

Nodular Sclerodermatous Chronic Cutaneous Graft-Versus-Host Disease (GvHD): A New Clinicopathological Variant of Cutaneous Sclerodermatous GvHD Resembling Nodular/Keloidal Scleroderma

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Abstract: Cutaneous chronic graft-versus-host disease (GvHD) has a broad spectrum of clinicopathological presentations, the most common ones being poikiloderma, lichen planus-like eruptions, lichen sclerosus-like lesions, morphea-like plaques, and deep sclerosis. New forms of chronic cutaneous GvHD with different clinicopathological characteristics have been described, most of them mimicking cutaneous manifestations of autoimmune diseases. We report the case of a 35-year-old man who underwent allogeneic stem cell transplantation for a therapy-associated acute myeloid leukemia and developed an acute GvHD with involvement of skin and gastrointestinal tract. He subsequently presented with chronic sclerodermatous cutaneous GvHD, followed by the appearance of indurated erythematous papules and plaques located on his back, resembling the nodular/keloidal form of cutaneous scleroderma on both clinical and histopathological grounds. This peculiar clinicopathologic presentation of chronic cutaneous GvHD was never described previously.

Key Words: nodular graft-versus-host disease, chronic graft-versus-host disease, sclerodermatous graft-versus-host disease, nodular scleroderma, keloidal scleroderma

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INTRODUCTION

Graft-versus-host disease (GvHD) is a multisystem disorder affecting recipients of allogeneic bone marrow transplantation, characterized by common involvement of skin and mucous membranes.¹ Two main types of GvHD are typically recognized: the acute form that occurs within the first 100 days after the bone marrow transplantation and the chronic form that usually starts more than 100 days after transplantation.¹ However, overlap forms characterized by features of

both acute and chronic types may be observed.¹ GvHD is still the primary cause of morbidity and mortality in patients who undergo bone marrow transplantation, and despite measures to avoid it, continues to have a significant incidence representing the main limitation for the more extensive use of this therapeutic option.²

Chronic GvHD can occur de novo, but more frequently follows an acute GvHD immediately after it (progressive chronic form) or after a disease-free period (quiescent form).² The more frequent clinical presentations include poikiloderma, lichen planus-like eruptions, lichen sclerosus-like lesions, morphea-like plaques, and deep sclerosis.³ Among these types of chronic GvHD, the sclerodermatous form usually appears later and is characterized by the most severe skin involvement, requiring a complex therapeutic management. Besides the aforementioned variants, other forms of cutaneous chronic GvHD with different clinicopathological features have been described (Table 1), many of them mimicking cutaneous manifestations of autoimmune diseases, prompting some authors to consider cutaneous GvHD as “the new great simulator.”^{4–18}

We report a case of a sclerodermatous GvHD resembling the nodular/keloidal type of cutaneous scleroderma and propose the term nodular sclerodermatous GvHD for this new variant of the disorder.

CASE REPORT

A 35-year-old man underwent allogeneic stem cell transplantation in October 2014 for a therapy-associated acute myeloid leukemia diagnosed in July 2014, 3 years after semi-castration and chemotherapy for a testicular carcinoma. In February 2015, he suffered an episode of acute GvHD followed by cytomegalovirus and Epstein-Barr virus reactivation and was treated with plasmapheresis. More than 1 year later, in April 2016, he presented with a recurrent GvHD (skin grade 1, gastrointestinal grade 4), for which he was treated with extracorporeal photopheresis and ultraviolet 1 (UV1). Since then, he started to notice a progressive induration of the skin with areas of hyperpigmentation and hypopigmentation. In the following months, hard erythematous papules and plaques developed on his back in the absence of trauma or other causative factors (Fig. 1). A biopsy of one of the lesions was performed in November 2016 with the clinical suspicion of specific cutaneous manifestations of his hematological disease.

Histopathologically, the superficial part of the lesion resembled a hypertrophic scar with loss of the epidermal rete ridges,

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TABLE 1. Variants of Chronic GvHD With Their Main Clinicopathological Features

Author Group	Type	Main Sites of Involvement	Clinical Features	Histopathology
Kawakami et al ⁴	Papulosquamous/psoriasiform	Trunk, extremities	Guttate, annular or erythematous scaly patches	Psoriasiform epidermal hyperplasia and vacuolar degeneration of the basal layer
Creamer et al ⁵	Ecematous	Trunk, extremities	Scaly erythroderma	Spongiosis and vacuolar degeneration of the basal layer
Wei et al ⁶	Atopic dermatitis–like	Back, abdomen, extremities	Dry skin, erythema, papules with perifollicular accentuation and pronounced pruritus; in some cases, elevated IgE and peripheral eosinophilia	Acanthosis, parakeratosis, spongiosis, necrotic keratinocytes, lymphocyte exocytosis, and vacuolar degeneration of the basal layer; superficial and mid-dermis inflammatory infiltrate admixed with eosinophils and melanophages
Goiriz et al ⁷	Lupus erythematosus–like	Face	Malar rash	Similar to lichenoid chronic GvHD
Hu et al ⁸	Hypertrophic lupus erythematosus–like	Head and neck area, trunk	Scaly verrucous plaques	Pseudoepitheliomatous squamous epithelium with lichenoid infiltrates; follicular plugging, focal basement membrane thickening, and dermal mucin deposition
Peñas et al ⁹	Leopard skin	Generalized	Well-defined hyperpigmented macules	Sclerosis in the reticular dermis and slight vacuolar degeneration of the basal layer
Naschitz et al ¹⁰	Panniculitis and fasciitis	Extremities	Panniculitis-like	Deep dermal sclerosis, septal panniculitis, and fasciitis
Kaffenberger et al ¹¹	Eruptive angiomatous	Lower extremities, trunk	Vascular plaques and nodules with a tendency to ulcerate	Anastomosing networks of thin-walled vessels with vague lobular growth pattern; epidermal acanthosis, peripheral collarette, disorganized fibroblast-rich, fibrotic stroma
Haemel et al ¹²	GvHD with keratinocyte-derived amyloidosis	Lower extremities	Reticulate hyperpigmentation, erosions, and sclerodermatous changes	Vacuolar degeneration of the basal layer, necrotic keratinocytes and amyloid-K in the papillary dermis; sparse inflammatory infiltrate with melanophages
Beroukhim et al ¹³	Sclerodermatous with mucin deposition	Thigh	Indurated elevated lesion	Dermal fibrosis with associated mucinosis
Ifrah et al ¹⁴	Acanthosis nigricans–like	Neck, large folds	Brown hyperkeratotic papules and plaques	Hyperkeratosis, papillomatosis and acanthosis with keratinocyte necrosis
Doherty et al ¹⁵	Erythema multiforme–like	Palmoplantar, fingers, palatal	Tender targetoid, erythematous papules, and vesicles	Similar to conventional GvHD
Park et al ¹⁶	Acral wart-like	Palms and soles	Hyperkeratotic papules and plaques	Epidermal acanthosis with dyskeratotic keratinocytes; vacuolar alteration of the basal layer and necrotic keratinocytes around follicles and eccrine glands
Valks et al ¹⁷	Follicular keratosis/keratosis pilaris–like	Extensor surfaces of extremities, face	Perifollicular erythema with hyperkeratotic, spiny papules and hyperpigmentation	Overlapping features between conventional lichenoid and sclerodermatous GvHD
Llamas-Velasco et al ¹⁸	Comedonal GvHD	Face, trunk	Follicular papules and open comedones	Sclerotic dermis and dilated follicular infundibula with keratotic plugging
Present case	Nodular sclerodermatous GvHD	Back	Indurated, erythematous papules and plaques	Superficial and mid-dermis similar to hypertrophic scar with vertically oriented vessels and proliferation of myofibroblasts

vertically oriented blood vessels, and a proliferation of myofibroblasts. In the deeper part of the biopsy, sclerodermatous changes with thickening of the collagen bundles and a sparse inflammatory infiltrate could be observed (Fig. 2).

On the basis of the clinical and histopathological findings, a diagnosis of nodular sclerodermatous cutaneous chronic GvHD was made. The patient is still treated with extracorporeal photopheresis with stable lesions 2 months after the diagnosis of this peculiar form of the disease.

DISCUSSION

Our patient had a chronic sclerodermatous GvHD and developed irregular, indurated papules and plaques characterized histopathologically by changes similar to those observed

in a hypertrophic scar lying over a sclerodermatous area. Although chronic cutaneous GvHD is characterized by a large number of presentations (Table 1), to the best of our knowledge, the clinicopathological features observed in our patient were never reported before and reveal striking similarities to nodular/keloidal scleroderma.

The nodular or keloidal type is one of the rarest variant of scleroderma, with only 17 cases published in the last 12 years.^{19–31} The majority of these patients are women presenting with lesions located mostly on the trunk (particularly the back) and the neck.^{19–31} Most patients with nodular or keloidal scleroderma had systemic sclerosis, but some had localized cutaneous scleroderma,^{19–31} and in one case, the lesions were arising in the context of linear scleroderma.²¹ The histological



FIGURE 1. A, Sclerodermatous skin changes with areas of hyperpigmentation and hypopigmentation and presence of numerous, hyper-trophic scar-like erythematous papules and plaques; (B) Detail of the scar-like lesions.

features range from scleroderma with keloidal-like nodules to scar-like tissue. Patients usually have a poor response to common treatments, such as methotrexate, psoralen and ultraviolet A, and systemic or intralesional steroids.^{19–31} The nomenclature of nodular/keloidal scleroderma has been the subject of debate, and some authors suggested that there are histopathological differences between a purely nodular and a purely keloidal form.³² In addition, there has been an attempt to differentiate cases associated with systemic sclerosis from those associated with cutaneous scleroderma (morphea),³² but the presence of overlap cases and of different histopathological features in different lesions from the same patient suggests that nodular/keloidal scleroderma represents a variant of the disease with variable clinicopathological presentation.²⁹ In this context, Rencic et al³³ in 2003 suggested that 2 clinical variants should be distinguished: one characterized by keloidal or nodular lesions arising directly on sclerodermatous skin and the other showing typical keloids on normal skin in scleroderma patients who have a family history of keloids. However, in our opinion, only the first variant represents a genuine nodular/keloidal form of scleroderma.

Sclerodermatous GvHD usually has a later onset than lichenoid GvHD and it may be more disabling because

patients experience limitations in their movements, often seriously compromising their quality of life.¹ The trunk is commonly affected and, besides sclerodermatous induration, shows typically widespread hyperpigmentation and hypopigmentation,¹ as observed in our patient. Unlike scleroderma, acral involvement is uncommon.¹ Histologically, mild lichenoid or vacuolar epidermal changes may be observed in a proportion of cases.¹ The main pathological findings are observed in the dermis, characterized by thickened collagen fibers and variably dense inflammatory infiltrates. Depending on the type of sclerodermatous GvHD, the sclerotic changes may be more prominent in the upper dermis (lichen sclerosus-like type) or in the mid-dermis and deep dermis (morphea-like type).¹ Two further variants present with sclerosis located predominantly in the subcutaneous fat (panniculitis-like type) or in the fascia (fasciitis-like type).¹⁰ In all of these variants, it is common to observe a slight increase of dermal fibroblasts and a variable lymphohistiocytic and plasmacytic inflammatory response. The nodular variant observed in our patient, in contrast to the aforementioned types, was characterized by a scar-like tissue located in the upper part of the dermis overlying a more conventional sclerodermatous area in the deeper dermis. In fact, a superficial biopsy would

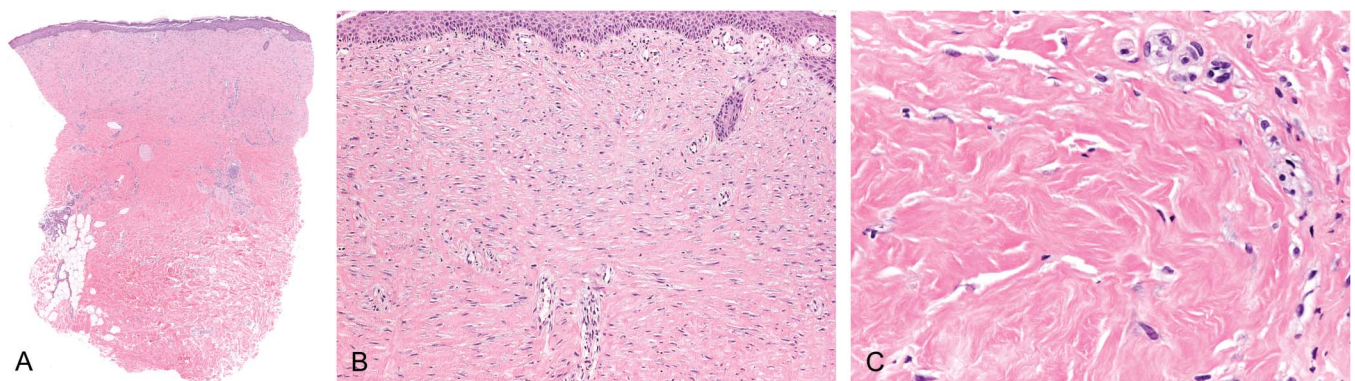


FIGURE 2. Histology (A) shows 2 different areas characterized by (B) vertically oriented blood vessels and a proliferation of myofibroblasts in the superficial part of the biopsy, and (C) thickening of the collagen bundles with a sparse inflammatory infiltrate in the deeper part.

fail to show the diagnostic features and may be thus misinterpreted as a scar.

The pathogenesis of nodular lesions in patients with sclerodermatous GvHD is not known. Even in nodular/keloidal scleroderma, the exact mechanism for the formation of scar-like tissue is unclear, although a complex interaction between cytokines, matrix cellular proteins, and local factors are considered crucial triggers for an exaggerated response to injury.³¹ In 2011, Arndt et al³⁴ described the aberrant overexpression of Fussel-15 in fibroblast of keloidal lesions and localized scleroderma. This member of the Ski/Sno family of transforming growth factor-beta/bone morphogenic protein (TGF- β /BMP) signaling repressors is involved in the early phase of wound healing, and its permanent expression could be implicated in the pathogenesis of both keloids and scleroderma.³⁴

In sum, the clinicopathological features observed in our patient and characterized by nodular, scar-like aspects represent a new variant of chronic cutaneous sclerodermatous GvHD, once again underlying the similarities between GvHD and autoimmune skin disorders, and showing that these unfortunate patients may present with lesions that overlap with all variants, even the least common ones, of these conditions.

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