Successful treatment of refractory tumor necrosis factor inhibitor-induced palmoplantar pustulosis with tofacitinib: Report of case

Yixin Ally Wang, BA,[a] and Misha Rosenbach, MD[b]
Philadelphia, Pennsylvania

Key words: palmoplantar pustulosis; tofacitinib.

INTRODUCTION

Tumor necrosis factor (TNF) inhibitor—induced palmoplantar pustulosis (PPP) can present with debilitating, refractory disease that requires changing or stopping anti-TNF agents or adding systemic treatments. Here, we report an update of a previously reported case of severely recalcitrant PPP successfully treated with the Janus kinase (JAK) inhibitor tofacitinib.

CASE REPORT

A white woman in her 40s initially presented with vesiculopustules on her palms and soles, clinically diagnosed as PPP, in the setting of adalimumab treatment for Crohn's disease. Despite cessation of adalimumab, the patient's eruption persisted. Throughout the course of her care, she failed to respond to multiple treatment regimens (Table I). Eventually, she had complete clearance after 4 doses of ustekinumab 45 mg subcutaneous injections, with remission achieved for several months, and her case was reported in *Archives of Dermatology*.[1]

Over time, however, the patient experienced worsening of her disease and subsequently failed to improve despite an increased dose of 90 mg ustekinumab. Because of debilitating symptoms, she was intermittently treated with cyclosporine at low doses. She had complete clearance temporarily while taking a combination of apremilast and tocilizumab, but she was unable to be tapered off either medication without a recurrence of symptoms, and she ultimately relapsed with active disease despite combination therapy. She was started on tofacitinib 5 mg tablets twice daily. Since initiation of this medication, her PPP has cleared completely without intermittent flares (Fig 1, *A-D*). During a follow-up period of 1 year after initiation of tofacitinib, she was able to discontinue all other topical and systemic immunosuppressive agents. Her Crohn's disease was in remission for the duration of her treatment for PPP, without flares of her gastrointestinal disease on any of the medications.

Abbreviations used:

JAK: Janus kinase
PPP: palmoplantar pustulosis
TNF: tumor necrosis factor

DISCUSSION

Because TNF inhibitor—induced PPP remains a relatively uncommon, understudied phenomenon, its pathophysiology and long-term treatment have

From the Perelman School of Medicine, University of Pennsylvania,[a] and Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia.[b]

Funding sources: None.

Disclosures: Dr Rosenbach is the deputy editor of *JAMA Dermatology*. He has received research support from Processa Pharma and consulting fees from Merck, aTyr, and Processa. Ms Wang has no conflicts of interest to declare.

Correspondence to: Misha Rosenbach, MD, Perelman Center for Advanced Medicine, Department of Dermatology, University of Pennsylvania, 3400 Civic Center Blvd, South Tower, 7th Floor, Ste 723, Philadelphia, PA 19104. E-mail: Misha.rosenbach@pennmedicine.upenn.edu.

JAAD Case Reports 2020;6:115-8.
2352-5126

https://doi.org/10.1016/j.jdcr.2019.12.006

Table I. Therapies and treatment response

Date started	Date ended	Medication	Reason for discontinuation
Before first appointment	June 2008	Efalizumab	Worsening of symptoms
June 2008	July 2008	Cyclosporine 400 mg	Esophagitis
July 2008	August 2008	Intravenous cyclosporine	Issues with midline access, pain
August 2008	August 2008	Mycophenolic acid	Worsening of symptoms
August 2008	October 2008	Psoralen plus ultraviolet A with oxsoralen ×8	Sustained burn and stopped Mild improvement
October 2008	March 2009	Topical steroid and oral steroid taper	Worsening of symptoms
May 2009	July 2009	Alefacept	Worsening of symptoms
August 2009	February 2010	Cyclosporine 200 mg	Creatinine rise
October 2009	February 2010	Isotretinoin	No improvement
February 2010	November 2010	Ustekinumab 45 mg ×4 injections	Completely clear with residual response
November 2010	February 2013	Topical dapsone, cyclosporine	Residual response from ustekinumab
February 2013	June 2013	Cyclosporine 200 mg	Creatinine rise
June 2013	November 2013	Ustekinumab 90 mg ×4 injections	No improvement
January 2014	March 2014	Anakinra	National Institutes of Health trial, limited by adverse effects (severe injection site reaction, headache)
April 2014	July 2014	Cyclosporine 200 mg	Creatinine rise
April 2014	July 2014	Methotrexate	Creatinine rise
September 2014	December 2014	Acitretin	No improvement
September 2014	December 2014	Cyclosporine 200 mg	Nausea and vomiting
January 2015	November 2017	Apremilast	No improvement by itself Clear in combination with tocilizumab initially Ultimately relapsed with residual disease
May 2015	November 2017	Tocilizumab	No improvement by itself Clear in combination with apremilast initially Ultimately relapsed with residual disease
November 2017	November 2017	Cyclosporine 200 mg	Flare requiring short-term cyclosporine
December 2017	December 2017	Guselkumab 100 mg ×1 injection	No improvement
June 2018	Present	Tofacitinib	Completely clear

not been well established. Here, we present a case of refractory TNF inhibitor–induced PPP that improved with tofacitinib, a JAK inhibitor.

Tofacitinib is an oral JAK inhibitor that inhibits the JAK–signal transducer and activator of transcription pathway, with the greatest effect on JAK1 and JAK3. It decreases the production of a multitude of cytokines, most notably interferon γ, interleukin 6, and interleukin 17A,[2] which have been shown to play a role in the pathogenesis of PPP.[3] However, because tofacitinib has also been implicated as a trigger for PPP, additional cytokines may be involved.[4]

Consistent with our current findings, a previous case report has shown the success of tofacitinib for recalcitrant TNF inhibitor–induced PPP in the setting of rheumatoid arthritis treatment.[5] We recommend consideration of the use of tofacitinib as a potential long-term management agent for refractory TNF inhibitor–induced PPP. We also hope to encourage further investigation of this agent.

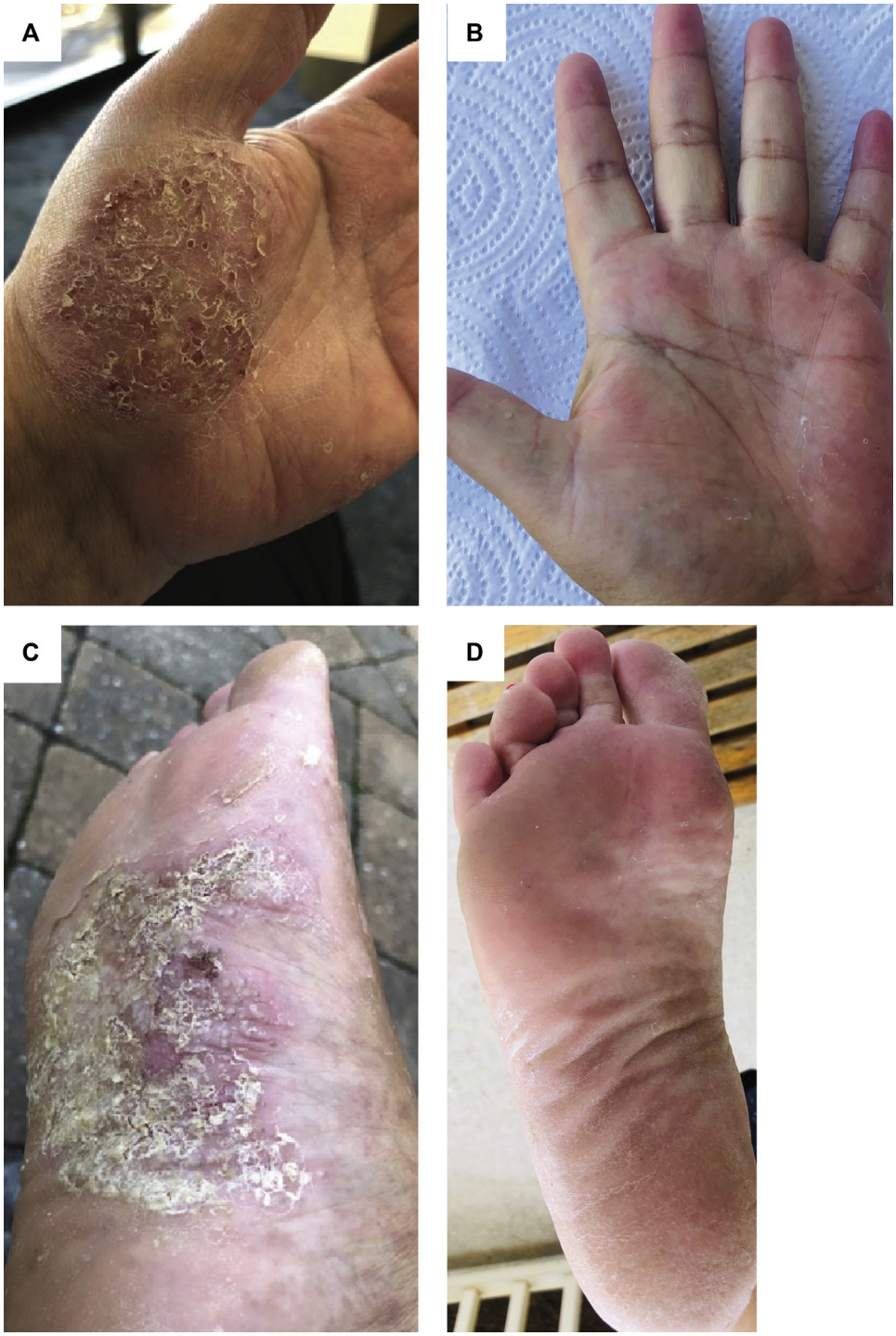

Fig 1. The left hand (**A**) before and (**B**) after tofacitinib initiation and the right foot (**C**) before and (**D**) after tofacitinib initiation.

REFERENCES

1. Chu DH, Van Voorhees AS, Rosenbach M. Treatment of refractory tumor necrosis factor inhibitor—induced palmoplantar pustulosis: a report of 2 cases. *Arch Dermatol*. 2011;147(10):1228-1230.
2. Ghoreschi K, Gadina M. Jakpot! New small molecules in autoimmune and inflammatory diseases. *Exp Dermatol*. 2014;23(1):7-11.
3. Bissonnette R, Nigen S, Langley RG, et al. Increased expression of IL-17A and limited involvement of IL-23 in patients with palmo-plantar (PP) pustular psoriasis or PP pustulosis; results

from a randomised controlled trial. *J Eur Acad Dermatol Venereol*. 2014;28(10):1298-1305.

4. Shibata T, Muto J, Hirano Y, et al. Palmoplantar pustulosis—like eruption following tofacitinib therapy for juvenile idiopathic arthritis. *JAAD Case Rep*. 2019;5(6):518-521.
5. Koga T, Sato T, Umeda M, et al. Successful treatment of palmoplantar pustulosis with rheumatoid arthritis, with tofacitinib: impact of this JAK inhibitor on T-cell differentiation. *Clin Immunol*. 2016;173:147.