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CORRESPONDENCE

Dupilumab aggravates Sézary syndrome: The importance of accurate pathological diagnosis

A 72-year-old woman was referred for evaluation of erythema over her entire body. She had received a diagnosis of atopic dermatitis (AD) based on skin biopsy elsewhere 7 years earlier. Since her symptoms were resistant to topical corticosteroids and oral antihistamines, dupilumab was started. She noticed peripheral lymph node enlargement 11 months after the commencement of dupilumab. Physical examination revealed generalized erythroderma with desquamation (Figure 1A,B) and lymphadenopathy in the neck, axilla, and inguinal region. A biopsy from her abdomen showed dense infiltrations of atypical lymphoid cells in the upper dermis with epidermotropism (Figure 1C,D). Immunohistochemically, the infiltrating cells were positive for CD3 and CD4; CD8 was almost negative. There was a 50% deletion of CD7 (Figure 1E–H). Her peripheral blood (PB) white blood cell count was 7660/μL, with 35% abnormal lymphocytes (2681/μL). Although $CD4^+/CD26^-$ or $CD4^+/CD7^-$ cells were not assessed, CD4/CD8 ratio was 10.59.[1,2] Human T-lymphotropic virus-1 antibody was negative. Monoclonal gene rearrangement of T-cell receptor β-chain was identified in her PB by Southern blot analysis. Inguinal lymph node biopsy showed partial effacement by atypical lymphocytes. The diagnosis was Sézary syndrome (SS), stage IVA2 (T4N3MXB2). Taking into account the risk of tumor lysis syndrome due to high tumor burden, we selected conventional multiagent chemotherapy as an initial therapy before using a molecular-targeted drug. Dupilumab was discontinued; cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) were started. After two cycles of CHOP, biweekly intravenous mogamulizumab was introduced. Her skin lesions gradually improved. The PB abnormal lymphocyte count decreased. Her disease was well controlled with mogamulizumab for 17 months.

We reviewed the previous biopsy specimen. Dense dermal infiltrates with atypical cells and epidermotropism were seen (Figure 1I,J). These infiltrates were positive for CD3 and CD4. CD8-positive cells were sparse. There was a 30% deletion of CD7 (Figure 1K–N). The atypical cells were $CCR4^+$ and $CD68^-$. Although a diagnosis of AD was made previously, our retrospective diagnosis was cutaneous T-cell lymphoma (CTCL).

Dupilumab is a monoclonal antibody which inhibits both IL-4 and IL-13 signaling pathways by binding specifically to the α subunit of the IL-4 receptor. Several cases of CTCL that developed or worsened after dupilumab use have been reported. A proposed mechanism of CTCL due to dupilumab is the involvement of IL-13 receptor α2 (IL-13Rα2), which is expressed on CTCL cells and promotes tumor progression. When dupilumab blocks IL-4 and IL-13 receptors, serum IL-13 levels increase. Because dupilumab inhibits IL-13Rα1 but not IL-13Rα2 signaling, increased IL-13 levels due to dupilumab stimulate IL-13Rα2, leading to the activation and proliferation of lymphoma cells.[3] To our knowledge, there are 36 cases[3–19] of CTCL worsened by dupilumab based on the diagnosis of AD or eczema have been reported. Of these 36 patients, 18 underwent skin biopsy prior to dupilumab therapy; no evidence of CTCL was described in 16 patients.[3–10] In one remaining patient, the authors re-evaluated the biopsy specimen taken before dupilumab treatment and revised the diagnosis to early CTCL-not otherwise specified.[10] In another patient, the first skin biopsy taken before dupilumab was compatible with AD; however, the diagnosis of mycosis fungoides was made by the second biopsy taken on the first day of dupilumab treatment. After 6 months of dupilumab treatment, the third biopsy turned out CD30-positive anaplastic large-cell lymphoma.[11]

When using dupilumab for AD, clinicians should be alert to the development or worsening of CTCL. Skin biopsy with immunohistochemical examination is strongly recommended before dupilumab therapy, especially in patients with erythroderma and elderly patients.

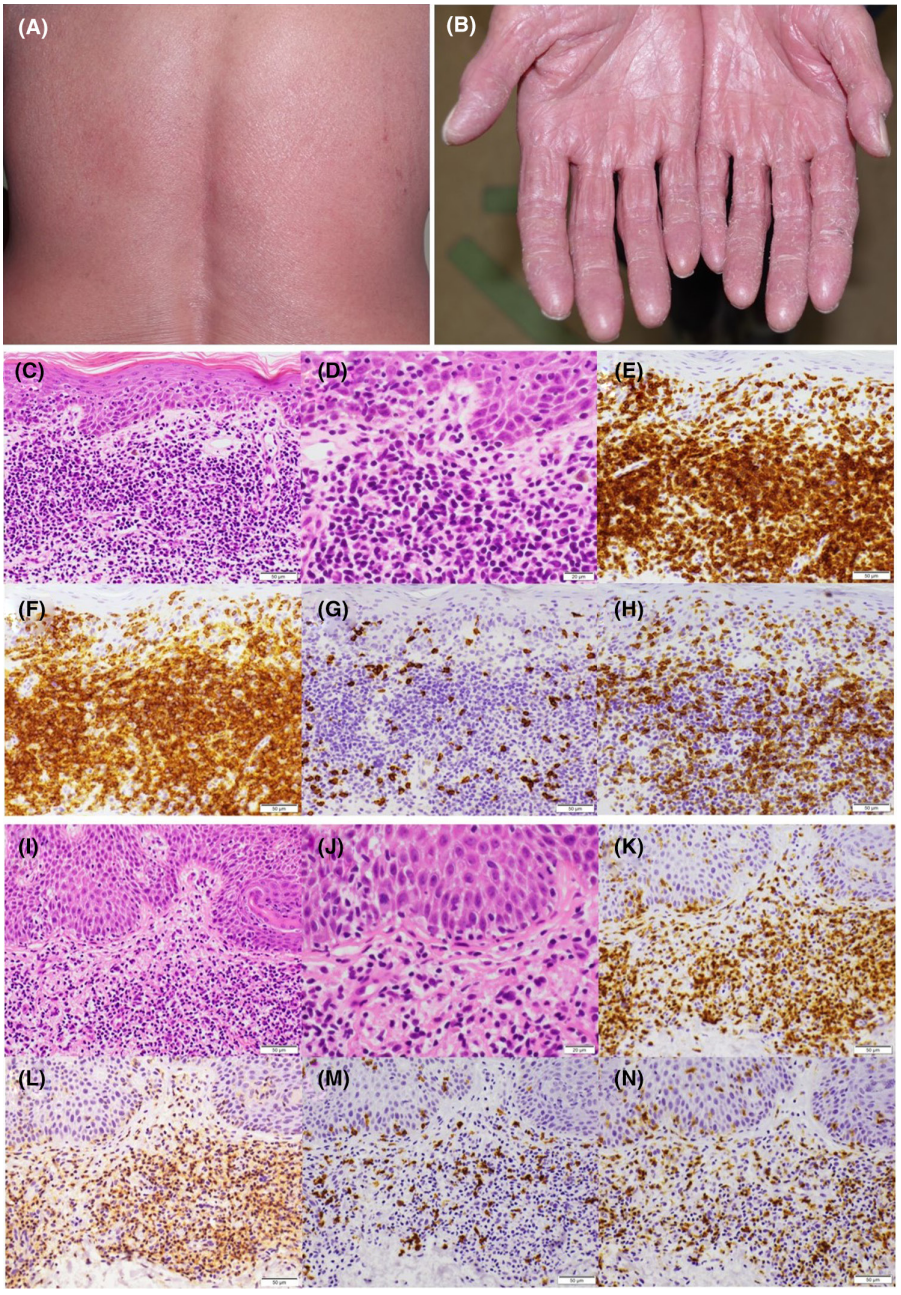

FIGURE 1 Diffuse erythema on the back (A) and palms (B) at the first visit. The biopsy from her abdomen revealed dense infiltrations of atypical lymphoid cells in the upper dermis with epidermotropism (C, D) (Hematoxylin and eosin [HE] stain). Immunohistochemical staining for CD3 (E), CD4 (F), CD8 (G), and CD7 (H). The infiltrating cells were positive for CD3 and CD4. CD8 was almost negative. There was 50% deletion of CD7. Histopathology of the skin biopsy obtained 7 years earlier. Dense dermal infiltrates with atypical cells and epidermotropism were seen (I, J) (HE stain). Immunohistochemical staining for CD3 (K), CD4 (L), CD8 (M), and CD7 (N). These infiltrates were positive for CD3 and CD4. CD8-positive cells were sparse. There was 30% deletion of CD7.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Approval of the research protocol: N/A.
Informed Consent: N/A.
Registry and the Registration No.: N/A.
Animal Studies: N/A.

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