Amicrobial pustulosis of the folds and palmoplantar pustulosis simultaneously induced by different tumor necrosis factor-α inhibitors: Demonstration of a shared pathophysiology

Matthew Zirwas, MD,[a] Hershel E. Dobkin, BS,[b] and Smita Krishnamurthy, MD[b]
Columbus and Dayton, Ohio

Key words: amicrobial pustulosis of the folds; palmoplantar pustulosis; tumor necrosis factor-α blocker.

INTRODUCTION

Amicrobial pustulosis of the folds (APF) and palmoplantar pustulosis (PPP) are 2 rare autoinflammatory neutrophilic dermatoses. Many studies report PPP triggered by treatment of inflammatory bowel disease (IBD) with tumor necrosis factor-α (TNF-α) blockers.[1,2] APF is much rarer and predominantly affects young women with autoimmune conditions.[3] Both conditions share histologic features of superficial spongiform pustulation associated with perivascular neutrophilic infiltration, without evidence of infection or vasculitis.[3] The clinical differentiation of these disorders is largely based on anatomic location. APF commonly occurs on cutaneous folds of the skin, the scalp, and the periorificial areas of the head. PPP, as the name suggests, primarily occurs on the palms and soles.

These 2 conditions are currently considered separate entities. TNF-α blockers are used in a variety of diseases, notably IBD, psoriasis, and rheumatoid arthritis. Pustular reactions, whether PPP or APF, occur in less than 1% of patients treated with TNF-α inhibitors.[4] We report a novel case of APF and PPP occurring and relapsing together in a patient after treatment with adalimumab and certolizumab.

Abbreviations used:

APF:	amicrobial pustulosis of the folds
IBD:	inflammatory bowel disease
IFN-α:	interferon-α
PPP:	palmoplantar pustulosis
TNF-α:	tumor necrosis factor-α

CASE REPORT

A 27-year-old white woman presented to our clinic with a rash that was present for approximately 6 weeks. Therapy with adalimumab for a new diagnosis of Crohn's disease began 5 months before presentation. Soon after initial onset of the rash, her gastroenterologist discontinued the adalimumab owing to suspicion it was the etiology, and a short course of prednisone was given, leading to rapid clearance. Certolizumab pegol was initiated approximately 2 months before presentation, with the rash reoccurring with increased severity shortly after initiation, prompting her visit to our dermatology office.

At presentation, the eruption involved her trunk, axillae, groin, proximal extremities, palms, soles, face, and scalp (Figs 1-4). Examination found newly formed white pustules and older brown lesions on acral skin with small erythematous pustules in skin folds and on the trunk and proximal extremities. Results of a bacterial culture were normal. Based on the unique clinical findings, TNF-α inhibitor—induced PPP and APF were diagnosed.

The certolizumab pegol was discontinued. Oral prednisone was restarted at 40 mg/d then increased to 60 mg because of lack of improvement. The eruption improved but relapsed when the dose

Dermatologists of Greater Columbus[a] and Wright State University Boonshoft School of Medicine.[b]
Funding sources: None.
Conflicts of interest: None declared.
Correspondence to: Matthew Zirwas, MD, Dermatologist, Dermatologists of Greater Columbus, 2359 East Main Street, Columbus, OH 43209. E-mail: matt.zirwas@gmail.com.

JAAD Case Reports 2017;3:401-3.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2017.06.003

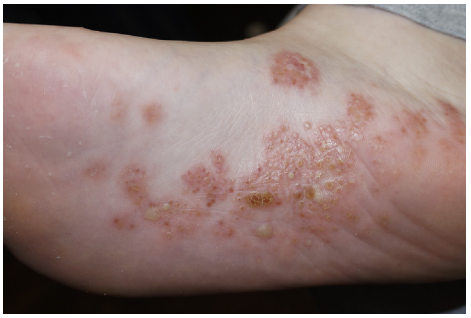

Fig 1. Erythematous, crusted plaque with papulopustules on the plantar surface of the foot.

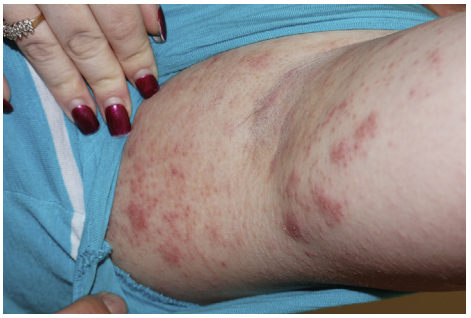

Fig 2. Axillary erythematous pustules.

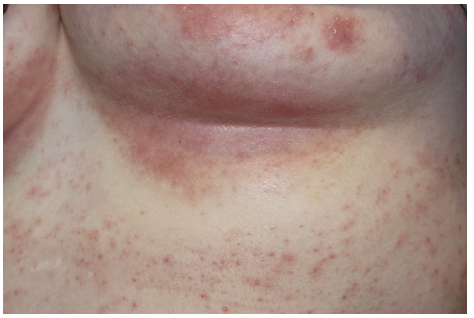

Fig 3. Erythematous pustules with surrounding erythema on inframammary fold continuous with abdominal lesions.

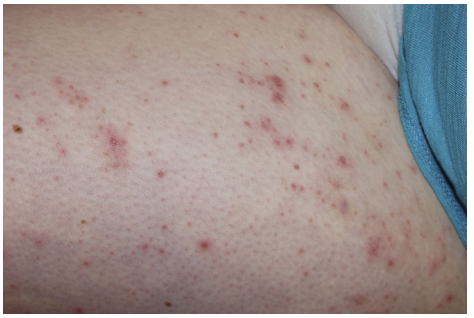

Fig 4. Scattered erythematous papulopustules over the abdomen.

decreased to less than 40 mg/d. After 2 months, prednisone still could not be tapered below 40 mg/d without significant flaring of the eruption, and her Crohn's disease was flaring. Intramuscular methotrexate at 25 mg weekly and colchicine at 0.6 mg twice daily were added. After several months, both her Crohn's disease and skin eruptions were still flaring when the prednisone dose decreased to below 20 mg/d, despite the concomitant use of methotrexate and colchicine. At this point, ustekinumab was initiated at 90 mg subcutaneously (patient's weight was 68 kg). The ustekinumab dosing regimen was primarily based on the patient's severe relapsing pustular cutaneous condition and not on the comorbid IBD. The patient's condition had dramatically improved when she presented for her second injection in 4 weeks. Methotrexate and colchicine were discontinued, a second dose of 90 mg ustekinumab was administered, and the prednisone was rapidly tapered. Her Crohn's disease, PPP, and APF all remained in good control over the ensuing year with ustekinumab, 90 mg every 3 months, with only minor cutaneous flares in the 2 weeks before each ustekinumab injection.

DISCUSSION

The concurrent occurrence of APF and PPP in our case suggests that the 2 disorders may share a common pathophysiologic mechanism, representing different clinical manifestations of the same disorder. The existence of these auto-inflammatory processes after treatment with TNF-α blockers represents a paradox, as this class of medication normally treats autoimmune conditions, including those mediated by neutrophils. All reported cases of TNF-α—induced APF have occurred during treatment for IBD, as opposed to PPP, which can arise in postinfectious or other inflammatory contexts.[2-4]

Our patient was treated with 2 separate TNF-α blockers for her Crohn's disease, both of which seemed to trigger or exacerbate both PPP and APF, suggesting strongly that these eruptions were caused by the shared mechanism of the agents rather than being an idiosyncratic reaction to an agent. The eruptions continued to be severe and recalcitrant to treatment for almost a year after discontinuing TNF-α inhibitors, suggesting that the TNF-α inhibitors triggered these autoinflammatory conditions but that they were self-sustaining once initiated. The fact that she still had minor flares of pustular eruptions approximately 2.5 months after each injection of ustekinumab suggests that the APF and PPP were still ongoing but were controlled by the ustekinumab rather than going into remission.

With respect to the pathophysiology of APF and PPP, it is theorized that because of TNF-α blockade,

there is an upregulation of interferon-α (IFN-α) from plasmacytic dendritic cells perpetuating an inflammatory response in genetically susceptible individuals.[3,4] The presence of this cell type in the skin is believed to be an early step in the pathogenesis of psoriatic lesions.[2] IFN-α has an important role in neutrophil recruitment and chemotaxis, which could account for the pustular nature of the lesions in APF and PPP. Immunohistochemical analysis of skin biopsy specimens from both conditions has shown an increase in IFN-α and various other nonspecific cytokines and extracellular inflammatory components when compared with normal skin.[2,3] Various other neutrophilic dermatoses share the sterile neutrophilic pustules and nonvasculitic histopathology seen in these 2 conditions.[2,3] However, the clinical correlation of bodily location, medical history, and therapeutic context differentiates these 2 entities from other related neutrophilic dermatoses.

Our novel case illustrates the concurrent presentation of 2 uncommon neutrophilic eruptions resulting from TNF-α—antagonizing medications. Although APF and PPP are currently thought of as separate disorders, the parallel occurrence in our case and other similar histopathologies suggests these may be 2 manifestations of a shared pathway. The mechanism concerning IFN-α overexpression underlying development of pustular lesions in patients on TNF-α blockers is an area that clinicians and researchers can further explore to understand the mechanisms underlying these conditions.

REFERENCES

1. Shmidt E, Wetter DA, Ferguson SB, Pittelkow MR. Psoriasis and palmoplantar pustulosis associated with tumor necrosis factor-α inhibitors: the Mayo Clinic experience, 1998 to 2010. *J Am Acad Dermatol*. 2012;67(5):e179-e185.
2. Mössner R, Thaci D, Mohr J, et al. Manifestation of palmoplantar pustulosis during or after infliximab therapy for plaque-type psoriasis: report on five cases. *Arch Dermatol Res*. 2008;300(3):101-105.
3. Marzano AV, Tavecchio S, Berti E, Gelmetti C, Cugno M. Paradoxical Autoinflammatory skin reaction to tumor necrosis factor alpha blockers manifesting as amicrobial pustulosis of the folds in patients with inflammatory bowel diseases. Cheng. X, ed. *Medicine*. 2015;94(45):e1818.
4. Lee HY, Pelivani N, Beltraminelli H, Hegyi I, Yawalkar N, Borradori L. Amicrobial Pustulosis-like rash in a patient with Crohn's disease under anti-TNF-alpha blocker. *Dermatology*. 2011;222:304-310.