Ibrutinib for the Management of Schnitzler Syndrome: A Novel Therapy for a Rare Condition

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Schnitzler syndrome is a rare dermatologic disorder that accompanies IgM monoclonal gammopathy and is characterized by a chronic urticarial-type eruption in association with intermittent fever, arthralgia or arthritis, and lymphadenopathy.[1] The etiology of Schnitzler syndrome remains unknown; however, most hypotheses suggest the involvement of autoreactive antibodies.[2] The interleukin-1 (IL-1) cellular pathway is implicated in its pathogenesis, and IL-1 receptor blockade results in rapid skin clearance. Recurrences are the norm within 48 to 72 hours after the discontinuation of anti–IL-1 treatment.[1]

Case Report

An 86-year-old man presented with minimally persistent urticarial papules and plaques for several years (Fig 1A). There was no evidence of dermatographism or postinflammatory patches on exam. Laboratory studies revealed mild leukocytosis and IgM monoclonal gammopathy. Prior management with topical corticosteroids and systemic antihistamines were ineffective. A bone marrow biopsy revealed involvement of 8% to 10% by a lymphoplasmacytic lymphoma but was negative for MYD88 mutation. A 4-mm punch skin biopsy demonstrated moderate superficial perivascular neutrophilic inflammation without vasculitis that is characteristic of Schnitzler syndrome (Fig 1B). The patient was started on daily subcutaneous anakinra, a humanized IL-1 receptor antagonist, which resulted in rapid skin clearance that was maintained with anakinra injections 3 times per week. After approximately 18 months of use, anakinra was no longer readily accessible to the patient, and with the discontinuation of this treatment, the patient experienced significant skin flaring with a generalized urticarial eruption. Rituximab was initiated as a result of the accompanying lymphoplasmacytic lymphoma, with weekly intravenous administrations of 375 mg/m^2 for six doses, but skin lesions did not improve. As a result of the lack of a durable treatment option, and given the underlying lymphoplasmacytic lymphoma, the patient was started on treatment with ibrutinib 420 mg by mouth daily. After approximately 2 months of ibrutinib use, the patient noted a moderation of skin involvement, with the slow resolution of existing lesions and fewer new onset lesions. The patient continued to improve and, after 6 months of ibrutinib use, has $<$ 10% of body surface involvement, which is significantly less than his presenting baseline.

Ibrutinib, an irreversible Bruton tyrosine kinase inhibitor, is US Food and Drug Administration–approved for the treatment of Waldenström macroglobulinemia, a rare disorder that is characterized by monoclonal gammopathy and the accumulation of IgM-producing lymphoplasmacytic cells in bone marrow and other organs.[3] In addition, ibrutinib is used for the management of several other B-cell malignancies, including chronic lymphocytic leukemia

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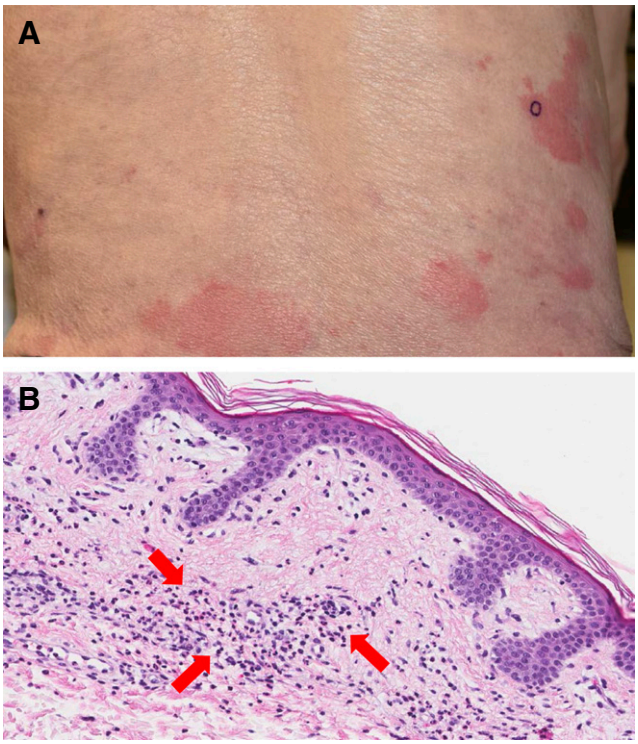

Fig 1. (A) Urticarial rash manifestation of Schnitzler syndrome on the patient's lower back. (B) Characteristic histopathologic features observed in Schnitzler syndrome with prominent superficial perivascular neutrophilic inflammation (marked by arrows). Magnification, ×20.

and non-Hodgkin lymphoma.[4] A recent study established that IL-1β processing and release from immune cells is inhibited in patients who receive ibrutinib therapy.[5] This may explain the observed therapeutic benefit in the case of our patient with Schnitzler syndrome, as anti–IL-1 therapy conventionally induces the rapid clearance of skin lesions with improvement other constitutional symptoms, notably fever and fatigue. Although this patient did not achieve complete clearance or full symptomatic relief, ibrutinib may be a useful treatment option in patients who are unable to receive other biologic agents, including IL-1 inhibitors. JOP

Authors' Disclosures of Potential Conflicts of Interest
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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