SKIN

BRIEF ARTICLE

A Unique Case of Heat-Induced Livedo Reticularis Following Initiation of Upadacitinib

Anya Patel[1], Kateryna Karpoff, BS[1], Mark Lebwohl, MD[1]

[1] The Kimberly and Eric J. Waldman Department of Dermatology, Icahn School of Medicine at Mount Sinai Hospital, New York, New York, USA

ABSTRACT

Livedo reticularis is a benign condition characterized by a mottled appearance of the skin that is most frequently triggered by exposure to cold temperatures. It is painless and often self-resolves after trigger avoidance. Upadacitinib is a Janus kinase inhibitor approved for the treatment of several inflammatory and autoimmune diseases including atopic dermatitis and psoriatic arthritis. Here, we report a case of heat-induced livedo reticularis following initiation of treatment with upadacitinib for an ixekizumab-triggered paradoxical eczematous flare. This presentation expands the spectrum of cutaneous vascular changes potentially associated with JAK-inhibitors and underscores the importance of clinician awareness to support counseling, avoid unnecessary workup, and guide ongoing monitoring.

INTRODUCTION

Livedo reticularis (LR) is a primarily benign, painless cutaneous manifestation characterized by reddish-blue discoloration in a net-like pattern. LR is most commonly observed on the lower extremities, however it can also present on the trunk, arms, and buttocks. Primary (physiologic) LR, also referred to as cutis marmorata, is often transient and triggered by cold temperatures. Persistent LR is referred to as secondary (pathologic) LR, or livedo racemosa, and is often associated with underlying autoimmune diseases such as antiphospholipid syndrome or vasculitides.[1]

Primary LR is often attributed to physiologic arterial vasospasm, venous dilation, or microvascular thrombi, and is exacerbated by exposure to cold temperatures.[1,2] Secondary cases have been reported in association with amantadine use and surrounding coronavirus disease 2019 (COVID-19) vaccine injection sites.[2,3] For primary prevention, patients are advised to avoid cold exposure, however pharmacologic intervention is generally unnecessary.[1] Janus kinase (JAK) inhibitors have been employed successfully in the treatment of inflammatory and autoimmune conditions including vitiligo and psoriasis. We report a case of heat-induced livedo reticularis in a patient who had initiated treatment with upadacitinib for a paradoxical eczematous flare following initiation of ixekizumab for psoriasis.

CASE REPORT

A 63-year-old male with a past medical history of psoriasis, Graves' disease, hypertension, and hyperlipidemia presented

to the clinic with one year of psoriatic plaques on the bilateral knees and elbows as well as severe involvement of the scalp. Upon presentation, he had been using calcipotriene/betamethasone foam and clobetasol solution for his scalp, and betamethasone dipropionate on his knees and elbows. Following evaluation, he was advised to start ixekizumab with a 160 mg loading dose, followed by 80 mg every two weeks for three months, and then 80mg every four weeks. He maintained this treatment for one year and seven months, during which he achieved complete clearance of psoriatic plaques. He was prescribed tapinarof 1% cream once daily for irritated patches. One month later, the patient experienced a sudden onset of severely pruritic erythematous and eczematous patches on the anterior and medial thighs, popliteal fossae, and forearms, at which point he was diagnosed with atopic dermatitis. The patient was advised to discontinue ixekizumab and was initiated on upadacitinib 15 mg daily.

Shortly after initiating upadacitinib, the patient developed a painless, mottled reddish discoloration on his bilateral lower extremities, characteristic of primary livedo reticularis (**Figure 1**). Notably, the rash occurred only following hot showers and spontaneously resolved within five minutes. A complete blood count, metabolic panel, and lipid panel were unremarkable. Five months later, the patient remained clear of atopic dermatitis, with remission maintained for one year. Upadacitinib 15 mg daily was continued, and given the benign nature of livedo reticularis, the manifestation required no specific treatment. In light of the temporal association, upadacitinib was suspected as the precipitating factor for the livedo reticularis.

This case is notable for heat-induced primary LR, suggesting vasodilation rather than the vasospastic mechanism of cold-induced LR. Diagnosis of LR is clinical, and further evaluation is typically only warranted if history or examination suggests a secondary cause.[1] Transient LR, such as in this case, requires no additional testing or treatment. To date, livedo reticularis has not been reported in association with JAK inhibitor therapy. JAK inhibitors function by suppressing cytokine signaling via the JAK-STAT pathway. Upadacitinib selectively targets JAK1-dependent cytokines, including IL-6, IL-7, and interferon γ, which play key roles in inflammatory diseases and vascular function.[4] Although rare, suppression of IL-6 and INF-γ has been implicated in vascular complications such as deep vein thrombosis.[5] While the mechanism remains unclear, we propose that in rare cases, upadacitinib may transiently alter vascular regulation, leading to manifestations such as LR.

CONCLUSION

In summary, we describe a unique case of heat-induced, transient livedo reticularis temporally associated with initiation of upadacitinib therapy. Although benign and self-resolving in this patient, this presentation broadens the spectrum of cutaneous vascular changes potentially associated with JAK inhibition. Clinicians should be aware of this phenomenon to avoid unnecessary workup, appropriately counsel patients, and continue monitoring for additional vascular sequelae with wider use of JAK inhibitors.

Conflict of Interest Disclosures: Anya Patel and Kateryna Karpoff have no disclosures. Mark Lebwohl is an employee of Mount Sinai and receives research funds from: Abbvie, Arcutis, Avotres, Boehringer Ingelheim, Cara therapeutics, Clexio, Dermavant Sciences, Eli Lilly, Incyte, Inozyme, Johnson & Johnson, Oruka, Pfizer, Sanofi-Regeneron, and UCB,

Figure 1. Livedo reticularis reaction in the bilateral lower extremities following heat exposure in a patient on upadacitinib.

and is a consultant for Added Health, Aikium, Almirall, AltruBio Inc., Alumis, Amgen, Apogee, Arcutis, Inc., AstraZeneca, Atomwise, Avotres Therapeutics, Boehringer-Ingelheim, Bristol-Myers Squibb, Castle Biosciences, Celltrion, Corevitas, Dermavant Sciences, Dermsquared, Evommune, Inc., Facilitation of International Dermatology Education, Forte biosciences, Galderma, Genentech, Incyte, LEO Pharma, Mayne Pharmaceuticals, Meiji Seika Pharma, Mindera, Mirium Pharmaceuticals, Moonlake, Oruka, Pfizer, Sanofi-Regeneron, Revolo, Seanergy, Strata, Sunpharma, Takeda, Trevi, and Verrica.

Funding: None

Corresponding Author:
Kateryna Karpoff
5 E 98th St
5th Floor
New York, NY 10029
Email: Kateryna.karpoff@gmail.com

References:

1. Sajjan VV, Lunge S, Swamy MB, Pandit AM. Livedo reticularis: A review of the literature. *Indian Dermatol Online J*. 2015;6(5):315-321. doi:10.4103/2229-5178.164493
2. Quaresma MV, Gomes AC, Serruya A, Vendramini DL, Braga L, Buçard AM. Amantadine-induced livedo reticularis--Case report. *An Bras Dermatol*. 2015;90(5):745-747. doi:10.1590/abd1806-4841.20153394
3. Horino T, Inotani S, Nakajima K, Terada Y. Livedo Reticularis After COVID-19 Vaccination. *J Rheumatol*. 2023;50(5):709. doi:10.3899/jrheum.220584
4. Miot HA, Criado PR, de Castro CCS, Ianhez M, Talhari C, Ramos PM. JAK-STAT pathway inhibitors in dermatology. *An Bras Dermatol*. 2023;98(5):656-677. doi:10.1016/j.abd.2023.03.001
5. Mytheen S, Varghese A, Joy J, Shaji A, Tom AA. Investigating the risk of deep vein thrombosis with JAK inhibitors: a disproportionality analysis using FDA Adverse Event Reporting System Database (FAERS). *Expert Opin Drug Saf*. 2023;22(10):985-994. doi:10.1080/14740338.2023.2223955