Letters to the Editors

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 (5x10^9/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 4mm² 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 10x10^9/L and 70x10^9/L.

In June 2010, the patient underwent UCMS Cs transfusion. However, in the following three years, the platelet count continued to fluctuate between 50x10^9/L and 70x10^9/L, occasionally dropping below 20x10^9/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 EU LAR 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 ≤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 Th1 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±25.5 months), could still derive benefits from MSCs therapy(9). However, there are still some patients who...
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do not respond to MSCs therapy, which re-
mains a challenging issue and is often as-
associated with poor outcomes.

ASCT is considered an alternative thera-
peutic 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 ref-
fractory and severe thrombocytopenia sec-
ondary to pSS who did not respond well to
other treatments, including glucocorticoids,
gamma globulin, immunosuppressants,
rituximab, and UCMSCs. Specifically, pa-
tients 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 lym-
phocyte count with normal lymphocyte
subsets, which may be attributed to the in-
crease in Treg cells and functional recovery.
However, since our study did not monitor
Treg cell levels, further verification is nec-
essary to confirm this correlation. Addi-
tionally, previous research has suggested that
MSCs can improve the therapeutic effect of
ASCT (12). Therefore, we cannot deter-
mine whether the observed effect is solely
attributed to ASCT or the amalgamation of
stem cell therapy.

Antithymocyte globulin (ATG) has tradi-
tionally been recommended for transplanta-
tion in rheumatic diseases due to its ability
to deplete T-cells. However, its use has also
been linked to a high risk of treatment-re-
lated 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 trans-
plantation. This approach offers a potential
alternative to ATG for patients with refrac-
tory and severe thrombocytopenia second-
ary 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 throm-
boctopenia and provides evidence of pro-
found regeneration of the adaptive immune
system after transplantation. Although it
cannot be definitively inferred that the ef-
ficacy is solely due to ASCT, our findings
suggest that this therapy is safe and effec-
tive 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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References
1. TSUKAMOTO M, SUZUKI K, TAKEUCHI T: Ten-
year observation of patients with primary Sjögren’s
syndrome: Initial presenting characteristics and the
929-33. https://doi.org/10.1111/1756-185X.13464
2. MARIETTE X, BARONE F, BALDINI C et al.: A ran-
donized, phase II study of sequential belimumab
and rituximab in primary Sjögren’s syndrome. JCI
Insight 2022; 7(23): e163030.
https://doi.org/10.1172/jci.insight.163030
3. VITALI C, BOMBARDIERI S, JONSSON K et al.: Classi-
fication criteria for Sjögren’s syndrome: a
revised version of the European criteria proposed
by the American-European Consensus Group. Ann
https://doi.org/10.1136/ard.61.6.554
4. CORNEC D, DÉVAUCHELLE-PENSEC V, TORON
GI, PERS JO, JOUSE-JOULIN S, SARAUX A: B
cells in Sjögren’s syndrome: from pathophysi-
ology to diagnosis and treatment. J Autoimmun 2012;
https://doi.org/10.1016/j.jaut.2012.05.014
5. LIU Y, CHEN S, SUN Y et al.: Clinical character-
istics of immune thrombocytopenia associated with
autoimmune disease: A retrospective study. Medi-
cine (Baltimore) 2016; 95(50): e5565.
https://doi.org/10.1097/MD.0000000000005565
6. VRIENSKY JR, NAZY I, CLARE R, LARCHE M,
ARNOLD DM: T cell-mediated autoimmunity in
immune thrombocytopenia. Eur J Haematol 2022;
7. ZHONG H, XUE Y, ZHANG L et al.: Predictive value
of bone marrow megakaryocyte count for immuno-
therapy responsive in primary Sjögren’s syndrome
patients with severe immune thrombocytopenia:
A single-center case-control study in China. Int J
https://doi.org/10.1111/1756-185x.14707
8. MANFRE V, CHATZIS LG, CAFARO G et al.: Sjögren’s
syndrome: one year in review 2022. Clin Exp Rheu-
https://doi.org/10.55563/clinexp rheumatol/43z8gu
9. XU J, WANG D, LIU D et al.: Allogeneic mesenchy-
mal stem cell treatment alleviates experimental and
clinical Sjögren syndrome. Blood 2012; 120(15):
3142-51.
https://doi.org/10.1182/blood-2011-11-391144
10. SNOWDEN JA, BADOGlio M, ALEXANDER T: The
rise of autologous HCT for autoimmune dis-
eseases: what is behind it and what does it mean for
the future of treatment? An update on behalf of the
EBMT Autoimmune Diseases Working Party. Ex-
https://doi.org/10.1080/1744666X.2019.1656526
11. TYNDALL A, GRATWOHL A: Haemopoietic stem
and progenitor cells in the treatment of severe au-
149-51. https://doi.org/10.1136/ ard.55.3.149
12. LIU RH, LI YQ, ZHOU WJ, SHI YJ, NI L, LIU GX:
Supplementing mesenchymal stem cells improves
the therapeutic effect of hematopoietic stem cell
transplantation in the treatment of murine systemic
lupus erythematosus. Transplant Proc 2014; 46(5):
1621-7.
https://doi.org/10.1016/j.transproceed.2014.03.003