Successful Treatment of Chronic Sclerotic-Type Graft-Versus-Host Disease Localized to Areas of Breast Irradiation After Breast Cancer: A Report of Two Cases

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Abstract

Chronic sclerotic-type graft-versus-host disease (csGVHD) is a rare yet severe complication of allogeneic stem-cell transplant (allo-SCT), characterized by localized fibrosis and inflammation. This condition can manifest in areas of prior skin injury, including sites of therapeutic radiation, posing significant diagnostic and therapeutic challenges. Here, we report two unique cases of csGVHD confined to prior breast cancer radiation sites in women who underwent allo-SCT for hematologic malignancies. Both cases were managed with a multimodal therapeutic approach involving topical and intralesional corticosteroids, systemic immunosuppression, and phototherapy, resulting in symptom resolution and improved skin pliability. In this article, we discuss these cases and summarize the literature related to instances of localized csGVHD linked to radiation, exploring elements of the isoradiotopic phenomenon and radiation-induced injury treatment outcomes of immune mediated disease.

Keywords: GVHD, irradiation, sclerotic, wound healing, transplant, myelofibrosis, leukemia.

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INTRODUCTION

Chronic sclerotic-type graft-versus-host disease (csGVHD) is a severe and often debilitating complication of allogeneic stem-cell transplant (allo-SCT).[1] The cutaneous manifestations of csGVHD are characterized by fibrosis and inflammation, often localized to previous skin injury sites, including areas of prior irradiation.[2] Despite its clinical severity and increased mortality risk, evidence-based treatment strategies remain limited. In this report, we present two cases of csGVHD confined to sites previously irradiated for breast cancer and their successful management. Additionally, we provide a review of other reported cases of chronic csGVHD localized to radiation sites.

CASE REPORTS

Case 1

A 50-year-old female with a history of stage 3 breast cancer diagnosed 7 years prior, bilateral mastectomy, adjuvant chemotherapy with letrozole, localized radiation therapy, and myeloproliferative disease complicated by post-essential thrombocythemia/polycythemia vera myelofibrosis underwent allo-SCT. About one year after allo-SCT, she complained of 2 months of chest wall pruritus, depigmentation and hypopigmentation on her upper back and inframammary chest, and thickened plaques of tight skin on her right breast. The patient had since relapsed and re-initiated ruxolitinib for myelofibrosis. A biopsy showed sclerosing dermatitis consistent with csGVHD. Morphea, scleroderma, and chronic radiation changes were excluded based on the patient's clinical history and morphology.

Treatment began with fluocinonide 0.05% cream and administrations of intralesional triamcinolone over 3 months. The patient received two photopheresis sessions per week for 9 months. The patient's csGVHD showed gradual improvement with ongoing therapy, and one year into treatment, the deep sclerotic breast changes further improved following bilateral implant removal for infection. By 18 months from diagnosis, pruritus and sclerosis had completely resolved, suggesting a combined effect of medical therapy and implant removal.

Case 2

A 54-year-old woman with history of stage 1 invasive breast cancer, treated 11 years prior with a right mastectomy, adjuvant paclitaxel chemotherapy, and local radiation therapy, subsequently developed acute lymphoblastic leukemia and underwent allo-SCT. Eight months after allo-SCT, she presented with itchy, painful skin on her right breast and chest wall. Notably, this patient had no breast implants. A biopsy showed basal layer vacuolar alteration with apoptosis and associated perivascular lymphoid infiltrate consistent with acute GVHD; however, sclerotic changes developed within 3 months of biopsy, consistent with progression to csGVHD. This progression, in conjunction with the histopathological findings, helped to rule out drug eruption, chronic radiation dermatitis, and morphea. The patient was started on topical triamcinolone 0.1% for three months, then advanced to triamcinolone intralesional injection, topical tacrolimus and fluocinonide ointment, and narrowband ultraviolet B phototherapy (NBUVB) for enhanced disease control. A final combination for 18 months of daily hydrocolloid dressing, fluocinonide ointment, topical tacrolimus, and lidocaine ointment coupled with continued NBUVB phototherapy, bimonthly intralesional steroid injections, 100 mg daily prednisone tapered to 30 mg over five months, and 200 mg daily hydroxychloroquine resulted in successful ulcer resolution.

Figure 1. *Before and after images from two patients.*

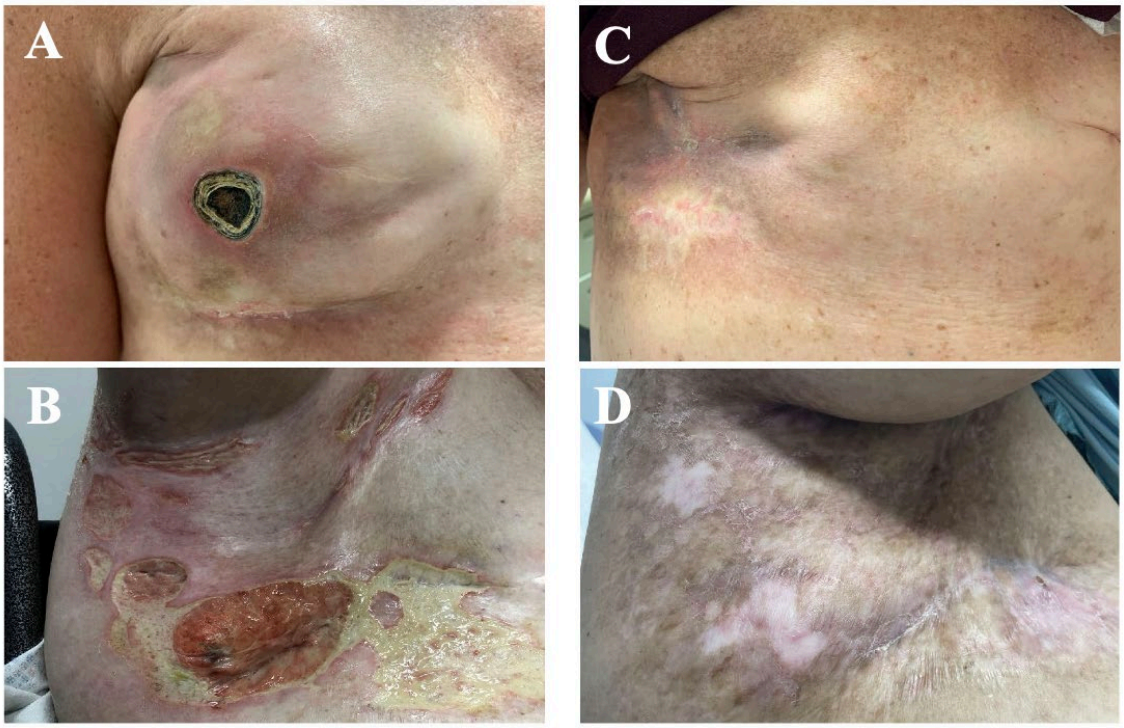

Figure 1 Legend. *1a: Initial presentation of csGVHD (patient 1); 1b: at presentation (patient 2); 1c: 3 months of topical triamcinolone treatment (patient 1); 1d: after completion of a high dose steroid taper (patient 2).*

METHODS

We completed a search through PubMed to identify other reported cases of chronic sclerotic-type graft-versus-host-disease (GVHD) developing at sites of prior radiation. The search strategy was ((GVHD OR graft-versus-host-disease) AND (cutaneous) AND (radiation OR isomorphic)). Articles were included if they met the following inclusion criteria: a localized cutaneous response specifically associated with external beam radiation therapy (EBRT) or other therapeutic radiation modalities used in oncology. Exclusion criteria were as follows: 1) cases involving full-body radiation; and 2) cases attributed to phototherapy, such as narrowband UVB, PUVA, or other light-based radiation therapies.

RESULTS

A total of six patients were identified across three studies (Table 1). Four patients received thoraco-abdominal irradiation, one received total lymphoid radiation, and another received external beam radiotherapy. In all patients, csGVHD was diagnosed between eight months to two years following allo-SCT. Of the five patients with available management data, four experienced significant improvement. Treatment strategies included cyclosporine, prednisone, azathioprine, anti-CD8 monoclonal antibody, and additional radiation.

Table 1. *Cases of chronic type graft-versus-host-disease (GVHD) developing at sites of prior radiation reported in the literature.*

Case ID	Patient characteristics	Radiation	Presentation	History of Acute GVHD	Management
Case 1: Martires et al. (2011)	54-year-old man with B-cell lymphoma	External beam radiotherapy to left thigh and left humerus for bony metastasis four months prior to HCT	Sclerotic-type cGVHD presenting 1 year after HCT corresponding to precise area of thigh radiation. No involvement of irradiated upper extremity.	No	Not published
Case 2: Okamoto et al. (1996)	20-year-old woman with aplastic anemia	Total lymphoid irradiation over the trunk and upper extremities	8 months after transplant, developed progressive, pigmented plaques with slight infiltration on the trunk, neck, back, and upper extremities 3 weeks after discontinuing cyclosporine for GVHD prophylaxis. Lesions were localized to limit of irradiation field.	No	5mg/kg cyclosporine daily. Resolution of cutaneous lesions seen at four months. Cyclosporine therapy discontinued after a total of ten months with no recurrence of cGVHD.
Case 3: Socie et al. (1989)	12-year-old boy with aplastic anemia	Thoraco-abdominal radiation (TAI)	cGVHD developing 15 months after TAI localized to the neck, trunk, and thighs with particularly clear border at inferior limit of irradiated field on thighs.	Yes	No improvement with cyclosporine, prednisone, or azathioprine. Dramatic improvement within weeks of starting TAI followed by cyclosporine and prednisone maintenance with no recurrence.

Case ID	Patient characteristics	Radiation	Presentation	History of Acute GVHD	Management
Case 4: Socie et al. (1989)	14-year-old boy with aplastic anemia	Thoraco-abdominal radiation (TAI)	cGVHD developed 15 months after TAI, beginning with lichen-planus-like features followed by "scleroderma" located precisely in radiation fields.	Yes	No improvement with cyclosporine, prednisone, azathioprine, or anti-CD8 antibody. Minor improvement with TAI. Death due to infectious and metabolic complications of cGVHD within 2 years of diagnosis.
Case 5: Socie et al. (1989)	9-year-old boy with aplastic anemia	Thoraco-abdominal radiation (TAI)	cGVHD 6 months after TAI beginning with lichen-planus like cutaneous lesions in radiation fields with increasing subcutaneous sclerosis during attempted treatment.	Yes	Unsuccessful treatment with cyclosporine, prednisone, and azathioprine followed by failure of anti-CD8 antibody. Dramatic improvement within months of TAI with near complete disappearance and no recurrence.
Case 6: Socie et al. (1989)	20-year-old male with aplastic anemia	Thoraco-abdominal radiation (TAI)	Appearance of "scleroderma" within radiation fields with eosinophilic fasciitis on biopsy more than 2 years after undergoing a second transplant due to bone marrow failure.	No	Received 1Gy fraction to pelvis and upper third of thighs where lesions delineated radiation field. Patient improved greatly with minimal subcutaneous sclerosis.

DISCUSSION

Selective Localization

Chronic sclerotic graft-versus-host disease (csGVHD) is a well-recognized complication of allo-SCT that can be localized to areas of prior radiation.[1-4] In such cases, the phenomenon is referred to as an isoradiotopic response, where radiation-induced skin injury acts as a trigger for subsequent csGVHD.[2] This process has been observed across diverse oncologic and transplant contexts with varying degrees of selective localization. In one case, a patient with B-cell lymphoma presented with csGVHD at a single irradiated site, despite receiving external beam radiotherapy to two separate areas.[2] Another case described cutaneous GVHD in the craniospinal irradiation field 8 months after allo-SCT during acute lymphoblastic leukemia treatment. Interestingly, this case initially involved acute GVHD confined to the irradiated area but later recurred as chronic GVHD affecting both irradiated and non-irradiated sites.[5] Given that removal of the infected breast implant appeared to contribute to improvement in Case 1, implant-related inflammation may represent a potential confounder in localized breast csGVHD. However, in Case 2, no implants were present, supporting an isoradiotopic mechanism for the observed localization. The cause of this selective localization remains unclear, underscoring the need for further investigation into potential underlying mechanisms such as immune activation, tissue damage, or variations in radiation dose. These cases highlight the role of radiation as a priming factor for localized csGVHD while emphasizing the complexity of this response.

Treatment Outcomes and Variability

Clinical outcomes in csGVHD localized to radiation fields show significant variability, reflecting the complex interplay between disease pathogenesis and patient-specific factors. Published reports show that some patients experience significant improvement with standard systemic therapies such as cyclosporine and prednisone, while others remain refractory despite escalating immunosuppressive regimens.[2-6] As seen in Table 1, additional reports describe the paradoxical use of thoracoabdominal irradiation to successfully treat csGVHD induced by prior radiation, highlighting the intricate relationship between radiation therapy and immune-mediated disease.[4]

Notably, prior reports of chronic GVHD post-radiation did not include phototherapy or photopheresis in their treatment regimens. However, growing evidence supports the efficacy of photopheresis in reducing fibrosis and improving skin pliability in GVHD more broadly. For example, Oliveri et al. demonstrated its benefit in steroid refractory cutaneous GVHD, with pooled response rates of up to 68% for skin involvement.[6] These data highlight the potential role of photopheresis, along with corticosteroids (topical, intralesional, and systemic), calcineurin inhibitors, and adjunctive agents, such as hydroxychloroquine, in managing post-radiation csGVHD, even though it has not yet been reported in radiation-associated cases.

Broader Implications

The observed variability in treatment responses highlights the importance of individualized therapeutic approaches in managing csGVHD.[1-6] Our cases expand upon this evidence by demonstrating the effectiveness of combining phototherapy and photopheresis with systemic and topical therapies to manage csGVHD in anatomically challenging areas like the breast. This approach not only resolved localized sclerotic changes but also alleviated associated symptoms, underscoring its potential as a strategy for csGVHD in niche contexts.

CONCLUSIONS

To our knowledge, this is the first report of csGVHD confined to prior breast cancer irradiation sites. Recognizing localized csGVHD as a distinct manifestation is critical, particularly in patients with a history of radiation. Chronic GVHD occurs in approximately 35-50% of allo-HCT recipients, and within this group, the 5-year cumulative incidence of csGVHD is about 15.5%.[7,8] In the Skert et al. series, csGVHD cases were evenly divided between generalized and localized variants.[8] Our cases and review of the literature suggest that treatment protocols for unique anatomical locations are essential. Given the variability in treatment responses, early recognition and aggressive, multimodal therapies— including breast implant removal and a combination of systemic, topical, and intralesional immunosuppression—are advisable for achieving resolution. Future efforts should focus on refining protocols for localized csGVHD, with particular attention to emerging treatments like photopheresis and NBUVB, which showed promise in our cases.

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