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Dupilumab as a targeted therapeutic strategy for Th2-driven cutaneous manifestations in Kimura disease

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Dear Editor,

Kimura disease (KD) is a rare, chronic inflammatory condition characterized by subcutaneous nodules, lymphadenopathy, peripheral and tissue eosinophilia, and markedly elevated serum IgE concentrations. Although its precise etiopathogenesis remains incompletely defined, accumulating evidence supports its classification as a type 2 immune-mediated disorder, sustained by Th2 lymphocyte activation and overexpression of interleukin (IL)-4 and IL-13 signaling pathways. This immunological milieu promotes eosinophilic infiltration, vascular proliferation, IgE overproduction, and persistent pruritus, ultimately driving both systemic and cutaneous manifestations of the disease.¹⁻⁴ Cutaneous involvement, frequently displaying clinicopathological overlap with angiolymphoid hyperplasia with eosinophilia (ALHE), represents a major source of morbidity and therapeutic complexity.

We describe the case of a young woman affected by KD with severe and refractory cutaneous involvement, in whom dupilumab achieved significant and sustained disease control. The patient was referred for multiple nodular lesions of the scalp, predominantly affecting the left occipital and nuchal regions. The lesions were progressively enlarging, intensely pruritic, and complicated by recurrent spontaneous bleeding (Figure 1A). Scratching behavior was compulsive and persistent, leading to chronic blood loss and secondary iron-deficiency anemia confirmed by hematologic evaluation. Clinical examination additionally revealed marked laterocervical lymphadenopathy. Her medical history was notable for chronic spontaneous urticaria, psoriasis, and renal involvement. Laboratory investigations demonstrated peripheral eosinophilia and markedly elevated total serum IgE levels, consistent with a systemic Th2-skewed inflammatory profile. Histopathological examination of a representative scalp nodule revealed features consistent with ALHE, including benign lobular vascular proliferation composed of epithelioid endothelial cells and a dense perivascular inflammatory infiltrate rich in eosinophils and lymphocytes, without cytologic atypia. Concurrent renal biopsy established a diagnosis of minimal change glomerulonephritis.

The convergence of dermatologic, histologic, immunologic, and nephrologic findings supported a unifying diagnosis of KD. Therapeutically, the patient had undergone multiple unsuccessful interventions. Local treatments consisted of repeated cryotherapy sessions and intralesional triamcinolone acetonide injections administered every three weeks for approximately three to four months, without meaningful clinical improvement. Systemic antihistamine therapy was also implemented, comprising a double daily regimen of rupatadine in the morning and cetirizine in the evening, targeting both urticaria and pruritus. Despite this intensified antihistaminic approach, neither pruritus nor bleeding showed significant improvement. High-dose systemic corticosteroids

were introduced primarily for renal disease management, with the expectation of secondary benefit on the cutaneous lesions; however, corticosteroid therapy resulted only in partial urticaria control, exacerbation of psoriasis, and no substantial impact on the angiolymphoid nodules, which continued to bleed spontaneously.

Given the coexistence of KD, ALHE-like cutaneous lesions, chronic urticaria, peripheral eosinophilia, and elevated IgE levels, a shared Th2-driven immunopathogenic mechanism was strongly suspected. On this basis, dupilumab, a fully human monoclonal antibody directed against the IL-4 receptor α subunit and capable of inhibiting both IL-4 and IL-13 signaling, was initiated off-label as a pathway-oriented therapeutic intervention. Following initiation of dupilumab, the patient experienced rapid and complete resolution of pruritus, with immediate cessation of scratching behavior. Within 3 months, treatment resulted in sustained arrest of spontaneous bleeding and visible reduction in nodular volume (Figure 1B). These clinical improvements translated into stabilization of hemoglobin levels, correction of iron-deficiency anemia, and marked enhancement in overall quality of life. Cutaneous inflammation became clinically quiescent, and disease activity remained stable throughout a follow-up of 12 months after initiation of dupilumab, without recurrence of bleeding, severe pruritus, or progression of the cutaneous lesions. Cervical lymphadenopathy progressively improved during follow-up, while renal involvement remained stable under nephrological monitoring. Chronic spontaneous urticaria also demonstrated significant and durable improvement. Notably, these benefits persisted despite progressive corticosteroid tapering. Follow-up laboratory evaluation demonstrated a reduction in peripheral eosinophilia and serum IgE levels compared with baseline values.

This case underscores a critical clinical consideration: in KD-associated cutaneous disease, therapeutic success should not be defined exclusively by lesion size reduction. In patients presenting with hemorrhagic, intensely pruritic ALHE-like nodules, effective control of inflammation, pruritus, and bleeding constitutes a clinically meaningful endpoint. By acting upstream on the Th2 inflammatory axis, dupilumab appears to neutralize the central immunologic driver responsible for eosinophilic infiltration, IgE overproduction, endothelial activation, and neuroimmune signaling of pruritus.¹⁻⁴

Consistent with emerging literature documenting dupilumab responsiveness in KD,¹⁻⁴ our case expands the currently available evidence by describing a particularly severe cutaneous phenotype characterized by hemorrhagic ALHE-like scalp nodules associated with compulsive pruritus, chronic blood loss leading to iron-deficiency anemia, chronic spontaneous urticaria, psoriasis, and concomitant renal involvement. Unlike previously published reports, the most clinically meaningful therapeutic benefit was not limited to lesion regression but also included complete control of

pruritus and spontaneous bleeding, allowing correction of anemia, corticosteroid tapering, and substantial improvement in quality of life. Although evidence remains limited to isolated case reports and small case series, the growing consistency of clinical responses observed with dupilumab suggests that IL-4/IL-13 blockade may represent a promising steroid-sparing therapeutic option for selected patients with refractory Th2-driven KD.

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Figure 1. Clinical response to dupilumab in KD with ALHE-like scalp lesions. **A)** Baseline presentation before initiation of dupilumab. Multiple erythematous, nodular, angiolymphoid hyperplasia-like lesions of the occipital scalp are visible. The patient had previously undergone cryotherapy and repeated intralesional triamcinolone acetonide injections without achieving disease control. Lesions were intensely pruritic and characterized by recurrent spontaneous bleeding, contributing to chronic iron-deficiency anemia. **B)** Clinical appearance after 3 months of dupilumab therapy. Marked reduction in lesion volume and inflammatory activity is observed, with complete cessation of spontaneous bleeding and resolution of pruritus. Hemorrhagic episodes did not recur, allowing stabilization of hemoglobin levels and improvement in overall clinical status.

