Complete clinical and serological remission of anti-synthetase syndrome after autologous haematopoietic stem cell transplantation

Sirs,

Anti-synthetase syndrome (ASS) is a chronic, rare, systemic autoimmune rheumatic disease. It is typically characterised by the presence of autoantibodies against different aminoacyl-transfer RNA synthetase (ARS), along with a range of clinical manifestations, including arthritis, myositis, skin involvement, and interstitial lung disease (ILD), among others (1). Management of ASS is often challenging due to disease heterogeneity, limited scientific evidence for treatment, and the lack of standardised guidelines (2). Long-term treatment is generally required. Severe cases carry an uncertain prognosis, although stabilisation or improvement is achievable. ILD progression is the main prognostic factor, occurring in up to 20% of cases despite treatment, particularly in patients with non-anti-Jo-1 autoantibodies.

We report the case of a patient with ASS who achieved drug-free remission and seroconversion following autologous haematopoietic stem cell transplantation (HSCT) for multiple myeloma.

A 59-year-old woman was referred to our rheumatology department in March 2023. At that time, she reported a long-standing history of recurrent (3-4 per year) episodes of fever and joint pain with swelling affecting hands, wrists and knees, and general malaise. Prior to our assessment, she had been diagnosed with seronegative undifferentiated arthritis and was being treated with oral methotrexate (10 mg weekly).

Upon re-evaluation**,** the patient reported that the last episode of polyarthritis and fever had occurred two months before. Physical examination revealed joint pain in the hands and wrists, but no swelling, and no skin involvement, or muscle weakness. Blood tests showed normal muscle enzyme levels and a positive cytoplasmic dense fine speckled pattern (AC19) (titre 1:160) by indirect immunofluorescence on HEp-2 cells, with positivity for anti-Ro52 and anti-PL12 autoantibodies. Anti-PL12 autoantibodies were confirmed by line- and dot-blot from two different manufacturers (Fig. 1). x-rays of the hands and feet revealed no erosions. Pulmonary function tests were normal, and high-resolution computed tomography (HRCT) of the chest showed limited ILD with a non-specific interstitial pneumonia pattern.

At the same time, the patient was diagnosed with IgA kappa oligosecretory multiple myeloma, ISS stage 1, R-ISS stage 2, with a TP53 gene deletion. In June 2023, treatment with D-VRD (daratumumab, bortezomib, lenalidomide, and dexamethasone) was initiated. After seven cycles, complete remission was achieved, although minimal residual disease persisted. Autologous haematopoietic stem cell transplantation

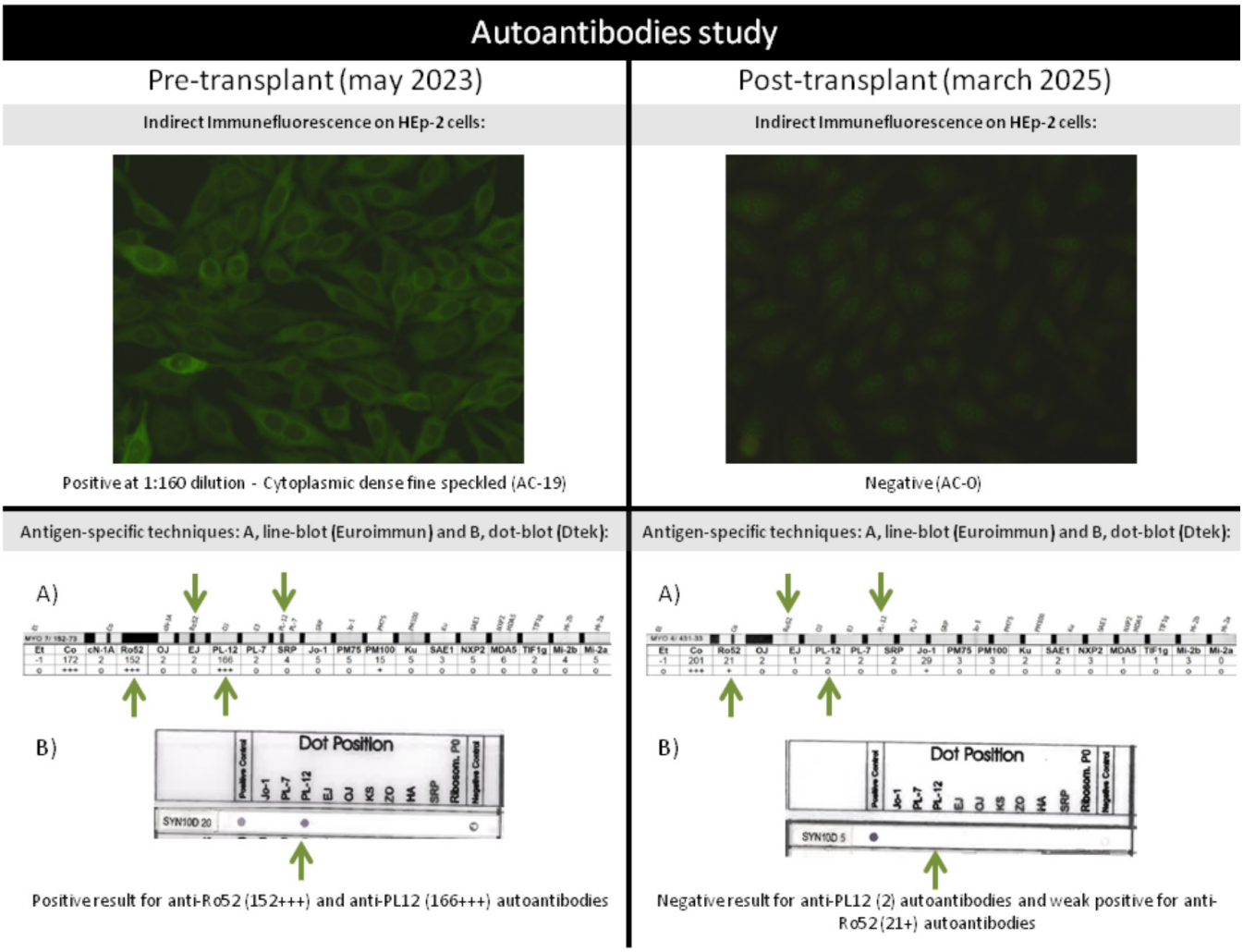

Fig. 1. Autoantibodies study before and after autologous haematopoietic stem cell transplantation.
The upper panel shows image of indirect immunofluorescence on Hep-2 cells pretransplant on May 2023 and post-transplant in March 2025. It can be seen on pre-transplant a positive result at 1:160 dilution, with a cytoplasmatic dense fine and speckled pattern, that is negative post-treatment. In lower-cases line-blot and dot-blot pre- and post-transplant are showed. Pre-treatment high positivity for anti-Ro52 and antiPL12 is detected and post-transplant these autoantibodies are negative.

(HSCT) with melphalan (200 mg/m²) conditioning was performed in February and June 2024, resulting in complete remission with no detectable minimal residual disease (<0.00023%). Maintenance therapy with lenalidomide and dexamethasone was started in October 2024.

The patient was regularly followed up by rheumatology throughout treatment for multiple myeloma. She remained asymptomatic with regard to ASS. Nine months after HSCT, repeat autoantibody testing showed negativisation of anti-Ro52 and anti-PL12 autoantibodies (Fig. 1), and follow-up HRCT showed no progression of ILD. At the last follow-up in July 2025, the patient still remained asymptomatic, reported no episodes of arthritis or other symptoms, physical examination revealed no signs of active disease.

ASS is a rare disorder characterised by immune-mediated organ damage. Its clinical presentation typically includes a triad of myositis, ILD, and arthritis, which may not be fully present at disease onset and can evolve over time (1). Despite therapeutic advances, treatment remains challenging, mainly due to clinical heterogeneity and unpredictable treatment responses (2).

There is growing evidence that B cells and autoantibodies play a central role in ASS pathogenesis (3). In line with this, B-cell-depleting therapy using the anti-CD20 monoclonal antibody rituximab has demonstrated efficacy in patients with idiopathic inflammatory myopathies and ASS who are refractory to conventional synthetic disease-modifying anti-rheumatic drugs (4). However, some patients experience refractory disease, potentially due to CD20-negative plasmablasts and plasma cells, or the persistence of CD19- and CD20-positive B cells in lymph nodes despite systemic B-cell depletion (5, 6). This suggests the need for broader and more profound B-cell-targeted therapies in selected patients.

Cell-based therapy with autologous chimeric antigen receptor (CAR) T cells has recently emerged as a promising treatment for autoimmune diseases refractory to conventional therapies, including ASS (7). Moreover, autologous HSCT has been used in various refractory autoimmune diseases, as it can eliminate autoreactive immune cells and regenerate a more tolerant immune system (8). In our case, although HSCT was not indicated for ASS treatment, shortly after it, clinical and serological remission was achieved. Most likely, the negativisation of anti-Ro52 and anti-PL12 autoantibodies reflects an immune reconstitution process induced by autologous HSCT, rather than a direct effect of immunosuppressive therapy, which, even when intensive, rarely leads to such early serological changes. To our knowledge, this is the first published report of ASS responding to this therapy, thereby broadening the range of potential therapeutic options for patients with refractory disease.

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