Eosinophilic Pustular Folliculitis With Underlying Mantle Cell Lymphoma

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PRACTICE **POINTS**

- Recalcitrant folliculocentric papules and pustules involving the head, trunk, arms, and legs should raise suspicion of possible eosinophilic pustular folliculitis (EPF).
- Underlying hematopoietic malignancy may be associated with cases of EPF.

Eosinophilic pustular folliculitis (EPF) is a noninfectious condition characterized by folliculocentric papules, pustules, and plaques on the head, trunk, and extremities. Three subtypes of EPF have been described. Histopathology predominantly shows abundant eosinophils concentrated at the follicle, and treatment typically consists of topical corticosteroids or oral indomethacin. We present an unusual case of EPF in a 52-year-old man that preceded the diagnosis of mantle cell lymphoma.

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Eosinophilic pustular folliculitis (EPF) was originally described in 1965 and has since evolved into 3 distinct subtypes: classic, immunosuppressed (IS), and infantile types. Immunosuppressed EPF can be further subdivided into human immunodeficiency virus (HIV) associated (IS-HIV) and non-HIV associated. Human immunodeficiency virus–seronegative cases have been associated with underlying malignancies (IS-heme) or chronic immunosuppression, such as that seen in transplant patients.

Case Report

A 52-year-old man with a medical history limited to prostate adenocarcinoma treated with a robotic prostatectomy presented with a pruritic red rash on the face, neck, shoulders, and chest of 1 month's duration. The patient previously completed a course of azithromycin 250 mg, intramuscular triamcinolone, and oral prednisone with only minor improvement. Physical examination demonstrated multiple pink folliculocentric papules and pustules scattered on the head (Figure 1A), neck, and chest (Figure 1B), as well as edematous pink papules and plaques on the forehead (Figures 1C and 1D). The palms, soles, and oral mucosa were clear.

Initial biopsy of the right side of the chest was nonspecific and most consistent with a reaction to an arthropod bite. The patient was started on oral doxycycline 100 mg twice daily for 2 weeks. With no improvement seen, additional biopsies were obtained from the left side of the chest and forehead. The biopsy of the chest showed ruptured folliculitis with evidence of acute and chronic inflammation. The biopsy of the forehead demonstrated eosinophilic follicular spongiosis with intrafollicular Langerhans cell microgranulomas along with abundant eosinophils adjacent to follicles, consistent with EPF (Figure 2). Serum HIV testing was negative. Serum white blood cell count was normal at 6400/μL (reference range, 4500–11,000/μL) with mild elevation of eosinophils (8%). The remaining complete blood cell count and comprehensive metabolic panel were within reference range. The patient was subsequently started on oral indomethacin 25 mg twice daily and triamcinolone cream 0.1%. Within a few days he experienced initial improvement in his symptoms of pruritus and diminution in the number of inflammatory follicular papules.

Approximately 1 month after presentation, he began to experience symptoms of dysphagia and fatigue. In addition, tonsillar hypertrophy and palpable neck and axillary lymphadenopathy were present. Computed

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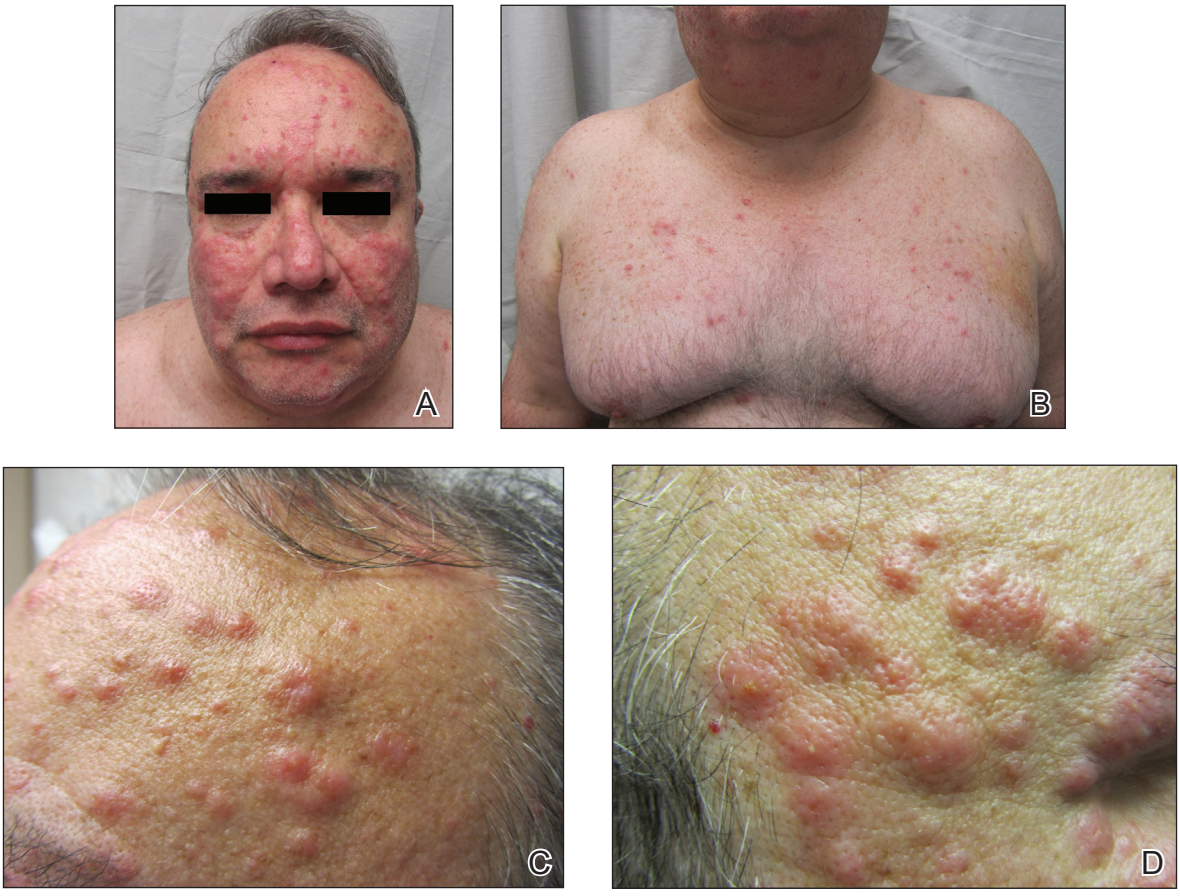

FIGURE 1. Multiple pink folliculocentric papules and pustules on the head (A), neck, and chest (B), as well as edematous pink papules and plaques on the forehead (C and D).

tomography of the neck, chest, and abdomen showed diffuse lymphadenopathy. Full-body positron emission tomography–computed tomography demonstrated extensive metabolically active lymphoma in multiple nodal groups above and below the diaphragm. There also was lymphomatous involvement of the spleen. An axillary lymph node biopsy was diagnostic for mantle cell lymphoma (CD4:CD8, 1:1; CD45 negative; CD20 positive; CD5 positive). He was subsequently initiated on a rituximab chemotherapeutic regimen via intravenous infusion and completed a total of 8 cycles. Although chemotherapy treatment improved the EPF, oral indomethacin and topical triamcinolone were useful in clearing disease.

Comment

Subtypes of EPF—Eosinophilic pustular folliculitis was first described in a Japanese female presenting with folliculocentric pustules distributed on the face, torso, and arms.[1] This noninfectious eosinophilic infiltration of hair follicles predominantly seen in the Japanese population is now regarded as the classic form. Three distinct subtypes of EPF now exist, including the originally described classic variant (Ofuji disease), an IS variant, and a rare infantile form.[1]

All 3 subtypes of EPF are more commonly seen in men than women. The classic form has a peak incidence between the third and fourth decades of life. It presents as chronic annular papules and sterile pustules exhibiting peripheral extension, with individual lesions lasting for approximately 7 to 10 days with frequent relapses. The face is the most common area of involvement, followed by the trunk, extremities, and more rarely the palmoplantar surfaces. Concomitant leukocytosis with eosinophilia is seen in up to 35% of patients.[1] The infantile type represents the rarest EPF form. The average age of onset is 5 months, with most cases resolving by 14 months of age.[1]

Clinically, EPF is characterized by recurrent papules and pustules predominantly on the scalp without annular or polycyclic ring formation, as seen in the classic type. The palms and soles may be involved, which can clinically mimic infantile acropustulosis and scabies infection. Most patients exhibit a concomitant peripheral eosinophilia.[1,2]

In the late 1980s, the IS variant of EPF was recognized in HIV-positive (IS-HIV) and HIV-negative

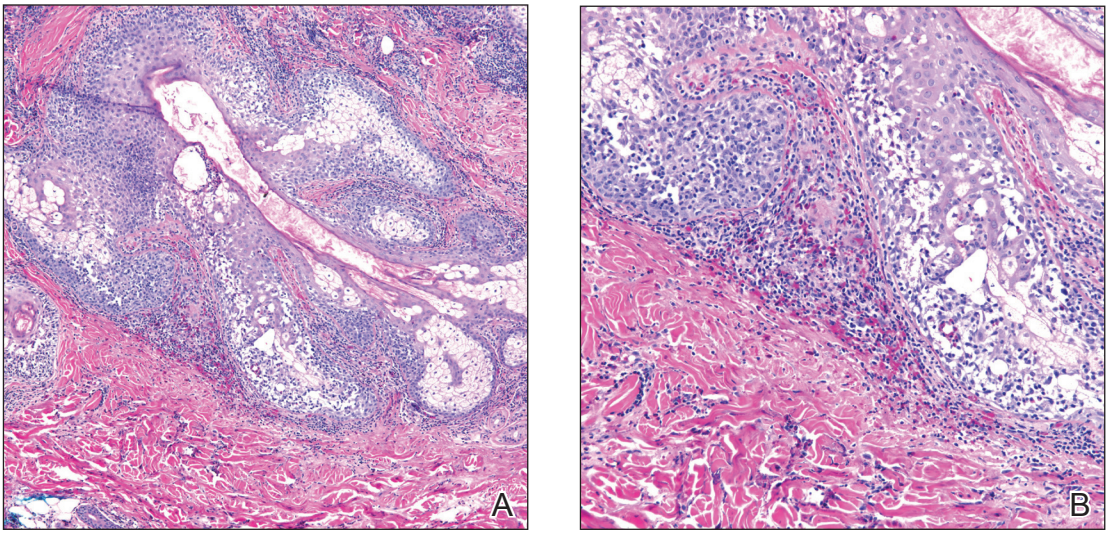

FIGURE 2. Follicular spongiosis and abundant perifollicular eosinophils admixed with lymphohistiocytes and neutrophils (A and B)(H&E, original magnifications ×10 and ×20).

malignancy-associated (IS-heme) populations.[1,3] This newly characterized form differs morphologically and biologically from the classic and infantile subtypes. The IS subtype has a unique presentation including intensely pruritic, discrete, erythematous, follicular papules with palmoplantar sparing and infrequent annular or circinate plaque forms.[1] Frequently, with the IS-HIV form, $CD4^+$ T-cell counts are below 300 cells/mL, and 25% to 50% of patients have lymphopenia with eosinophilia.[3] Highly active antiretroviral therapy has been associated with EPF resolution in HIV-positive individuals; however, it also has been shown to induce transient EPF during the first 3 to 6 months of initiation.[1,3,4]

Unlike the IS-HIV form, the IS-heme form has occurred solely in males and is predominantly associated with hematologic malignancies (eg, non-Hodgkin lymphoma, acute lymphoblastic leukemia, acute myeloid leukemia, myelodysplastic syndrome) 30 to 90 days following bone marrow transplant, peripheral blood stem cell transplant, or chemotherapy treatment.[5,6] Unlike the chronic and persistent IS-HIV form, prior cases of IS-heme EPF have been predominantly self-limited. Interestingly, only 2 reported cases of EPF have occurred prior to the diagnosis of malignancy including B-cell leukemia and myelodysplastic syndrome.[5]

Histopathology—All 3 identified forms of EPF histopathologically show acute and chronic lymphoeosinophilic infiltrate concentrated at the follicular isthmus, which can lead to follicular destruction. Scattered mononuclear cells, eosinophils, and neutrophils are found within the pilar outer root sheath, sebaceous glands, and ducts. Approximately 40% of cases demonstrate follicular mucinosis.[1] Histopathology of lesional palmar skin in classic-type EPF demonstrates intraepidermal pustule formation with abundant eosinophils and neutrophils adjacent to the acrosyringium.[7,8]

Pathogenesis—Although the pathophysiology of EPF is largely unknown, it is thought to represent a helper T cell (T_H2) response involving IL-4, IL-5, and IL-13 cytokines.[9] Chemoattractant receptor homologous molecule 2, which is expressed on eosinophils and lymphocytes, is believed to play a role in the pruritus, edema, and inflammatory response seen adjacent to pilosebaceous units in EPF.[10] Moreover, immunohistochemical and flow cytometry analysis has revealed a prevalence of prostaglandin D2 within the perisebocyte infiltrate in EPF.[9] Prostaglandin D2 induces eotaxin-3 production within sebocytes via peroxisome proliferator-activated receptor γ, which enhances chemoattraction of eosinophils. This pathogenesis represents a prostaglandin-based mechanism and potentially explains the efficacy of indomethacin treatment of EPF through its cyclooxygenase inhibition and reduction of chemoattractant receptor homologous molecule 2 expression.[9-11]

Treatment—Multiple therapeutic modalities have been reported for the treatment of EPF. For all 3 subtypes, moderate- to high-potency topical corticosteroids are considered first-line therapy. UVB phototherapy 2 to 3 times weekly remains the gold standard, given its consistent efficacy.[1,12] Indomethacin (50–75 mg daily) remains first-line treatment of classic EPF.[4,12] Previously reported cases of classic EPF and IS-EPF have responded well to oral prednisone (1 mg/kg daily).[12,13] In a retrospective review of EPF treatment data, the following treatments also have been reported to be successful: psoralen plus UVA, oral cetirizine (20–40 mg daily, particularly for IS-EPF cases), metronidazole (250 mg 3 times daily), minocycline (150 mg daily), itraconazole (200–400 mg daily,

dapsone (50–200 mg daily), systemic retinoids, tacrolimus ointment 0.1%, and permethrin cream.[4,12]

Malignancy—Although the entity of IS-heme EPF is rare, the morphology and treatment are unique and can potentially unmask an underlying hematologic malignancy. In patients with EPF and associated malignancy, such as our patient, a differential diagnosis to consider is eosinophilic dermatosis of hematologic malignancy (EDHM). Eosinophilic dermatosis of hematologic malignancy is most commonly associated with chronic lymphocytic leukemia and can be differentiated from EPF clinically, histopathologically, and by treatment response. Eosinophilic dermatosis of hematologic malignancy clinically presents with nonspecific papules, pustules, and/or vesicles on the head, trunk, and extremities. On histopathology, EDHM shows a superficial and deep perivascular and interstitial lymphoeosinophilic infiltration. Furthermore, EDHM patients typically exhibit a poor treatment response to oral indomethacin.[14]

Conclusion

Eosinophilic pustular folliculitis is a noninfectious folliculocentric process comprised of 3 distinct types. The histopathology shows follicular spongiosis with increased eosinophils. The pathogenesis is most likely related to a multifactorial immune system dysregulation involving T_H2 T cells, prostaglandin D2, and eotaxin-3. The treatment of EPF may involve topical corticosteroids, UVB phototherapy, or most notably oral indomethacin. In patients with EPF and malignancy, EDHM is a differential diagnosis to consider. Our case serves as a reminder that rare eosinophilic dermatoses may represent manifestations of underlying hematopoietic malignancy and, when investigated early, can lead to appropriate life-saving treatment.

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