# FEATURED NEW INVESTIGATOR

## Allogeneic stem cell transplantation for the treatment of refractory scleromyxedema

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**Scleromyxedema is a rare disorder of connective tissue with unknown etiology. Its manifestation includes a generalized mucin deposition, which is frequently associated with paraproteinemia. The course of scleromyxedema is progressive and often lethal. As a result of its poorly understood pathogenesis, there is no causative treatment option. The efficacy of cytoreductive agents and autologous stem cell transplantation has been reported, but so far allografting as a treatment option has not yet been documented. Herein, we report on a patient with severe neurologic involvement and refractory course attaining durable remission after receiving an allogeneic hematopoietic cell transplant from an human leukocyte antigen-matched sibling. This case not only illustrates a potential new treatment option for selected patients, but also provides insights into the pathogenesis of this rare disease. (Translational Research 2015;165:321–324)**

**Abbreviations:** G-CSF = Granulocyte-colony stimulating factor; GvD = Graft versus disease; GVHD = Graft-versus-host disease; HLA = Human leukocyte antigen; IgG kappa = Immunoglobulin G kappa; MRI = Magnetic resonance imaging; SCT = Stem cell transplantation; SM = Scleromyxedema; WBC = White blood cell

### INTRODUCTION

The clinical manifestation of scleromyxedema (SM) involves a generalized papular and sclerodermoid eruption. This condition was first described in 1906 by Dubreuilh, and its association with monoclonal gammopathy has been known since the early 1960s.[1,2] The diagnosis of SM requires the histology of the involved areas showing a triad of a marked interstitial mucin deposition, increased fibroblasts, and collagen.[3] Mild perivascular lymphoplasmacytic inflammatory infiltrates can also be observed. These patients often have monoclonal gammopathy, in the absence of thyroid disease.[4] Systemic implications including neurologic, hematologic, and cardiologic involvement are common and determine the prognosis.[5] In particular the outcome is poor if neurologic impairment such as encephalopathy, convulsions, and coma occur. Recent case series report a fatal outcome for most patients with SM with systemic disease

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## AT A GLANCE COMMENTARY

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### Background

Scleromyxedema is a rare disorder of connective tissue. Its course is progressive and often lethal. Because of its poorly understood pathogenesis, there is no causative treatment option.

### Translational Significance

The successful clinical course in our patient provides direct evidence that there is a rationale for allografting in otherwise fatal cases of scleromyxedema. It can be hypothesized that cellular components of the bone marrow and secondary lymphatic organs may be involved. The combination of immunomodulation induced by allogeneic effector cells (graft-vs-disease effect) with unspecific cytoreductive conditioning therapy may be a strategy inducing stable remission in carefully selected patients.

manifestations.[5,6] Among the 26 cases of SM with neurologic involvement reported in the literature, 8 patients died during neurologic episodes.[6] To the best of our knowledge, we report the first patient with SM successfully treated by allogeneic hematopoietic cell transplantation. The procedure provided long-term remission after an otherwise refractory course with severe neurologic involvement.

## CASE REPORT

We report the case of a 44-year-old man, developing sclerodermoid skin changes unknown etiology. Two months later because of the onset of coma he was admitted to the intensive care unit. The patient immediately received supportive care, mechanical ventilation, and thrombolytic therapy on suspicion of a stroke. Magnetic resonance imaging (MRI) did not support the suspected diagnosis of a stroke. Findings of an extensive workup including analysis of autoimmune markers, thyroid studies, and urine were unrevealing except for immunoglobulin G kappa (IgG kappa) monoclonal gammopathy. Echocardiography, chest radiograph, and abdominal ultrasound showed no abnormalities. Bone marrow aspiration and biopsy were nondiagnostic. Furthermore, cerebrospinal fluid analysis indicated pleocytosis (20 white blood cell/$\mu$L; normal range, $<5/\mu$L), and positivity for monoclonal IgG kappa. Physical examination revealed progression of the sclerodermoid skin changes. Biopsy specimens of the papular and sclerodermoid eruptions from abdominal wall and forearms led to the diagnosis of SM, showing histologically with fibroblast proliferation, fibrosis, and mucin deposition in the upper reticular dermis without evidence of amyloidosis. The abnormalities of a second MRI performed 10 days after admission were consistent with the diagnosis of limbic encephalitis. Tracheotomy had to be performed because the patient still presented with significantly illness. A treatment regimen was initiated with high-dose steroids and plasmapheresis, which rapidly resolved the monoclonal gammopathy. Five weeks later, the MRI findings disappeared and his condition began to ameliorate so that he finally could be released from the intensive care unit. Four months later, he presented again with rapidly progressive skin changes. High-dose steroids, intravenous immunoglobulins, mycophenolate mofetil, and finally plasmapheresis were not able to stop the progressive course. The treatment of his refractory disease with 2 courses of doxorubicin, bortezomib, and dexamethasone showed no response, and because of that the regimen was switched to bortezomib and bendamustine. Meanwhile, his mental functions deteriorated progressively, leading to dysarthria. Fortunately, the patient achieved complete remission after cyclophosphamide stem cell mobilization and conditioning with high-dose melphalan for autologous stem cell transplant. Maintenance therapy with mycophenolate mofetil was initiated. One year after the stem cell transplant, he developed serious central nervous system (CNS) disturbances, characterized by tetraplegia and generalized seizures, followed by coma. His condition was temporarily stabilized by high-dose immunoglobulins, steroids, and continuous bortezomib and bendamustine infusion. To prevent further deterioration and a fatal outcome, the patient received allogeneic hematopoietic cells from an human leukocyte antigen-matched sister, after conditioning therapy with 150 mg/m$^2$ fludarabine and 140 mg/m$^2$ melphalan. Graft-vs-host-disease prophylaxis consisted of tacrolimus, bortezomib, and methotrexate. He achieved rapid hematologic engraftment associated with clinical remission and full and long-lasting lymphohematopoietic donor chimerism during at least 530 days (Figs 1 and 2). At his latest follow-up, 18 months after allografting, the skin changes had dissipated completely, and he remained free of CNS disturbance. Ten months after allografting, when tacrolimus was tapered, there was an isolated flare of hepatic GvD that was successfully treated with prednisolone. During steroid therapy, infectious complications included 2 episodes of pneumonia (*Pneumocystis*