

CASE REPORTS

Chronic Graft-Versus-Host Disease Presenting as Bullous Lesions

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Abstract. Graft-vs-host disease is still the leading cause of morbidity and mortality in patients undergoing bone marrow transplantation. It is important to start treatment early to reduce the severity and consequences of this complication. Cutaneous lesions are often the presenting complaint of graft-vs-host disease and presage visceral involvement.

We present the case of a 45-year-old woman with multiple myeloma who underwent autologous and subsequently allogeneic bone marrow transplantation with hematopoietic precursors. She developed bullous lesions with fluid elimination on the abdomen and legs. Biopsy findings were compatible with graft-vs-host disease and immunosuppressive therapy was increased. She subsequently presented oral lichenoid lesions and sicca syndrome. The bullous lesions progressed to painful ulcers that healed leaving highly sclerodermatous skin with substantial hyperpigmentation.

Bullous lesions are a rare form of presentation of chronic graft-vs-host disease. In such cases, the diagnosis may not be suspected initially, particularly when the lesions are isolated and internal organs are not involved.

Key words: chronic graft-vs-host disease, bullous lesions.

LESIONES AMPOLLOSAS COMO FORMA DE PRESENTACIÓN DE UNA ENFERMEDAD DE INJERTO CONTRA HUÉSPED CRÓNICA

Resumen. La enfermedad de injerto contra huésped (EICH) continúa siendo la primera causa de morbilidad y mortalidad en los enfermos con trasplante de médula ósea, de modo que un tratamiento precoz es importante para reducir la gravedad y las consecuencias de esta complicación.

Las lesiones cutáneas son en muchas ocasiones la forma de presentación de una EICH y anuncian la afectación visceral.

Presentamos el caso de una paciente de 45 años con mieloma múltiple a la que se realizó primero un trasplante autólogo y posteriormente un trasplante alogénico de médula ósea con precursores hematopoyéticos. Desarrolló lesiones ampollasas con eliminación de líquido en el abdomen y los miembros inferiores. Se realizó una biopsia que fue compatible con una EICH y se aumentó el tratamiento inmunodepresor. La paciente posteriormente presentó lesiones liquenoides orales, síndrome seco y las lesiones ampollasas que evolucionaron a úlceras dolorosas, que cicatrizaron con un intenso aspecto esclerodermiforme e importante hiperpigmentación.

Las lesiones ampollasas son una forma de presentación excepcional en la EICH crónica, y en estos casos la sospecha inicial del diagnóstico puede ser difícil, sobre todo cuando se presentan de forma aislada sin afectación de órganos internos.

Palabras clave: enfermedad injerto contra huésped crónica, lesiones ampollasas.

Introduction

Despite constant advances, graft-vs-host disease (GVHD) continues to be the primary cause of morbidity and mortality in bone marrow transplantation (BMT).¹

Chronic GVHD is an immunologic complication of allogeneic BMT that occurs in 30% to 50% of patients who survive the acute phase of transplantation.² It usually develops more than 100 days after transplantation, and between 90%

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Table 1. Mucocutaneous Manifestations of Chronic Graft-Versus-Host Disease

Specific Lesions
<i>Typical specific skin lesions</i>
Lichenoid lesions of early or late presentation
Sclerodermatous lesions
Precursor lesions: Leopard skin eruption-like lesions, intense follicular keratosis, inflammatory plaques
Localized sclerodermatous lesions
Generalized sclerodermatous lesions
Eosinophilic fasciitis-like lesions
Lichen sclerosus et atrophicus-like lesions
<i>Atypical specific skin lesions</i>
Mucinosis
Bullous lesions
Morbilliform rash
Pigmentary changes: diffuse melanoderma, total leukoderma, etc.
Pityriasis rosea-type lesions
Ichthyosiform lesions
Recall phenomenon-type lesions
Angiomatous lesions
<i>Oral lesions</i>
Focal or diffuse reddening of the oral mucosa, xerostomia, leukoplakia, lichenoid lesions, mucosal atrophy or ulcers, mucosal sclerosis, caries, and periodontal disease
<i>Nail lesions</i>
Ulceration of the lunula, periungual erythema, nail atrophy, pterygium, longitudinal striations, trachyonychia, nail fragility, onycholysis, and opacification and thickening of the nail plate
Nonspecific Lesions Simulating Autoimmune Diseases
Sjögren Syndrome: xerophthalmia and xerostomia
Lupus erythematosus: malar erythema, photosensitivity, cicatricial alopecia, discoid lupus-type lesions
Dermatomyositis: Gottron papules, periungual erythema, poikiloderma
Systemic sclerosis: sclerodermatous lesions, reticulated hyperpigmentation
Others: overlap syndrome
Higher Incidence of Infectious Diseases
Bacterial infections due to gram-positive cocci
Infections due to Candida species and opportunistic deep mycoses
Herpesvirus infections: varicella zoster, herpes simplex, and cytomegalovirus
Higher Incidence of Malignant Diseases
Oral squamous cell carcinoma, melanoma, nonmelanoma skin cancer, and Kaposi sarcoma



Figure 1. Bullous lesions on the lower abdomen.



Figure 2. Bullous lesions on the lower limbs with a spontaneous nonpurulent exudate.

and 100% of cases have mucocutaneous manifestations (Table).

In 25% to 50% of cases, chronic GVHD is preceded by acute GVHD, which is therefore the principal risk factor for suffering this chronic complication. However, in other patients, chronic GVHD develops with no previous lesions; this situation has been called *de novo* chronic GVHD.

Chronic GVHD typically presents with an early lichenoid phase and a late sclerodermatous phase, though sclerodermatous lesions can develop with no previous lichenoid phase, and can also occur in the final phase of other forms characterized by bullous or ichthyosiform lesions.

The sclerodermatous phase, therefore, usually develops in late stages of BMT (500 days post-transplant), and is frequently preceded by a leopard skin-like eruption, follicular keratosis, an erythematous or violaceous rash, patchy hyperpigmentation, or inflammatory plaques. Sclerodermatous lesions may be localized but are more commonly widespread.

To our knowledge, bullous lesions have been reported as the form of presentation of *de novo* chronic GVHD in only 2 cases, neither of which was associated with hematopoietic stem cell transplantation as in our patient. We present the case of a patient with multiple myeloma, treated by autologous transplantation and later by mini allogeneic transplantation; she developed bullous lesions as the first sign of chronic GVHD.

Case Description

The patient was a 45-year-old woman who, in March 2000, based on a lytic lesion in the right femur, was diagnosed with plasmacytoma and subsequently with multiple myeloma. A femoral prosthesis was implanted and she was treated with chemotherapy and radiation therapy.

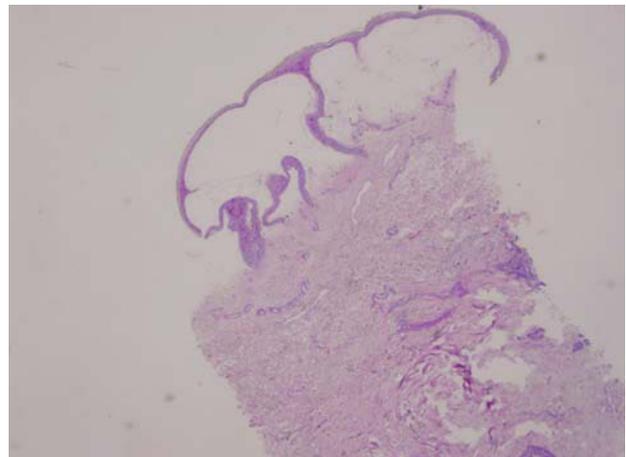


Figure 3. Low-magnification (x4) photomicrograph in which staining with hematoxylin-eosin shows a large bulla with subepidermal cleavage.

In May 2001, autologous hematopoietic stem cell transplantation was performed, achieving partial remission. In March 2002, she underwent mini allogeneic hematopoietic stem cell transplantation with complete remission of the myeloma.

She was first seen in the dermatology department in July 2003 for widespread, painful bullous lesions on the lower abdomen and lower limbs (Figures 1 and 2); a clear, nonpurulent exudate spontaneously drained from these lesions. At this time there was no systemic disease and no mucosal lesions.

Fresh skin biopsy was performed for histopathologic study and immunofluorescence. Histopathology revealed a large bulla with a subepidermal plane of cleavage and which did not contain acantholytic cells (Figure 3). The epidermis presented necrotic keratinocytes (Figure 4) and hydropic changes in the basal layer, but with no necrosis with adjacent lymphocytes (satellite cell necrosis). The

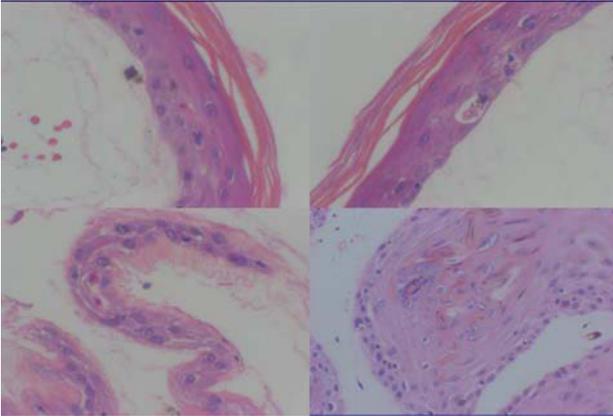


Figure 4. The epidermis contains necrotic keratinocytes, but with no satellite cell necrosis, characteristic of graft-vs-host disease. The eccrine ducts are also affected, with changes similar to those observed in the epidermis. Hematoxylin-eosin, original magnification $\times 20$.

eccrine ducts were involved and showed changes similar to those found in the epidermis. There was minimal sclerosis and a minimal inflammatory infiltrate in the dermis, and melanophages and telangiectatic vessels were seen. Direct immunofluorescence was negative. These nonspecific changes were considered to be compatible with an early phase of GVHD.

The complementary studies performed at that time did not show other organs to be involved and there were no signs of recurrence of the myeloma. Tissue cultures were also performed, and these were negative.

With the diagnosis of chronic bullous GVHD, treatment was started with oral prednisone and cyclosporine. Despite this, the skin lesions developed into large, indurated, intensely painful ulcers with progressive hyperpigmentation.

In September 2003, the patient developed lichenoid lesions on the oral mucosa and a sicca syndrome. In April 2004, the skin ulcers had almost completely resolved, and the skin acquired a sclerodermatous appearance with intense hyperpigmentation.

Treatment was given with psoralen-UV-A (PUVA) (a total of 40 sessions) with a significant improvement in the pain, in the induration, and in some of the lichenoid lesions that began to appear on the sclerodermatous lesions.

Discussion

Hematopoietic stem cells are the most primitive cells and are able to establish a complete renewal of the cell population as they retain their potential for lymphopoietic and hematopoietic differentiation. In contrast to bone marrow cells, these cell populations do not contain mature lymphocytes able to induce GVHD, and their use in this

type of transplant has been shown to reduce the risk of GVHD.

In recent years, there has been an increasing use of peripheral blood stem cells instead of bone marrow cells as they achieve adequate hematopoietic reconstitution and there has been a fall in the incidence of acute GVHD. However, the association with chronic GVHD is unclear. Some authors have suggested that allogeneic BMT with peripheral blood stem cells may be associated with a higher risk of developing chronic GVHD³; others report that the skin and female genital tract are more commonly affected in recipients of BMT with peripheral blood stem cells who develop a chronic GVHD than in recipients of BMT with bone marrow cells.⁴ There are also authors who have found no significant differences in the frequency of chronic GVHD or lesions of the skin or female genital tract.⁵

Extensive skin disease (more than 50% of the body surface) is a variable associated with a poorer prognosis in patients with chronic GVHD.⁶ Furthermore, cutaneous chronic GVHD usually heralds extracutaneous involvement. For this reason, early diagnosis is of great importance in order to start treatment as soon as possible. A number of atypical skin manifestations of chronic GVHD have been described, such as mucinosis,⁷ morbilliform rash,⁸ pigmentary changes (diffuse melanoderma or total leukoderma),⁹⁻¹¹ pityriasis rosea-type lesions,¹² ichthyosiform lesions,¹³ recall phenomenon,¹⁴ angiomatous lesions,^{15,16} and bullous lesions.^{17,18}

The presence of bullous lesions as the first manifestation of chronic GVHD has been reported very rarely,^{17,18} However, these lesions have been observed in grade IV acute GVHD and progress to toxic epidermal necrolysis.¹⁹ As occurred in our case, bullous lesions that develop in cases of chronic GVHD appear late with respect to when BMT was performed, after 500 days, and all cases subsequently progress to a sclerodermatous form. Unusually, our patient developed bullous lesions as the first manifestation of GVHD, and this was followed by lichenoid lesions in the mouth and on the legs, over the sclerodermatous lesions. The presence of bullous lesions in GVHD may be explained by the presence in the dermis of intense edema that induces the formation of bullae.

The initial diagnosis of chronic GVHD presenting with bullous lesions without extracutaneous manifestations can be difficult, as the histopathologic findings are compatible but not diagnostic. A high index of suspicion is therefore necessary to make the diagnosis early and start treatment as soon as possible.

Peñas et al²⁰ reviewed 17 cases of sclerodermatous GVHD in a series of 457 BMT patients. The mean time to the onset of sclerotic lesions was 529 days. In some cases, these lesions were preceded by leopard skin eruption-like lesions or by follicular keratosis. No previous lesions were identified in our case, and the bullous lesions that developed into ulcers and then to sclerodermatous lesions appeared de novo.

It has been reported that UVA-1 has beneficial effects in patients with chronic sclerodermatous GVHD that does not respond to other therapies, such as systemic treatments or extracorporeal photochemotherapy.²¹ In our patient, treatment was started with PUVA due to the persistent pain and the appearance of lichenoid lesions; after 40 sessions, this achieved a good clinical result, which enabled systemic immunosuppression to be reduced.

In summary, we report a case of chronic GVHD that presented with bullous skin lesions that subsequently progressed to ulcers and then to sclerodermatous lesions. Despite the usually poor response to treatment in these patients, the response to PUVA in our case was excellent.

Conflicts of Interest

The authors declare no conflicts of interest.

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