Incidence and Risk Factors Defined for Sclerotic GVHD after Transplant

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Allogeneic hematopoietic cell transplantation (HCT) is used to treat hematologic disorders and malignancies; however, half of the transplant recipients develop chronic graft-versus-host disease (GVHD). Chronic GVHD is an immune disorder in which the transplanted donor T cells recognize transplant recipient cells as foreign and kill them, including those in the skin, mouth, eyes, liver, lungs, and other organs. Chronic GVHD is treated with immunosuppressive drugs to dampen the attack on transplant recipient cells. Sclerosis is a distinct clinical phenotype of chronic GVHD, and is associated with severe morbidity and disability among transplant survivors. Sclerosis begins in superficial layers of the skin and extends to deeper layers, developing from skin thickening (cutaneous sclerosis), to inflammation of connective tissue (fibrosis), and then muscle and joint tightening (joint contracture). The incidence, risk factors, and transplant outcomes of sclerotic GVHD in HCT recipients had not been extensively examined until a recent study published in the journal *Blood* by Dr. Yoshihiro Inamoto (postdoctoral fellow in the Long-Term Follow Up Program), Dr. Mary Flowers (senior author), and colleagues from the Clinical Research Division.

The researchers examined a cohort of 977 HCT recipients that were treated with immunosuppressive drugs for chronic GVHD from May 2000 to December 2009. At initial treatment, 7% of patients presented with sclerosis, and the cumulative incidence of sclerosis reached 20% within 3 years after initial treatment of GVHD (95% CI, 17.5%-22.5%). Previous smaller studies had reported a sclerotic GVHD incidence of 10% to 15%. "This result is important to alert hematologists and oncologists who may not be familiar with this complication, and will help to counsel patients about this complication when considering an allogeneic transplant and, after transplant, when they develop chronic GVHD," according to Drs. Flowers and Inamoto.

Using multivariate analysis, the investigators identified two factors that increase the risk of developing sclerosis: the use of mobilized blood stem cells for the graft (hazard ratio [HR] 1.99; 95% CI, 1.20-3.31; $P = 0.008$), and total body irradiation greater than 450 centigray when preparing patients for transplant (HR 1.62; 95% CI, 1.14-2.31; $P = 0.008$). Mobilized blood stem cell transplant increases the risk of developing chronic GVHD overall. The cytokine treatment used to mobilize

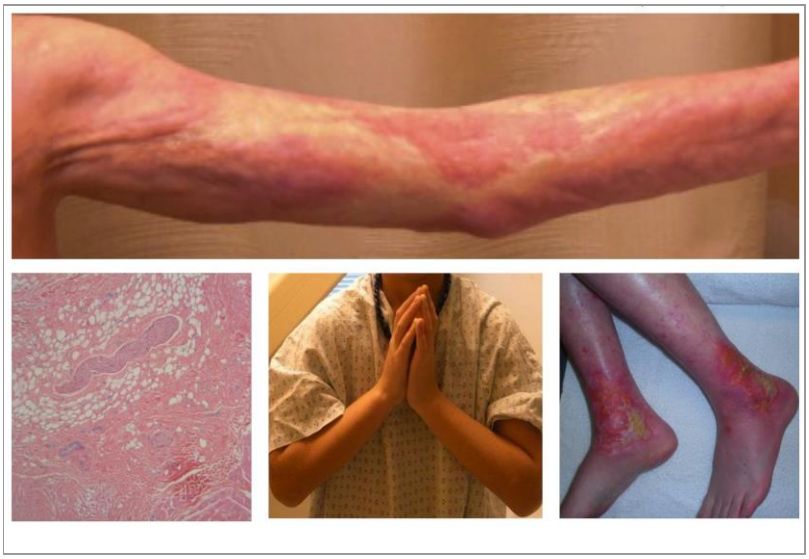
stem cells from the bone marrow to the blood stream was previously shown to cause a certain type of T cell differentiation that contributes to sclerotic GVHD in murine transplant models. The researchers speculate that irradiation of skin could also contribute to sclerosis through increased presentation of sclerotic antigens to donor T cells through epidermal damage and cytokine production.

Decreased risk of sclerosis was associated with human leukocyte antigen (HLA)-mismatched donor (HR 0.57; 95% CI, 0.37-0.89; *P* = 0.01) and with the use of a major ABO-mismatched donor (HR 0.65; 95% CI, 0.45-0.94; *P* = 0.02) compared to matched donors. The ABO antigens are sugars on red blood cells that determine blood type, and have been shown to increase risk for acute but not chronic GVHD, but the mechanisms remain unclear. HLA subtype determines immune cell recognition of self and non-self. HLA mismatch increases the risk of chronic GVHD, making the association with decreased risk of sclerosis surprising. The authors speculate that HLA mismatching may decrease the presentation of sclerotic antigens to donor T cells, thus decreasing the risk of sclerosis. However, the precise mechanism for the decreased risk of sclerosis with ABO and HLA mismatching remains unclear.

The presence of sclerosis in chronic GVHD patients had no effect on the risk of overall mortality, nonrelapse mortality or malignancy relapse post-transplant. However, developing sclerosis increased the time patients were treated with immunosuppressive drugs, which can increase the risk of infections and other complications in transplant survivors. While sclerotic GVHD does not affect the prognosis of HCT recipients, sclerosis can cause pain and disability in patients.

"Our findings will help to identify candidates for early interventional studies aimed to reduce disability related to sclerosis," according to Drs. Flowers and Inamoto, and "will foster future studies exploring pathogenic mechanisms of sclerosis, genetic risk factors for sclerosis, and proteomic profile associated with sclerosis."

Inamoto Y, Storer BE, Petersdorf EW, Nelson JL, Lee SJ, Carpenter PA, Sandmaier BM, Hansen JA, Martin PJ, Flowers ME. 2013. Incidence, risk factors and outcomes of sclerosis in patients with chronic graft-versus-host disease. *Blood*. Epub ahead of print, doi: 10.1182/blood-2012-10-464198



Images provided by Yoshiro Inamoto and Mary Flowers

Clinical and histological manifestations of sclerotic chronic graft-versus-host disease (GVHD): dimpling signs with erythema in the arm (top), histological findings (left), limited range of motion associated with fasciitis (middle), and sclerosis and ulcers in the legs (right).