SKIN

BRIEF ARTICLE

A case of pityriasis rubra pilaris following atorvastatin therapy

Gretchen D. Ball BS[1], Scott Stratman MD MPH[1], Alice B. Gottlieb MD PhD[1]

[1] Department of Dermatology, Icahn School of Medicine at Mount Sinai, NY, New York, USA

ABSTRACT

Background: Pityriasis rubra pilaris (PRP) is a rare dermatologic disorder of unknown etiology characterized by distinct red-orange scaly plaques, red follicular papules, and palmoplantar keratoderma. The occurrence of PRP following statin therapy is exceptionally uncommon, with only a few cases reported in the literature.
Case Presentation: An 83-year-old male developed PRP within one month of initiating atorvastatin therapy. Detailed history revealed no other new medications or identifiable triggers. Initially misdiagnosed with psoriasis, the patient underwent multiple biopsies and several unsuccessful treatment regimens before receiving a clinical diagnosis of PRP. He ultimately responded well to a combination of methotrexate and secukinumab therapy.
Discussion: PRP is often challenging to diagnose due to clinical and histologic overlap with other dermatoses, particularly psoriasis, and is misdiagnosed in a high percentage of cases. Although rare, drug-induced pityriasis rubra pilaris has been reported in association with several medication classes, including tyrosine kinase inhibitors and immunomodulatory agents. The mechanisms behind statin-induced PRP remain speculative; recent insights suggest a possible involvement of the interleukin (IL)-23/T-helper 17 cell (Th17) inflammatory pathway.
Conclusion: This case underscores the diagnostic challenges associated with PRP and proposes a potential association between statin use and PRP onset.

INTRODUCTION

Pityriasis rubra pilaris (PRP) is an inflammatory, papulosquamous dermatosis with clinical features of follicular keratotic papules, orange-red erythematous plaques, and palmoplantar keratoderma with red-orange hue.[1] PRP can be further subdivided into six different subtypes based on age of onset, disease extent, prognosis, and other associated features.[1]

Although a comprehensive spectrum of clinical variations in PRP has been previously described, its pathogenesis and etiology remain unclear. Several possible mechanisms have been suggested. Genetics, vitamin A metabolism abnormalities, and infections (i.e., HIV) have been associated with PRP onset.[1] Other factors associated with PRP onset include preceding trauma and multiple drugs, such as antivirals for hepatitis C and tyrosine kinase inhibitors.[1,2] Through modification of inflammatory pathways, these drugs can cause potential alterations in the immune system and abnormal epidermal growth.[2]
For other cases of drug-induced PRP, the pathogenic mechanisms are less clear.

Statin-induced PRP is a rare phenomenon, and its mechanism has yet to be fully elucidated. To date, there are only two documented case reports of statin-induced PRP.[3,4] Herein, we describe a male patient who developed PRP approximately one month after starting atorvastatin therapy for hypercholesterolemia.

CASE REPORT

An 83-year-old male with a past medical history of nonmelanoma skin cancer, hypertension, and hypercholesterolemia presented to our outpatient dermatology practice with an extensive rash that began 1 month after starting atorvastatin therapy and persisted for six months prior to our encounter. His rash reportedly started with desquamation involving his face, which later progressed to areas on his back. Over a few months, his rash acutely worsened and spread to his chest, bilateral upper and lower extremities, and acral sites. On presentation, the patient had generalized orange-red papules and plaques on his back (**Figure 1A**). He had similar plaques involving the entirety of his distal upper and lower extremities (**Figure 1B,C**) with unique waxy, orange-red hued palmoplantar keratoderma (**Figure 1D**). He reported associated peeling and swelling of his hands and feet, greatly impacting his mobility and quality of life.

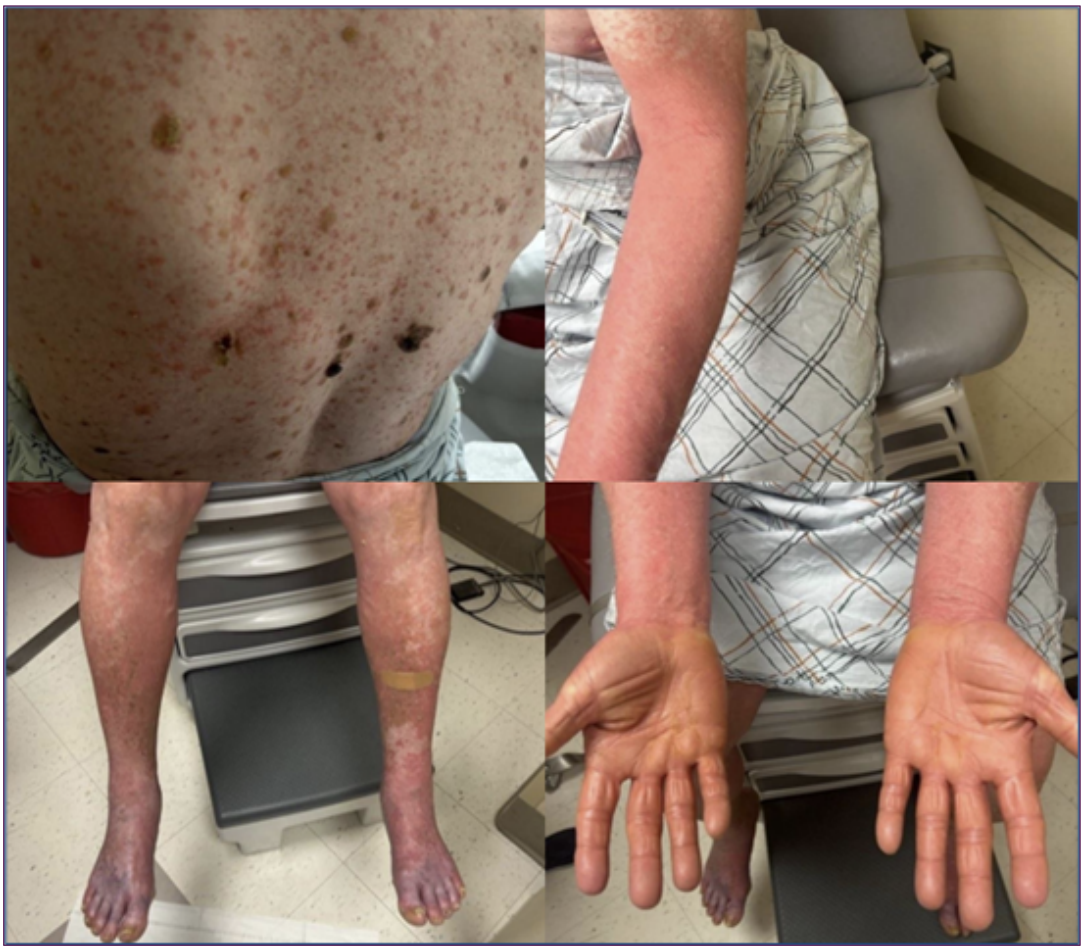

Figure 1. (A) Orange-red papules and plaques on the back (B,C) and upper and lower extremities with (D) waxy, orange-red hued palmoplantar keratoderma

Given his clinical history and physical examination, his presentation was consistent with PRP. A comprehensive history of present illness was taken at the initial encounter; of note, he reported being in a monogamous relationship and denied a history of psoriasis. He also denied a history of known viral or bacterial illness prior to rash onset. The only new medication he started before his symptoms started was atorvastatin. Within one week of rash onset, the patient discontinued atorvastatin, suspecting a connection between the two.

Prior to visiting our clinic, the patient was evaluated at three different dermatology practices for the same concern. At the first two clinics, biopsies were performed on the left lateral upper arm and mid-upper back, revealing an eczematized lesion of psoriasis and psoriasiform dermatitis consistent with psoriasis, respectively. He was started on topical corticosteroids of varying potency, a topical calcineurin inhibitor, and a short taper of oral prednisone for 5 days; however, these medications exacerbated his symptoms, and he stopped using them. He was also started on oral acitretin for two weeks but discontinued this medication again due to worsening symptoms.

At his third dermatologic visit, he was clinically diagnosed with PRP and began treatment with methotrexate (15 mg per week), folic acid, and a loading dose of secukinumab. After presenting to our clinic, he continued with methotrexate and secukinumab (150 mg every 4 weeks). His condition improved after approximately 3 months of therapy.

DISCUSSION

Diagnosing PRP presents significant challenges due to its clinical and histological similarities with other dermatoses. Both PRP and psoriasis are characterized by altered epidermal differentiation and increased keratinocyte proliferation. However, distinguishing PRP from psoriasis and other conditions relies on recognizing histopathological features unique to PRP, such as hypergranulosis, orthokeratosis, parakeratosis, thickened suprapapillary plates, and keratotic plugs.[5] A recent review indicated that PRP is misdiagnosed in 60.7% to 91.3% of cases, most commonly as psoriasis[1], which was the initial misdiagnosis in our case.

Statin-induced PRP is rare, with only a few documented cases. The first case reported in 2013 involved a 61-year-old male who developed a pruritic, erythematous scaling eruption after starting simvastatin. Despite discontinuing the medication, the eruption progressed to erythroderma with palmoplantar keratoderma and eyelid ectropion, ultimately diagnosed as classical adult PRP type 1. Treatment with acitretin led to complete clearance within three months.[3] A second case in 2022 involved a 57-year-old male who developed PRP confirmed by biopsy one month after starting atorvastatin. Despite ongoing treatment with acitretin and secukinumab, the PRP had not resolved after six months.[4]

Drug-induced PRP has been infrequently evaluated, but a systematic review in 2020 identified several implicated drug classes, including tyrosine kinase inhibitors, topical Toll-like receptor 7 agonists, phosphoinositide 3-kinase inhibitors, antivirals, biologics, programmed cell death protein 1 inhibitors, vascular endothelial growth factor inhibitors, statins, insulin, and angiotensin-converting enzyme inhibitors.[6] The mechanisms by which statins may induce PRP are not well understood. However, statins have been associated with

several drug-induced autoimmune reactions involving the skin, such as systemic lupus erythematosus, subacute cutaneous lupus erythematosus, dermatomyositis, and lichen planus pemphigoides.[7]

Statins have been shown to influence the Interleukin-23 (IL-23)/Th17 pathway through immunomodulatory mechanisms,[8] and recent literature has identified the dysregulation of the IL-23/Th17 cell axis as a mediator of PRP pathogenesis. Strunck et al. found that two IL-23/Th17 pathway proteins, IL-17C and CCL20, were upregulated in tissue samples from PRP patients compared to healthy controls. Moreover, these elevated levels appeared to correlate with PRP disease severity and responsiveness to IL-17A blockade.[9] This common inflammatory pathway may explain a relationship between statin use and the development of PRP.

Treating PRP is challenging. Evidence supports the effectiveness of isotretinoin and the IL-17 inhibitors ixekizumab and secukinumab, while other medications have shown inconsistent results.[10] Our patient improved on a regimen of methotrexate and secukinumab. A deeper understanding of the genetic and immunologic underpinnings of PRP may help develop targeted therapies and improve patient outcomes.

Conflict of Interest Disclosures: GBD: None, SS: None, ABG: honoraria as an advisory board member and consultant for Amgen, AnaptypsBio, Avotres Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Dice Therapeutics, Eli Lilly, Highlights Therapeutics, Janssen, Novartis, Sanofi, Teva, UCB, and Xbiotech (stock options for a rheumatoid arthritis project).

Funding: None

Corresponding Author:
Gretchen D. Ball
18 Ivy Hill Road, Ridgefield, CT 06877
Phone: 203-240-5808
Email: gretchen.ball@einsteinmed.edu

References:

1. Zhou T, Al Muqrin A, Abu-Hilal M. Updates on Pityriasis Rubra Pilaris: A Scoping Review. *J Cutan Med Surg*. Mar-Apr 2024;28(2):158-166. doi:10.1177/12034754231223159
2. Mufti A, Lytvyn Y, Maliyar K, et al. Drugs associated with development of pityriasis rubra pilaris: A systematic review. *J Am Acad Dermatol*. Apr 2021;84(4):1071-1081. doi:10.1016/j.jaad.2020.07.052
3. Gajinov ZT, Matic MB, Duran VD, et al. Drug-related pityriasis rubra pilaris with acantholysis. *Vojnosanit Pregl*. Sep 2013;70(9):871-3. doi:10.2298/vsp1309871g
4. Reich IK, Keller KL. A Debilitating Adverse Reaction of Pityriasis Rubra Pilaris Due to Statin Therapy in A Low-Risk Patient: Case Report *Frontiers in Medical Case Reports*. 2022;3(6):1-07. doi:10.47746/FMCR.2022.3603
5. Balan R, Grigoraş A, Popovici D, Amălinei C. The histopathological landscape of the major psoriasiform dermatoses. *Arch Clin Cases*. 2021;6(3):59-68. doi: 10.22551/2019.24.0603.10155
6. Mufti A, Lytvyn Y, Maliyar K, et al. Drugs associated with development of pityriasis rubra pilaris: A systematic review. *J Am Acad Dermatol*. 2021;84(4):1071-1081. doi:10.1016/j.jaad.2020.07.052
7. Noel B. Lupus erythematosus and other autoimmune diseases related to statin therapy. J Eur Acad Dermatol Venereol 2007; 21(1): 17-24.
8. Zhang X, Jin J, Peng X, et al. Simvastatin inhibits IL-17 secretion by targeting multiple IL-17-regulatory cytokines and by inhibiting the expression of IL-17 transcription factor RORC in CD4+ lymphocytes. *J Immunol*. 2008;180(10):6988-6996. doi:10.4049/jimmunol.180.10.6988
9. Strunck JL, Cutler B, Rajpal B, et al. Pityriasis rubra pilaris response to IL-17A inhibition is associated with IL-17C and CCL20 protein levels. *J Invest Dermatol*. 2022;142(1):235-239. doi: 10.1016/j.jid.2021.06.009

10. Joshi TP, Duvic M. Pityriasis Rubra Pilaris: An Updated Review of Clinical Presentation, Etiopathogenesis, and Treatment Options. *Am J Clin Dermatol*. 2024;25(2):243-259. doi:10.1007/s40257-023-00836-x