3,10,13].

Classic Form

Classic EPF may relapse over a period of several years. Pharmacological control of inflammation does not guarantee sustained remission; therefore, follow-up is necessary to assess the frequency of recurrences and treatment tolerability [3,32].

Indomethacin is one of the best-documented systemic treatment options for the classic form and may produce a rapid and substantial clinical response. In a retrospective series of 23 adult patients, 90% of those treated with oral indomethacin achieved a good response within 2–4 weeks; however, relapses were observed in 82.6% of patients. In some patients, maintenance therapy with indomethacin or ketoprofen proved beneficial [3,32].

An initial therapeutic response does not necessarily indicate definitive resolution of the disease. Discontinuation of treatment is often followed by a new flare, with the frequency and severity of relapses varying among individual patients. Therefore, therapeutic success should be assessed not only in terms of the reduction in skin lesions but also by the duration of remission, control of pruritus, treatment tolerability, and the need for maintenance therapy [3,32].

In the event of a change in the clinical phenotype, the development of systemic manifestations, or a lack of the expected response to a treatment that was previously effective, a repeat diagnostic evaluation is warranted [4].

Immunosuppression-Associated Form

The prognosis of IS-EPF is closely related to the underlying disease, the nature and extent of immune dysregulation, and the ability to control the underlying condition. Accordingly, the outcome of the cutaneous disease should be considered in the context of the patient's overall clinical and immunological status [9].

In HIV-associated EPF, effective ART and subsequent restoration of immune function may be associated with improvement or remission of cutaneous manifestations. However, initiation of ART does not always lead to immediate improvement, and in some patients EPF may develop or flare during the period of early immune reconstitution [9].

In a retrospective study of 57 patients with biopsy-confirmed eosinophilic folliculitis, 28 of the 34 patients receiving ART developed the disease within six months of initiating treatment, with an increase in CD4+ T-lymphocyte counts reported in most cases. These observations support an association between EPF and the dynamics of immune reconstitution but do not establish an adverse long-term effect of ART. Control of HIV infection, virological response, and restoration of immune function remain essential to the overall prognosis [9].

In IS-EPF associated with other immunosuppressive conditions, including following HSCT or solid organ transplantation, the prognosis depends on both control of cutaneous inflammation and the underlying hematological or systemic disease, as well as the degree of immunosuppression. In a series of 11 patients with IS-EPF following HSCT, nine achieved complete resolution of cutaneous manifestations, whereas two had an incomplete response. Time to resolution ranged from several weeks to months, highlighting the individualized nature of the disease course [10,12].

In immunosuppressed patients with persistent or recurrent lesions, the diagnosis should be reconfirmed, and infectious, drug-induced, GVHD, and other immune-mediated dermatoses should be excluded. Immunosuppressive therapy should not be modified or reduced solely because EPF is present; any such decision should be individualized and made in consultation with the treating specialist [10,12].

Infantile Form

I-EPF generally follows a favorable natural course, resolving in most children during early childhood. However, the heterogeneity of reported cases should be taken into account, and the diagnosis should be reconsidered in the presence of a persistent or atypical eruption [13,14].

Given the tendency toward spontaneous remission, aggressive systemic treatment is usually unnecessary. A conservative approach aimed at controlling pruritus and inflammation is appropriate for most children, with topical corticosteroids considered in symptomatic cases [13].

The prognosis should also be considered in light of the diagnostic heterogeneity of infantile EPF as historically defined. In a series of 61 cases, tissue eosinophilia was identified in all patients, but convincing follicular involvement was found in only 62% of cases for which histological examination was available. This raises the question of whether all historically reported cases represent the same clinicopathological entity [23,30].

In cases of atypical clinical presentation, persistence beyond the usual age range, absence of convincing folliculocentric eosinophilic inflammation, or an atypical therapeutic response, the diagnosis should be reassessed clinically and, where indicated, histopathologically [23,30].

Impact on Quality of Life

Despite the generally favorable prognosis of the cutaneous disease, EPF may have a significant functional and psychosocial impact. Intense, persistent pruritus, visible papulopustular lesions, a chronic-relapsing course, and the need for repeated treatment courses may lead to sleep disturbances, daily discomfort, psychological distress, and difficulties with social functioning [25].

Accordingly, therapeutic success should not be assessed solely by a reduction in the number or size of cutaneous lesions. During follow-up, it is appropriate to assess pruritus intensity, sleep disturbances, daily functioning, relapse frequency, the duration of flare-free periods, and the need for systemic or maintenance therapy [25].

Discussion

EPF represents a clinically and immunologically heterogeneous inflammatory disorder, suggesting that its pathogenesis cannot be explained by a single mechanism [3,15]. The proposed involvement of the PGD_2–PPARγ–CCL26 axis provides an experimentally supported explanation for eosinophil recruitment within the pilosebaceous unit, while findings concerning IL-36 signaling suggest an additional potential mechanism of local inflammatory regulation [17,18]. Nevertheless, the relative contribution of these pathways across different clinical variants remains incompletely defined. The diversity of clinical presentations and immunological contexts further complicates the development of a unified pathogenetic model, highlighting the need to clarify the relationship between inflammatory pathways and individual disease phenotypes [15,18].

The management of EPF remains challenging because the available therapeutic evidence is limited and largely derived from case reports, small case series, retrospective studies, and analyses of published cases [3,32,37]. Although indomethacin is among the best-documented systemic treatments for classic EPF, the available evidence does not permit robust comparisons of efficacy across treatment options [32,37]. Differences in clinical subtype, patient characteristics, treatment regimens, outcome assessment, and follow-up restrict the interpretation of published results. Furthermore, the predominance of uncontrolled observations and the potential for publication bias may lead to an overestimation of treatment benefits. Consequently, reported responses should be interpreted cautiously, and treatment decisions should be individualized rather than based on an assumed hierarchy of therapeutic efficacy [3,32,37].

Emerging targeted approaches offer a potential opportunity to address specific inflammatory pathways implicated in EPF. Successful responses to dupilumab and JAK inhibitors have been reported in selected refractory cases, while isolated reports have also described the use of apremilast and mepolizumab [39-44]. These observations are of interest because they may help identify pathways relevant to particular disease phenotypes. However, the evidence remains preliminary and is insufficient to establish the efficacy, long-term safety, or appropriate place of these agents in standard treatment algorithms. It also remains uncertain whether targeted interventions will provide consistent benefits across the heterogeneous EPF spectrum or whether their effectiveness will depend on specific clinical or immunological subtypes [15,39-44].

Several important gaps in the literature remain. Small study populations, inconsistent terminology and diagnostic criteria, and heterogeneous outcome measures limit the comparability of published findings and impede the identification of reliable prognostic or predictive factors [14,32]. Multicenter prospective studies and collaborative registries are needed to characterize disease course, improve clinical and immunological stratification, and establish standardized definitions of treatment response, remission, and relapse. Future research should also prioritize the validation of candidate biomarkers and investigate whether mediators involved in eosinophil recruitment, prostanoid signaling, CCL26, CRTH2, and IL-36 can help predict disease course or treatment response [17,18,32,35,36]. These efforts are essential to strengthen the evidence base and support a more individualized approach to EPF management.

Conclusion

EPF is a rare, clinically and pathogenetically heterogeneous dermatosis whose recognition requires assessment of lesion morphology, immune status, and histopathological changes. Differentiating the classic, immunosuppression-associated, and infantile forms has direct implications for the diagnostic and therapeutic approach.

In the classic variant, indomethacin remains the best-documented systemic treatment, whereas in HIV-associated EPF, optimization of ART is of primary importance. In infants, a conservative, symptom-oriented approach is often sufficient. Novel targeted agents offer potential options for refractory cases, but their efficacy and safety still require confirmation.

Future research should clarify the significance of immunological subtypes, pathogenetic pathways, and predictors of therapeutic response. Until more robust evidence becomes available, individualized clinicopathological assessment and follow-up remain the cornerstones of good clinical practice [3,14,32].

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