Sclerotic-Type Chronic Graft-Versus-Host Disease: A Case Presentation and Discussion

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Abstract

Background: Hematopoietic stem cell transplants (HSCT) are becoming more common; therefore, graft-versus-host disease (GVHD) is becoming a more prevalent dermatologic condition. Objective: To educate current dermatologists on the most current recommendations for chronic GVHD (cGVHD), specifically sclerotic-type chronic GVHD (ScGVHD). Methods: A patient with ScGVHD is presented. A literature review was performed for ScGVHD. Results: A discussion is provided on the presentation, treatment, and management of ScGVHD. Limitations: This is a case report of one patient. The mechanism of action of ScGVHD is not well-known, and there are no FDA-approved therapies with indications for cGVHD. Conclusion: Due to the increased morbidity and mortality of ScGVHD patients, research on the mechanism of action and optimization of currently used therapies is imperative.

Introduction

Hematopoietic stem cell transplants (HSCT) are becoming more common for treatment of multiple medical conditions. One of the most common complications of HSCT is graft-versus-host disease (GVHD). GVHD is distinguished as either acute or chronic, and both types frequently affect the skin. Due to the increased prevalence of GVHD patients, dermatologists need to be aware of the multiple presentations and the current recommendations for treatment and management. This case presentation and discussion focus on chronic GVHD (cGVHD), specifically sclerotic-type chronic GVHD (ScGVHD), and the difficulties of its treatment and management.

Case Presentation

A 61-year-old male presented with a past medical history of multiple myeloma, status post autologous stem cell transplant with subsequent allogeneic sibling peripheral stem cell transplant. One year later, the patient was diagnosed with acute graft-versus-host disease (aGVHD) of the esophagus and small and large intestines. Two years after the aGVHD, the patient presented with symmetrical diffuse, bound down, woody plaques with hypopigmentation and alopecia of the upper and lower extremities (Figure 1). Involving the bilateral anterior lower legs were multiple pink-colored papules (Figure 2). On the plantar surface of the left foot, there were punched-out ulcerations with yellow adherent film (Figure 3). There was decreased capillary refill of the fingers and toes. Wrist dorsiflexion was 15 degrees, and hand grasp was 75 percent of normal. Pathology revealed mild epidermal changes, thickening of dermal collagen bundles, and dermal fibrosis extending into the subcutis resulting in septal hyalinization (Figure 4). These findings were consistent with sclerotic-type chronic graft-versus-host disease.

The patient has been treated aggressively by Oncology with multiple immunosuppressive therapies, including topical ointments (tacrolimus and triamcinolone), oral corticosteroids, imatinib, cyclosporine, sirolimus, narrow-band UVB phototherapy, extracorporeal photopheresis, intravenous immunoglobulin (IVIG), and rituximab infusions. Long-term oral corticosteroids and cyclosporine usage resulted in adrenal insufficiency and hypertension, respectively. The patient is currently receiving rituximab infusions. In addition, the patient follows a strict exercise and stretching regimen to maintain his upper and lower extremity range of motion, uses compression stockings to assist with his chronic lymphedema, and receives wound care for his chronic plantar wounds.

Discussion

In 1968, the first successful allogeneic bone marrow transplant was performed. There are now approximately 25,000 allogeneic hematopoietic stem cell transplants (HSCT) performed worldwide each year. In the past, acute and chronic GVHD were distinguished by time of onset following HSCT,
with acute appearing in fewer than 100 days, and chronic presenting more than 100 days after HSCT. However, this changed with the NIH consensus conference on cGVHD in 2005, where the acute and chronic GVHD definitions were reclassified based on clinical and histologic findings. The NIH definitions can now better indicate prognosis, guide treatment, and define eligibility for clinical trials.

Cutaneous cGVHD is a polymorphic condition that often has multiple presentations within one patient. Non-sclerotic cGVHD can resemble lichen planus, poikiloderma, psoriasis or papulosquamous lesions, subacute cutaneous lupus, and keratosis pilaris. Sclerotic-type cGVHD manifestations appear more bound down, and can resemble lichen sclerosus, morphea, and eosinophilic fasciitis. Although sclerotic-type cGVHD is not an acute, life-threatening condition, widespread involvement may lead to significant disability and morbidity. Deep-seated fibrosis of the subcutaneous tissue and fascia may result in loss of range of motion. Longstanding fibrosis may result in skin ulceration and proliferation of benign angiomatous nodules. Due to the increased risk of developing cutaneous malignancies secondary to immunosuppression, chronic scarring, and potentially photosensitizing agents, the importance of sun protection and regular skin examinations should be emphasized.

Because the exact mechanism of action of cGVHD is unknown, it is difficult to treat. Cutaneous sclerotic type cGVHD is particularly resistant to systemic immunotherapy. First-line therapy for chronic GVHD includes systemic corticosteroids with or without a calcineurin inhibitor, which is based on controlled trials; however, at least 50 percent of these patients will not respond adequately. For steroid-refractory cGVHD, there are no therapies with level I evidence from randomized, controlled trials. There are a few with level II evidence from clinical trials without randomization, including photopheresis, rituximab, pentostatin and thalidomide. Steroid-refractory cGVHD therapies all have level C recommendations, where evidence is insufficient to support for or against treatment, or evidence may not outweigh adverse consequences or cost of treatment. The second-line therapies for steroid-refractory cGVHD are generally approached through trial and error. More than 10 years after the initial NIH Consensus Conference in 2005, there are still no FDA-approved agents with indication for cGVHD. Therefore, there is a strong need for clinical trials to optimize the currently used therapies or to develop new agents.

A recent study using the new NIH cGVHD definitions revealed a possible association between ScGVHD and the presence of total body irradiation (TBI) conditioning prior to transplantation. It also suggested that elevated C3 may stimulate fibrotic processes, and that increased platelets may act as acute-phase reactants, triggering synthesis of collagens and other matrix proteins. These predictors were either unknown or absent in our patient. Of note, previous acute or chronic GVHD did not predispose patients to an increased risk of ScGVHD. This study also revealed that ScGVHD patients with a body surface area (BSA) sclerosis greater than the median 37.4 percent had poorer survival than those with less than median BSA sclerosis. In this population, it is possible that restriction of the chest and abdominal wall secondary to sclerosis may lead to decreased lung vital capacity and therefore decreased survival. Although cGVHD is not generally viewed as an acute, life-threatening condition, it can be lethal for ScGVHD patients.

**Conclusion**

As cGVHD becomes a more common dermatologic condition, resulting from the increased prevalence of HSCTs, dermatologists must be aware of the diverse presentations of cGVHD, as early involvement can greatly decrease the sequelae of cGVHD. However, due to the unknown exact mechanism of action of cGVHD, it is very difficult to treat. There are no FDA-approved therapies with indications for cGVHD, and most steroid-refractory treatments are approached through trial and error. Therefore, it is imperative that our community supports increased research on the mechanism of action and optimization of currently used therapies for cGVHD.

**References**


