of microvascular involvement, compared with a classical NVC pattern definition showing longer time to progression between different patterns [7]. In our study we found very low levels of VEGF-A but high levels of E-Selectin and VCAM-1. A plausible explanation of this finding might be the large variability observed in serum levels of these molecules when compared between different studies [3, 6–8]. However, we observed a significant improvement of microvascular involvement achieved with 3 months of HCQ treatment. This is a novel finding in SSc, which could represent a new therapeutic possibility for the prevention of microvascular complications of the disease.

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References

1 Andracco R, Irace R, Zaccara E *et al*. The cumulative number of micro-haemorrhages and micro-thromboses in nailfold videocapillaroscopy is a good indicator of disease activity in systemic sclerosis: a validation study of the NEMO score. Arthritis Res Ther 2017;19:133.

2 Rahman R, Murthi P, Singh H *et al*. The effects of hydroxychloroquine on endothelial dysfunction. Pregnancy Hypertens 2016;6:259–62.

3 Kuryliszyn-Moskal A, Klimiuk PA, Sierakowski S. Soluble adhesion molecules (sVCAM-1, sE-selectin), vascular endothelial growth factor (VEGF) and endothelin-1 in patients with systemic sclerosis: relationship to organ systemic involvement. Clin Rheumatol 2005;24:111–6.

4 Dooley A, Gao B, Bradley N *et al*. Abnormal nitric oxide metabolism in systemic sclerosis: increased levels of nitrated proteins and asymmetric dimethylarginine. Rheumatology (Oxford) 2006;45:676–84.

5 Schreiber K, Breen K, Parmar K *et al*. The effect of hydroxychloroquine on haemostasis, complement, inflammation and angiogenesis in patients with antiphospholipid antibodies. Rheumatology (Oxford) 2018;57:120–4.

6 Cerinic MM, Valentini G, Sorano GG *et al*. Blood coagulation, fibrinolysis, and markers of endothelial dysfunction in systemic sclerosis. Semin Arthritis Rheum 2003;32:285–95.

7 Avouac J, Vallucci M, Smith V *et al*. Correlations between angiogenic factors and capillaroscopic patterns in systemic sclerosis. Arthritis Res Ther 2013;15:R55.

8 Thakkar V, Patterson KA, Stevens W *et al*. Increased serum levels of adhesion molecules ICAM-1 and VCAM-1 in systemic sclerosis are not specific for pulmonary manifestations. Clin Rheumatol 2018;37:1563–71.

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Second autologous haematopoietic stem cell transplantation in systemic sclerosis—a case report

Rheumatology key message

- A second haematopoietic stem cell transplantation (HSCT) with post-HSCT immunosuppression can be considered in SSc relapse after HSCT.

Sir, Autologous haematopoietic stem cell transplantation (HSCT) is an effective treatment in patients with progressive diffuse cutaneous systemic sclerosis (dcSSc) [1, 2]. Unfortunately, some patients experience a relapse, which can be managed with conventional immunosuppressants in most cases. In refractory cases a second HSCT may be considered; however, data on safety and efficacy are lacking. Here, we present the case of a dcSSc patient who underwent a second HSCT and discuss our management of the patient in light of current evidence.

A 35-year-old woman with a history of RP for 1 year presented with rapidly progressive skin thickening despite treatment with MMF. Physical examination showed anterior tibial tendon friction rubs and generalized skin involvement with a modified Rodnan skin score of 26. Nailfold capillaroscopy revealed an early scleroderma pattern. Immunology showed a positive ANA, anti-RNP III and anti-SSA-52 autoantibodies. The diagnosis of dcSSc was made. There was no visceral involvement.

Taking into consideration the poor prognosis of this patient (progressive skin involvement, tendon friction rubs) and non-responsiveness to MMF, she was counselled about available treatment options and the decision to perform HSCT was made. Mobilization and pre-transplant conditioning were conducted according to the Autologous Stem Cell Transplantation International Scleroderma Trial protocol [1]. After conditioning with i.v. CYC and rabbit antithymocyte globulin (ATG), 315×10^6 $CD34^+$ cells were infused (5.25×10^6/kg bodyweight). There were no adverse events during the procedure apart from a self-limiting viral respiratory tract infection.

Skin thickening significantly decreased after HSCT (Fig. 1). However, almost 12 months post-HSCT, the patient developed clinical signs of a relapse; the modified Rodnan skin score had increased to 22, and tibial

tendon friction rubs had returned. The patient developed severe itching, which was refractory to standard supportive and pharmacological treatment. Pulmonary function tests were unchanged, but an ECG revealed new onset of a first degree atrioventricular block. MMF, MTX and rituximab were initiated but were not effective.

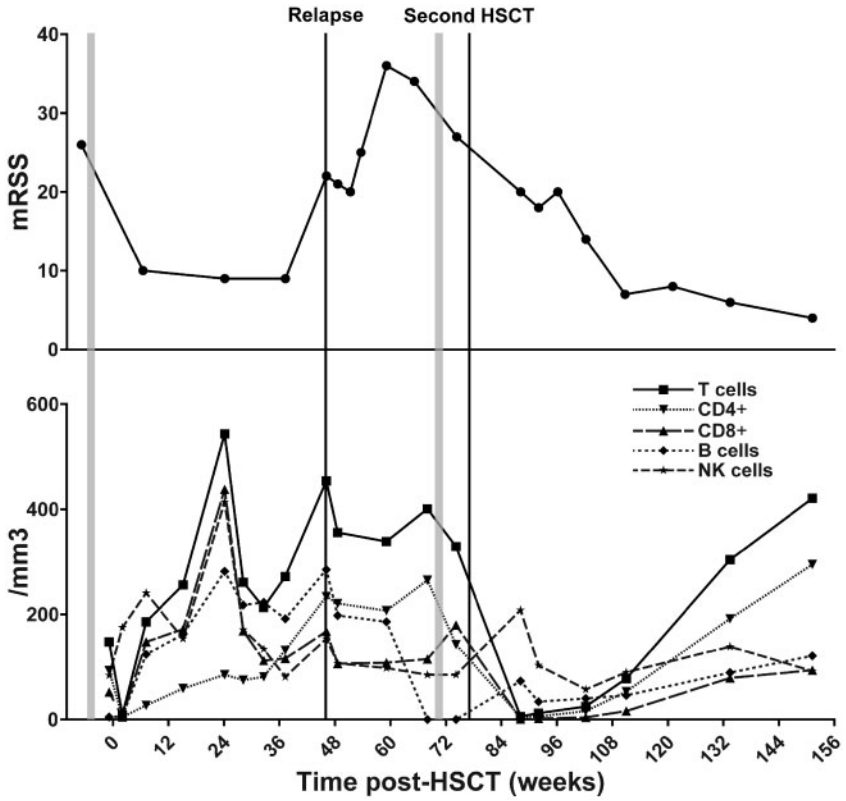
There is little evidence to guide treatment decisions in relapse of SSc after HSCT. Data from clinical trials shows that most relapses can be treated with oral MTX and MMF [1]. Additionally, a small study suggested that rituximab can be used to manage post-HSCT relapse in RA [3]. Unfortunately, neither MTX nor rituximab were effective in our patient.

Given that symptoms recurred with T cell repopulation (see Fig. 1), and the brief but very favourable response on the first HSCT, a second autologous HSCT was considered. Information on both the efficacy and safety of second HSCT is scarce [4]. The European Group for Blood and Marrow Transplantation Working Party on Autoimmune Diseases reports nine second HSCTs, but no clinical outcome data were presented [5]. A single case report described a second HSCT in SSc, which induced clinical remission, but long-term follow-up data on safety was not available [6]. Therefore, we extensively counselled the patient about the possible risks of a second HSCT, which include secondary malignancy and cardiotoxicity as a complication of high-dose CYC administration. Other important considerations were anticipated difficulties with stem cell mobilization, and possible sensitization to ATG. It was decided to start immune suppression with ciclosporin and MMF immediately post-HSCT to maintain T cell suppression after immunological reconstitution.

The second HSCT was initiated at 18 months after the first HSCT, using the same protocol as the first HSCT. The mobilization was uneventful; no changes to the mobilization regimen were needed to harvest the required number of $CD34^+$ cells through leukapheresis. No adverse events occurred during the conditioning. A total of 172×10^6 cells were infused (2.93×10^6/kg bodyweight). During the neutropenic phase after graft infusion, the patient developed an infected digital ulcer complicated with osteomyelitis, which was successfully treated with i.v. antibiotics.

At 18 months after the second HSCT, skin thickening has almost disappeared (modified Rodnan skin score of 4) and no new visceral involvement has occurred. Despite the favourable outcome on these aspects of the disease, the patient still experiences significant disability due to severe RP.

Fig. 1 Immunological reconstitution and the mRSS



The vertical lines denote the start of the relapse and the second HSCT. The grey bars represent mobilization phases. After HSCT, the mRSS rapidly decreased, to increase again at the onset of relapse. This coincided with immunological reconstitution. After the second HSCT, the mRSS remained low, despite reconstitution of the T cell compartment. HSCT: haematopoietic stem cell transplantation; mRSS: modified Rodnan skin score.

The pathophysiology of post-HSCT relapse is unclear, but the temporal relationship of the relapse in our patient with immune reconstitution suggests a relationship with re-emergence of autoreactive clones (Fig. 1). Studies regarding correlations between immunological parameters and relapse after HSCT for dcSSc are conflicting [7]. At baseline, our patient had a positive ANA test (1:100), anti-RNP III antibodies and anti-SSA antibodies. Anti-SSA antibodies disappeared after the first HSCT and remained absent during the relapse, although the ANA test remained weakly positive (granular staining pattern) and RNP III antibodies persist up until now.

In conclusion, our case underscores the potential benefit of a second HSCT with post-HSCT immunosuppression in SSc patients who relapse after HSCT. However, caution should be used regarding possible toxicity and long-term side-effects and a careful screening procedure remains essential, as described by us recently [8]. Ultimately, the decision to perform a second HSCT requires good multidisciplinary support as well as shared decision making with the patient.

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References

1 van Laar JM, Farge D, Sont JK *et al*. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis. JAMA 2014;311:2490–8.

2 Kowal-Bielecka O, Fransen J, Avouac J *et al*. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis 2017;76:1327–39.

3 Moore J, Ma D, Will R *et al*. A phase II study of rituximab in rheumatoid arthritis patients with recurrent disease following haematopoietic stem cell transplantation. Bone Marrow Transplant 2004;34:241–7.

4 Naumann-Winter F, Greb A, Borchmann P *et al*. First-line tandem high-dose chemotherapy and autologous stem cell transplantation versus single high-dose chemotherapy and autologous stem cell transplantation in multiple myeloma, a systematic review of controlled studies. Cochrane Database Syst Rev 2012; Issue 10. Art. No.: CD004626. Doi: 10.1002/14651858.CD004626.pub3.

5 Farge D, Labopin M, Tyndall A *et al*. Autologous hematopoietic stem cell transplantation for autoimmune diseases: an observational study on 12 years' experience from the European Group for Blood and Marrow Transplantation Working Party on Autoimmune Diseases. Haematologica 2010;95:284–92.

6 Hou Y, Li H-J, Li M-T *et al*. A successful case of second autologous haematopoietic stem cell transplantation for post-transplant systemic sclerosis relapse. Clin Exp Rheumatol 2016;34:207.

7 van Rhijn-Brouwer FCC, Spierings J, van Laar JM. Autologous hematopoietic stem cell transplantation in systemic sclerosis: a reset to tolerance? Immunol Lett 2018;195:88–96.

8 Swart JF, Delemarre EM, van Wijk F *et al*. Haematopoietic stem cell transplantation for autoimmune diseases. Nat Rev Rheumatol 2017;13:244–56.

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Successful treatment of refractory mechanic's hands with ustekinumab in a patient with the antisynthetase syndrome

Rheumatology key message

- Ustekinumab may be useful to treat mechanic's hands in patients with the antisynthetase syndrome.

Sir, A 29-year-old non-smoker male presented with a history of progressively worsening arthralgia, arthritis and proximal weakness. He also had hyperkeratotic scaly lesions on his fingers and hands characteristic of mechanic's hands, with no other skin manifestations. Creatine kinase levels were increased and a muscle biopsy revealed an inflammatory myopathy. The patient had no signs of lung involvement and pulmonary function tests were normal. Anti-histidyl-tRNA synthetase (i.e. anti-Jo1) autoantibodies were positive and the patient was diagnosed with the antisynthetase syndrome. Following treatment with mycophenolate and prednisone, the patient's muscle and joint involvement improved and his muscle enzyme levels normalized. However, over the next 3 years, the skin lesions continued to worsen despite treatment with multiple drugs, including corticosteroid ointments, topical tacrolimus, adalimumab and methotrexate (Fig. 1a and b). Given the refractory nature of the mechanic's hands, treatment with subcutaneous ustekinumab was initiated as recommended (45 mg initially and 4 weeks later, followed by 45 mg/12 weeks) with a dramatic improvement of the skin lesions over the following