Tofacitinib as a novel therapeutic option for refractory Schnitzler's syndrome: a case report

Sir,

A 55-year-old Chinese man presented with recurrent fever up to 39°C in August 2023. Associated symptoms included recurrent pruritic urticaria-like lesions on the extremities and trunk (Fig. 1A), shoulder pain, fatigue, and unintentional weight loss of 2 kg over three months. Investigations showed neutrophilic leucocytosis, CRP 140 mg/L, ESR 108 mm/h, IL-6 9.0 pg/mL and ferritin 500 ng/mL, while procalcitonin was normal. Autoimmune serologies, including ANA, ANCA, RF, anti-CCP, ASO, and IgG4, were negative. An elevated IgM level of 6.42 g/L (normal: 0.3–2.2 g/L) was noted, with normal IgG and IgA level. Comprehensive infectious workup and serum tumour markers returned negative. PET/CT showed increased bone density in the bilateral sternoclavicular joints without elevated FDG uptake, along with reactive hyperplasia of bilateral inguinal lymph nodes. Bone marrow biopsy revealed active proliferation without evidence of lymphoproliferative malignancy. Whole-exome sequencing of blood detected no pathogenic germline variants. Histopathology of a skin biopsy from a back lesion showed perivascular infiltration of lymphocytes and neutrophils, consistent with chronic urticaria. A provisional diagnosis of SAPHO syndrome was made. The patient was started on regular NSAIDs, leading to partial symptomatic improvement: CRP decreased, and fever and pain resolved, although the urticarial rash continued to recur.

By June 2024, the patient experienced recurrent shoulder pain, with CRP rising to 85 mg/L and ESR to 107 mm/h. MRI of the right shoulder demonstrated multiple bone marrow oedema sites in the humerus, clavicle and scapula. Serum protein electrophoresis revealed an M protein, identified as IgM-κ type. This constellation of findings was most consistent with Schnitzler's syndrome (SchS), meeting two obligate and four minor criteria of the Strasbourg criteria: chronic urticarial rash, monoclonal IgM gammopathy, recurrent fever >38°C, elevated CRP >30 mg/L, bone pain with radiographic evidence of remodelling, and neutrophilic dermal infiltration on biopsy. The diagnosis was therefore revised to SchS.

The patient initially received intravenous tocilizumab (an IL-6 inhibitor) 80 mg, a reduced dose, due to his financial constraints. While CRP and ESR decreased within two

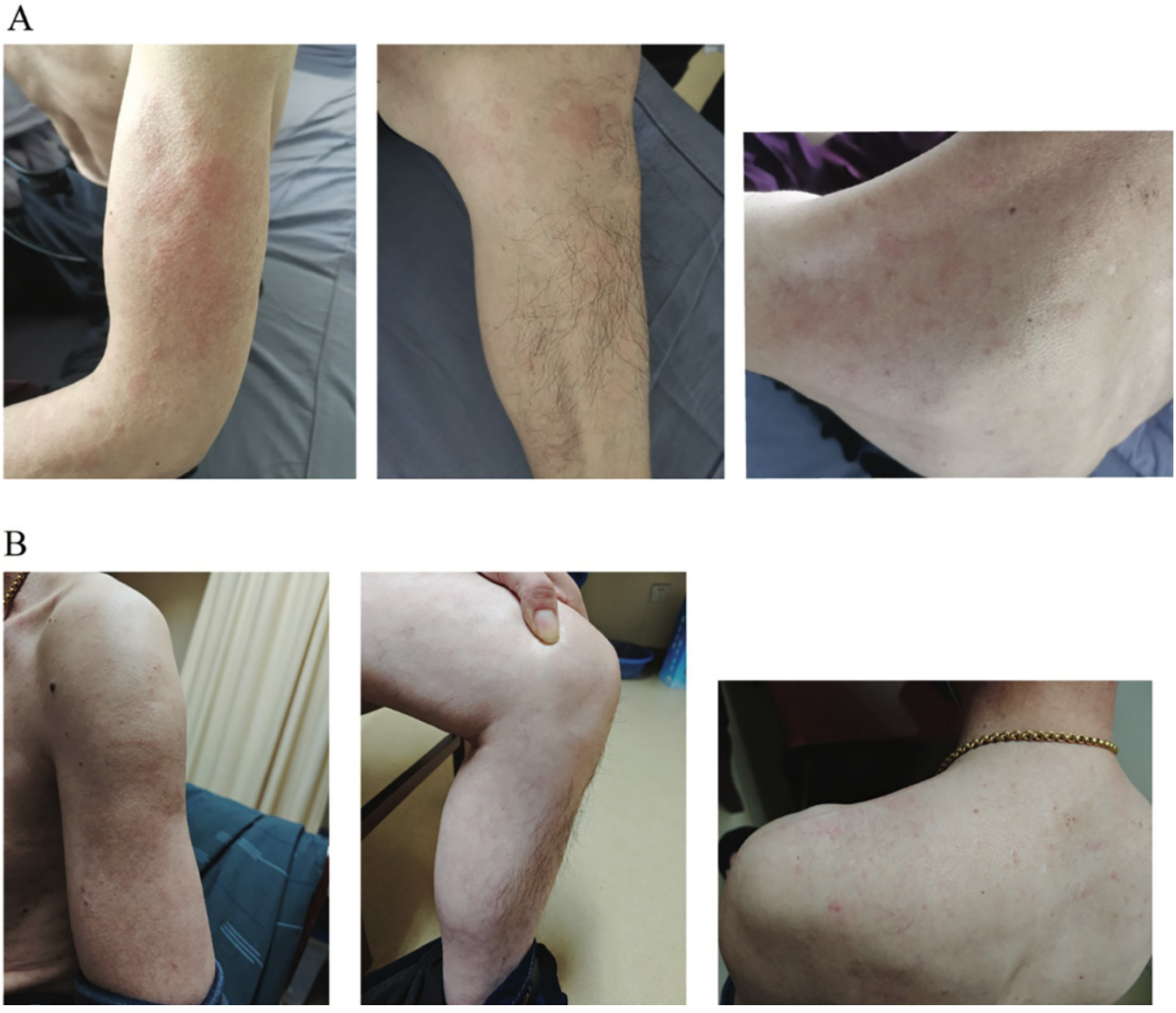

Fig. 1. Clinical presentation of urticarial lesions on the left arm, left leg, and trunk before (**A**) and after (**B**) treatment.

weeks, fever, shoulder pain, and rash recurred. One month after the first dose, he was given 320 mg tocilizumab. However, rash recurrence prompted him to switch treatments. He was started on oral prednisone 30 mg daily and tofacitinib 5 mg twice daily. His symptoms gradually improved, and CRP levels declined. However, when prednisone was tapered to 12.5 mg daily, the rash relapsed mildly, and IgM remained elevated at 12.9 g/L. Methotrexate 10 mg weekly was added at that point. After three months, the urticaria resolved, but IgM levels remained high and inflammatory markers fluctuated. Methotrexate was discontinued and replaced with colchicine 1 mg daily. At the most recent follow-up, the patient is in good general condition with no fever, shoulder pain, or new rash (Fig. 1B). He is maintained on prednisone 5 mg daily, colchicine 1 mg daily, and tofacitinib 5 mg twice daily. Laboratory studies showed CRP 0.79 mg/L, ESR 36 mm/h, and IgM 9.65 g/L.

SchS is a rare acquired autoinflammatory disorder, characterised by chronic urticarial rash associated with an IgM monoclonal gammopathy. To date, only approximately 700 cases have been reported (1). IL-1 inhibitors are considered first-line treatments for SchS (2). The patient was subsequently treated with tofacitinib, a Janus kinase (JAK) inhibitor. There are limited reports on the use of JAK inhibitors in SchS (3).

In summary, we report a case of SchS with an initial diagnostic delay. During treatment, the patient's rash proved recalcitrant and recurred during corticosteroid tapering but eventually responded to a combination of a JAK inhibitor and colchicine. Besides IL-1 and IL-6 inhibitors, JAK inhibitors and colchicine may represent alternative therapeutic options.

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