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Unraveling the spectrum of paradoxical Th1-mediated dermatoses under IL-4/IL-13 or IL-13 blockade: Two Cases and a Review of the Literature

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Introduction

Interleukin-4 (IL-4) and interleukin-13 (IL-13) are key cytokines in T-helper 2 (Th2)–mediated immunity, driving the pathogenesis of atopic dermatitis (AD) and related diseases (3,4). Both cytokines signal through receptor complexes containing the IL-4 receptor alpha subunit (IL-4Rα), activatingthe JAK/STAT pathway and promoting type 2 inflammation. Dysregulated IL-4 and IL-13 signaling is therefore a hallmark of Th2-driven inflammatory disorders, including AD, asthma, and related atopic conditions(2). Moreover, IL-4 and IL-13 exert important immunoregulatory effects by suppressing T-helper 1 (Th1) and T-helper 17 (Th17) pathways, inhibiting Th1Th1 differentiation, reducing Th1-associated chemokines, and modulating interferon-γ production (6,7). Dupilumab (anti-IL-4Rα) and more recently the selective IL-13 inhibitors tralokinumab und lebrikizumab have been introduced as an additional targeted therapeutic option, by reducing type 2 inflammation while maintaining a favorable safety profile (1,2,5,6). However, blockade of the IL-4/IL-13 axis may disrupt immune homeostasis, potentially triggering paradoxical Th1-mediated inflammatory conditions. We report two cases and review the literature on paradoxical Th1-driven dermatoses emerging under IL-4/IL-13 and IL-13 blockade. (8).

Materials and Methods

We present two patients with manifestations of moderate-to-severe AD treated with IL-4/IL-13 or IL-13 inhibitors who developed new-onset Th1-mediated inflammatory dermatoses. Clinical presentation, histopathological findings, and therapeutic outcomes were documented and presented in a consolidated format. A comprehensive literature review was performed to identify similar paradoxical cutaneous reactions reported under dupilumab, tralokinumab, and lebrikizumab therapy.

Results

Both patients developed paradoxical Th1-mediated dermatoses following initiation of biologic therapy targeting the IL-4/IL-13 axis. Clinical manifestations included psoriasiform eruptions and other inflammatory skin conditions consistent with Th1/Th17 immune activation. Histopathology supported a shift toward Th1-driven inflammation. Literature review revealed increasing reports of similar paradoxical reactions, including psoriasis, alopecia areata, vitiligo, and granulomatous dermatitis, occurring under IL-4/IL-13 blockade. Management strategies varied from continuation of therapy with adjunctive treatment to biologic discontinuation. NanoString-based transcriptomic profiling of the skin biopsies revealed the immunopathogenic signatures underlying both conditions.

Conclusions

Paradoxical Th1-mediated dermatoses are an emerging complication of IL-4/IL-13–targeted therapies for atopic dermatitis and related disorders. Our two cases, supported by NanoString- based gene expression profiling of lesional biopsies, provide insights tp the postulated shift from Th2- to Th1/Th17-skewed immune signatures under IL-4/IL-13 or IL-13 blockade, providing mechanistic insight into these reactions. These findings underscore the need for vigilant clinical monitoring, awareness of paradoxical inflammatory events, and individualized management rather than automatic

discontinuation of biologic therapy. Larger prospective studies are warranted to define risk factors, clarify immunopathogenic pathways, and guide safer use of IL-4/IL-13 inhibitors in clinical practice.