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CASE REPORT

Autologous Hematopoietic Cell Transplant as an Effective Treatment Modality for Systemic Sclerosis and Multiple Myeloma

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Abstract: Systemic sclerosis (SSc) is a multi-system disease characterized by a dysregulated immune system. Autologous hematopoietic cell transplantation (AHCT) is the only treatment that has been shown to confer significant benefit in controlling disease and improving survival for patients with SSc. A diagnosis of multiple myeloma (MM) after the diagnosis of SSc is rare and optimal treatment in such cases remains unclear. We here report a case of a female patient who was diagnosed with MM while she was undergoing evaluation for AHCT due to SSc. A novel conditioning regimen for AHCT, with therapeutic efficacy in SSc and MM was offered to the patient, resulting in long term remission of both diseases.

Keywords: systemic sclerosis, autologous hematopoietic cell transplantation, multiple myeloma

Introduction

Systemic sclerosis (SSc), also commonly known as scleroderma, is a chronic multi-system disorder involving inflammatory, vascular, and fibrotic processes. The underlying pathophysiology is dysregulation of the adaptive immune system where tolerance to self-antigens is broken and self-reactive effector T-cells cause cellular and antibody mediated injury to host organs.[1] Characteristic skin thickening (scleroderma) and distinct organ involvement, particularly of the lungs, gastrointestinal tract, heart, and kidneys are seen, resulting in progressive organ damage and impaired quality of life (QoL). The treatment of SSc poses a significant challenge and commonly involves immunosuppressive drugs.[2,3] However, these approaches offer modest benefits in delaying disease progression or improving QoL, often failing to reverse the fatal natural course of the disease. Furthermore, they need to be given over prolonged periods of time and are associated with a huge economic burden.[4–6]

Several studies have demonstrated the ability of high-dose chemotherapy and autologous hematopoietic cell transplantation (AHCT) to halt and potentially reverse organ damage in SSc.[7] The efficacy of AHCT in SSc is secondary to an ablative effect on the T cell compartment, facilitating the regeneration of a new, tolerant repertoire from the reinfused stem cells. It has also been associated with regeneration of regulatory T-cell repertoire and reactivation of thymic function (12–14). Three randomized controlled trials, American Scleroderma Stem Cell versus Immune Suppression Trial, Phase II (ASSIST), Autologous Stem Cell Transplantation International Scleroderma Trial, Phase III (ASTIS) and Scleroderma: Cyclophosphamide or Transplantation, phase II (SCOT), have shown improvement in overall survival, event-free survival and QoL with AHCT in comparison to the standard of care treatment.[8–10] Patients eligible for inclusion in these trials were those who had advanced SSc, as evidenced by internal organ involvement in addition to skin involvement.[8–10] The ASTIS trial also allowed inclusion of patients with skin-only involvement if they had a modified Rodnan skin score (mRSS) of at least 20 and an erythrocyte sedimentation rate greater than 25mm and/or hemoglobin less than 11g/dL.[9] European League Against Rheumatism guidelines and the American Society for Blood and Marrow

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Transplantation recognize AHCT as a standard of care treatment for patients with SSc who have advanced and rapidly progressive disease, placing them at risk of organ failure.[11,12]

Interestingly, associations have been reported between SSc and monoclonal gammopathy (typically IgG-κ) and multiple myeloma (MM).[13] Inflammation, immune dysregulation, and use of immunosuppressive drugs for the treatment of SSc can be a potential explanation for subsequent clonal proliferation of plasma cells leading to MM.[13] While the association between SSc and MM is rare, there have been anecdotal cases published in the literature (Table 1). We here report a case of a female patient who was diagnosed with MM while undergoing evaluation for AHCT for the diagnosis of SSc. The uniqueness of our case is secondary to the subsequent treatment approach adopted. Post systemic treatment of MM, our patient proceeded to receive AHCT with a unique conditioning regimen, one that included therapeutic agents with efficacy in both MM and SSc, namely melphalan and anti-thymocyte globulin (ATG). This treatment approach has not been previously described in literature.[14]

Case Presentation

Symptoms at Presentation

A 58-year-old female presented with a 5-year history of gastrointestinal symptomatology including trouble swallowing, regurgitation and intermittent vomiting. She additionally reported tightening of the rings on her fingers. This was accompanied by thickening and tightening of her skin, which was most predominant on her lower extremities. She also reported Raynaud's phenomena and intermittent shortness of breath.

Physical Examination and Investigations

Her physical exam was notable for hyperpigmented plaques in the lower extremities and healed ulcers at the ankles alongside sclerodactyly with flexion contraction of the hands bilaterally. Also noted were dry crackles posteriorly in the mid to bases of her lungs. Of note, at the time of her examination she was also noted to have proximal muscle weakness. Her diagnosis based on her presentation was assessed to be most consistent with SSc with multi-system involvement. This was subsequently confirmed with additional investigations, and she was noted to have evidence of gastrointestinal, vascular, pulmonary, muscular, and skin involvement. Of note, she had not previously received any immunosuppressive treatment for her symptoms. Her mRSS was assessed to be 33. Autoimmune antibody panel was negative, but interestingly her complete blood count and general chemistry were notable for anemia with a hemoglobin of 9 gm/dl and elevated total protein at 9.2 g/dL. Renal function was normal. Serum protein electrophoresis was subsequently requested and was notable for an M spike of 3.8 g/dL with immunofixation positive for IgG lambda monoclonal protein. Immunoglobulin G level was elevated at 6050 mg/Dl and kappa/lambda light chain ratio was normal. Urine protein electrophoresis was notable for 25 mg of monoclonal IgG lambda protein per 24 hours. Bone marrow biopsy was positive for involvement by plasma cell myeloma at 70–90%. Imaging was negative for any bone lesions. Patient was diagnosed with international staging system (ISS) stage II standard risk, IgG lambda MM.

Treatment

She was initiated on treatment with cyclophosphamide, bortezomib and dexamethasone for the treatment of MM and was assessed to have a partial response after 3 cycles of treatment. She was then recommended to proceed with AHCT. Her conditioning regimen included melphalan (200mg/m^2) and rabbit ATG. Her autologous graft was CD34 selected, and she received a total of 5.05×10^6 cells/kg. Her transplant course was without significant complications, and she was discharged from the hospital 14 days post cell infusion.

Outcome and Treatment Response Assessment

At the time of vital organ testing and pre AHCT, her computed tomography (CT) of the chest was notable for mild mosaic attenuation and cylindrical bronchiectasis. Expiratory imaging showed diffuse air trapping throughout the lungs with greater than 75% collapse of the mainstem bronchi, bronchus intermedius and segmental bronchi. The main pulmonary artery measured 32 mm. Right heart catheterization was subsequently completed but was consistent with

Table 1 Literature Review of Cases That Developed SSc Followed by MM

	Age/Gender	Duration Between the Diagnosis of SSc and MM	Treatment Administered for SSc	Outcome for SSc	Treatment Administered for MM	Outcome for MM
Gajendra et al[13]	24/M	8 years	Dexamethasone (40 mg/day weekly)	Improvement in skin thickening and increased range of movements after 9 months of therapy.	Thalidomide (100 mg/day)	
Ohta et al[15]	64/M		Prednisone, 80 mg/ day for 4 days and repeated monthly	After 6th cycle, clinical evidence of softening of the skin and improved joint mobility	Melphalan, 14 mg/ day, given for 4 days and repeated monthly	Partial response
Hodak et al[16]	74/F	4 years		Skin lesions improved after receiving chemotherapy for MM	Melphalan given for 1.5 years	Partial response
Salisbury et al[17]	76/F	1 month		After the third cycle of treatment for MM, the skin became softened and after completing treatment, mobility was significantly improved	Six pulses of IV cyclophosphamide 750 mg given over 3 days with prednisone 30 mg daily for three days, each pulse at an interval of three weeks	MM in remission after the treatment
Pujol et al[18]	74/M	15 years		Marked improvement of the skin after MM therapy, such that affected skin was softer, and only a slight induration over his neck remained.	4 day cycle of intravenous vincristine 1 mg and cyclophosphamide 0.5 g (day l), together with oral melphalan 10 mg daily and prednisone 90 mg daily (days 2–4).	After the sixth chemotherapy cycle his myeloma was in remission.
Bachleitner Hoffman et al[19]	73/F	24 years		Substantial skin softening in with a > 50% reduction in the skin thickness score following VMCP treatment	VMCP (vincristine, melphalan, cyclophosphamide and prednisolone) polychemotherapy	Partial response
Colovic et al[20]	55/F	20 years		Symptom-free of SSc after receiving treatment for MM	Treated with CTD protocol (Cyclophosphamide 500 mg I.V. 1 and 8 days, Thalidomide 100 mg per os and Dexamethasone 40 mg i.v. from 1 to 4 days)	After 6 courses of CTD protocol, she achieved complete remission of MM
Basu et al[21]	59/F	5 months			Bortezomib, cyclophosphamide and dexamethasone	Overall response observed for both conditions

(*Continued*)

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Table 1 (Continued).

	Age/Gender	Duration Between the Diagnosis of SSc and MM	Treatment Administered for SSc	Outcome for SSc	Treatment Administered for MM	Outcome for MM
Hilal et al[22]	66/M	28 years			Bortezomib, dexamethasone, and zoledronic acid	After six cycles of treatment, there was a major improvement in his disease condition with amelioration of anemia and normalization of globulin levels
Alsamarrai et al[23]	58/F	10 years	Dexamethasone (20 mg/day weekly)	Improvement in skin thickening and increased range of movements after 6 months of therapy.	Thalidomide (100 mg/day)	
Owlia et al[24]	58/M	15 years			Treated with two cycles of combination chemotherapy (VAD) with Vincristine 0.4 mg, Adriamycin 9 mg/m2, and Dexamethasone 40 mg. Subsequently he received two cycles of Bortezomide 1.3 mg/m2.	Had a fair response with VAD. However, he died following an acute illness with sepsis-like feature, 2 months later

normal pulmonary artery pressure. Pulmonary lung function tests showed a forced expiratory volume (FEV1) of 94%, forced vital capacity (FVC) of 90% and diffusion capacity (DLCO) of 66%. Electrocardiogram showed voltage criteria for LVH, ST and T wave abnormality. Echocardiogram showed an ejection fraction of 76% with no wall motion abnormalities or significant valve disease. She underwent disease restaging at 100 days post-transplant. She had maintained a partial response for MM. For her SSc, mRSS had decreased to 17, CT of the chest was consistent with stable exam, FEV1 and FVC were now at 108% and DLCO was stable at 64%. She then initiated lenalidomide maintenance as per standard for MM. At the time of writing, the patient is 2 years and 2 months post AHCT. At her last follow-up for MM, her response was consistent with minimal residual disease (MRD) negative complete remission. Minimal residual disease was assessed by flow cytometry with a sensitivity of 10^{-5}. Regarding SSc, her mRSS had further improved and was at 13, FEV1, FVC and DLCO remained stable. Chest CT showed mild stable chronic changes. She also reported significant improvement in her QoL and had returned to working full time.

Discussion

We here present a unique case of a 61-year-old African American female who was diagnosed with both SSc and MM. Anecdotal reports of patients developing SSc and MM have been reported in the literature, but there is limited understanding on how to best approach treatment in this situation (Table 1).

SSc is a connective tissue disease with an unknown etiology, it is more prevalent in African American women and involves multiple organs with diverse clinical manifestations, these ultimately contribute to an impaired QoL and reduced survival.[25,26] There remains a lack of effective therapeutics for the disease and based on the results from the 3 randomized controlled trials, which have been subsequently confirmed in a meta-analysis, AHCT is considered a "standard of care" treatment for patients with severe SSc.[8–12,27] In the ASSIST trial, AHCT led to

significant improvement in skin and lung function when compared to the standard arm of monthly IV cyclophosphamide.[8] Similar results were demonstrated in the ASTIS trial, which is the largest published clinical trial, randomizing a total of 156 patients between the two groups.[9] The SCOT trial utilized a myeloablative conditioning regimen unlike the ASSIST and ASTIS trial but again showed improved event-free and overall survival with AHCT, when compared to the control group.[10] Of note, conditioning regimen in ASSIST and ASTIS trial was cyclophosphamide at 200 mg/kg in combination with ATG (non-myeloablative), while in the SCOT trial cyclophosphamide at 120 mg/kg in combination with total body irradiation at 800 cGy and ATG (myeloablative) was utilized.[8–10]

MM, a plasma cell dyscrasia, is the second most common hematologic malignancy with an estimated 35,780 new cases per year.[28,29] While survival has improved considerably over the past two decades due to the introduction of a multitude of novel therapies, the disease remains incurable.[30] Despite the introduction of novel therapies, AHCT with melphalan 200mg/m^2 has remained a mainstay of treatment for newly diagnosed patients with MM. Two large phase III clinical trials have demonstrated a substantial progression free survival (PFS) benefit with upfront AHCT compared to novel agent therapy alone with bortezomib, lenalidomide and dexamethasone.[31,32] While survival outcomes of patients with MM continue to improve as novel agents are incorporated into front-line therapy, AHCT with melphalan 200mg/m^2 remains a pivotal treatment modality for transplant eligible patients.

The coexistence of SSc and MM in our patient was a unique and rare situation where both diseases required treatment. We decided to combine therapeutic agents in the conditioning regimen for AHCT that have proven efficacy in each of the respective diseases, with melphalan in MM and ATG in SSc. Melphalan, an alkylating agent, has been integral to the treatment of MM since its introduction in 1958.[33] The results of the Intergroupe Francophone du Myelome 9502 randomized trial established melphalan 200mg/m^2 as the conditioning regimen for MM as melphalan 200mg/m^2 resulted in superior PFS compared to melphalan 140mg/m2 plus 8 Gy total body irradiation.[34] Cyclophosphamide is typically the chemotherapeutic agent used in the conditioning regimens in AHCT for SSc due to its lymphodepleting effect. It has alkylating properties similar to melphalan and causes nonspecific depletion of both quiescent and active T and B lymphocytes. This has resulted in cyclophosphamide being the most common chemotherapeutic agent of choice in SSc.[35] Given the overlapping properties of melphalan and cyclophosphamide, we decided to combine melphalan with ATG to achieve a plasma cell ablative and a lymphocyte ablative effect. This allowed us to provide effective disease control in both MM and SSc concurrently. As noted, at 2 years follow-up, our patient continues to maintain remission for both MM and SSc.

We conducted a thorough review of the literature and found less than 20 cases of SSc that were followed by diagnosis of MM. They are summarized in Table 1. These cases did not include the use of AHCT. The etiology is not fully understood, but it is speculated that the use of immunosuppressive drugs and a dysregulated immune system, perpetuates the clonal proliferation of plasma cells.[13] Variability was noted in the time duration between the diagnosis of SSc and MM, ranging from 1 month to up to 28 years. Treatment for MM in the reviewed cases was noted to often result in improvement in the signs and symptoms secondary to SSc (Table 1). Immunomodulators such as thalidomide and lenalidomide can shift the balance of T- helper cells from Th^2 to Th^1 preventing fibroblast production of collagen, which in turn reduces the skin thickening and fibrosis central to the pathophysiology of SSc.[36]

The diagnosis of two concurrent or sequential diseases is challenging for the patient and clinician alike and is also associated with increased healthcare-related costs and impact on QoL. However, AHCT offers a potential advantage especially in the management of SSc as patients who achieve long-term durable remission, do not require lifelong immunosuppressive medications with resultant decrease in healthcare-related costs and overall improvement in QoL. Our report has several limitations, including limited follow-up, difficulty in generalizability given the heterogeneity of SSc and MM in their clinical presentations and the risks inherent in an intensive chemotherapy-based procedure such as AHCT.

Conclusion

In summary, to our knowledge, a conditioning regimen involving melphalan and ATG for AHCT in cases of synchronic MM and SSc has not been reported in the literature. While this case confirms AHCT as an effective treatment for both MM and SSc, long-term follow-up and vigilance for complications and disease relapse remains crucial. It also suggests that melphalan may be an effective lymphodepleting alternative for patients with SSc. Further research in similar complex cases is essential in understanding long-term outcomes and contributing to the evolving treatment landscape in patients with concurrent hematologic and autoimmune diseases.

Consent

Patient has provided consent for publication of this case report.

Disclosure

The authors have no relevant conflicts of interest.

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