Clinical features, treatment and long-term outcomes of Schnitzler syndrome: a report from China

Dear Editors,

Schnitzler syndrome (SchS) is a rare acquired autoinflammatory disorder characterised by chronic urticarial rash, monoclonal gammopathy and systemic inflammation, diagnosed by the Strasbourg criteria (1). Most reported cohorts are European; data from China are scarce, and the prolonged unavailability of interleukin-1 (IL-1) inhibitors has restricted access to first-line therapy. We report eight consecutive patients fulfilling these criteria at Peking Union Medical College Hospital (2018-2025), the largest Chinese series to date.

The study has been approved by the Institutional Review Board of Peking Union Medical College Hospital. All methods followed the principles outlined in the Declaration of Helsinki for human. Written and informed consent was obtained from all participants.

Demographic, clinical, laboratory, treatment and outcome data were retrieved retrospectively from the medical records. Genetic testing was performed by whole-exome sequencing (WES) of genomic DNA from peripheral blood (n=4) or bone marrow (n=2). Treatment response was assessed at each follow-up visit, usually at six-month intervals, and categorized as complete, partial, or no response based on clinical remission and normalization of inflammatory markers by more than 80%, 20–80%, or less than 20%, respectively.

All eight patients were Han Chinese and seven were male. Median age at onset was 52 years and median diagnostic delay 5.5 years. All had chronic urticaria; fever occurred in seven, arthralgia or bone pain in seven, lymphadenopathy in five and hearing loss in one. In four patients, fever developed a median of 2 years after rash onset. All had leukocytosis and raised inflammatory markers (median CRP 119 mg/L, ESR 95 mm/h). Monoclonal gammopathy was IgM-κ in seven and IgM-λ in one. Neutrophilic urticarial dermatosis was demonstrated in five patients and bone-imaging abnormalities in six. One patient carried an *NLRP3* c.386A>G variant of uncertain significance; none of the six patients tested carried *MYD88 L265P*, reported in approximately 30% of patients with SchS (2). Only one patient received an IL-1 inhibitor (canakinumab, obtained overseas) and achieved complete remission; four received tocilizumab with partial responses. Conventional agents and off-label Janus kinase (JAK) or Bruton tyrosine kinase (BTK) inhibitors gave partial benefit only (Table I). Over a mean follow-up of 14 months (range 3–24), one patient developed Waldenström macroglobulinaemia (WM).

Within the limits of a small, single-centre series, our patients showed a male predominance (7:1) and exclusively IgM gammopathy, more pronounced than in Western cohorts (male-to-female ratio 1.2–1.8:1; IgG in 7–15%) (3, 4). This may reflect the small sample and referral bias rather than true ethnic variation and requires confirmation in larger cohorts. The absence of *MYD88 L265P* warrants particular caution: only six patients were tested, not including the one who developed WM, and the mutation in SchS is largely B-cell-restricted and, without B-cell enrichment, is readily missed by WES, whereas the reported prevalence of around 30% derives from targeted allele-specific PCR with a sensitivity of about 1% (2). Our negative result therefore probably reflects assay sensitivity rather than true absence, and targeted allele-specific or droplet-digital PCR on purified B cells would be preferable in future studies.

The most striking finding is the treatment gap: only one of eight patients received IL-1 blockade, far below utilisation in Western practice (5), reflecting drug availability rather than clinical indication. Where IL-1 inhibitors were inaccessible, IL-6 blockade (6) and JAK or BTK inhibitors (7, 8) achieved partial control only, consistent with previous Chinese reports (9). The short follow-up also limits assessment of long-term complications: SchS carries an estimated 15% 10-year risk of WM, a 15–20% risk of haematological malignancy and a risk of AA amyloidosis (10). These outcomes cannot yet be captured here and mandate prolonged surveillance.

In conclusion, this Chinese series confirms the classic SchS phenotype while exposing a critical shortfall in access to first-line IL-1 inhibitors. Expanded access, evaluation of alternatives such as IL-6, JAK and BTK inhibitors, comprehensive genetic testing and long-term monitoring are urgently needed.

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Table I. Genetic, therapeutic and outcome data of eight patients with Schnitzler syndrome.

Pt	Sex/age at onset (y)	Delay (y)	M-protein	Genetic testing	Key clinical features	Post-diagnosis targeted therapy (dose)	Follow-up (mo.)	Response
1	M/55	11	IgM-κ	WES (blood): negative	Rash, fever, LN, hearing loss	Tocilizumab 400 mg q4w + prednisone + MTX	18	Partial
2	M/53	5	IgM-λ	WES (blood): negative	Rash, fever, arthralgia, LN	Tocilizumab 560 mg q4w + prednisone + HCQ → canakinumab 150 mg q8w	24	Complete
3	F/35	5	IgM-κ	WES (blood): negative	Rash, fever, arthralgia	Prednisone + Tripterygium wilfordii glycosides	17	Partial
4	M/52	7	IgM-κ	WES (bone marrow): negative	Rash, fever, arthralgia, LN	Tocilizumab 400 mg q4w + prednisone + colchicine + tofacitinib + HCQ	18	Partial
5	M/44	1	IgM-κ	Not performed	Rash, fever, arthralgia, LN	Zanubrutinib + prednisone + thalidomide	6	Partial
6	M/60	6	IgM-κ	WES (bone marrow): negative	Rash, fever, arthralgia, LN	Tofacitinib + prednisone + colchicine + thalidomide	3	Partial
7	M/54	8	IgM-κ	Not performed	Rash, arthralgia; developed WM during follow-up	Prednisone + Tripterygium wilfordii glycosides	10	Partial
8	M/62	0.1	IgM-κ	WES (blood): *NLRP3* c.386A>G (VUS)	Rash, fever, arthralgia	Tocilizumab 400 mg, irregular intervals + prednisone	16	Partial

Pt: patient; y: years; LN: lymphadenopathy; WES: whole-exome sequencing; VUS: variant of uncertain significance; MTX: methotrexate; HCQ: hydroxychloroquine; WM: Waldenström macroglobulinaemia; q4w/q8w: every 4/8 weeks.

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