

## Case Report

# Sclerodermatous Graft-Versus-Host Disease-Related Angiomatosis

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Chronic graft-versus-host disease (cGVHD) is a relatively common complication of allogeneic hematopoietic stem cell transplantation, although the exact incidence is unknown. The disease most commonly affects the skin, liver, and gastrointestinal tract, but any organ may be involved. Cutaneous manifestations are varied and rarely include vascular eruptions now characterized by the term “graft-versus-host disease associated angiomatosis” (GVHD-AA). We present a 70 year-old male with bleeding violaceous plaques and papules in the setting of sclerodermatous cGVHD. Biopsy of these lesions revealed angiomas with focal organizing thrombosis in a background of marked dermal sclerosis. Ulceration and progression of lesions continued despite treatment with local excision, prednisone, extracorporeal photopheresis, and hydroxychloroquine. GVHD-AA likely represents reactive vascular proliferation in areas of dermal sclerosis.<sup>1</sup> We report this case to raise awareness of GVHD-AA as a potential diagnosis in patients who present with vascular eruptions in the setting of cGVHD, and to encourage research into the etiology and potential treatment of reactive angiomatosis.

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## INTRODUCTION

Graft-versus-host disease (GvHD) is a common complication of allogeneic hematopoietic stem cell transplantation. Transplanted leukocytes become sensitized to host antigens and initiate an immune reaction which results in multisystem disease. GvHD is divided into acute and chronic forms which differ in clinical features and average time from transplant to symptom onset. Chronic graft versus host disease (cGvHD) begins at least 100 days after transplant and commonly affects the skin, liver, and gastrointestinal tract.<sup>2</sup> Cutaneous manifestations are classically grouped into early lichenoid and late sclerodermatous forms. However, a wide variety of cutaneous findings have been reported and a spectrum of disease presentation is increasingly being recognized. In rare cases, angiomatous eruptions have occurred in patients with cGvHD. The etiology of angiomatosis in this setting is poorly understood and has proven difficult to treat. This “graft-versus-host disease-associated angiomatosis” (GvHD-AA) was recently characterized by Kaffenberger et al.<sup>1</sup> We report an additional case of GvHD-AA occurring in a patient who underwent bone marrow transplant and donor lymphocyte infusion.

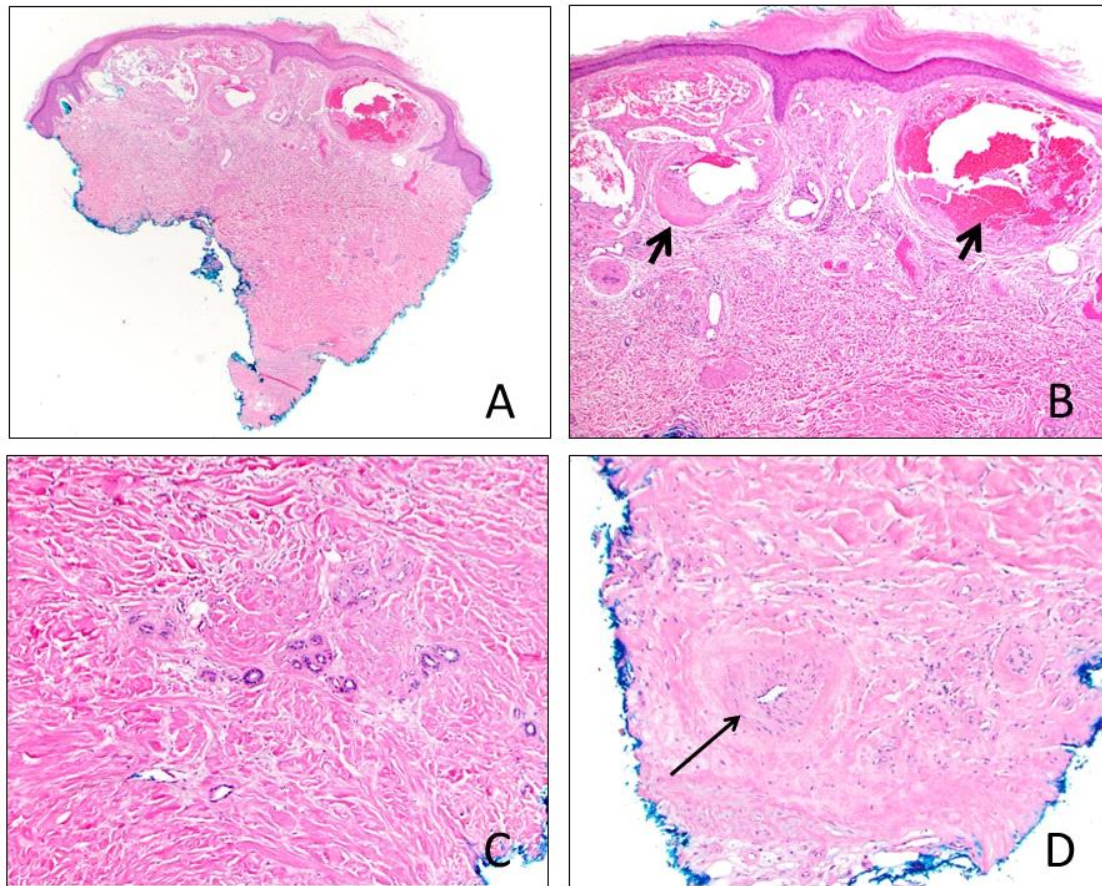
## CASE REPORT

The patient is a 70 year-old Caucasian male with a history of stage IV mantle cell lymphoma diagnosed ten years previously. He initially achieved full remission with chemotherapy and autologous stem cell transplantation. He relapsed three years later and underwent reduced-intensity allogeneic stem cell transplantation from a sibling. A second relapse occurred after three additional years which was treated with donor lymphocyte infusion. His therapy was complicated by GvHD including extensive cutaneous involvement. He developed multiple indurated sclerodermatous plaques on his upper and lower extremities. Fascial fibrosis also developed, leading to contractures of his knees and ankles bilaterally. Additionally, dermal nodules with violaceous plaques and papules developed in areas of sclerosis. These nodules were most notable on his left elbow, left thigh, and right lower leg. Hemorrhage and dark eschar formation followed with some progressing to form draining ulcers. Microscopic examination of skin biopsy specimens from the right leg revealed angiomas with focal organizing thrombosis in a background of marked dermal sclerosis (**Figure 1**). Treatment with prednisone, extracorporeal photopheresis, and hydroxychloroquine was unsuccessful in controlling the formation and progression of endothelial proliferations.

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**Figure 1.** Histopathologic features of sclerodermatous Graft-Versus-Host Disease-Related Angiomatosis (GVHD-AA): **A.** Low power view of GVHD-AA showing a proliferation of dilated vascular spaces expanding the superficial dermis accompanied by dermal sclerosis. **B.** Higher power view showing organizing vascular thromboses (short arrows). **C & D.** Dermal sclerosis surrounding eccrine coils and involving a deep dermal blood vessel (long arrow).

## DISCUSSION

GVHD is a major source of morbidity and mortality following allogeneic hematopoietic stem cell transplantation. The disease represents an overly robust graft cell immune response against host antigens. Despite the favorable graft-versus-tumor effect, treatment-related mortality is increased in GVHD.<sup>3</sup> Chronic GVHD may develop with or without preceding acute GVHD. Incidence rates of cGVHD following hematopoietic stem cell transplant vary widely and true disease incidence is unknown. Incidence is decreased by close HLA matching, but higher rates are seen in patients who undergo peripheral blood progenitor cell transplant or donor lymphocyte infusion.<sup>4,5</sup>

Cutaneous manifestations of cGVHD display both clinical and histologic heterogeneity. Poikiloderma, lichenoid disease, dermal and fascial fibrosis are diagnostic features.<sup>2,4</sup> Although traditional distinction between early lichenoid and late sclerodermatous cGVHD has been made, the disease is increasingly recognized as a spectrum of cutaneous features with overlapping presentations. Atypical findings such as

comedones, bullae, and atopic dermatitis-like involvement have been reported.<sup>6,7</sup> In rare cases, endothelial proliferations have been described. Clinically, these vascular lesions appear as brown to violaceous papules, plaques, and nodules which may bleed or ulcerate.<sup>1,5,8,9</sup> As in our case, these lesions arise exclusively in areas of longstanding sclerosis and occur most frequently in patients with severe, refractory cGVHD.<sup>1</sup> The trunk and lower extremities are the most commonly involved areas. Histologically, lesions reveal endothelial proliferation with vague lobular architecture in a background of dermal fibrosis and fibroblast proliferation. Endoluminal proliferation is minimal. No cytologic atypia is present. Organizing thrombi and pericyte proliferation may be seen. The epidermis may appear atrophic or display irregular acanthosis.<sup>1</sup>

The precise pathophysiologic mechanism underlying angiomatosis in the setting of cGVHD is unknown. It has been suggested that the disease is a form of cutaneous reactive angiomatosis.<sup>1,10</sup> As the name suggests, the reactive

angiomatoses are a group of vascular proliferations that develop in response to vaso- or veno-occlusion caused by a variety of local or systemic disease processes. Unlike vascular tumors, the reactive angiomatoses appear to be reversible with the restoration of adequate tissue perfusion.<sup>11,12</sup> Therefore, these diseases appear to be an exaggerated response to tissue hypoxia rather than true neoplasia.

Similar to GVHD-AA, the cutaneous reactive angiomatoses present with ecchymoses and multiple erythematous, violaceous, and purpuric papules and plaques with the potential for necrosis and ulceration.<sup>10,11</sup> These lesions appear to preferentially involve the limbs, but have also been noted on the trunk and face. Many forms of cutaneous reactive angiomatosis have been described, including reactive angioendotheliomatosis, diffuse dermal angiomatosis, acroangiodermatitis, glomeruloid reactive angioendotheliomatosis, reactive intralymphatic histiocytosis, and angiopericytomatosis.<sup>11,13</sup> The primary differences between these conditions are based upon their microscopic appearance, each having varying degrees of intravascular or extravascular endothelial proliferation in lobular or diffuse patterns throughout the dermis.<sup>10,11</sup> Some subtypes display a component of pericyte or histiocyte proliferation. Organizing thrombi, extravasation of erythrocytes, and formation of new vascular channels may be seen.<sup>11</sup> The specific histopathology of each subtype is beyond the scope of this article.

Cutaneous reactive angiomatoses have been described in a variety of systemic diseases including subacute bacterial endocarditis, hepatitis, tuberculosis, cryoglobulinemia, renal failure, rheumatoid arthritis, systemic lupus erythematosus with antiphospholipid syndrome, monoclonal gammopathy, lymphoproliferative disorders, and chronic lymphocytic leukemia. Subtypes of reactive angiomatosis have also been described in localized processes such as arteriovenous fistula, venous stasis, and cholesterol embolism.<sup>10,11</sup> Angiomatosis in cGVHD may represent an additional variant of this process in which local hypoxia caused by dermal sclerosis leads to reactive vascular proliferation. Lymphatic obstruction secondary to sclerosis and resulting tissue edema may also play a role.<sup>1</sup> In one case report, the authors found high levels of vascular endothelial growth factor (VEGF) and  $\beta$ -fibroblastic growth factor in a patient with GVHD-AA.<sup>9</sup> A similar association has been noted in other reactive angiomatoses. High levels of epidermal VEGF expression were noted in a patient with glomeruloid reactive angioendotheliomatosis. Vascular proliferations in the same case displayed increased endothelial expression of VEGF receptor-2.<sup>14</sup> These findings suggest an exaggerated tissue healing response underlying reactive vascular proliferation. This is theory is supported by the observation that lesions of GVHD-AA occur exclusively in areas of longstanding sclerosis.<sup>1</sup>

Clinical correlation is critical in arriving at an accurate histologic diagnosis. Prior to formal characterization of 11

cases by Kaffenberger et al, a wide variety of diagnoses were initially rendered to biopsy specimens of GVHD-AA. Traumatized pyogenic granuloma (lobular capillary hemangioma), cavernous hemangioma with Masson tumor, lymphangioma, and angiokeratoma are specifically noted by the authors.<sup>1</sup> Differential diagnosis also includes Kaposi sarcoma and bacillary angiomatosis which may occur in immunocompromised patients.<sup>8,11</sup> These entities may be ruled out with a negative Human Herpes Virus-8 immunostain and negative Warthin-Starry stain respectively.<sup>5</sup> Kaposi sarcoma is rare in hematopoietic stem cell transplant patients, and can be identified histologically by its fascicular proliferation of spindle cells with slit-like vascular spaces.<sup>1,5</sup>

Attempts to treat the vascular proliferations of GVHD-AA have been largely unsuccessful. Excision, curettage, and cautery have not prevented recurrence and proliferation of skin lesions.<sup>8</sup> Thalidomide was also found to be ineffective in several patients.<sup>1,5,9</sup> One patient experienced resolution with radiation treatment and tacrolimus, but skin lesions recurred over the next few years.<sup>8</sup> Some authors have noted partial benefit with a combination of sirolimus and propranolol.<sup>1</sup>

## CONCLUSION

GVHD-AA is a rare, recently described condition with limited representation in medical literature. We present an additional case in the setting of chronic sclerodermatous GVHD with limited response to treatment with glucocorticoids, extracorporeal photopheresis, and hydroxychloroquine. Lack of treatment success is likely related to the secondary, reactive etiology of vascular proliferations. Treatment does not correct underlying tissue fibrosis, and thus the drive for vascular proliferation remains. Further examination of biochemical signaling involved in reactive angiomatosis may lead to more pointed therapies for uncontrolled vascular proliferations in all settings. Due to past difficulty in diagnosis, the present report intends to highlight GVHD-AA as a potential diagnosis in patients with cGVHD.

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## CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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