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Dyshidrotic eczema associated with Upadacitinib use: a paradoxical adverse event or serendipity?

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Dear editor,

Janus kinase inhibitors (JAKi) have emerged as a therapeutic alternative in inflammatory bowel disease (IBD). Upadacitinib (UPA), a selective JAK1 inhibitor, has been licensed for both induction and maintenance of remission in moderate-to-severe ulcerative colitis (UC) and Crohn's disease, with a rapid onset of action (1).

We report the case of a 39-year-old man with ileocolic Crohn's disease diagnosed 25 years ago, with ileocecal resection`s history (2005). He received long-term infliximab-azathioprine combination therapy (2012–2024), followed by ustekinumab due to secondary loss of response. However, he developed clinical, biological (fecal calprotectin 1091 µg/g, C-reactive protein 101 mg/L) and endoscopic (Rutgeerts i4) recurrence, prompting a switch to UPA 45 mg/day. The patient achieved a marked symptomatic improvement within 48 hours, clinical remission by day 7 and biochemical normalization after one month. However, two weeks after UPA initiation developed pruritic vesicles on both palms and fingers, diagnosed with a new-onset dyshidrotic eczema (DE) by an expert dermatologist (**Figure 1**). Considering clinical presentation and absence of atopic personal history other differential diagnosis were excluded. Topical methylprednisolone led to rapid resolution ED, without stopping UPA. After 9 months he remained in clinical and biological remission.

In addition to IBD, UPA is also approved for the treatment of other immune-mediated diseases such as atopic dermatitis (AD) (2), although paradoxical UPA-induced AD has been recently reported, suggesting a plausible mechanism explaining by a Th1/Th2 dysregulation. JAK1i acts interfering the signaling of key Th2 cytokines, such as IL-4 and IL-13. In susceptible individuals, this may favor a relative shift toward Th1/Th17 responses, with increased production of proinflammatory cutaneous cytokines such as IFN-γ and IL-17 (3).

UPA has been exceptionally used off-label in refractory DE, a recurrent vesicular palmoplantar eruption characterized by intense pruritus and multifactorial etiology (4,5). Given the

chronologic association in our patient, this event may represent an adverse (paradoxical?) reaction to UPA or, less likely, environmentally triggered DE. Although environmental factors such as heat, hyperhidrosis, contact allergens or ultraviolet light have been reported to trigger DE, none of them were present in our patient. Moreover, we did not find any relationship between IBD and DE in the literature. Even more, DE was reported as an uncommon adverse event in UPA UC pivotal trials (data on file, Upadacitinib Ulcerative Colitis Integrated Summary of Safety for Investigator Brochure V14, August 2023, AbbVie). To our knowledge, this is the first reported case of UPA-induced DE in Crohn's disease.

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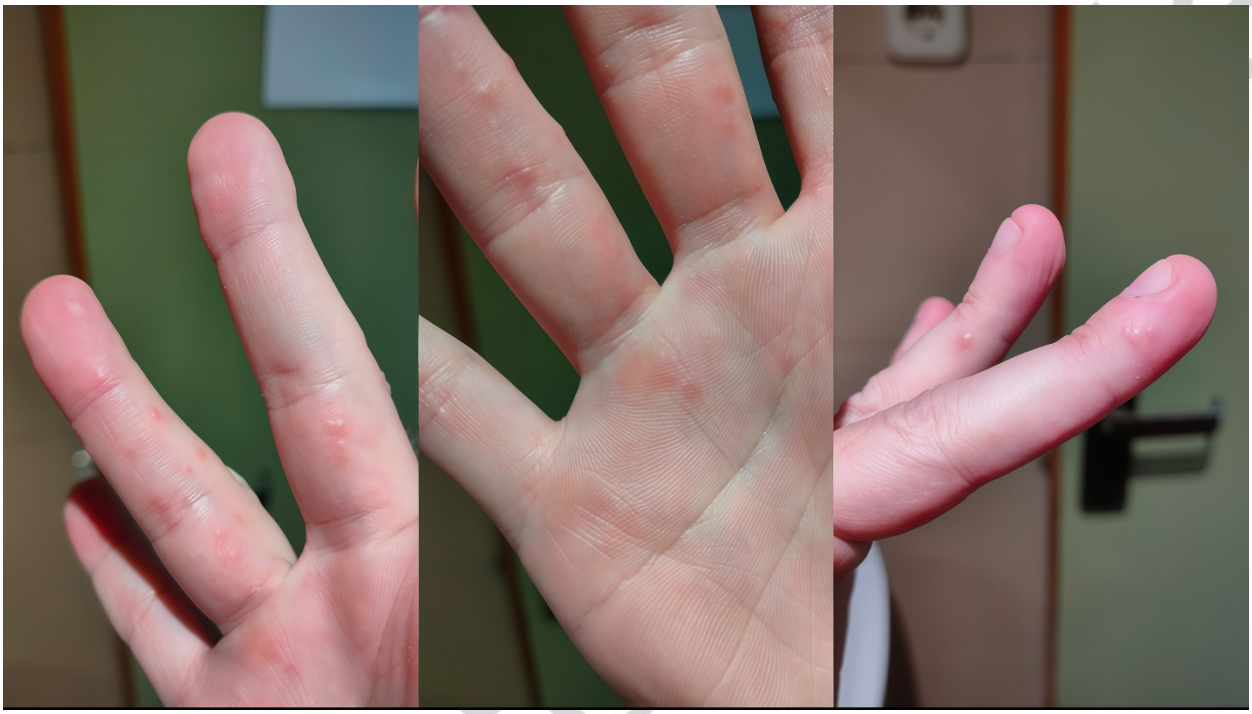

Figure 1. Dyshidrotic eczema vesicles in our patient.