

## Resolution of Schnitzler's syndrome after haematopoietic stem cell transplantation

Sirs,

Schnitzler's syndrome (SS) is a rare multifactorial adult-onset autoinflammatory disorder. Patients with SS are characterised by fever episodes, urticarial skin rash, severe arthralgia, monoclonal gammopathy along with highly increased inflammatory markers possibly leading to AA amyloidosis as long-term complication. An overt lymphoproliferation occurs in about 15% of patients over time (1, 2). Since no diagnostic biomarkers are currently available, diagnosis is based on the fulfillment of clinical criteria proposed by Simon and colleagues in 2013 (Strasburg criteria) (1).

Patients should be treated with glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and antihistamine drugs; conventional disease-modifying anti-rheumatic drugs (cDMARDs) may be used as steroid sparing agents or in severe cases. More recently, the interleukin (IL)-1 receptor antagonist anakinra and the monoclonal IL-1 $\beta$  inhibitor canakinumab have proved to be highly effective in controlling both clinical and laboratory inflammatory manifestations in SS (3, 4). Conversely, the role of the anti-IL-6 agent tocilizumab is contradictory (5).

To date, no data are available on haematopoietic stem cell transplantation (HSCT) in SS patients. In this regard, we report herein the first case of SS experiencing complete disease remission after HSCT.

A 56-year-old Caucasian female was admitted to our Unit for a history of prolonged fever episodes (up to 39°C) with chronic urticarial rash, arthralgia and bone pain. Laboratory investigations showed increased inflammatory markers, including erythrocyte sedimentation rate (88 mm/1h) and C-reactive protein (CRP, 4.3 mg/dl), elevated white cell count and a monoclonal IgM gammopathy. No evidences of autoimmunity, infections and solid neoplasms had been identified. Conversely, superficial dermal infiltrate with perivascular and interstitial lymphocytes, neutrophils and eosinophils was observed on skin biopsy. These findings are part of the heterogeneous histopathological spectrum identified in urticarial lesions from patients with SS, which may range from mild perivascular inflammation to leukocytoclastic vasculitis, while skin infiltrates may vary depending on the age and dynamic evolution of skin lesions (6, 7). Therefore, based on the fulfillment of the Strasburg criteria (1), diagnosis of SS was made. Subsequently, the patient was

treated with antihistamines, NSAIDs and low-dose corticosteroids for a 2-year period of disease activity. This treatment approach allowed a satisfactory disease control despite occasional exacerbations dealt with a temporary increase in corticosteroid dosage (up to 50 mg/die prednisone or equivalent). Haematological assessment performed during follow-up included a bone marrow biopsy that showed osteomyelosclerosis and severe marrow cavity sclerosis; the cellularity, where assessable, was characterised by elements of the erythrocyte series, megakaryocytes, neutrophils, lymphocytes, and plasma cells. Molecular analysis identified Jak-2 positivity, while cytogenetic assessment highlighted a complex karyotype corresponding to a 47 XX +9 and a 47 XX der(7)t(1;7). Due to the haematological picture, the patient underwent allogeneic peripheral HSCT from a HLA-matched related donor after reduced intensity conditioning with thiotepa, fludarabine and busulfan. The patient received 5.9 x 10<sup>6</sup> CD34+ stem cells/Kg bodyweight and a total of 1.43 x 10<sup>8</sup> CD3+ cells/kg bodyweight.

Soon after HSCT, the patient no longer complained of fever and urticarial skin rash. Likewise, inflammatory markers significantly reduced. A few months after HSCT, the patient started cyclosporine 2.5 mg/kg/day because of chronic graft versus host disease for a 6-month period. During a 12-month follow-up from cyclosporine discontinuation and from 48 months from HSCT the patient did not show any clinical sign of disease activity. Moreover, laboratory workout revealed the disappearance of the previous gammopathy with polyclonal normal serum immunoglobulins and persistently decreased circulating markers of inflammation.

During the last decade, HSCT has been increasingly suggested for treating patients with autoimmune disorders, especially for rapidly progressive systemic sclerosis at risk of organ failure (8, 9). Among autoinflammatory diseases, HSCT has been proposed as curative therapeutic option for patients with deficiency of adenosine deaminase 2 and Behçet's syndrome (10, 11). Accordingly, the present case report suggest that HSCT may be a successful treatment option also in patients with SS, thus widening the number of autoinflammatory conditions potentially responsive to such therapeutic approach.

In conclusion, HSCT may represent a promising treatment opportunity for SS patients, especially when an accompanying haematological condition leads to transplantation or in case of patients refractory to current therapeutic strategies.

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