Tegumentary manifestations of graft-versus-host disease in bone marrow transplantation recipients*

*Manifestações tegumentares da doença enxerto contra hospedeiro em pacientes transplantados de medula óssea**

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Abstract: Graft-versus-host disease (GVHD) is a systemic disease that occurs in patients that receive immunocompetent lymphocytes. Pathophysiology involves an immunologic reaction between transplanted lymphocytes and tissues of the host, through an immune attack of donor T cells against recipient cells that differ from the donor's by histocompatibility antigens. It is a major complication of allogeneic hematopoietic stem cell transplantation. GVHD skin involvement is frequent and contributes to morbidity and mortality of bone marrow transplantation. Dermatologists have an important role on patient´s evaluation, providing early diagnosis of GVHD disease and its complications, so as to follow-up these patients. In this review, we emphasize the skin manifestations of GVHD, taking into account our 14-year personal experience at Centro Nacional de Transplante de Medula Óssea/INCA/MS.
Keywords: Graft vs host disease; Bone marrow transplantation; Transplantation, homologous.

Resumo: *A doença enxerto contra hospedeiro (DECH) é uma síndrome sistêmica que ocorre em pacientes que recebem linfócitos imunocompetentes. A fisiopatologia envolve uma reação imunológica entre linfócitos transplantados e tecidos do hospedeiro, e ocorre por ataque imune das células T do doador às células do hospedeiro, as quais diferem daquelas pelos antígenos de histocompatibilidade. É, assim, uma complicação primária do transplante de medula óssea (TMO) alogênico. O envolvimento cutâneo é freqüente na DECH e contribui para a morbidade e mortalidade do TMO. O dermatologista tem papel importante na avaliação dos pacientes auxiliando no reconhecimento precoce da DECH e suas complicações e no acompanhamento clínico desses pacientes. Nesta revisão os autores enfatizam as manifestações cutâneas da DECH, tendo como base sua experiência pessoal no acompanhamento de pacientes portadores de DECH transplantados de medula óssea no Centro Nacional de Transplante de Medula Óssea/Inca/MS, no Rio de Janeiro, nos últimos 14 anos.*
Palavras-chave: Doença enxerto contra hospedeiro; Transplante de medula óssea; Transplante alogênico.

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INTRODUCTION

Bone marrow transplantation (BMT) is an effective treatment against several types of diseases, whether hematological or not. Infusion of bone marrow, however, can generate countless complications with associated cutaneous manifestations, some of which due to the process of recognizing the introduced graft.[4-6] In addition, even in the pre-transplantation phase (conditioning regimen), the drugs used in the ablation of the marrow may also lead to specific mucocutaneous alterations.[7] Furthermore, while new immunosuppressant drugs and antibiotics enable greater safety in the performing of bone marrow transplantations, they may also generate dermatological complications (Chart 1). Thus the precise differential diagnosis between these various dermatological manifestations is fundamental for early recognition of the most frequent and often serious complication of the transplantation, namely graft-versus-host disease (GVHD).

GRAFT-VERSUS-HOST DISEASE

Graft-versus-host disease is the major complication of allogeneic bone marrow transplantation and an impediment to extending the application of allotransplantations.

GVHD was first described in experimental animals, in which it was observed that the infusion of genetically matched splenic cells, transplanted from animals with bone marrow aplasia induced by radiation, was followed by serious disease, the most common clinical manifestations of which were asthenia, diarrhea and cutaneous lesions.[8]

CHART 1: Mucocutaneous complications related to bone marrow transplant

1. Cutaneous manifestations of HVGD	● Acute ● Chronic
2. Drug induced	● Immediate type hypersensitivity, for example, urticaria with ATG* ● Cutaneous reactions to drugs, for example, penicillin and allopurinol ● Chemotherapy-induced acral dermatitis ● Erythema induced by busulfan/hyperpigmentation in the axillae and groin ● Erythema induced by TBI ● Erythema induced by nifedipine ● Erythema induced by vancomycin (venous infusion) ● Acneiform eruption due to corticoids ● Facial Hypertrichosis due to cyclosporine ● Alopecia secondary to chemotherapy/c-GVHD*/ TBI*
3. Infections	● Bacterial: cellulitis / furunculosis / local catheter infection/ Septic embolia/ paronychia ● Fungal: dermatophyte, Candida, Aspergillus, Malassezia furfur ● Viral: herpes simplex; herpes-zoster; CMV (rare)
4. Immunologically mediated lesions	● Erythema multiforme (for example, response to infection by herpes simplex ● Eczema ● Transference of contact hypersensitivity by donor
5. Neoplasias	● Relapse of base disease, for example, subcutaneous chloroma as seen in ANL*/CML*/leukemia cutis ● Basal cell and squamous cell carcinomas, actinic keratosis (above all in extremely immunocompromised patients with c-GVHD*)

* ATG: antithymocyte globulin; TBI: total corporal irradiation; c-GVHD: chronic graft-versus-host disease; CMV: cytomegalovirus; ANL: acute non-lymphoblastic leukemia; CML: chronic myeloid leukemia

The first human BMTs were performed by Thomas *et al*.[9] in 1957. Now hundreds of BMTs are performed annually around the world. The failure of the graft and GVH disease were the two main reasons why BMTs were discontinued until techniques for defining human histocompatibility were developed.[10-14] In 1966, Billingham[15] formulated prerequisites for the development of GVHD. First, the graft should contain immunologically competent cells; second, the host should be unable to present an effective response to destroy the transplanted cells; and third, the host should express tissue-specific antigens that are not extant in the donor. Thus in accordance with these criteria, GVHD may occur in any situation in which tissues containing immunocompetent cells (blood components, bone marrow, solid organs) are transferred between individuals. The age of the host, allotransplantation, the fact that the donor is female and the host male, the use of radiation in the conditioning regimen along with inadequate dosages of immunosuppressant drugs, all increase the risk for developing GVHD (Chart 2).

Around 1970, the tests for evaluation of histocompatibility and the immunosuppressive regimens reduced the rate of graft failure. Transplants from donors that had matched human leukocytic antigens (histocompatibility antigens or HCA, also known as antigens of the major histocompatibility complex or MHC) greatly increased the success of transplantation and reduced mortality from GVHD.[14] Prophylactic immunosuppressive regimens with methotrexate and cyclosporine also reduced the incidence of acute GVHD (a-GVHD).[16] However, GVHD is still the most important problem following the performance of an allogeneic BMT, since it occurs in a percentile that varies from 40 to 50% of those receiving grafts and is responsible for 15 to 40% of the acute BMT mortality.[13,14,16,17]

GVHD is divided into acute and chronic forms, in accordance with time lapse and histopathological clinical findings. It is classified as acute when it develops within the first 100 days after the allogeneic BMT. It is characterized clinically by the exanthema triad: hepatitis (jaundice) and gastroenteritis (abdominal pain, diarrhea). Chronic GVHD (c-GVHD) is a multiorganic syndrome, with characteristics similar to those of autoimmune and collagen diseases. It usually occurs 100 days after the BMT. These distinctions are important, because the treatment regimens vary, and the prognosis is different for each form. The incidence of tumoral relapse decreases with the development of GVHD due to the known effect of the graft against disease.[18]

IMMUNOPHYSIOPATHOLOGY OF GRAFT-VERSUS-HOST DISEASE

GVHD results from activation of the T lymphocytes derived from the donor through histocompatibility antigens originating from the tissues of the host. The immunological mechanisms that promote acute or chronic lesions, however, are not identical. The current theory for the immune response of GVHD suggests that a-GVHD results from the activation of T lymphocytes alloreactive of the graft; while c-GVHD may involve mechanisms that are as much alloreactive as autoreactive.[19]

ACUTE GRAFT-VERSUS-HOST DISEASE

The immune response of a-GVHD occurs in two phases, (Figure 1) one afferent and the other efferent. In the afferent phase, CD4+ and CD8+ T cells react to the class I and II alloantigens of the host; this occurs on the surface of the antigen-presenting

CHART 2: Procedures associated with increased risk of GVHD

Procedure	High-risk groups
BMT	Patients without prophylaxis for GVHD; elderly; non identical recipient of BMT
Infusion of leukocytes from donor (containing mature cells or T cells of the donor)	Patients that received infusion of leukocytes to prevent or treat hematological malignancy after allogenic BMT
Transplant of solid organs (organs containing lymphoid tissues)	Recipients of small intestine transplant
Transfusion of non-irradiated blood components	Neonates and fetuses; patients with congenital immunodeficiency syndromes; patients undergoing immunosuppressive chemoradiotherapy; patients receiving blood transfusions directly from partially matched HLA

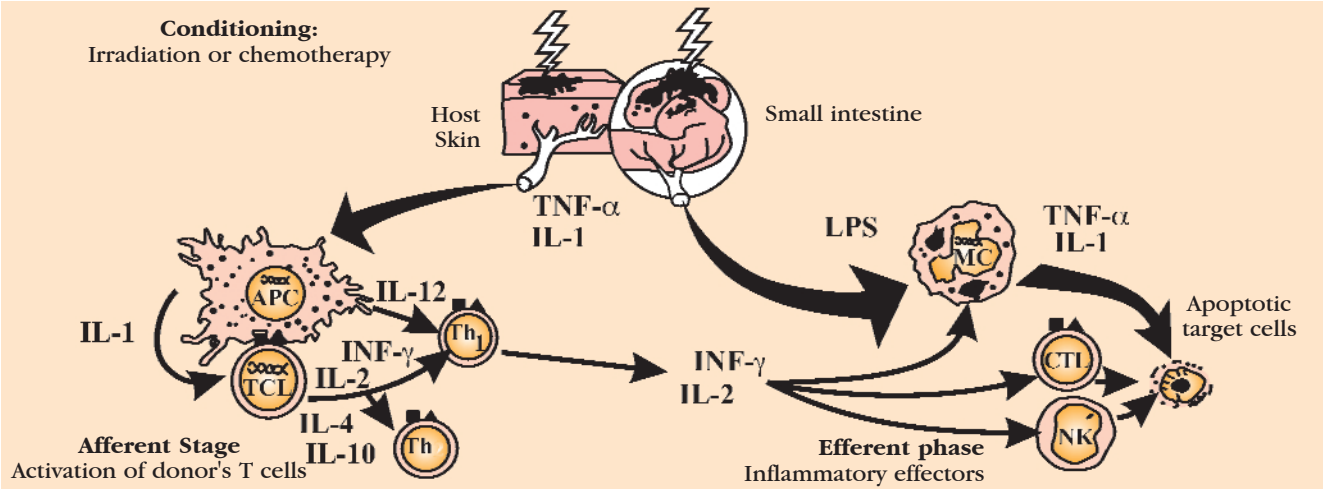

FIGURE 1: Immunophysiopathology of GVHD: immune response occurs in two phases: afferent and efferent.

cells (APC). The exact mechanism for the formation of these alloantigens is still not well understood. The conditioning regimen seems to initiate the immune response by damaging the tissues of the host, such as the intestinal mucous membrane, liver and other organs, by inducing the liberation of cytokines, especially interleukin-1 (IL1) and tumoral necrosis factor (TNF-α), as well as permitting the penetration of enteric bacterial liposaccharides. The T cells are stimulated by IL-1 and by co-stimulating signals to produce interleukin-2 (IL-2). Under influence of IL-2, the CD4+ and CD8+ T cells expand clonally. They differentiate into efferent cells, which induce the graft-versus-host response. These efferent cells are activated by co-stimulators and proinflammatory cytokines, such as interferon gamma (IFN-γ) and interleukin 12 (IL-12), into efferent T helper cells 1 (including cytotoxic lymphocytes CD4+ and CD8+), which direct the graft-versus-host response. The allogeneic T cells can also transform themselves into suppressor T helper 2 cells that are antigen-specific, under the influence of the interleukins 4 and 10 (IL4 and IL10).

The efferent phase of a-GVHD is not yet well understood. Activated T cells produce a cytokine storm, including IL-2, IL-3, IL-4, IFN-γ and others. These mediators recruit and activate effector cells, including additional lymphocytes, macrophages, and natural killer cells (NK) that attack both the donor's tissues and those of the host. MHC class II alloantigens are preferentially formed in the skin, intestine and in the epithelium of the biliary duct by the action of IFN-γ They can facilitate the attack on the epithelial cells. NK cells are considered responsible, as much in experimental models as in humans, for the epithelial damage of GVHD, targeting cells that do not express antigens from autologous (their own) surfaces. They are activated during GVHD by cytokines IL-2, IL-12 and IFN-γ, starting from which they produce numerous other cytokines, such as hematopoietic colony-stimulating factors, TNF-α and IFN-γ. Thus, the beginning of a-GVHD is dependent on the NK cells present in the grafted marrow, whose activity has been augmented.

CHRONIC GRAFT-VERSUS-HOST DISEASE

T cells from the donor present in the host usually suffer a thymic selection, in which auto-reactive clones are eliminated. However, the post-fetal thymus is not efficient in the elimination of reactive T cells of the host; they can also be compromised still further by various other factors, such as advanced age, conditioning regimes, previous a-GVHD or the use of cyclosporine. In c-GVHD, some mature T cells from the host escape elimination and target histocompatibility antigens, resulting in the persistence of clones allo and auto-reactive T cells.

c-GVHD is characterized by epithelial damage caused by mononuclear and fibrose cells. CD8+ cytotoxic T lymphocytes predominate in the infiltrate and can directly induce tissue damage. However, other effector cells (NK cells, macrophages and mastocytes) and cytokines (TNF-α) can mediate the cytotoxicity. Soluble mediators induce MHC molecules in the target tissues and stimulate the proliferation and production of collagen by the fibroblasts. The chronic activation and degranulation of the mastocytes contribute to the induction of fibrosis in c-GVHD. The polyclonal activation of B cells can result in the formation of several autoantibodies, including antinuclear, antiplaque, antierythropoietic, antiepithelial and rheumatoid factor.

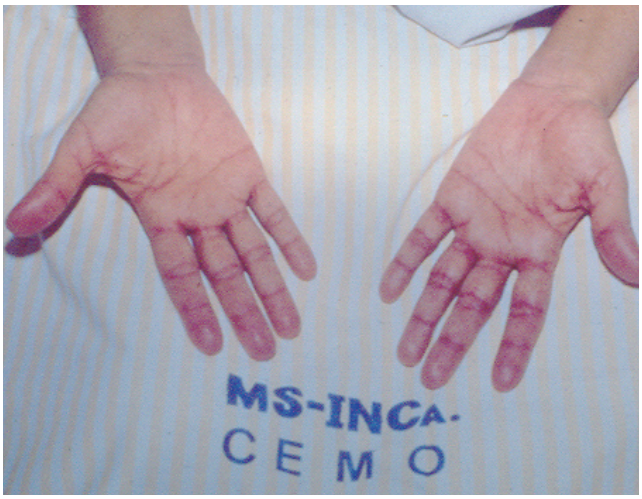

FIGURE 2: a-HVGD - palmar erythema

TEGUMENTARY MANIFESTATIONS OF GRAFT-VERSUS-HOST-DISEASE

Acute Graft-Versus-Host Disease (a-GVHD)

It occurs in the first three months following BMT, frequently between day 7 and 21. The principal organs involved are the immune system, skin, liver, gastrointestinal tract and lungs.[20] Cutaneous manifestations are generally the first sign, characterized by erythema on the palmoplantar regions, preceded commonly by ardor or pruritus. (Figure 2) As the disease progresses, maculopapular exanthema involves the thorax, neck, cheeks and causes a violaceous coloration of the ears (Figure 3).[20,21] Involvement of the mucosa is difficult to distinguish from chemotherapy-induced mucositis. There may also be erythroderma exfoliativa or a cutaneous picture that resembles toxic epidermal necrolysis, which may remain localized in the pressure areas or may be disseminated (Figure 4).[22]

a-GVHD may be graded according to the gravity of the disease[23] into four stages, and the prognosis is related to the clinical stage, as demonstrated in charts 3 and 4.

Histologically a-GVHD is characterized by four degrees of damage to the epidermis: Degree I - vacuolization of the basal keratinocytes; Degree II - vacuolization of the basal keratinocytes and the presence of dyskeratotic keratinocytes; Degree III - focal rifts of the basal layer; and Degree IV - epidermis totally separated from the dermis. The interpretation of the results from the skin biopsy, mainly in the initial phase after the BMT may be difficult, due to the similarity with findings after the use of high doses of radiation or chemotherapy in the preparatory pre-transplant regimen or treatment with other drugs.[24,25] The situation is also complicated by the fact that frequently there is a lack of correlation between the clinical and histological characteristics.[24,26] For example, the skin in a clinically affected area may not present a significant alteration histologically; or a skin area without clinical alterations may exhibit vacuolization of keratinocytes and necrosis compatible with GVHD.[24] For this reason, the diagnostic value of cutaneous biopsies in the initial phase of BMT has been questioned.[24,27] Additionally, the prognostic value of the findings by skin biopsy after BMT is also debatable. In

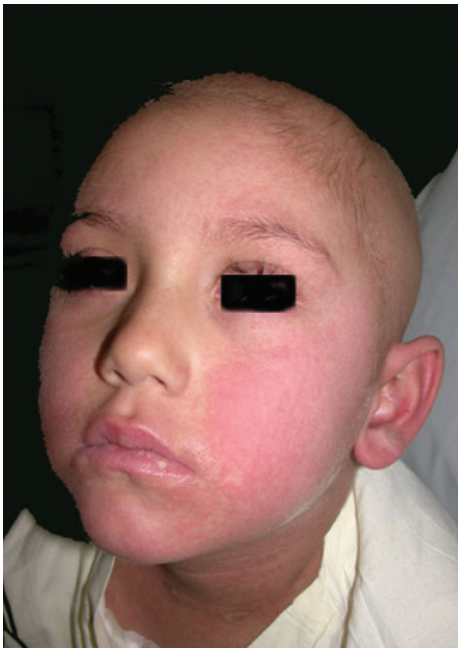

FIGURE 3: a-HVGD - disseminated - violaceous - papular - erythematous - lesions

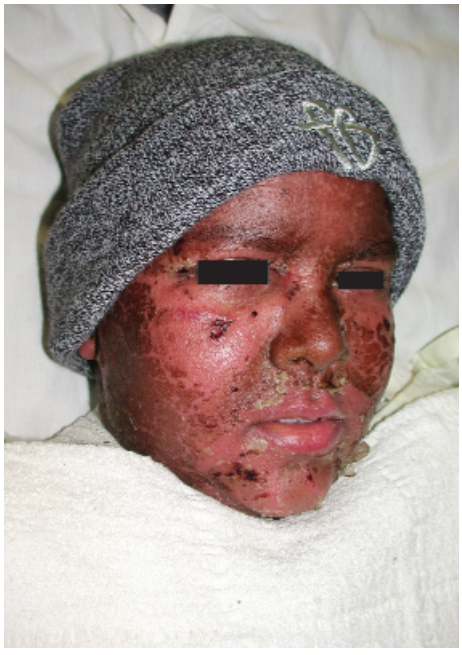

FIGURE 4: a-HVGD - bullous vesicular lesions - similar to toxic epidermal necrolysis

CHART 3: Clinical stage of a-HVGD

Stage	Skin	Liver	Intestine
1.	Maculopapular rash - 25% of body surface	Bilirubin 2-2.9 mg/dl	Diarrhea 0.5-1 L/d persistent with positive intestine biopsy
2.	Maculopapular rash - 25-50% of body surface	Bilirubin 3-5.8 mg/dl	Diarrhea 1-1.5 L/d
3.	Maculopapular rash - more than 50%	Bilirubin 5.9-14.9 mg/dl	Diarrhea >1.5 L/d
4.	Generalized erythema with desquamation and/or presence of blisters	Bilirubin > 15 mg/dl	Serious abdominal pain

the findings of one report, the dyskeratotic keratinocytes, the number of exocyted lymphocytes and the presence of follicular involvement were not correlated to clinical improvement.[28]

A differential diagnosis should be made with cutaneous reactions from chemo- or radiotherapy, with pharmacodermias and even with some viral infections. This is difficult, because the clinical symptoms and the histological aspects are not specific. The presence of extracutaneous involvement may be useful in the differentiation.

CHRONIC GRAFT-VERSUS-HOST DISEASE (c-GVHD)

It occurs three months or more after the transplant, resulting from active a-GVHD (progressive form), after a disease-free interval (quiescent form) or without previous a-GVHD (*de novo* form). As to the extension, it is classified as localized when only skin and/or hepatic involvement are present, and as extensive, when other organs are involved. The mortality from c-GVHD is more than 30% during the five years after transplantation.[29]

The dermatologist needs to be attentive to the spectrum of chronic cutaneous GVHD (Chart 5), because it appears in various clinical forms. The tegumentary manifestations of c-GVHD are multiple, frequently mimicking well-known dermatological diseases. The most common manifestations of the disease are the lichenoid, sclerodermoid and vitiligoid forms, however ungual dystrophy and permanent alopecia of the scalp are frequent. Extensive follicular keratosis, mainly on the back, is a common manifestation in the authors' experience.

In the histology, both show interface alterations with common characteristics of lymphocytes, basal vacuolization and necrosis of the epidermal cells.

CHRONIC LICHENOID GRAFT-VERSUS-HOST DISEASE

Clinical manifestations generally occur early in the course of the disease and have the appearance of idiopathic lichen planus (Figure 5). Violaceous papules that are pruriginous with fine, adherent scales may be observed on the palmoplantar regions, although the eruptions may converge, forming elevated plaques with large violaceous areas. The lesions are less marked and angular than those seen in classic lichen planus. The periorbital area, ears and palmoplantar regions are areas typically affected. Sometimes, vesicles form in the center of the lesions, reminiscent of dyshidrosis when they involve the palms. When affecting the nails, onychoatrophy and pterygium unguis occur, while in the genitalia it may lead to phimosis and vaginal constriction. In the oral mucous membrane there may coexist whitish arboriform marks that are at times exulcerated. Usually these

CHART 4: Clinical staging of a-HVGD

Degree	Cutaneous stage	Hepatic stage	Intestinal stage
I (mild)	1 to 2		0 0
II (moderate)	3 or 4	1 or above	1
III (serious)	0 to 3	2 or above	2 to 4
IV (life threatening)	4	4	0 to 4 + skin or liver

CHART 5: Manifestations of cutaneous chronic graft-versus-host disease

- **Lichenoid**
  - Blaschko lines localized or generalized
  - Vesiculae
- **Scleroderma**
  - Localized or generalized
  - Bullous
- **Pigmentary alterations**
  - Hyperpigmentation
  - Generalized
  - Flexural
  - Exposed areas
  - Periorbital
  - Hypopigmentation
  - Vitiligo
  - Reticulate
  - Lichen sclerosus et atrophicus-like
  - Guttate hypomelanosis
  - Poikiloderma
- **Connective tissue diseases-like**
  - Cutaneous lupus erythematosus-like
  - Dermatomyositis-like
  - Lichen sclerosus et atrophicus-like
  - Fasciitis
- **Oral manifestations**
  - Xerostomia, cavities, taste dysfunction, infection
  - Erythema in plaques
  - Lichenoid
  - Atrophic mucositis
- **Ungual alterations**
  - Beau's lines
  - Atrophy, dystrophy, thickening, fragility, exfoliation
  - Pterygium unguis
- **Hair alterations**
  - Alopecia, temporary or progressive of the scalp hair, eyebrows, eyelashes, body hair
  - Premature hair greying
  - Vitiligo-like depigmentation
- **Miscellaneous**
  - Xerosis, ichthyosis vulgaris, follicular GVHD, pityriasis rosea-like, bullous pemphigoid, acquired epidermolysis bullosa, pyoderma gangrenosum, cytophagic histiocytic panniculitis

are in the mucous membranes of the lips and jugal area, similar to those of oral lichen planus associated with xerostomia (Figure 6). It may be dermatomal[30] or it may follow the lines of Blaschko.[31] Subclinical viral infections of herpes zoster, with alterations of the histocompatibility antigens in the affected area, have been implicated in the pathogenesis of this clinical presentation. Histologically, distinguishing between

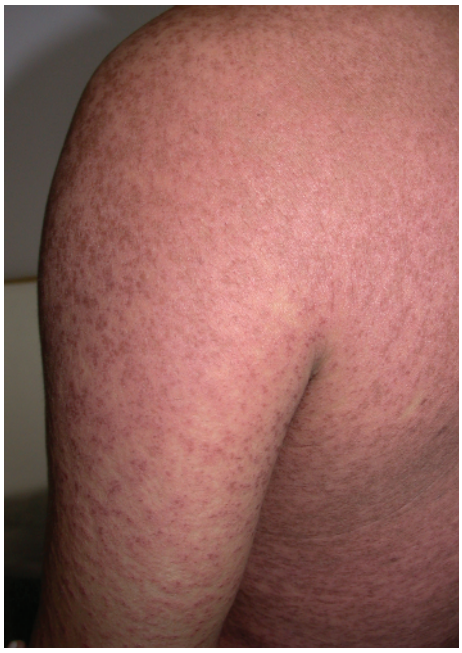

FIGURE 5: c-HVGD dorsal lichenoid

idiopathic lichen planus and lichenoid GVHD can be difficult, because both exhibit hyperkeratosis, hypergranulosis, acanthosis, vacuolar alteration of the basal layer, dyskeratosis and infiltrate in the band of the papillar dermis. The Infiltrate in lichenoid GVHD is frequently less intense and more perivascular, plasmatic and eosinophilic cells may be present.[32] (Figure 7). Chronic lichenoid GVHD can progress into sclerodermatous GVHD, or it may stabilize or spontaneously resolve after several months or years. Post-inflammatory hyperpigmentation frequently occurs during the resolution of the picture, and it can occur inside or outside of the violaceous papules.

CHRONIC SCLERODERMATOUS GRAFT-VERSUS-HOST DISEASE

Described for the first time in 1979,[33] it is a less frequent form of clinical presentation of chronic GVHD than lichenoid GVHD. It commonly develops progressively after acute GVHD and in locations previously affected by chronic lichenoid GVHD. It has also been described as occurring without previous cutaneous GVHD and in places previously affected by herpes zoster and radiotherapy.[34]

Clinically it may be generalized or localized. The localized lesions resemble those of localized scleroderma, but without the characteristic lilac colored ring. They appear on the trunk (Figure 8) and upper members. Initial lesions may be guttate or confetti-like and/or present hypopigmentation or hyperpigmentation on top of the sclerotic plaques. It may be preceded by periorbicular hyperpigmentation, which may be predictive of extensive chronic scleroderma-

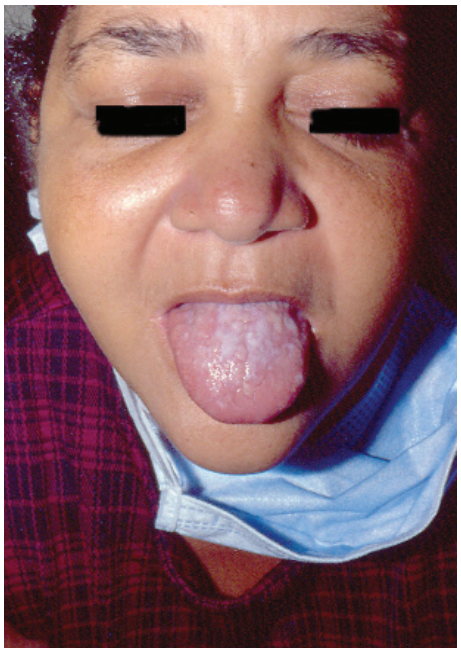

Figure 6: oral lichen - whitish stains on back of tongue

tous GVHD. There can occur generalized hardening, hyperpigmentation, poikiloderma, contractures and cutaneous ulceration (Figure 9). Cutaneous alterations similar to those of bullous scleroderma, with hundreds of small vesicles spreading from the sclerotic lesions have been described in generalized sclerodermatous GVHD.[35] Extracutaneous manifestations include Raynaud's phenomenon, xerophthalmia, xerostomia and dysphagia. Sclerodermatous GVHD can clinically resemble idiopathic scleroderma, and, although the distinction is difficult (Chart 6), the two can have histological differences. Alterations in the epidermis are more frequent in sclerodermatous GVHD, with acanthosis or atrophy, dyskeratotic cells and vacuolar alterations of the basal layer.[36,37] Differences in the dermic collagen may also be noticed. In sclerodermatous GVHD, the dermal thickening can be less significant, since the collagen deposit is in the profound dermis below the level of the sudoriferous glands. In contrast, idiopathic scleroderma is characterized by a more uniform deposit of collagen with important dermal thickening. Antinuclear antibodies are frequently absent or they are nonspecific in sclerodermatous GVHD. Antibodies against topoisomerase 1(Scl-70) and PM-Scl, found in 70% of the patients with systemic idiopathic scleroderma, may also be present in patients with sclerodermatous GVHD. This may be a predictive factor for extensive cutaneous and internal involvement.[38]

Pigmentary Disturbances

Alterations of the pigmentation are frequent in c-GVHD and vary in accordance with the post-transplantation period.[39] Diffuse hyperpigmentation with exacerbation in the flexurae may be observed at the onset of the chronic phase, generally in those patients that present acute exanthematous GVHD.

Extensive reticulated hyperpigmentation, juxtaposed on areas of leukoderma, is frequent after lichenoid GVHD.

Periorbital hyperpigmentation, dyspigmentation vitiligoid and total leukoderma (Figure 10) have been described.[40]

PROPHYLAXIS AND TREATMENT

The strategies for prevention and treatment of GVHD usually aim to interfere with the afferent phase

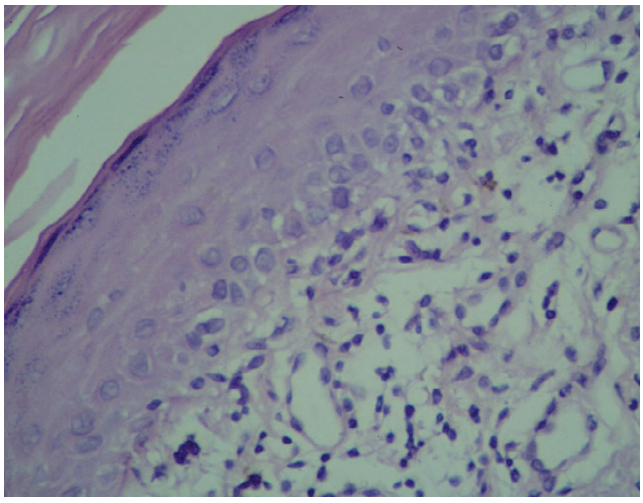

Figure 7: c-HVGD lichenoid - acanthosis, infiltrate in a band in the papillary dermis (100x)

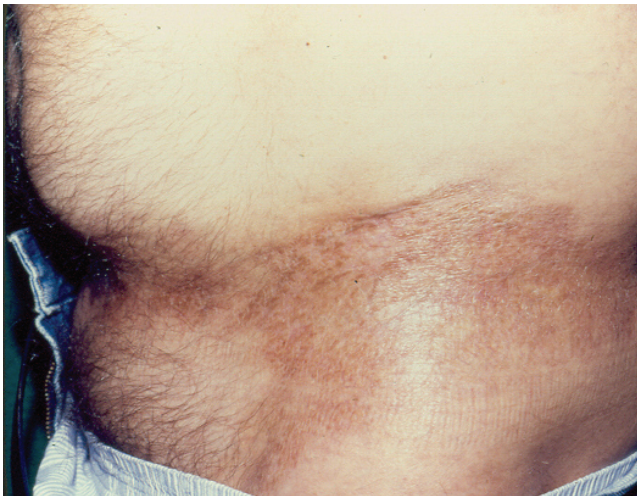

Figure 8: c-HVGD localized sclerodermatous in trunk

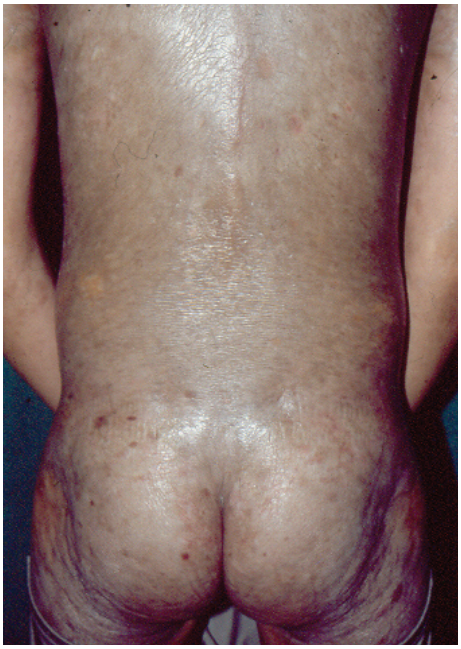

FIGURE 9: c-HVGD extensive scleroderma

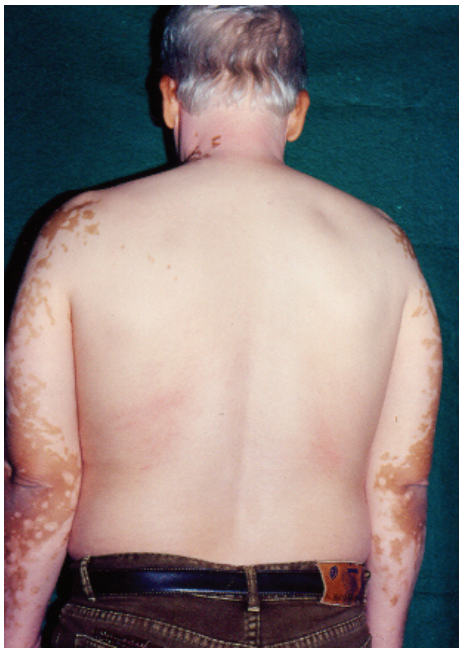

FIGURE 10: c-HVGD vitiligo-like - total leukoderma

of the response, in an attempt to eliminate the donor's T cells or to block their activation. The prophylaxis of GVHD is made with immunosuppressors such as corticoid, cyclosporine and methotrexate used in combination. Oral antihistamines and topical corticotherapy are used for mild cases. Recently, cyclosporine administered in the form of mouthwashes has been used for oral lichen. In the treatment of GVHD, the first-line drugs are cyclosporine and corticoids, whether or not used in combination. For patients that are resistant, strategies may be developed using tacrolimus, mycophenolate, azathioprine, thalidomide and PUVA photochemotherapy,[41-43] in an attempt to control the disease. Extracorporeal photopheresis has an effect on extensive c-GVHD, when refractory to the first and second-line drugs.[44,45]

CHART 6: Differences between sclerodermatous GVHD and systemic scleroderma

Sclerodermatous GVHD	Systemic scleroderma
Infrequent Raynaud's phenomenon	Frequent Raynaud's phenomenon
Rarely seen acrosclerosis	Frequent acrosclerosis
Dermal papillae fibrosis	Dermal reticular fibrosis
Normal collagen fibrils	Fine collagen fibrils
Absence of pericapillary fibrosis	Pericapillary fibrosis
Descending fibrosis	Ascending fibrosis

DISCUSSION

Despite the therapeutic progress regarding post-transplantation immunosuppression, GVHD ranks after infectious processes as the most frequent complication of allogeneic BMT, increasing the morbidity and mortality rates of the procedure. It has as target organs, the liver and epithelial cells of the intestines and skin. GVHD is classified as acute when it develops in the first 100 days (beginning generally around day 20) after allogeneic BMT. It is characterized clinically by exanthema, jaundice, abdominal pain and diarrhea. After the skin, the liver is the organ most involved by a-GVHD, a condition which is observed clinically as cholestatic jaundice. More than 30% of the patients submitted to allogeneic BMT with matched HLA, and more than 90% of those that receive a BMT from donors that are not related, develop a-GVHD. Chronic GVHD is a multiorgan syndrome, with characteristics similar to those of the autoimmune and collagen diseases. This occurs occasionally before the first 100 days following BMT but rarely after 500 days. The average period leading to the onset of c-GVHD is 201 days after BMT with matched HLA, and 159 days after BMT with a non-identical related HLA donor, and 133 days after BMT with HLA from an unrelated donor.[46] In the long term, it affects 50% of the patients submitted to BMT and is lethal in a percentile that varies from 20 to 40% of the affected patients, in spite of the treatments instituted. The following factors are associated with

increased risk of developing c-GVHD: histocompatibility differences, type of prophylaxis for a-GVHD, prior a-GVHD, cyclosporine A (CsA) prophylaxis, latent herpetic infections either in donor or recipient, and advanced age.[46]

Clinically the tegumentary involvement of c-GVHD is characterized by hyperpigmentation, hypopigmentation, violaceous papules with whitish striae similar to those of lichen planus (lichenoid forms). In the oral mucous membrane, there may occur whitish stains on the mucous membrane of the jugal area, lips and palate. These are at times associated with vesicles, exulcerations and xerostomia. Dermal and subcutaneous fibrosis can cause hardening of the skin, reminiscent of localized morphea or systemic scleroderma (sclerodermoid forms). Lichenoid and sclerodermoid forms may occur simultaneously. As for the histopathology of the skin, two phases are recognized, one early and one late. The early phase is characterized by epidermal alterations indistinguishable from lichen planus; with vacuolization of the basal layer, necrosis of keratinocytes, hyperkeratosis and acanthosis associated to a sparse band of infiltrate composed of mononuclear cells in the dermoepidermal junction.[32] The late phase is characterized by sclerodermoid alterations, with involution of the epidermal alterations, accompanied by fibrosis of the dermis and loss of the annexes. The epidermis becomes atrophic, and vacuolization of the basal layer, the necrotic keratinocytes and the eosinophílic bodies are rarely observed. The final appearance is similar to that of scleroderma, however with some differences. In scleroderma, the epidermis is frequently normal, unlike that observed in c-GVHD, when it presents residual alterations in the epidermis, with persistence of the atrophy and pigmentary incontinence.[47] Besides this, it seems that in c-GVHD the fibrosis begins higher in the superior dermis.[48] It is worth remembering that the histopathology of the skin offers subjective signs for evaluating the response to treatment, but it is not an appropriate method for response quantification.

The conventional first-line treatment of c-GVHD comprises corticoids and cyclosporine, which are associated, frequently, with serious side effects, such as Cushing's syndrome, secondary infections or neoplasias. When this therapeutic scheme fails, one should resort to second line therapeutic alternatives, such as thalidomide, azathioprine, tacrolimus, PUVA and, more recently, extracorporeal photopheresis.

CONCLUSION

GVHD presents a variety of clinical forms, making the dermatologist's role in the transplant centers important, by aiding in the early diagnosis of the disease and in the differentiation of other manifestations in the mucocutaneous membranes. ❑

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