

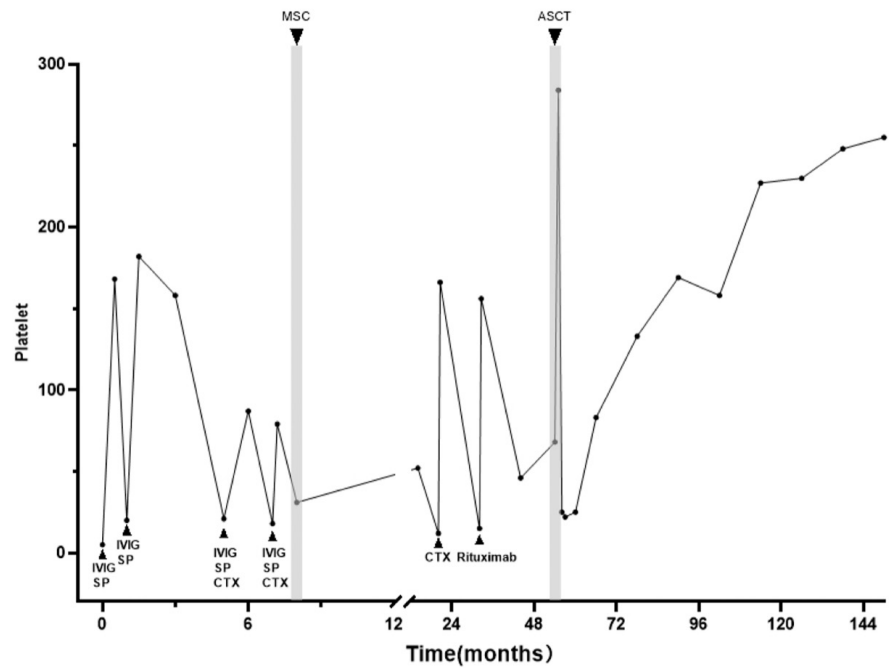
**Autologous haematopoietic stem cell transplantation for primary Sjögren’s syndrome with severe refractory thrombocytopenia: a case report**

Sirs,

Primary Sjögren’s syndrome (pSS) is a chronic systemic autoimmune disease characterised by inflammation of exocrine glands and functional impairment of the salivary and lacrimal glands, resulting in xerostomia and xerophthalmia. Thrombocytopenia occurs in approximately 8% of patients with pSS (1). Currently, managing patients with severe, refractory systemic disease remains a significant challenge, despite the utilisation of systemic therapy, including the sequential or combined administration of glucocorticoids, immunosuppressive agents, and biologic agents like CD20 monoclonal antibody (2). Autologous haematopoietic stem cell transplantation (ASCT) has emerged as a promising therapy for various autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, and systemic sclerosis, but its effectiveness in treating pSS remains uncertain. Herein, we present the case of a patient with severe refractory thrombocytopenia secondary to pSS, who show unsatisfactory response to conventional therapy and umbilical cord blood mesenchymal stem cells (UCMSCs), but achieved successful treatment through ASCT.

In 2009, a 40-year-old woman presented with various symptoms, including an extremely dry mouth, dysphagia, photophobia, arthralgia, and gingival bleeding. Laboratory investigations revealed thrombocytopenia ( $5 \times 10^9/L$ ), positive anti-nucleic antibodies (ANA), positive anti-SSA antibodies, positive parotid sialography, and a lower lip biopsy indicating a focus score of 1 per  $4 \text{ mm}^2$  of glandular tissue (3). The Schirmer test showed 0 mm/5min in the right eye and 1mm/5min in the left eye. Bone marrow aspiration revealed a significant increase in the number of megakaryocytes (46 per slide). After ruling out other potential causes of thrombocytopenia such as haematological disorders, other autoimmune diseases, hypersplenism, viral infections, and drug-induced thrombocytopenia, the patient was diagnosed with pSS with severe thrombocytopenia according to the 2002 American and European Consensus Group (AECG) criteria (3). Despite receiving glucocorticoid pulse therapy, gamma globulin therapy (20g/d for 5 days), immunosuppressants (including cyclophosphamide (CTX) and cyclosporine), and rituximab repeatedly, the patient failed to achieve sustained remission. The platelet count fluctuated between  $10 \times 10^9/L$  and  $70 \times 10^9/L$ .

In June 2010, the patient underwent UCMSCs transfusion. However, in the following



**Fig. 1.** Changes in platelet count over the follow-up period from the date of diagnosis. MSC: mesenchymal stem cell; ASCT: autologous haematopoietic stem cell transplantation; IVIG: intravenous immunoglobulin; SP: steroid pulse therapy; CTX: cyclophosphamide.

three years, the platelet count continued to fluctuate between  $50 \times 10^9/L$  and  $70 \times 10^9/L$ , occasionally dropping below  $20 \times 10^9/L$ . The patient experienced persistent symptoms such as fatigue, dry mouth, and arthralgia. Meanwhile, previous treatments had not yielded satisfactory results. There was no significant decrease observed in the EULAR Sjögren’s Syndrome Disease Activity Index (ESSDAI) and EULAR Sjögren’s Syndrome Patient Reported Index (ESSPRI). The patient has received a cumulative amount of 25g CTX.

In April 2014, the patient underwent an ASCT. Prior to the transplant, she received intravenous ifosfamide (5g) and etoposide (0.2g) for three days as a mobilisation regimen, followed by collecting and freezing blood cells. The pretransplant conditioning regimen involved intravenous administration of CTX (1g) and cytarabine (Ara-C) (1g) on days -2 and -1. On day 0, the frozen blood cells were defrosted and infused.

After undergoing ASCT in 2014, the patient’s lymphocyte subsets and platelet counts returned to normal after 2 years of transplantation and this normalisation remained consistent throughout the 5-year follow-up period. Consequently, the patient’s symptoms of fatigue, dry mouth, and joint pain resolved, and the ESSDAI and ESSPRI scores declined to 0 after 2 years post-transplant. Additionally, we found that the presence of anti-SSA antibodies and ANA persisted throughout the follow-up period. No adverse reactions occurred during the treatment, and the use of glucocorticoids was ceased in April 2019. As of January 2023, there has been no recurrence of symptoms.

The pathogenesis of thrombocytopenia secondary to pSS is not fully understood. The main reason for thrombocytopenia in pSS is likely attributed to increased peripheral platelet destruction involving antiplatelet antibodies and immune complex-mediated mechanisms (4-6). Thrombocytopenia secondary to pSS is a challenging issue and is usually associated with a poor prognosis, especially in patients with bone marrow megakaryocytes  $\leq 6.5$  per slide (7). However, in our case, active hyperplasia of megakaryocytes in the bone marrow before ASCT contradicts this conclusion, thereby further prospective studies are needed to explore other predictors of treatment response to pSS with severe refractory thrombocytopenia.

In recent years, mesenchymal stem cells (MSCs) have shown potential in treating pSS, owing to their immunomodulatory effects on activated lymphoid cells, including T cells, B cells, natural killer cells, and dendritic cells. Specifically, MSCs promote the development of CD4 T cells that favour T regulatory (Treg) and Th2 responses while simultaneously inhibiting Th17 and Tfh inflammatory responses and maintaining the differentiation and suppressive function of Treg cells (8). Xu’s study demonstrated that patients with pSS, even those who had a poor response to glucocorticoids and immunosuppressants (with a mean disease duration of  $76.7 \pm 82.5$  months), could still derive benefits from MSCs therapy (9). However, there are still some patients who do not respond to MSCs therapy, which remains a challenging issue and is often associated with poor outcomes.

ASCT is considered an alternative therapeutic option for autoimmune diseases due to its ability to deplete inflammatory and auto-reactive T and B cells. The *de novo* generation of naive T cells induced by ASCT can also lead to immune tolerance to autoantigens through immune system reconstruction (10, 11). Our study shows that ASCT yielded remarkable clinical and serologic improvements in patients with refractory and severe thrombocytopenia secondary to pSS who did not respond well to other treatments, including glucocorticoids, gamma globulin, immunosuppressants, rituximab, and UCM-SCs. Specifically, patients showed normal platelet counts and decreased ESSDAI and ESSPRI scores at 1-year post-transplant. At 24 months after ASCT, the patient exhibited a normal lymphocyte count with normal lymphocyte subsets, which may be attributed to the increase in Treg cells and functional recovery. However, since our study did not monitor Treg cell levels, further verification is necessary to confirm this correlation. Additionally, previous research has suggested that MSCs can improve the therapeutic effect of ASCT (12). Therefore, we cannot determine whether the observed effect is solely attributed to ASCT or the amalgamation of stem cell therapy. Antithymocyte globulin (ATG) has traditionally been recommended for transplantation in rheumatic diseases due to its ability to deplete T-cells. However, its use has also been linked to a high risk of treatment-related mortality. In our study, we opted for a conditioning regimen consisting of Ara-c and CTX, which we found to be effective in rebuilding the immune system by depleting T cells, B cells, and NK cells after transplantation. This approach offers a potential alternative to ATG for patients with refractory and severe thrombocytopenia secondary to pSS, offering a potentially safer and more efficacious treatment option.

In conclusion, this study represents the first reported case of using ASCT to treat a patient with pSS complicated with thrombocytopenia and provides evidence of profound regeneration of the adaptive immune system after transplantation. Although it cannot be definitively inferred that the efficacy is solely due to ASCT, our findings suggest that this therapy is safe and effective in achieving remission and even curing the disease. Further research is warranted to compare the effectiveness of ASCT alone *versus* the combination of MSCs, and to validate these findings in larger series.

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