Dermatol Ther (Heidelb) (2013) 3:215–222
DOI 10.1007/s13555-013-0029-7

CASE REPORT

Isomorphic Sclerotic-Type Cutaneous Chronic Graft-Versus-Host Disease: Report and Review of Chronic Graft-Versus-Host Disease in a Cutaneous Immunocompromised District

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Received: May 21, 2013 / Published online: July 2, 2013

ABSTRACT

Background: Patients who have received a hematopoietic cell transplantation can develop graft-versus-host disease (GVHD). The liver, the gastrointestinal tract, and/or the skin can be affected by GVHD. Chronic sclerotic-type cutaneous GVHD can occur at sites of repetitive skin friction.

Purpose: To describe isomorphic sclerotic-type GVHD and review chronic GVHD appearing in a cutaneous immunocompromised district.

Methods: The clinical features of a 74-year-old man with mantle cell lymphoma who developed chronic sclerotic-type cutaneous GVHD localized to the waistband area—which had been exposed to repetitive skin injury—after a second hematopoietic cell transplantation are reported. Using the PubMed database, an extensive literature search was performed on chronic GVHD.

Case report and review: The cutaneous immunocompromised district is an area of skin whose local effective immunity has been altered, thereby permitting the development of a dysimmune reaction, infection, or tumor at the site. A cutaneous isomorphic response refers to a disease-associated skin lesion occurring at the site of physical injury that is morphologically similar to the existing condition. Cutaneous chronic GVHD can occur at sites of repetitive skin trauma as an isomorphic response. The patient developed sclerotic-type GVHD in a cutaneous area that had previously experienced repeated irritation, friction, and pressure. Isomorphic sclerotic-type GVHD—in either the waistband area or brassiere area or both—has also been observed in other patients. In addition, cutaneous chronic GVHD has been described not only at the location of a previous, unrelated, and healed skin disease as an isotopic response, but also at the cutaneous site of earlier exposure to radiotherapy or ultraviolet radiation as an isoradiotopic response.

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Conclusion: Sclerotic and nonsclerotic skin lesions of chronic GVHD can occur not only as an isomorphic response, but also as either an isotopic response or an isoradiotopic response in a cutaneous immunocompromised district.

Keywords: Dermatology; Graft-versus-host disease; Immunocompromised district; Isomorphic response; Isoradiotopic response; Isotropic response; Sclerosis

INTRODUCTION

Graft-versus-host disease (GVHD) may affect the liver, gastrointestinal tract, and/or skin of patients who have received a hematopoietic cell transplantation [1]. Chronic sclerotic-type cutaneous GVHD can occur at sites of repetitive skin friction [2]. A man with isomorphic cutaneous GVHD presenting as sclerotic-type skin lesions on the waistband is described and chronic GVHD of the skin appearing in a cutaneous immunocompromised district is reviewed.

METHODS

Informed consent was obtained from the patient for being included in the study. Using the PubMed database, an extensive literature search was performed for the following topics: chronic cutaneous GVHD, isomorphic response, isotopic response, isoradiotopic response, and immunocompromised district. The results of the search were used to secure reports of chronic GVHD appearing in a cutaneous immunocompromised district.

CASE REPORT

A 74-year-old man with a history of mantle cell lymphoma had received two prior hematopoietic cell transplants. The patient experienced several weeks of asymptomatic, yet progressive, stiffening of the skin on the distal right extremity and lower abdomen. The patient also noted that the skin on the lateral lower chest and upper abdomen had a rippled appearance.

The mantle cell lymphoma was diagnosed in 2005. In September 2008, the patient underwent an autologous stem cell transplant using BEAM (carmustine, etoposide, cytarabine, and melphalan) as a conditioning regimen. The patient achieved a complete remission.

The patient's lymphoma relapsed in July 2009 and he participated in a clinical trial receiving intranodal injections of an immunotherapy Ad-ISF35 (immune stimulating factor 35). The patient was withdrawn from the study after injection #3 because of lack of clinical improvement. From October 2009 to April 2010, the patient completed six cycles of bendamustine and rituximab. The patient achieved a complete clinical response, but had residual inguinal lymphadenopathy; subsequently, new nodes were discovered.

The patient underwent an allogeneic hematopoietic peripheral blood stem cell transplant using a sex-matched unrelated donor in May 2010; the conditioning regimen was fludarabine, melphalan, and rituximab. The patient engrafted without complications and again achieved a complete remission. The patient subsequently developed biopsy-confirmed acute cutaneous GVHD that resolved after treatment with topical corticosteroids.

In early February 2013, the patient noted that his right forearm and hand were becoming stiff and indurated. Similarly, the area of his abdomen that came in contact with the waistband of his pants was becoming

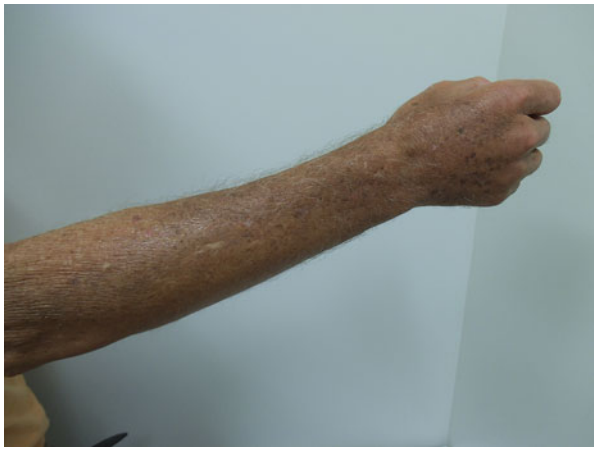

Fig. 1 Sclerotic-type chronic cutaneous graft-versus-host disease presenting with firm induration and hyperpigmentation of the extensor right forearm and dorsal hand

indurated. Also, the area of his lateral abdomen above his waistband became rippled. The observed changes continued to progress.

Cutaneous examination in late March 2013 showed the patient's right forearm to be hyperpigmented and indurated; similarly, his dorsal hand was also firm and there was no elasticity of the overlying skin (Fig. 1). The patient's lower abdomen, particularly the areas that came in contact with the waistband of his pants and belt, was smooth and hyperpigmented with areas of erythema; in addition, the lower abdomen had developed a confluent morphea-like sclerotic dermal induration (Figs. 2a, b, 3, 4). The skin of the patient's lateral lower chest and abdomen had a "cellulite" appearance (Figs. 2, 4).

Biopsy from the right forearm, the waistband area, and the lateral upper abdomen all showed similar findings: sclerotic and thickened collagen in the reticular dermis. In the waistband area, these changes were predominantly in the mid reticular dermis; there was also loss of the perieccrine fat and a sparse lymphocytic superficial perivascular infiltrate. In the forearm and the upper

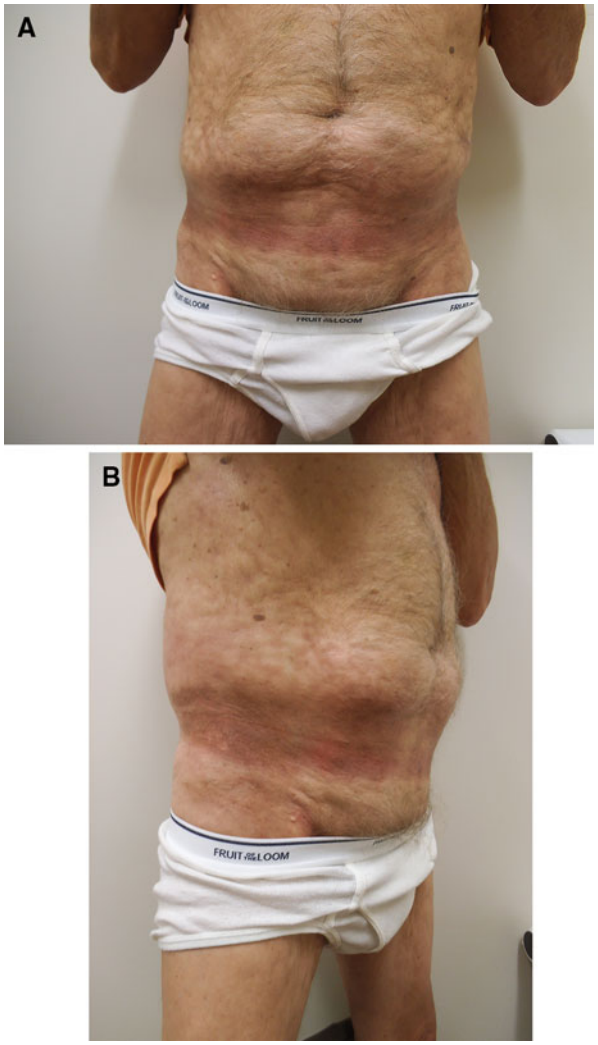

Fig. 2 Frontal (**a**) and right side (**b**) views of the lower chest and abdomen demonstrating sclerotic-type chronic cutaneous graft-versus-host disease. An isomorphic response to the repetitive 'trauma' from the patient's belt and pants shows a hyperpigmented—with areas of erythema—confluent zone of morphea-like induration involving the waistband area. The lateral areas of his lower chest and upper abdomen have a rippled, cellulite-like appearance

abdomen, the sclerosis began in the deep reticular and extended into the subcutaneous fat; lymphoplasmacytic inflammation was noted at the junction of the deep reticular dermis and subcutaneous fat in the forearm, and extravasated erythrocytes were observed in the reticular dermis of the abdomen.

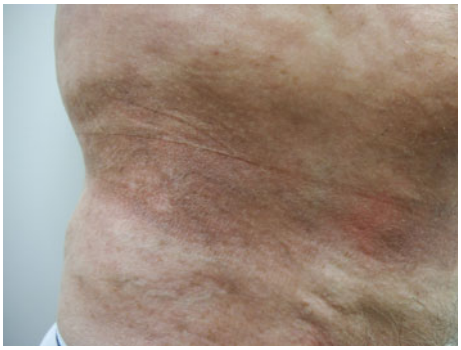

Fig. 3 Isomorphic sclerotic-type chronic cutaneous graft-versus-host disease. The closer view shows the extensive linear skin fibrosis in the right lower abdomen waistband area

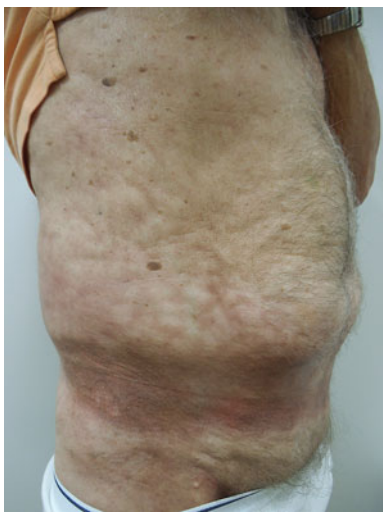

Fig. 4 A closer view of the sclerotic involvement of subcutaneous fat presenting with a rippled or 'cellulite' appearance of the skin in a patient with sclerotic-type chronic cutaneous graft-versus-host disease. Fibrosis of the skin in the waistband area demonstrating the patient's isomorphic sclerotic-type chronic cutaneous graft-versus-host disease can also be seen on the lower abdomen

Correlation of the clinical presentation and pathology findings established the diagnosis of chronic sclerotic-type cutaneous GVHD; the localization of GVHD to the waistband area demonstrates an isomorphic response to the repetitive irritation, friction, and pressure from the patient's belt and pants. The patient was treated with oral prednisone (initially at 10 mg per day for 2 weeks, and tapered to 5 mg per day and 2.5 mg per day for 2 weeks each) and topical tacrolimus 0.1% gel twice daily. Clinical improvement was observed, with the dermal plaques becoming less firm.

DISCUSSION

GVHD of the skin has traditionally been classified as either acute or chronic. The appearance of signs and symptoms of GVHD within the first 100 days after transplant is now referred to as classical acute GVHD. More recently, additional categories of late acute GVHD have been adopted: persistent (in which acute GVHD continues past day 100), recurrent (in which acute GVHD has resolved and then relapses), and late onset (in which acute GVHD appears after day 100) [1]. Acute GVHD can also occur as an overlap syndrome with chronic GVHD in which features of both can concurrently present.

Chronic GVHD includes sclerotic and nonsclerotic (such as eczematous, exfoliative, ichthyosiform, lichen planus-like, papulosquamous, poikilodermatous, and psoriasiform) skin lesions [1, 3–5]. To date, risk factors influencing cutaneous chronic GVHD have not been clearly elucidated. However, proposed markers of sclerotic-type GVHD include CD3 T-cell dose in the graft, eosinophilia, positive antinuclear antibodies, and antecedent nonsclerotic chronic GVHD skin involvement [6]. Also, the use of reduced-intensity conditioning regimens may result in survival of recipient antigen-presenting cells that could be associated with chronic GVHD.

Recently, total body irradiation—particularly in individuals who received a reduced-intensity conditioning regimen—has been proposed as an important risk factor for the subsequent

development of sclerotic-type GVHD [6]. Specific mechanisms that may account for sclerotic-type GVHD after total body irradiation include: (1) type I interferon (alpha/beta); (2) that radiotherapy produced elevated interferon gamma (which along with interferon-inducible chemokines is up regulated in sclerotic-type GVHD skin); and (3) promotion and maintaining of T-cell cytotoxicity secondary to local production of interferon and downstream factors. Also, nonspecific radiation effects may predispose patients to develop chronic GVHD; these include damage to keratinocytes, depletion of local immune regulatory factors, and stimulation of systemic cytokine production [6].

The immunocompromised district was introduced by Rucco et al. [7] to describe the occurrence of either dysimmune reactions, infections, or tumors in an area of skin that has been selectively damaged and immunologically marked as the result of either a reduction or induction of local effective immunity. Conceptually, the immunocompromised district unifies three types of skin responses: isomorphic, isotopic, and isoradiotopic [8].

The appearance of a skin lesion at the site of physical trauma or injury that is morphologically similar to an existing disease was originally presented by Koebner in 1872 with regard to psoriasis [9]. However, the Koebner phenomenon occurring at a localized area with diminished resistance to disease—a 'locus minoris resistentia'—has subsequently been observed to occur in several diseases [10]. In this setting, it has also been referred to as the isomorphic response [11].

Wolf's isotopic response, originally described in 1995, most commonly is associated with a herpetic infection. It refers to the development of a new cutaneous condition at the location of a previous, unrelated, and already healed skin disease [12]. In contrast, when the source of injury to the skin is ionizing radiotherapy (or subsequently expanded to also include conventional electron beam radiotherapy and ultraviolet radiation), the subsequent isomorphic phenomenon has been referred to as an isoradiotopic response [11, 13].

In addition to the patient in the present report who developed GVHD localized to areas of skin friction from the waistband of his pants, isomorphic chronic cutaneous GVDH has also been described in several patients with sclerotic-type GVHD skin lesions. The patients include other men with waistband-associated chronic GVHD and women with brassiere band and/or waistband-related chronic GVHD [1, 2, 11, 14]; of note, similar to the reported patient with isomorphic (waistband) and idiopathic (right forearm and hand) sclerotic-type GVHD, other individuals with concurrent isomorphic chronic cutaneous GVHD and idiopathic sclerotic-type GVHD have been observed [11]. The source of injury associated with isomorphic sclerotic-type GVHD has also been the sites of injections of subcutaneous interferon alpha on the abdomen [15], previous subclavian or central venous catheter placement without [14] or with [11] subsequent cellulitis, repeated needle sticks to obtain blood from the right antecubital fossa [11], suction blisters [16], and Bacillus Calmette Guerin therapy [16]. In addition, chronic GVHD with sclerotic-type skin lesions has been observed to occur at the healed sites of prior acute GVHD [16, 17].

Albeit rare, isomorphic nonsclerotic-type chronic GVHD has also been observed. If, as suggested by Girault et al. [18], striae distensae are accepted to represent traumatized dermal zones, then the lichenoid eruption of chronic GVHD that were observed would be an

isomorphic response. Clinically, the skin lesions presented as finely squamous, atrophic erythematous plaques in the striae distensae of a 23-year-old man who received a bone marrow transplant for acute leukemia at the age of 18; microscopically, the lesions showed a superficial lichenoid dermatitis [18].

Isotopic sclerotic-type and lichen planus-like chronic GVHD have both been reported in hematopoietic cell transplantation patients most commonly localized to the sites of prior varicella zoster virus infection [11, 16, 17, 19–23]. Dermatomal lichen planus-like chronic GVHD has also been observed in transplant patients who do not have a prior history of varicella zoster virus infection [24, 25]; it has been postulated that a subclinical viral infection may explain their distinctive presentation of chronic cutaneous GVHD [4].

Sclerotic-type GVHD has also occurred at the site of prior measles virus exanthema. A 14-year-old girl received an allogeneic bone marrow transplant for aplastic anemia. The patient developed measles 7 months post-transplant and the viral exanthema resolved over 3 weeks. However, within the next 2 months, poikiloderma and sclerotic-type chronic GVHD appeared in the same areas as her acute measles viral exanthem [26].

Sclerotic-type chronic GVHD within radiation ports of four patients was described by Socie et al. [27] in 1989. It was also reported more recently by Martires et al. [11] to occur on the left distal femur in a 58-year-old man with B-cell lymphoma who received electron beam radiotherapy to this location 4 months prior to an allogeneic peripheral blood hematopoietic cell transplant. Isoradiotopic sclerotic-type chronic GVHD also occurred following ultraviolet radiation from incidental sun exposure in a 51-year-old man with multiple myeloma following allogeneic stem cell transplant (which was preceded by an autologous peripheral blood stem cell transplant) [28]. Acute GVHD and nonsclerotic-type GVHD have also been described following either radiotherapy, narrow band ultraviolet B, or incidental sun exposure [27–29].

Recently, Martires et al. [11] described a 60-year-old man with both isomorphic and isotopic chronic sclerotic-type GVHD. The patient had received an allogeneic peripheral blood hematopoietic cell transplantation for treatment of B-cell lymphoma and developed a varicella zoster virus infection on the T9–T10 dermatomes of his left flank 8 months later. The patient subsequently developed sclerotic-type GVHD not only in the waistband areas (isomorphic response) but also in the healed varicella zoster virus infection scars (isotrophic response) 3 and 3.5 years after transplant, respectively [11]. Also, similar to the present patient with a cellulite-appearing abdomen, Martires et al's patient also had subcutaneous chronic GVHD involvement characterized by cutaneous rippling of the skin on both upper extremities [11].

CONCLUSION

The cutaneous immunocompromised district is an area of skin whose local effective immunity has been altered, thereby permitting the development of a dysimmune reaction, infection, or tumor at the site. A cutaneous isomorphic response refers to a disease-associated skin lesion occurring at the site of physical injury that is morphologically similar to the existing condition. A cutaneous isotopic response refers to the development of a new skin condition at the location of a previous, unrelated, and healed skin disease. An isoradiotopic response refers to a new skin disease appearing at the cutaneous site of earlier exposure to radiotherapy or ultraviolet

radiation. Cutaneous chronic GVHD can occur with sclerotic or nonsclerotic skin lesions. The present patient developed chronic sclerotic-type cutaneous GVHD localized to the waistband area—which had been exposed to repetitive skin injury—after his second hematopoietic cell transplantation. Similar to this patient, isomorphic sclerotic-type GVHD in either the waistband area or brassiere area, or both, has also been observed in other patients with localized and repeated skin trauma (such as irritation, friction, and pressure) to their skin. In summary, sclerotic and nonsclerotic skin lesions of chronic GVHD not only occur as an isomorphic response, but also can develop as an isotopic response or an isoradiotopic response in a cutaneous immunocompromised district.

ACKNOWLEDGMENTS

No funding or sponsorship was received for this study or publication of this article. Dr Cohen is the guarantor for this article and takes responsibility for the integrity of the work as a whole.

Conflict of interest. Dr Cohen declares no conflict of interest.

Compliance with Ethics Guidelines. Informed consent was obtained from the patient for being included in the study.

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