Treatment of sclerotic chronic graft-versus-host disease with injections of hyaluronidase

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INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a complication of allogenic hematopoietic cell transplant. cGVHD is caused by graft donor-T-cells identifying the host as a foreign entity, leading to the production of cytotoxic cells that later migrate to target organs, causing widespread inflammation and fibrosis.[1] The National Institutes of Health Consensus Working Group has developed organ-specific criteria for symptoms of cGVHD with skin manifestations, including features of poikiloderma and sclerosis.[2] Sclerotic cGVHD (ScGVHD) can mimic lichen sclerosus, morphea, and eosinophilic fasciitis.[3] Treatment options for ScGVHD include topical corticosteroids and calcineurin inhibitors, phototherapy, extracorporeal photopheresis, and systemic immunosuppressive agents. Long-term management often involves prolonged systemic immunosuppression.[4] Treatment of severe ScGVHD is exceedingly difficult with contraindications to immunosuppression.

Abbreviations used:

cGVHD:	Chronic graft-versus-host disease
HL:	Hodgkin lymphoma
IFRT:	Involved field radiation therapy
PBSCT:	peripheral blood stem cell transplant
RUE:	Right upper extremity
ScGVHD:	Sclerotic chronic graft-versus-host disease
TBI:	Total body irradiation

CASE REPORT

A 35-year-old man with history of Hodgkin lymphoma (HL) and melanoma presented to clinic with new, rapidly developing violaceous firm plaques on the trunk and extremities. HL was diagnosed 7 years prior to presentation; initial treatment included 30.6 Gy/17fx of involved field radiation therapy (IFRT) to the supraclavicular nodes. A 5.4 Gy/3fx boost to the right axilla was added because of residual soft tissue abnormality. Because of disease progression 2 years later, he was treated with an allogeneic peripheral blood stem cell transplant (PBSCT), including a conditioning course of total body irradiation (TBI). After PBSCT, he developed cGVHD involving the duodenum, descending colon, rectum, skin, and liver that was managed with long-term prednisone and mycophenolate mofetil. Three years after PBSCT, he was diagnosed with stage IIB melanoma on the right side of the neck. This was treated with wide local excision with negative right side of the neck sentinel lymph node biopsy; he was tapered off prednisone the same month.

Six months after immunosuppressant taper, he presented with new bound-down violaceous plaques on the trunk and extremities. The most severely affected area was the right upper extremity (RUE) that demonstrated severe edema from the midupper portion of the arm to the hand. Notably, patient had a history of RUE lymphedema post-HL IFRT. Groove sign was present at the biceps tendon. Skin biopsy showed sparse vacuolar interface dermatitis and perivascular inflammation with reticular dermal fibrosis, compatible with cGVHD with morphea-like features. Topical steroids and

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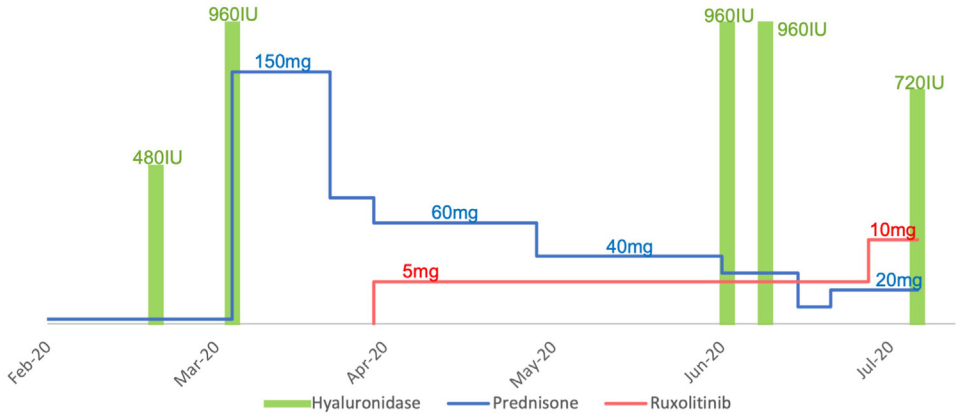

Fig 1. Timeline of immunosuppressants, immunotherapy, and administration of hyaluronidase injections.

calcineurin inhibitors did not slow plaque progression. A combination of systemic sirolimus and prednisone successfully limited progression. Unfortunately, 6 months later, he developed metastatic melanoma with innumerable liver and brain lesions, which required discontinuing all immunosuppression and initiating targeted melanoma therapy with Dabrafenib/Trametinib.

Options for managing ScGVHD were limited given metastatic melanoma. The RUE was particularly bothersome because of immobility from swelling. Intralesional injections of hyaluronidase, without dilution, were administered over 5 visits spaced 1 to 4 weeks apart (Fig 1). Injections were administered 1 cm apart in a grid-like pattern (Fig 2) at the areas with the least pliability, which varied each visit. Starting dose at the first visit was 480 IU total, which was increased to 960 IU at follow-up visits to allow for greater treatment area. There was mild pain with injection; no other adverse events occurred.

Circumferential measurements were recorded to monitor progress (Table I), revealing RUE size reduction. The elbow, midforearm, and wrist circumference decreased by 3 cm, 4 cm, and 2.25 cm, respectively. Fourteen days after the first injection, he was able to bend his right arm to touch his shoulder for the first time in 6 months and reported consistent improvement in swelling and range of motion at subsequent visits. Photographs show marked improvement in swelling (Fig 3). Notably, he received a single infusion of pembrolizumab for melanoma treatment hours after the first injection; 16 days after this infusion, he developed an acute GVHD flare secondary to immunotherapy and was started on varying doses of prednisone and ruxolitinib (Fig 1). Importantly, regular positron emission tomography scans throughout the patient's entire disease course

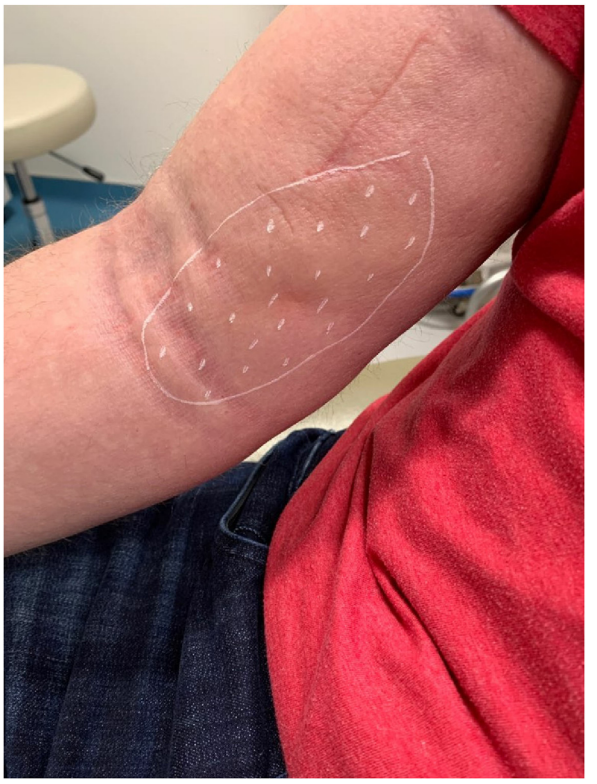

Fig 2. Injection pattern.

demonstrated that his right axillary and supraclavicular lymph nodes were disease-free prior to and after pembrolizumab infusion. Despite the concurrent systemic treatments, improvements were only noted in areas injected with hyaluronidase on the RUE and none of the ScGVHD plaques on the torso or left upper extremity improved during this time.

DISCUSSION

Management of ScGVHD is difficult, especially with contraindications to immunosuppression. Our

Table I. Circumferential measurements on the right upper extremity

Location	Before hyaluronidase	After first round of injections	After second round of injections	After fourth rounds of injections
Elbow	31 cm	35 cm	29.5 cm	28 cm
Midforearm	30 cm	28 cm	27 cm	26 cm
Wrist	21 cm	22 cm	19.5 cm	18.75 cm

Fig 3. Photographs prior to treatment (**A**) and after 4 rounds of injections (**B**).

patient with metastatic melanoma and ScGVHD treated with hyaluronidase injections had significant improvement in skin pliability and swelling. Although ScGVHD is often symmetric, our patient presented with asymmetric edema of the RUE. Lymphedema is a common side effect of axillary intensity-modulated radiation therapy, furthermore, radiation injury can exacerbate GVHD, with history of TBI associated with development of ScGVHD.[5,6] Given his past IFRT targeting the right axilla for HL treatment, TBI before PBSCT, and disease-free axillary lymph nodes on multiple imaging studies from time of metastatic melanoma diagnosis to patient's death, his presenting asymmetric RUE edema is more likely attributed to ScGVHD in context of radiation injury than metastatic melanoma.[5]

Hyaluronidase is Food and Drug Administration approved for treating hypodermoclysis and increasing absorption and dispersion of injected drugs.[7] Recently, hyaluronidase has been used off-label to treat sclerotic skin conditions, including scleredema, scleroderma, and myxedema.[7] Two recent case reports demonstrated use of hyaluronidase injections for sclerotic microstomia with amelioration of the reduced oral aperture.[8,9] The proposed mechanism of action is that these skin conditions have accumulations of hyaluronic acid in the extracellular matrix that can be degraded by hyaluronidase, allowing for fluid dispersal into the interstitial space and lymphatic drainage, potentially explaining our patient's decreased local RUE circumference and reported improved range of motion.[10]

One limitation is that the patient had concomitant systemic treatments for immune-related adverse events of immunotherapy during the same time of the hyaluronidase injections, including a course of high-dose prednisone and prolonged Janus kinase inhibitor treatment. However, the active ScGVHD on the torso and left upper extremity did not improve during this time. Therefore, the lack of improvement outside the areas injected with hyaluronidase supports our assertion that the effects seen on the RUE were due in part to hyaluronidase injections. Although it is difficult to definitively conclude that improvements in ScGVHD were because of hyaluronidase alone, injections were well tolerated, without significant adverse effects. This case report illustrates that hyaluronidase may have a role in

treatment of ScGVHD, but larger studies are needed to further clarify this.

Conflicts of interest

Dr. Sio is a member of Galera Therapeutics, Inc. and the Novocure, Inc. advisory boards and speaker bureau, which are not related to the content and scopes of this article. The other authors have no conflicts of interest to disclose.

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