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## Localization of Sclerotic-type Chronic Graft-vs-Host Disease to Sites of Skin Injury:

### Potential Insight Into the Mechanism of Isomorphic and Isotopic Responses

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### Abstract

**Background:** The mechanisms responsible for the variable manifestations of chronic cutaneous graft-vs-host disease (cGVHD) are poorly understood. Localization of sclerotic-type chronic graft-vs-host disease to sites of skin injury (isomorphic and isotopic responses), a recognized phenomenon in morphea, suggests a potential common pathway between cGVHD and other sclerotic skin conditions.

**Observations:** Four cases of sclerotic-type cGVHD developed at the site of disparate skin injuries (ionizing radiotherapy, repeated needle sticks, central catheter site, and varicella-zoster

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virus infection). We review the spectrum of previously reported cases of sclerotic and nonsclerotic cGVHD relating to external forces on the skin.

**Conclusions:** Localization of sclerotic-type cGVHD may occur after many types of skin injury, including UV and ionizing radiotherapy, needle sticks, viral infection, and pressure or friction. Recognition of this phenomenon may be helpful for the early diagnosis of sclerotic disease. Recent insights into the immunological consequences of minor skin injury may provide important clues to the underlying pathogenesis of cGVHD-mediated skin disease.

THE CUTANEOUS MANIFESTATIONS of chronic graft-vs-host disease (cGVHD) are polymorphic, ranging from epidermal disease mimicking lichen planus to sclerotic involvement of the dermis and deep connective tissue resembling morphea, systemic sclerosis, and eosinophilic fasciitis. Despite recent efforts to establish a single nomenclature of the diverse cutaneous manifestations of cGVHD,<sup>1</sup> however, the mechanisms responsible for differing cutaneous presentations remain unknown. Nonetheless, similarities between cGVHD and well-described dermatologic diseases associated with dermal and subcutaneous fibrosis suggest that a common pathogenesis may be shared by these disorders.

Previously, we described the occurrence of sclerotic-type cGVHD at sites of skin friction (eg, waistband, brassiere line) in a large series of patients who underwent allogeneic hematopoietic cell transplantation (HCT),<sup>2</sup> consistent with the isomorphic response of Koebner, a phenomenon that has been described in morphea<sup>3</sup> and a number of other dermatologic conditions.<sup>4</sup> Lichenoid-type cGVHD has also been reported at the site of previous varicella-zoster virus (VZV) infection,<sup>5-8</sup> consistent with the isotopic phenomenon, a process first proposed by Wolf et al<sup>9</sup> in 1995. However, evidence of the isotopic phenomenon associated with sclerotic-type cGVHD is not well described. Herein we report 4 additional cases that expand the spectrum of external factors associated with sclerotic-type cGVHD and suggest that the phenomenon of cGVHD at the site of skin injury may provide an important clue to the pathogenesis of cutaneous cGVHD.

## REPORT OF CASES

### CASE 1

A 34-year-old man with a history of acute myelogenous leukemia, treated with a matched allogeneic peripheral blood HCT, presented for evaluation of skin sclerosis approximately 3 years after HCT. Before HCT, chemotherapy was infused through a right subclavian venous catheter. This was complicated by cellulitis at the site of the catheter, and the line was removed. After HCT, he developed acute cutaneous GVHD that resolved with oral prednisone therapy.

On examination, a well-circumscribed 2×3-cm hypopigmented sclerotic plaque with a peripheral rim of pigmentation surrounded a small scar at the insertion site of the catheter on the lateral right side of the neck (Figure 1). Scattered indurated plaques with overlying hyperpigmentation were also present on the chest, arms, abdomen, flanks, and right ankle. A groove between fascial bundles was detected on the right forearm, as was a small sclerotic plaque above the right ankle. Biopsy findings of a plaque from the left abdomen

demonstrated thickened collagen in the deep dermis and superficial subcutaneous tissue, consistent with sclerotic-type cGVHD.

## CASE 2

A 52-year-old man with a history of chronic myelogenous leukemia and a bone marrow HCT, followed 2 years later by treatment with imatinib mesylate for relapse, presented for evaluation of progressive skin thickening approximately 8 years after HCT. Skin tightening of the abdomen, arms, and legs had begun 2 years before presentation. He had a history of multiple peripheral blood draws, most frequently from the right antecubital fossa.

Examination revealed a raised sclerotic band of the right antecubital fossa, limiting full extension at the elbow (Figure 2). The skin surrounding the band was also sclerotic. The left antecubital fossa demonstrated similar hyperpigmentation and sclerosis, without the prominent raised band. There were several areas of hyperpigmentation on the chest, lichen planus–like cGVHD changes of the axillae and neck, and diffuse subcutaneous fibrosis of the arms, lower abdomen, and lower extremities bilaterally.

## CASE 3

A 60-year-old man with a history of B-cell lymphoma treated by allogeneic peripheral blood HCT presented for evaluation of skin thickening. Eight months after HCT, the patient developed VZV reactivation of the left flank, corresponding to the T9-T10 dermatomes. He was treated with oral valacyclovir hydrochloride. After resolution, postherpetic neuralgia symptoms persisted. Eighteen months after HCT, the patient developed erythema and patchy hyperpigmentation of his chest and back. Skin fibrosis at the flanks and waistband was first reported 3 years after HCT.

At the time of examination 3½ years after HCT, multiple centrally hypopigmented sclerotic plaques of varying sizes with hyperpigmented borders corresponded to the distribution of previous VZV eruption (Figure 3). There was also diffuse firmness and rippling of the waistband area. Multiple superficial sclerotic plaques were noted on the patient's upper back and midabdomen. Subcutaneous rippling of the skin was seen on both upper arms. Skin biopsy findings of the plaque on the right abdomen demonstrated hyperkeratosis with necrotic keratinocytes in the lower epidermis, as well as collagen thickening of the dermis and thickening of the fat septae consistent with epidermal involvement of cGVHD with underlying cGVHD-related skin fibrosis.

## CASE 4

A 54-year-old man with a history of B-cell lymphoma presented for evaluation of a large sclerotic plaque involving his left thigh. His lymphoma treatment had consisted of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (the R-CHOP regimen), followed by induction chemotherapy consisting of etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone, and fludarabine phosphate before allogeneic peripheral blood HCT in October 2009. Four months before HCT, he received external beam radiotherapy consisting of 35 Gy in 15 fractions to the left thigh and 30 Gy in 10 fractions to the left humerus during the course of 1 month for

palliation of bony metastasis. He began experiencing swelling and tightening of the left thigh area approximately 7 months after HCT.

At the time of examination 1 year after HCT, a large, well-circumscribed, hyperpigmented sclerotic plaque extended circumferentially from the left midthigh to 5 cm inferior to the knee, corresponding precisely to the field of previous radiotherapy for the femoral lesion, as determined by review of the patient's radiation treatment records (Figure 4). The area was diffusely indurated without overlying surface textural changes or erythema. There was marked limitation in his range of motion at the left knee joint. There was no firmness or epidermal changes overlying the radiation treatment site of the left upper extremity. A biopsy specimen of the plaque on the left thigh demonstrated dermal and subcutaneous sclerosis, as well as necrotic keratinocytes in the basal epidermis, consistent with cGVHD. Findings suggestive of radiation fibrosis, including radiation fibroblasts, intimal thickening, or vessel dropout, were not observed. A magnetic resonance imaging study of the left thigh confirmed dermal thickening with subcutaneous edema.

## COMMENT

The geographic distribution of skin lesions on the body is a diagnostic clue to many dermatologic conditions, such as psoriasis, lichen planus, and pityriasis rosea. By the same token, recognition of diseases that demonstrate the isomorphic and isotopic phenomena in response to skin injury may be an important diagnostic clue. The Koebner isomorphic response, the appearance of a skin lesion at a site of injury that is morphologically similar to an existing skin disease, has been associated with many diseases, most frequently psoriasis.<sup>4</sup> Boyd and Neldner<sup>10</sup> proposed that, for a disease to be considered isomorphic, it must be reproducible in all patients by a variety of insults (excluding external infective or allergic elements), and it must duplicate the pathogenesis of the disease as it occurs naturally. In cases 1 and 2, minor external skin injury (subclavian venous catheter insertion with cellulitis on the neck and repeated blood draws in the antecubital fossa, respectively) was a localizing factor for the development of sclerotic-type cGVHD.

In 1995, Wolf et al<sup>9</sup> defined the term *isotopic* as the occurrence of a new, unrelated disease in the same location as a previously healed disease. The interval between the primary trauma and appearance of disease may be extremely variable, ranging from weeks to years, although most occur in the setting of active disease.<sup>11</sup> Most commonly, VZV infection has been reported as the initial skin insult; however, additional reports have described isotopic responses after herpes simplex virus infection and thrombophlebitis.<sup>9,12</sup> Although lichenoid-type cGVHD has been described at healed VZV sites,<sup>5-8</sup> (and in a dermatomal distribution on previously unaffected skin),<sup>13,14</sup> an isotopic presentation of sclerotic-type cGVHD occurring at the site of a previous VZV infection has not been frequently reported<sup>15</sup> (Table). In case 3, sclerosis developed in the dermatomal distribution of previous VZV reactivation; however, the patient exhibited other sites of skin involvement, including prominent sclerosis in the area of the waistband, demonstrating overlap between isomorphic and isotopic disease. Proposed mechanisms of the isotopic phenomenon include residual hypersensitivity to viral or tissue antigens, collagen rearrangement due to scarring, and damage to cutaneous nerves despite the presence of clinically normal-appearing skin.<sup>9,11</sup>

In case 4, the occurrence of sclerotic-type cGVHD was entirely limited to the site of a radiation portal, a phenomenon that has been termed an *isoradiotopic* response. Other diseases, including acne, lichen planus, and pemphigus vulgaris, have similarly been described at sites of ionizing radiotherapy, conventional external beam radiotherapy, and UV radiation.<sup>4,20–30</sup>

In 1989, Socie et al<sup>15</sup> described 4 patients with sclerotic-type cGVHD occurring within radiation portals. This phenomenon has been also observed with acute GVHD and lichenoid-type cGVHD.<sup>15,16</sup> Although ionizing radiotherapy may lead to radiation fibrosis,<sup>31</sup> the dose and fractionation of radiation given to this patient are unlikely to have led to fibrosis within 7 months.<sup>32</sup> Furthermore, skin biopsy findings did not demonstrate radiation fibroblasts (atypical stellate cells with large nuclei containing clumped chromatin). Radiation-induced morphea may also be considered in the differential diagnosis for this case. It is characterized by focal dermal and subcutaneous sclerosis indistinguishable from morphea and may occur within weeks to months of radiotherapy exposure.<sup>33</sup> However, radiation-induced morphea has been reported almost exclusively in the setting of radiotherapy for breast cancer,<sup>34,35</sup> and the presence of necrotic keratinocytes in the biopsy specimen favors a diagnosis of GVHD rather than radiation-induced morphea.<sup>33</sup> The other site of focal irradiation in this patient (left arm) did not develop sclerotic-type cGVHD despite receiving a comparable dose of radiation, suggesting an additional unknown localizing factor.

Although the present cases and those reported previously in the setting of GVHD demonstrate the challenge of differentiating isomorphic and isotopic phenomena based on their current definitions, the phenomena may offer avenues to explore underlying disease mechanisms. The isotopic mechanism may be related to dysregulation of the local immune response in an area of healing that renders it susceptible to the development of a second injury. This concept is similar to *locus minoris resistentiae*, that is, a localized area with diminished resistance to disease.<sup>36</sup> The 2 events need not share the same mechanism; rather, the first disease predisposes the area to development of the second. Ruocco et al<sup>37</sup> proposed that a vulnerable district of immune alteration occurs, resulting in a reduction (eg, tumor development) or induction (eg, autoimmune conditions) of effective immunity. Desbarats et al<sup>38</sup> theorized that irradiation nonspecifically depletes local immune regulatory factors, allowing a permissive environment for the development of GVHD.

The propensity of sclerotic-type cGVHD to develop at sites of skin injury, a phenomenon also observed in morphea, may also reflect shared disease pathways between cGVHD and other skin conditions. Recent analyses in cutaneous systemic lupus and systemic sclerosis implicate type I interferon (IFN) as a central factor in the initiation and maintenance of inflammatory and fibrotic autoimmune processes.<sup>39,40</sup> Immunohistochemical studies by our group and others suggest that type I IFN plays a similarly significant role in oral and cutaneous lichen planus–like cGVHD.<sup>41–43</sup> Signaling by IFN can be activated by pathogen- and damage-associated molecular patterns through toll-like receptor molecules.<sup>44,45</sup> Damage to skin produces an influx of plasmacytoid dendritic cells that produce type I IFN in response to toll-like receptor 7– and toll-like receptor 9–dependent recognition of nucleic acids from damaged cells; the inflammatory process is further exacerbated in hosts with ongoing autoimmune reactions.<sup>38,46,47</sup> Similarly, viral infection can have systemic and local

effects on IFN production. Cytomegalovirus infection is a well-recognized risk factor for the development of GVHD.<sup>48</sup> Locally, VZV has been shown to produce a massive recruitment of plasmacytoid dendritic cells into affected skin.<sup>49</sup> Therefore, if the overall levels of IFN production are elevated systemically owing to the ongoing inflammatory processes of cGVHD, as in systemic lupus erythematosus and systemic sclerosis, then local augmentation of the process may result in highly localized exacerbations of the inflammatory and fibrotic processes.

Much remains to be learned about the protean manifestations of cGVHD in the skin. The tendency of cGVHD to localize to areas of skin injury may prove a useful clinical clue to begin elucidating these intricacies. In addition, an awareness of isotopic and isomorphic presentations of cGVHD-mediated skin disease will allow for early disease detection in patients with sclerotic-type GVHD, prompting appropriate intervention before significant functional disability occurs.

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**Figure 1.**  
Sclerotic plaque localized to right side of the neck at the site of a previous subclavian venous catheter placement.



**Figure 2.** Morphealike chronic cutaneous graft-vs-host disease with a fibrous band at site of multiple previous needle sticks in the right antecubital fossa.



**Figure 3.** Localization of morphealike chronic cutaneous graft-vs-host disease to the distribution of a previous varicella-zoster virus infection.



**Figure 4.** Isoradiotoxic response in chronic cutaneous graft-vs-host disease presenting as a well-circumscribed plaque confined to the field of previous radiotherapy of the left distal femur.

Reported Cases of GVHD Localized to Sites of Injury

Table.

Source	No. of Patients	Sex/Age, y	Primary Disease	Type of Tx	Type of Localized GVHD	Antecedent Injury	Latency <sup>a</sup>	Other Skin GVHD Involvement	Other Organ GVHD Involvement <sup>b</sup>	Reaction Type
Case 1	1	M/34	AML	PBSC	Sc	Subclavian venous catheter cellulitis	3 y	Yes	Yes	Isomorphic/isotopic
Case 2	1	M/52	CML	BM	Sc	Repeated blood draws	Unknown	Yes	Yes	Isomorphic
Case 3	1	M/60	NHL	PBSC	Sc	VZV	2.5 y	Yes	Yes	Isotopic
Case 4	1	M/54	MHL	PBSC	Sc	External beam radiotherapy	7 mo	No	No	Isoradiotopic
Patel et al, <sup>2</sup> 2008	11	5M; 6 F/20–57	MM (n=3), NHL(n=3), ALL(n=2), MDS(n = 1), CML(n = 1), CLL(n=1)	PBSC (n=8), BM(n=3)	Sc	Waistband and brassiere band pressure/ friction	Variable	Yes (n=9), no(n=2)	Yes(n=10), no (n=1)	Isomorphic
Baselga et al, <sup>5</sup> 1996	1	F/16	MLD	BM	Non-Sc	2 Episodes VZV (48 days apart)	55 d <sup>b</sup>	Yes	NR	Isotopic
Lacour et al, <sup>6</sup> 1999	1	M/4	ALL	BM	IMon-Sc	2 Episodes VZV (2 months apart)	6–9 mo (est) <sup>b</sup>	NR	Yes	Isotopic
Cordoba et al, <sup>7</sup> 2000	1	F/34	ALL	BM	Mon-Sc	2 Episodes VZV (8 days apart)	1 mo <sup>b</sup>	No	No	Isotopic
Sanli et al, <sup>8</sup> 2003	2	F/23, 47	CML	BM	Non-Sc	VZV	3 mo	Yes	Yes(n=1), NR (n = 1)	Isotopic
Socie et al, <sup>16</sup> 1989	4	M/9–20	AA	BM	Sc	Thoracoab-dominal radiotherapy	5 mo to 3.5 y <sup>c</sup>	No	Yes(n=1), NR(n=3)	Isoradiotopic
Zwaan et al, <sup>17</sup> 1980	1	M/35	AA	BM	Non-Sc	Total nodal irradiation therapy	1–2 mo (est)	Yes	Yes	Isoradiotopic
Fenyk et al, <sup>18</sup> 1978	1	F/14	AA	BM	Sc	Measles exanthem	2 mo	No	No	Isotopic
Vasallo et al, <sup>19</sup> 2009	4	2M; 2 F/5–57	ALL (n = 1), Diamond-Blackfan anemia (n=1), MM(n=2)	BM	Sc(n=1), Non-Sc (n=3)	Narrow band UVB(n=1), sun exposure (n=3)	Immediate	Yes	Yes(n=1), NR(n=3)	Isomorphic

Abbreviations: AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; BM, bone marrow; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; est, estimated; GVHD, graft-vs-host disease; MDS, myelodysplastic syndrome; MLD, metachromatic leukodystrophy; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; Non-Sc,

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nonsclerotic (includes acute, erythematous, and lichenoid-types GVHD); NR, not reported; PBSC, peripheral blood stem cell; Sc, sclerotic (includes morphhealike cGVHD, sclerodermalike cGVHD, and cGVHD-related fasciitis); Tx, transplant; VZV, varicella-zoster virus.

<sup>a</sup> Indicates from injury to GVHD.

<sup>b</sup> Indicates after first outbreak of VZV.

<sup>c</sup> One patient in this series had 2 courses of transcatheter arterial infusion (TAI) before development of chronic GVHD due to recurrence of the underlying disease; the latency to chronic GVHD is reported as the time from first TAI conditioning.