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Microvascular remodeling after autologous stem cell transplant in an overlap of systemic sclerosis and systemic lupus erythematosus: A case report

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Abstract

Microvascular remodeling and capillary repopulation can occur after autologous hematopoietic stem cell transplant (HSCT) in patients with systemic sclerosis and systemic lupus erythematosus (SLE). We aim to report evidence for microvascular remodeling after autologous HSCT as observed by nailfold videocapillaroscopy (NVC). We describe a rare occurrence of features consistent with systemic sclerosis and SLE in a 33-year-old female with a complex clinical course refractory to conventional treatments, ultimately requiring autologous HSCT. We performed NVC before and after HSCT using optical video and light microscopy. At the microvascular level, morphologic changes in the capillary vascular bed were observed after HSCT. Pretransplant damage in capillary structure was noted as evidenced on NVC with architectural loss, ramifications, capillary drop, and decreased density. Posttransplant NVC revealed an increase in capillary density with evidence of microvascular remodeling. Further studies on the clinical use and impact of microvascular remodeling on disease progression are needed and looking into the application of NVC scoring to assess clinical response would be meaningful.

Keywords

Microvascular remodeling, nail videocapillaroscopy, scleroderma, systemic sclerosis, systemic lupus erythematosus, hematopoietic stem cell transplant

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Introduction

Systemic sclerosis is characterized by microvascular pathology and inflammation of vascular endothelial cells.[1] The pathogenesis of systemic sclerosis is driven by an autoimmune process manifesting as extensive fibrosis via fibroblast activation and micro- and macrovascular injury. In systemic lupus erythematosus (SLE) there is also endothelial cell activation and inflammation causing a change in the microvascular structure.[2]

Autologous stem cell transplant involves replacing part of the hematopoietic system with a graft sourced directly from the patient. Hematopoietic stem cell transplant (HSCT) for autoimmune conditions was first studied in clinical trials in 1990s.[3] Mortality associated with HSCT for autoimmune pathology has been reported as less than 10%.[3] Clinical trials with autologous HSCT for autoimmune diseases have reported exceptional results, with more evidence for use in scleroderma than SLE, and although it is not yet recognized as a universal standard therapeutic approach it is an option in severe refractory cases.

Nailfold videocapillaroscopy (NVC) allows for noninvasive direct visualization of dermal nail capillaries and instantaneous assessment for microvascular abnormalities using

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light microscopy and digital video camera.[4] NVC can identify structural abnormalities that represent microvascular distortion, such as giant capillaries, capillary dilatation, microhemorrhages, avascular beds, and angiogenesis.[5] A qualitative and quantitative assessment has been validated to measure microvascular damage at diagnosis and assess progression.[5] We evaluated improvement in microvasculature after autologous HSCT using NVC in a patient who had features of both systemic sclerosis and SLE refractory to conventional therapies.

Case description

A 33-year-old woman had a past medical history of SLE with a course complicated by biopsy-proven myositis. The patient experienced diffuse arthralgias, alopecia, oral ulcers, and photosensitive rash and was noted to have thrombocytopenia, positive serology for anti–double-stranded DNA, SSA/Ro, SSB/La antibodies, cardiolipin antibodies, β2 glycoprotein, and low complement C4, which led to her diagnosis of SLE. She was treated with corticosteroids, hydroxychloroquine, and leflunomide which controlled her symptoms well.

Two and a half years prior to her presentation, the patient developed dysphagia to solids and liquids and intermittent proximal muscle weakness. Laboratory results showed abnormal liver function test (LFT) levels, with aspartate aminotransferase (AST) of 135 IU/L, alanine aminotransferase (ALT) of 100 IU/L, elevated creatine kinase (CK) of 4074 U/L, and aldolase of 42.3 U/L. At that time, she was evaluated by a hepatologist; incidental liver lesions were seen on ultrasound, and magnetic resonance imaging liver protocol noted these findings may represent peliosis, although atypical hemangiomas were also considered. She was seen by a neuromuscular specialist and electromyography showed myopathic features. Muscle biopsy was consistent with myopathy, and she received treatment with intravenous immunoglobulin (IVIG) for 6 months along with mycophenolate mofetil.

The patient had three more SLE flares characterized by severe arthritis, and she was prescribed prednisone, mycophenolate mofetil, and hydroxychloroquine with IVIG monthly. Her LFTs worsened to AST level of 720 IU/L and ALT level of 1058 IU/L. Laboratory results included antinuclear antibody titers of 1:320, anti–smooth muscle antibody titers of 21 units (weakly positive), antimitochondrial antibody titers of 118.9 units (positive), and negative viral serologies. MyoMarker panel had positive U1RNP and she tested positive for RNP.

The patient's intermittent proximal muscle weakness progressed, and she was admitted for acute liver injury and jaundice. Liver biopsy was consistent with acute and subacute hepatitis with moderate activity concerning drug-induced liver injury or autoimmune hepatitis. She was exhibiting signs of active SLE flare with the development of dermatomyositis with mucocutaneous involvement, uptrending CK levels, inflammatory arthritis, Raynaud's phenomenon, and progressive dysphagia. She was prescribed intravenous methylprednisolone and continued on mycophenolate mofetil; hydroxychloroquine was withheld. Her LFT levels improved, and she was referred to Mayo Clinic for evaluation for HSCT.

An esophagogastroduodenoscopy demonstrated abnormal esophageal motility and pH impedance testing showed esophageal acid exposure above normal values. Esophageal manometry showed a lower esophageal sphincter pressure zone below normal resting pressures consistent with esophageal aperistalsis. High-resolution computed tomography of the chest showed minimal peripheral ground-glass opacities in the lung bases and reticulation changes consistent with interstitial lung disease. Pulmonary function tests showed compromised diffusing capacity of the lung for carbon monoxide (63 mL/min/mm Hg). Echocardiography and right heart catheterization were negative for pulmonary hypertension.

The patient's condition worsened as she developed ulceration of multiple fingers, diffuse joint and muscle pain with difficulty walking, and rash around her eyes and face. She was documented to have anti–double-stranded DNA antibodies and low complement 4 level. She resumed IVIG, prednisone daily, and mycophenolate mofetil. At the same time, she noticed progressive sclerodermatous changes in the skin of her abdomen and chest with tightness in her forearms.

NVC showed a decrease in capillary density (mean score, 5.8 (normal score, 0)) with areas of capillary drop. Numerous enlarged and several giant capillaries were visualized. Disorganization was noted in several fingers and the abnormal NVC was consistent with late-stage scleroderma. Capillaroscopy findings were defined by density, dimension, morphology, or hemorrhages. Density was defined as abnormal if there were <7 capillaries per 1 mm field, and dimension is abnormal if >20 μm, with 20–59 μm being defined as enlarged and >50 as giant. Morphology was considered abnormal if there was not a characteristic hairpin shape to the end of the capillary. The presence of micro or macrohemorrhages was considered abnormal.

She was referred to Hematology and Oncology for consideration for autologous HSCT in light of refractory scleroderma symptoms. She had developed evidence of inflammatory myopathy, autoimmune hepatitis, and progressive skin thickening, and features of a mixed connective tissue disease had been noted. Symptoms were nonresponsive to medical therapy, and she was decided to be an appropriate candidate for high-dose immune ablation and autologous HSCT. She underwent autologous bone marrow transplant with conditioning with cyclophosphamide and anti-thymocyte globulin and CD34/kg 6.36×10^6/kg was infused. Cyclophosphamide 50 mg/kg daily was given on days -5, -4, -3, -2 and Rabbit ATG 0.5 mg/kg on day -5, followed by 1.5 mg/kg daily on days -4, -3, -2, -1. Three-week posttransplant NVC showed marked improvement

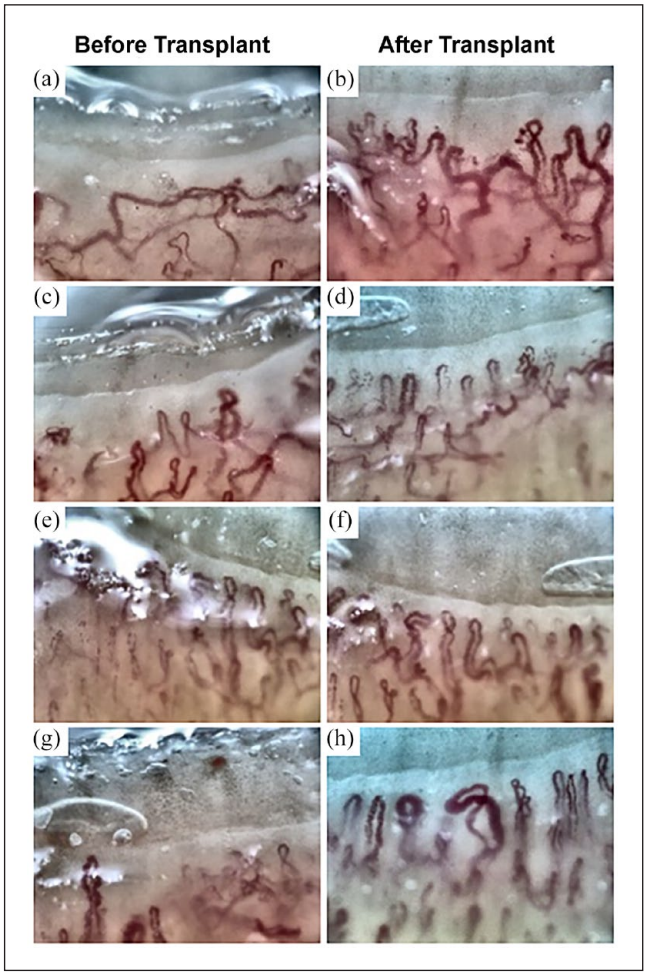

Figure 1. Right-hand nailfold videocapillaroscopy. (a) Capillary disorganization. (b) Microvascular remodeling with hairpin-like capillary repopulation. (c) Capillary drop with decrease in capillary density. (d) Increase in capillary density. (e, f) No significant changes in morphology. (g) Capillary disorganization. (h) Increase in capillary density and microvascular remodeling with hairpin-like capillary repopulation.

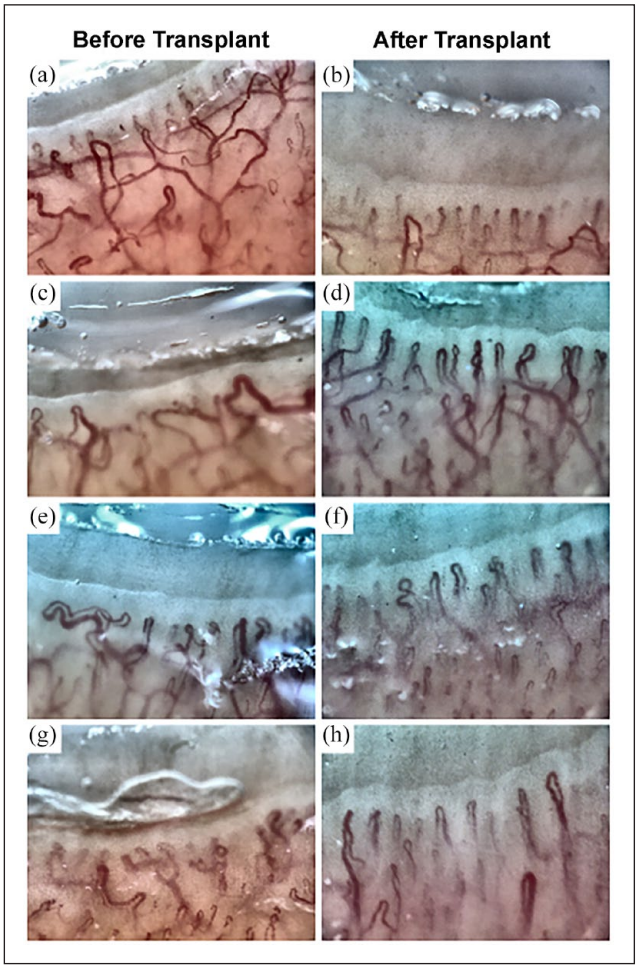

Figure 2. Left-hand nailfold videocapillaroscopy. (a, b) Normal nailfold videocapillaroscopy with normal density and morphology of the capillaries. (c) Capillary disorganization. (d) Increase in capillary density and microvascular remodeling with hairpin-like capillary repopulation. (e) Capillary drop and disorganization with ramification. (f) Increase in capillary density. (g) Ramifications and capillary drop. (h) Increase in capillary density.

in capillary architectural loss with an increase in capillary density and hairpin-like capillaries (mean score, 1.31). Figures 1 and 2 show NVC changes observed before and after HSCT in right and left hands. At posttransplant follow-up on day 188, the patient was doing well with no relapses of autoimmune hepatitis or dermatomyositis symptoms. Sclerodermatous changes in the skin had resolved. She returned to work full-time and started going to the gym.

Discussion

Scleroderma and SLE target multiple organ systems and though conventional immunosuppressive regimens have decreased morbidity and mortality rates, they still cause a substantial burden on health care systems globally. Three randomized control trials of autologous HSCT for patients with systemic sclerosis have noted objective improvement with increased long-term survival.[6] Based on current data, improved disease remission rates have been seen in patients with SLE who received HSCT compared to conventional immunosuppression alone, with reduction in SLE disease activity index scores.[7] However relapse rates have been concerning and incidences of patients requiring long-term immunosuppression after HSCT have been reported.[7]

Due to early onset of microvascular changes, NVC has become a standardized diagnostic tool for scleroderma, primary Raynaud phenomenon, and dermatomyositis. Microvascular abnormalities detected via NVC have been observed to correlate with disease progression and can precede clinical disease manifestation.[8] Capillary micro-hemorrhages and giant capillaries typically present in early disease course of systemic sclerosis, while avascular

regions, bushy capillaries, and ramifications develop later.[8] Correlation between NVC objective findings and disease activity has been described.[1] Presence of profound avascular areas, angiogenesis, and severe capillary structure loss has been observed with higher disease activity while giant capillaries with minimal architectural loss have been observed with lower disease activity.[1] Santana-Gonçalves et al.[8] retrospectively studied the effect of autologous HSCT on microvasculopathy for 27 patients with systemic sclerosis. The median number of capillaries per mm increased 12 months after autologous HSCT with reduction in the number of giant capillaries.[8]

Boonstra et al.[9] studied microangiopathy in 18 patients with systemic sclerosis who received autologous HSCT and noted a significantly lower number of giant capillaries and lower visual analog scale scores on microangiopathic assessment in the autologous HSCT group compared to controls. One-third of the patients treated with autologous HSCT showed improvement from a scleroderma pattern to normal NVC compared to 6% of the controls. A significant improvement in capillary loss and disorganization was recorded in the autologous HSCT treatment arm.[9]

NVC changes have been reported to occur as early as 1 month after autologous HSCT in patients with systemic sclerosis.[10] A sustained effect has been documented with improvement in vasculopathy seen up to 2 years after autologous HSCT.[11] NVC findings in patients with SLE are nonspecific, but abnormal capillary morphology is present. Studies have described correlation between abnormal NVC findings and SLE disease activity index scores.[12] A higher frequency of capillary hemorrhage has been observed in patients with SLE with higher disease activity. NVC scores were significantly higher in patients with SLE compared to controls.[12]

Haverkort et al.[13] described a patient with systemic sclerosis who underwent repeat autologous HSCT with increase in capillary density after transplant. This suggests that HSCT changes capillary morphology and causes vascular remodeling; however, the process by which it does so is not clear.

Our case is unique as it describes a patient with SLE who developed features of scleroderma and then underwent autologous HSCT. To our knowledge, no cases have described patients with coexistent scleroderma and SLE undergoing autologous HSCT with favorable outcomes. NVC assessment showed remarkable architectural improvement, with a drastic NVC mean score reduction from 5.8 before transplant to 1.31 three weeks after transplant.

Conclusion

The dynamic nature of microvasculature abnormalities makes NVC a valuable clinical tool for assessment of disease progression; however, no standardized tool is available for scoring, which remains subjective. The role of NVC in assessing post-HSCT response needs to be explored further. NVC diagnostic tools can be further developed for enhanced and further detailed assessment and to self-quantify against standardized scores to assess subtle changes in architecture.

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Conceptualization, A.A. and F.B.; Data curation, S.M., E.A., A.A., and F.B.; Formal analysis, S.M., A.A., and F.B.; Methodology, S.M., A.A., and F.B.; Resources, A.A. and F.B.; Supervision, A.A. and F.B.; Validation, A.A., R.R.B., and F.B.; Visualization, S.M.; Writing, S.M. and F.B.; Critical review, A.A., E.A., R.R.B., and F.B.

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Ethics statement

Mayo Clinic Institutional Review Board (IRB) approved the study. The approval IRB number is 22005403. This approval number was given by the IRB.

Consent

Written informed consent was received from the patient.

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