Autologous hematopoietic stem-cell transplantation in diffuse cutaneous systemic sclerosis: a single-center experience

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Summary

Systemic sclerosis (SSc) is a chronic autoimmune disorder characterized by multisystem involvement. Patients can be stratified into an indolent or rapidly progressive disease course. A progressive course warrants early and more aggressive treatment to prevent irreversible organ damage. Therapeutic strategies should be tailored to the presenting symptoms and organ involvement. Autologous hematopoietic stem cell transplantation (AHSCT) has proven to be an effective treatment modality for specific phenotypes of SSc, especially progressive diffuse cutaneous SSc. However, the optimal timing for the transplantation remains unknown. We present two cases of rapidly progressive diffuse cutaneous SSc (dcSSc) treated with AHSCT following inadequate response to conventional immunosuppressive therapy. While both patients experienced significant cutaneous improvement post-AHSCT, internal organ involvement progressed in one case, ultimately resulting in a fatal outcome due to severe sepsis, whereas the second patient remained clinically stable and without immunosuppressive therapy during long-term follow-up. This report contributes to the growing body of evidence supporting AHSCT as a therapeutic option in carefully selected cases of progressive dcSSc. To our knowledge, our cases are the first successful experiences with this treatment modality in Croatia and among the Slavic populations of the Balkan Peninsula, promoting the need for earlier interventions in patients who develop a progressive disease course, particularly with skin involvement.

Introduction

Systemic sclerosis (SSc) is a complex autoimmune disease characterized by immune dysregulation, vasculopathy, and progressive fibrosis, leading to multi-organ involvement with a heterogeneous clinical presentation. The disease course ranges from mild and slowly progressing to severe, rapidly progressive forms requiring early intervention. Indolent cases permit a gradual treatment approach, whereas rapidly progressive diffuse cutaneous SSc (dcSSc) necessitates prompt and aggressive management upon diagnosis. The initial symptom in most patients is Raynaud's phenomenon, followed by several non-Raynaud symptoms like skin thickening, dysphagia, palpitations, dyspnea, *etc*. (1, 2). Morbidity and mortality in patients with SSc are significantly higher than in the general population, with interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) being the leading causes of death (3, 4). Several high-risk factors for mortality include male sex, elevated C-reactive protein, proteinuria, high modified Rodnan Skin Score (mRSS), cardiac dysfunction, and pulmonary involvement (3, 4). Recent studies emphasize the increased cardiovascular risk in SSc patients, reinforcing the necessity for early assessment and intervention (5).

According to the latest European Alliance of Associations for Rheumatology 2023 recommendations, methotrexate (MTX) may be considered for the treatment of skin manifestations in early diffuse SSc, while autologous hematopoietic stem cell transplantation (AHSCT) is recommended for selected patients with rapidly progressive disease at risk of organ failure. The updated guidelines also emphasize the role of immunosuppressive agents such as mycophenolate mofetil (MMF), rituximab, and tocilizumab for skin fibrosis (6). Although only a limited number of controlled trials on AHSCT have been published, the medical literature continues to grow with an increasing number of case reports and case series. Despite associated risks, AHSCT remains the only disease-modifying therapy in SSc that can offer long-term remission despite being used in refractory and rapidly progressive cases. The aim of our single-center experience was to enhance the knowledge of AHSCT and further refine our understanding of its optimal indications and timing as a high-risk yet highly effective procedure.

Case Report 1

A 19-year-old male presented to our clinic with progressive skin tightening affecting both distal and proximal extremities, accompanied by a 10 kg weight loss over the past year. He exhibited Raynaud's phenomenon and flexion contractures of the fingers. Capillaroscopy revealed an active scleroderma pattern, and serology confirmed the presence of anti-topoisomerase 1 autoantibodies. Based on these findings, he was diagnosed with dcSSc (mRSS 16/51) with pulmonary and esophageal involvement. The patient was initially treated with low-dose prednisone (starting at 10 mg/day, tapered to 7.5 mg/day), hydroxychloroquine (HCQ),

calcium channel blocker (nifedipine 30 mg/day), proton pump inhibitor, D-penicillamine, and MTX (starting at 15 mg/week, increased to 25 mg/week). HCQ was discontinued after 6 months due to lack of efficacy. Due to the rapidly progressive disease, cyclophosphamide therapy (600 mg/m^2/month for six cycles) was initiated on two separate occasions (cumulative dose of 6000 mg), but no clinical or radiological improvement was observed. Pulmonary function tests (PFTs) showed a decline in forced vital capacity (FVC) from 66% to 47% and diffusion capacity for carbon monoxide (DLCO) from 60% to 41% over 12 months, indicating ILD progression. High-resolution computed tomography (HRCT) demonstrated worsening ground-glass opacities and interstitial thickening, consistent with progressive nonspecific interstitial pneumonia (NSIP). As the disease remained refractory, with worsening lung function and increased skin tightness (mRSS 20/51) along with digital ulcers, MMF 1 g twice daily was introduced as a replacement for MTX following foreign expert consultation. However, MMF was discontinued after 9 months due to a lack of significant benefit on skin involvement and continued ILD progression. Given the refractory disease course and poor prognosis, a decision was made to proceed with AHSCT. In January 2017, AHSCT was performed using a conditioning regimen of cyclophosphamide (50 mg/kg during 4 consecutive days) and rabbit anti-thymocyte globulin (ATG) (2.5 mg/kg/daily for 3 days). Twenty days post-transplantation, the patient reported noticeable improvement, including softer skin and increased finger mobility. mRSS improved from 20/51 before transplantation to 10/51. The therapy with low-dose prednisone (10 mg/day) was continued. One year later, capillaroscopy showed a reduction in capillary loss and decreased microhemorrhages. Despite skin improvements, HRCT demonstrated further fibrotic progression of NSIP, with persistent ground-glass opacities and worsening PFTs. FVC declined further to 30% and DLCO to 26%. Following further expert consultation, therapy was intensified with intravenous immunoglobulin (2 g/kg/month) and the endothelin receptor antagonist bosentan. Although MMF therapy had previously been discontinued due to lack of efficacy, it was reintroduced at a dose of 1 g twice daily due to disease progression. Rituximab (2×1000 mg) and nintedanib were also initiated later, as the condition continued to worsen. Additionally, cardiac function deteriorated, with frequent ventricular extrasystoles, occasionally occurring in the bigeminy and trigeminy patterns. Cardiac magnetic resonance (CMR) suggested possible cardiac involvement. Due to significant ventricular ectopic activity, an implantable cardioverter-defibrillator (ICD) was placed for

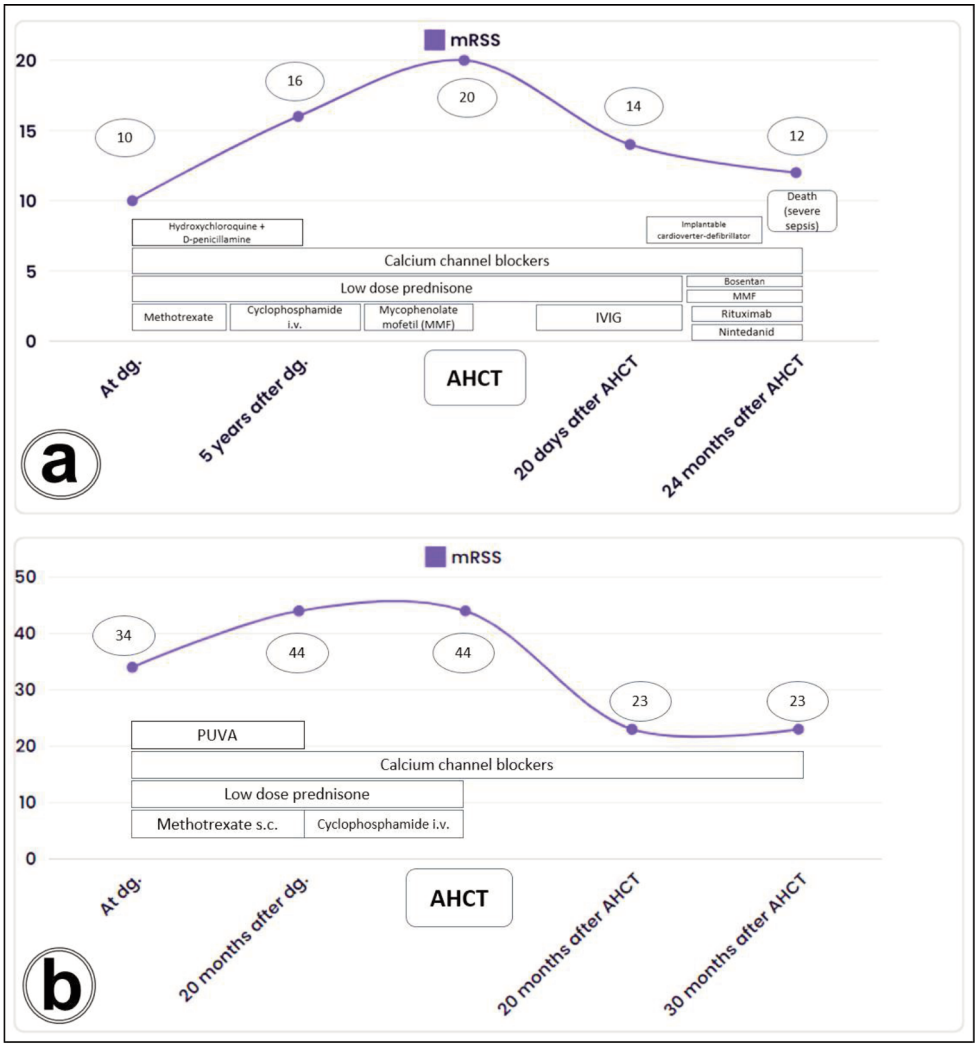

Figure 1. Clinical course and treatment history of patient 1 (**a**) and 2 (**b**). AHCT, autologous hematopoietic stem cell transplantation.

primary prevention of sudden cardiac death. Several months later, the patient developed atrial tachycardia (AT) and ventricular tachycardia, requiring successful AT ablation. Despite aggressive treatment and initial skin improvement, the disease continued to affect pulmonary and cardiac function. The patient ultimately developed severe sepsis, which was the cause of death. The course of the disease is presented in Figure 1.

Case Report 2

A 48-year-old woman with no significant medical history developed Raynaud's phenomenon and progressive skin thickening in her distal extremities. Over 9 months, her skin involvement worsened, prompting hospitalization. She exhibited mild esophageal involvement, presenting with mild pyrosis and no reported dysphagia. She primarily reported a progressive thickening of the skin. Her laboratory results were largely normal, except for positive antinuclear antibody and RNA polymerase III antibodies. Capillaroscopy revealed an active scleroderma pattern, leading to a diagnosis of dcSSC with mRSS of 44/51. HRCT revealed no lung involvement, and she did not report any digital ulcerations. Initial treatment included a calcium channel blocker (amlodipine 5 mg twice daily), low-dose prednisone (5-10 mg/day), subcutaneous MTX (to a maximum dose of 20 mg/week), PUVA baths, and cyclophosphamide pulses (cumulative dose of 9000 mg). However, immunosuppressive therapy proved to be ineffective, with her skin score remaining high (mRSS 42/51) (Figure 2). The patient's functional status declined, significantly affecting her overall quality of life. Following consultation with an international expert, a decision was made to proceed with AHSCT 2 years after disease onset, despite the emerging challenges of the newly unfolding COVID-19 pandemic. CD34+ stem cells were collected after the mobilization with cyclophosphamide and granulocyte-colony stimulating factor. Conditioning was performed using cyclophosphamide (50 mg/kg during 4 consecutive days) and ATG (7.5 mg/kg during 3 consecutive days), followed by stem cell reinfusion in June 2021. The patient experienced 9 days of aplasia, complicated by non-severe sepsis. All prior immunosuppressive treatments were discontinued before conditioning and were not resumed post-transplantation. During a 30-month follow-up period, she remained stable with a reduced mRSS of 23/51 (Figure 2) and no additional organ involvement beyond the skin and esophagus. The overall disease course is summarized in Figure 1.

Perspectives

Two additional patients recently underwent AHSCT but require a longer follow-up to assess treatment outcomes. The first, a 33-year-old female with progressive dcSSc (RNA polymerase III positive), underwent transplantation 4 months ago following an inadequate response to MTX and MMF. The second, a 53-year-old male with limited SSc (anticentromere positive), was diagnosed with multiple myeloma (solitary extramedullary plasmacytoma) and underwent transplantation 2 months ago in the Hematology Unit.

Discussion

AHSCT is an established treatment for rapidly progressive and aggressive phenotypes of SSc (7). It aims to eradicate autoreactive

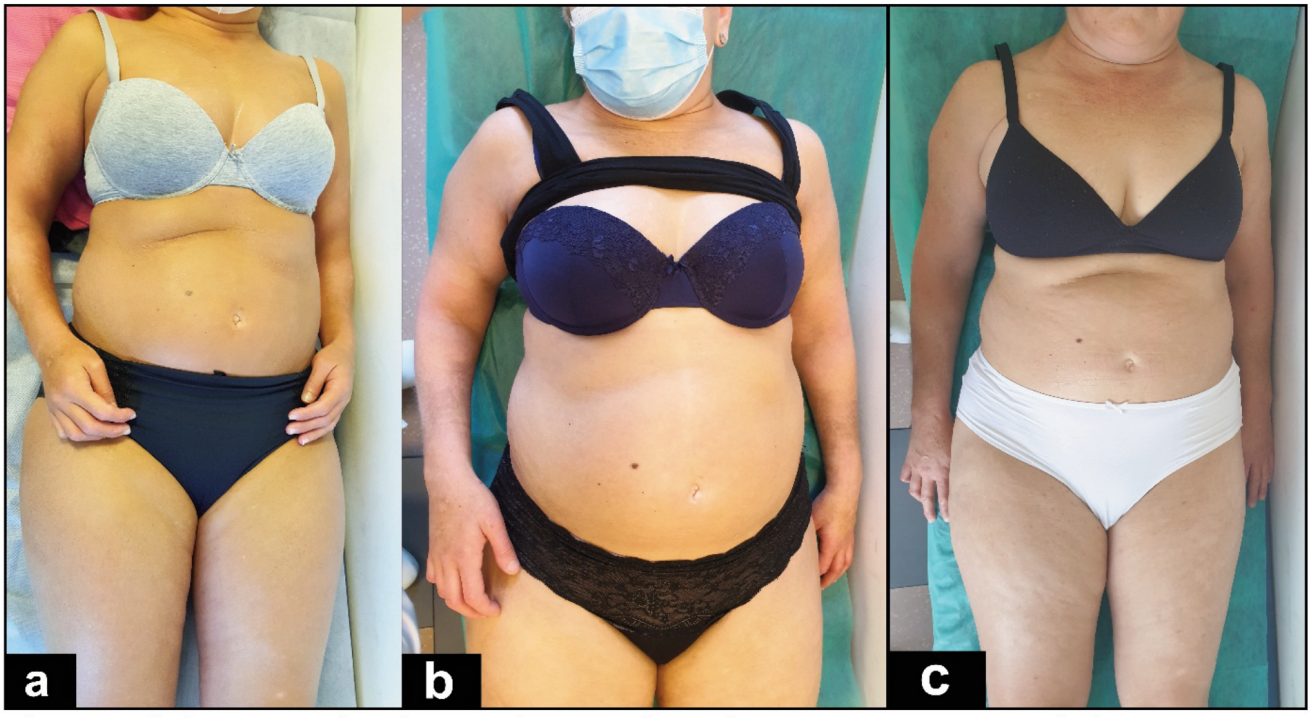

Figure 2. Skin status of patient 2: **a**) at the time of autologous hematopoietic stem cell transplantation (AHSCT); **b**) 20 months after AHSCT; **c**) 30 months after diagnosis.

T and B cells by high-dose immunosuppression and promote reconstitution of the immune system by infusion of the stem cells, resetting the system (8). However, optimal patient selection and timing of AHSCT significantly affect patient outcomes. Although fibrosis of the skin is the hallmark of SSc, the disease also affects internal organs, including the heart. Cardiac involvement occurs in 7-35% of patients and is a major cause of morbidity and mortality (9). Manifestations range from myocardial fibrosis and conduction abnormalities to pericardial effusion, heart failure, and PAH. Myocardial fibrosis can lead to diastolic dysfunction and arrhythmias, contributing to poor outcomes. Early detection of cardiac involvement is crucial in risk stratification for AHSCT. While echocardiography remains the first-line tool, CMR is emerging as the gold standard for detecting subclinical myocardial fibrosis, offering superior sensitivity in assessing cardiac structure and function. CMR-based detection of late gadolinium enhancement is particularly important, as it correlates with a higher risk of arrhythmias, heart failure, and transplant-related mortality. Additionally, biomarkers such as N-terminal pro-brain natriuretic peptide have been utilized for early identification of cardiac dysfunction in SSc patients (9-12). Management of cardiac involvement in SSc is multifaceted, addressing both the underlying autoimmune process and symptomatic cardiac manifestations. Cyclophosphamide and MMF are effective in reducing myocardial inflammation and fibrosis, while antiarrhythmic medications, ICD implantation, or catheter ablation may be required for arrhythmias (6, 11). Case Report 1 illustrates the challenges of managing myocardial involvement post-transplant. Regular cardiovascular monitoring, including serial echocardiography, CMR, and biomarker assessment, is essential to detect early progression and adjust treatment strategies accordingly (10-12).

Emerging evidence highlights that AHSCT is most effective when performed within a critical "window of opportunity" – before irreversible organ damage occurs. In our first case, delayed intervention resulted in persistent cardiac dysfunction and lung deterioration, despite an initial improvement in skin involvement. At the time of diagnosis, treatment options were limited, making AHSCT the last resort. The transplantation was carried out in January 2017 and, to our knowledge, was the first AHSCT for this indication in Croatia and the ex-Yugoslavia region. Conversely, our second patient underwent AHSCT two years after disease onset, before major organ involvement had developed. This resulted in significant skin amelioration, drug-free remission, and improved quality of life. She is the second transplanted (and still living) patient in Croatia for the indication of SSc. Recent studies suggest that AHSCT within 5 years of disease onset yields superior long-term outcomes, reinforcing the importance of early referral for transplantation in selected patients with progressive dcSSc (13, 14). Additionally, significant racial differences in SSc presentation and progression have been reported. Asian patients tend to develop disease features earlier, with a higher prevalence of PAH and reduced lung function, whereas Black patients exhibit the fastest disease onset and more frequent diffuse skin involvement. These findings highlight the importance of considering racial and ethnic factors in diagnosis, treatment selection, and timing of AHSCT to optimize patient outcomes (15).

One limitation of this study is the lack of standardized cardiac screening with CMR before AHSCT, which could have allowed for a more detailed baseline assessment of myocardial fibrosis. Moving forward, pre-transplant evaluation should include comprehensive cardiac imaging and biomarker analysis to refine patient selection and minimize transplant-related risks (16). These cases underscore the crucial role of AHSCT in severe SSc, the importance of timely intervention, and the need for thorough pre-transplant cardiac assessment. Other limitations of this study are the small number of cases, limiting the generalizability of conclusions to the broader population; patient selection was influenced by selection bias, as participants were chosen due to their progressive form of the disease; and the absence of a comparison group prevents the determination of causation or the true efficiency of the intervention.

Before the pivotal randomized controlled trials, early phase I-II trials reported positive results (17). The ASSIST trial (American Scleroderma Stem Cell *vs.* Immune Suppression Trial), published in 2011, included 19 patients: 10 underwent AHSCT and 9 received intravenous cyclophosphamide (18). The ASTIS trial (Autologous Stem Cell Transplantation International Scleroderma Trial) studied 156 patients, with 79 undergoing AHSCT and 77 receiving cyclophosphamide (19). A 2017 study by Del Papa *et al.* evaluated 18 patients with rapidly progressive dcSSc, comparing them to 36 demographically and clinically matched patients treated with conventional therapies (13). Lastly, the SCOT trial (Scleroderma: Cyclophosphamide or Transplantation), published in 2018, included 75 patients, of whom 36 received myeloablative AHSCT and 39 were treated with cyclophosphamide (14). All these trials demonstrated the superiority of AHSCT over standard cyclophosphamide therapy, with significant improvements in overall symptoms, primarily skin thickening progression, and event-free survival. These findings established AHSCT as a viable treatment option for patients with severe or rapidly progressive SSc. According to the European Alliance of Associations for Rheumatology recommendations, AHSCT should be considered for carefully selected patients with rapidly progressive dcSSc at risk of organ failure (6).

Conclusions

Over the past 15 years, AHSCT gained a foothold in phase I-II and pivotal phase III trials, becoming the treatment option for specific phenotypes of patients with SSc. The procedure is more widely utilized. However, it should be reserved for medical institutions with rheumatological and hematological centers with expertise in transplantation programs capable of dealing with pre- and post-procedural complications. The transplantation has shown superiority to the widely used cyclophosphamide, better outcomes, and improved quality of life, especially for patients with progressive skin phenotype. The results from our center illustrate the pivotal role of AHSCT in severe SSc, the importance of early intervention, and the need for comprehensive pre-transplant cardiac assessment. While AHSCT remains the most effective treatment for aggressive SSc phenotypes, optimal patient selection and timing remain critical factors for success.

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