Biology of Blood and Marrow Transplantation 12:1101-1113 (2006)

1083-8791/06/1211-0001$32.00/0
doi:10.1016/j.bbmt.2006.08.043

Cutaneous Manifestations of Chronic Graft-versus-Host Disease

Sharon R. Hymes,[1] Maria L. Turner,[3] Richard E. Champlin,[2] Daniel R. Couriel[2]

Departments of [1]Dermatology and [2]Blood and Marrow Transplantation, The MD Anderson Cancer Center, Houston, Texas; [3]Dermatology Branch, National Cancer Institute, Bethesda, Maryland

Correspondence and reprint requests: Sharon R. Hymes, MD, Department of Dermatology, The MD Anderson Cancer Center, Unit 434, FC5.3004, Houston, TX 77030 (e-mail: srhymes@mdanderson.org).

Received August 11, 2006; accepted August 29, 2006

ABSTRACT

Cutaneous chronic graft versus host disease has traditionally been classified into lichenoid and scleroderma-like forms. However, the initial presentation is sometimes subtle and a variety of less common cutaneous manifestation may be prevalent. This clinical review focuses on the lesional morphology of chronic graft versus host disease, and presents a classification system that may prove useful in early diagnosis. In addition, this approach may help to facilitate the correlation of different morphologic entities with outcome and response to therapy.

KEY WORDS

Stem cell transplant • GVHD • Dermatology

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) using peripheral blood, cord blood, or bone marrow is used to treat a wide variety of genetic and immunologic disorders and hematologic and solid organ malignancies. Significant advances in technology and immunology have improved the prognosis, rate of engraftment and quality of life for many stem cell recipients. Chronic graft-versus-host disease (cGVHD) is a multisystem disease often presenting with prominent skin involvement.

Traditionally, two types of cutaneous GVHD have been described: the acute form that occurs <100 days after transplantation and the chronic form that occurs >100 days. These rigid time-related criteria should serve only as a guide, especially as HSCT practices change. Since the availability of new, less intensive preparative regimens and the use of donor lymphocyte infusions, it is not uncommon to see a delayed or late acute GVHD (aGVHD; ie, >100 days after transplantation) and, in some cases, overlapping aGVHD and cGVHD, or other "atypical" forms of cGVHD. Acute GVHD and cGVHD in the skin are more accurately diagnosed by clinical and, less frequently, histopathologic features [1]. Based on similarities with other dermatologic diseases, we describe and summarize the diversity of cutaneous manifestations of cGVHD in Table 1. In our patients, the diagnosis of cutaneous GVHD was confirmed by a combination of elements including the clinical course and the presence of GVHD in other organ systems. All of our patients also had pathologic confirmation. By specifically describing lesional morphology, we hope to achieve a common, systematic, and consistent terminology for cutaneous cGVHD. This approach may also facilitate the correlation of different morphologic entities with outcome and response to therapy.

CLINICAL DESCRIPTION

Early on, the skin lesions of cGHVD are often subtle and the progression is insidious, characterized by the development of marked xerosis (skin dryness), follicular prominence (Figure 1), and ichthyosis (fish scale-like skin) (Figure 2). Papulosquamous lesions may simulate the appearance of keratosis pilaris (Figure 3) or present with pityriasiform (annular plaques demonstrating a branny scale), eczematous, or psoriasiform plaques (Figure 4).

Table 1. *Cutaneous Chronic Graft-versus-Host Disease*

Clinical Pattern	Description
Xerotic or asteatotic	Dry skin, frequently generalized; "dry dandruff" on scalp or fishlike scale as in ichthyosis
Keratosis pilaris-like	Perifollicular erythema or hyperpigmentation with papules or follicular keratotic, spiny protrusions
Lichen planus-like	Purplish to markedly hyperpigmented, polygonal papules with varying configurations: annular, reticulated or confluent; distribution may be follicular, linear, dermatomal or lupus-like; may be vesiculobullous at times
Lichen sclerosus-like	May be indistinguishable from the idiopathic variety with purple or gray-white smooth papules and plaques, plugged follicles and sclerosis of the papillary dermis; at times associated with fibrosis of deeper layers of the dermis or prominent atrophy
Papulosquamous/psoriasiform	Discrete guttate, annular or confluent erythematous scaly patches and plaques with micaceous scale that may involve any part of the body including scalp, face, hands and feet
Poikiloderma	Variegated colors: erythema, hypo- and hyperpigmentation with cigarette-paper epidermis; suggestive of lupus when on the face
Dyspigmentation	May be punctate or confetti-like; generally considered to be a postinflammatory phenomenon; may be associated with dermal fibrosis of varying depths and appear "leopard-like"; spontaneous depigmentation suggestive of vitiligo may be prominent
Reactive erythema	Urticarial or annular plaques with variable scale resembling erythema annulare centrifugum or lupus erythematosus
Erythroderma	Diffuse to generalized erythema over ≥80% of the body accompanied by scaling, localized bullae or superficial erosions
Acral erythema	Diffuse or patchy erythema, edema and pain of distal fingers, toes, palms and soles; may appear targetoid or erythema multiforme-like with variable hyperkeratosis and erosions; early cases may resemble hand or foot eczema
Dermal fibrosis, superficial	Superficial and mid-dermal sclerosis resulting in indurated plaques with variable pigmentation; epidermis may be normal, atrophic, or bullous and skin can be moved over underlying structures; resembles morphea clinically
Rippled or cellulite-like fibrosis	Skin appears to be rippled in areas rich in adipose tissue-volar arms, abdomen and lateral thighs; caused by fibrosis of septae of subcutaneous fat
Dermal/subcutaneous fibrosis	Sclerosis involves all layers of the skin with loss of subcutaneous tissue, making it fixed to underlying bone; early on may be preceded by edema/lymphedema resulting in a peau d'orange appearance, bullae, and occasionally vascular tumors; pipestem fibrosis of the extremities is frequently associated with neuropathy and painful ulcers
Fasciitis	Superficial skin may have varying degrees of fibrosis or may not be fibrotic at all; prominent grooves are seen along the course of tendons; causes marked reduction of range of motion at joints; "prayer sign" is positive
Nails	Nails are generally thin with vertical ridging and vertical pigment bands; pterygia may be seen and entire nail may be lost; periungual telangiectasia is variable
Scalp	Patchy or moth-eaten scarring alopecia with variable epidermal and pigmentary changes and scarring

The lichen planus-like lesions of cGVHD are indistinguishable clinically and histologically from classic lichen planus. The lesions can be focal (Figure 5a), confluent (Figure 5b), linear (Figure 5c) [2], follicular-centric, or even dermatomal. Often there is an overlap of lichen planus-like lesions and lichen sclerosis-like lesions as demonstrated in Figure 5b. Lichen planus-like GVHD may have vesicles, and these must be

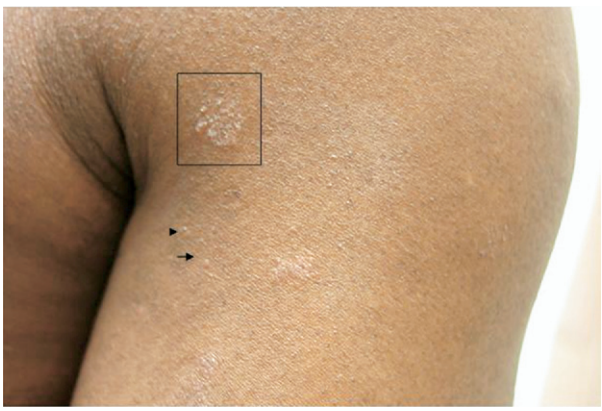

Figure 1. Early cGVHD with abrupt onset xerosis and follicular prominence in an annular distribution (rectangle) and small follicular papules (arrows).

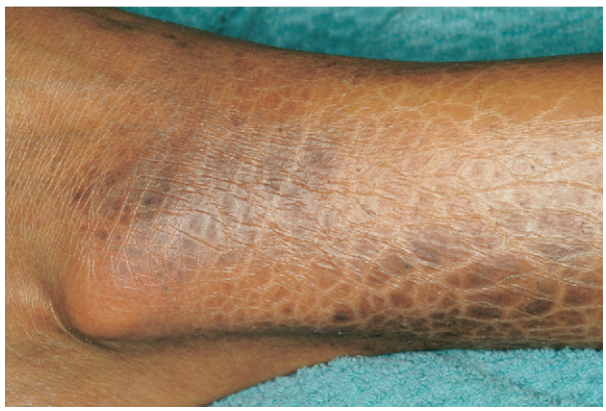

Figure 2. Early cGVHD with the new onset of ichthyosis (fish-like scaling).

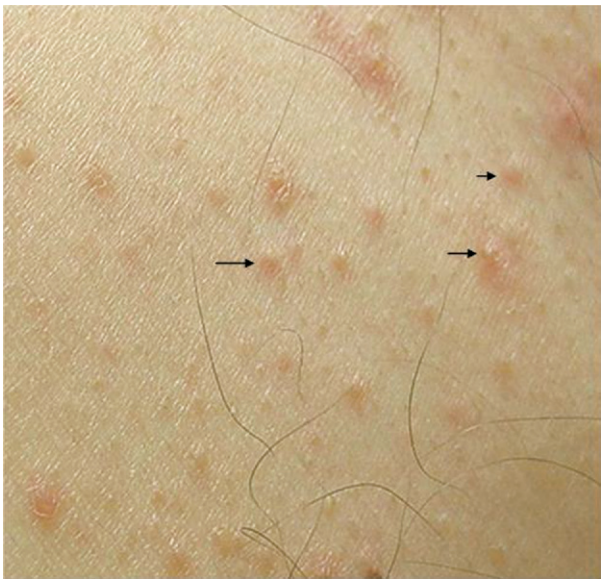

Figure 3. Early cGVHD presenting with new onset of a keratosis pilaris-like eruption (perifollicular papules with a central core marked by arrow).

distinguished from those of herpes simplex or varicella-zoster virus infection [3]. Disfiguring postinflammatory hyperpigmentation is a common problem with lichen planus and lichen planus-like GVHD, especially in darker skinned individuals, and this may persist despite intervention [4].

Other chronic eruptions that have traditionally been designated "lichenoid" are often polymorphic. If the epidermis is involved, the histologic picture will have lichenoid features; ie, there will be vacuolar degeneration of the basal layer, apoptotic cells within the epidermis, and a perivascular lymphohistiocytic infiltrate irregardless of the clinical presentation. Clinically, the morbilliform (measle-like papulosquamous) rash that is seen in aGVHD occurs in cGVHD, usually after donor lymphocyte infusion or decrease in immunosuppressive medications. Although it can be difficult to distinguish from drug eruptions, the presence of chronic lesions that persist despite elimination of possible drug culprits, along with documented GVHD in other organ systems, helps to confirm the diagnosis. Persistent annular lesions reminiscent of urticaria or other reactive erythemas such as erythema annulare centrifugum (Figure 6) is a striking presentation. Erythrodermic cGVHD is often preceded by papulosquamous, morbilliform, or annular eruptions (Figure 7).

Acral lesions are not uncommonly seen in cGVHD. The palms and soles may develop deep-seated vesicles and scale suggestive of hand and foot eczema (Figure 8a,b), an acral erythema-like picture with edema, pain, and erosions, acral keratoses [3,5], or erythema multiforme-like lesions.

The onset of cGVHD may also be marked by the appearance of lesions of cutaneous lupus and other connective tissue disorders (Figures 9a,b). When present, facial lesions may be crusted, lichen planus-like, or poikilodermatous (characterized by atrophy, dyspigmentation, and telangiectasia). Autoantibodies, especially antinuclear antibody, anti-Ro, and anti-La (Sjögren antibodies), are variably positive and their significance is unknown. Cutaneous cGVHD may also be photodistributed even in the absence of detectable autoantibodies.

Sclerotic skin changes are a prominent feature and a major source of morbidity in cGVHD. They may develop concurrently with other skin lesions or may occur independently. These can be divided by the extent of dermal, subcutaneous, and fascial involvement [6]. Dermal fibrosis may be superficial or deep and subcutaneous fibrosis may include the fascia, tendon, or fat septae. In some cases the onset is slow, with localized waxy, bound-down sclerotic plaques resembling morphea, preceded by variable erythema. When the dermis alone is sclerotic, these plaques can be moved over underlying structures such as bone. This may rarely occur in a linear distribution (Figure 10), or in a dermatomal distribution, sometimes but not always at the site of antecedent zoster eruption. This striking presentation may reflect changes in keratinocyte antigenicity due to the virus [7,8]. Leopard-like changes, with hyperpigmented, scaly macules, may be localized or widespread and precede the sclerotic eruption [9].

Widespread, deep sclerotic lesions, especially over joints and long bones, are devastating, and patients are literally "hidebound" with limited mobility. When present on the lower extremities, it results in the appearance of "pipestem legs" (Figure 11a), which may be accompanied by a painful neuropathy [10]. Eventually, benign angiomatous tumors may develop in this setting (Figure 11b) [11,12]. Bullae are a serious

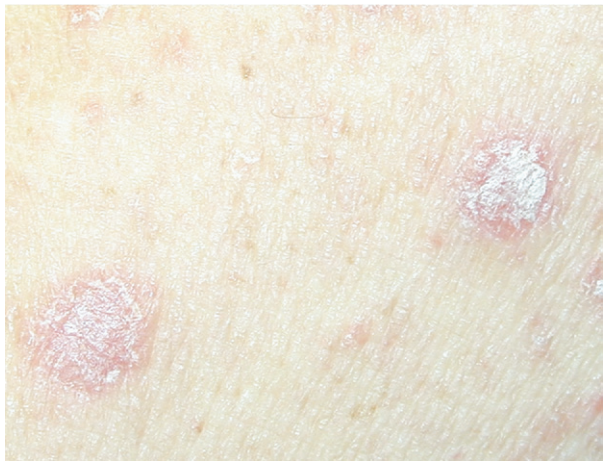

Figure 4. Psoriasiform GVHD. Note the well-defined plaques with silvery scaling.

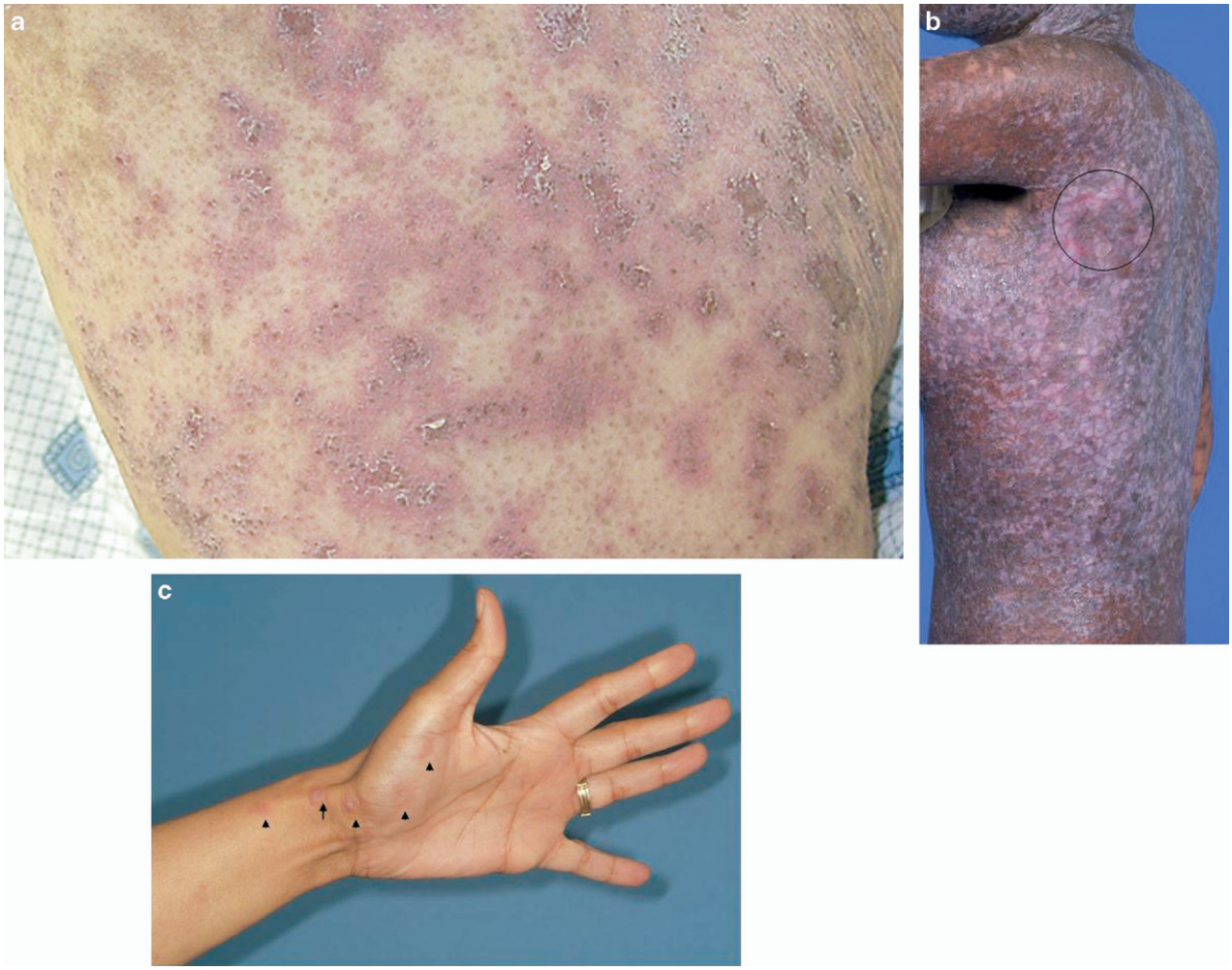

Figure 5. a, Lichen planus-like GVHD presenting with individual and confluent purple polygonal plaques. b, Confluent purple and atrophic white plaques. The thin, hypopigmented, wrinkled, atrophic plaques (circles) are characteristic of lichen sclerosis and the purple plaques on the shoulder with lichen planus. c, Chronic GVHD presenting with linear lichenoid papules. This patient had more typical lichen planus-like lesions elsewhere.

complication because they break down into ulcers that are painful, slow healing, and a nidus of infection [13]. Extensive deep sclerosis of the thorax may further contribute to the restrictive lung problems already associated with cGVHD. Fibrosis of tendons may produce a "grooving" sign (Figure 11c). Subcutaneous septal fibrosis by itself may produce a rippling or cellulite effect (Figure 11d) with little overlying epidermal and dermal change. Alopecia and loss of skin appendages occurs as the skin becomes more fibrotic, leading to decreased sweating and an often irreversible scaring alopecia.

Abrupt and painful skin swelling associated with erythema with or without subcutaneous edema or a peau d'orange appearance characterizes deep fascial involvement. This severe complication resembles the eosinophilia-myalgia syndromes and is resistant to therapy [14]. Figure 12 shows acute limitation of wrist dorsiflexion (positive prayer sign) secondary to fasciitis. The face is usually spared, and these changes may occur independently or concurrently with fibrosis of the dermis or fat. Fifty percent of affected patients also report myalgias, and laboratory evaluation may demonstrate peripheral eosinophilia [14]. A full-thickness biopsy can be used, but is not necessary, to confirm the diagnosis. We have found it helpful to objectively document disease progression and treatment response by serial photographs, measurements of joint mobility, and, in some cases, noninvasive 20-MHz sonography [15].

Nail dystrophy is a common manifestation of cGVHD, with thickening, ridging, onycholysis, pterygium, or complete nail loss. Periungual telangiectasias are occasionally present. These changes affect single or multiple nails, often correlate with the duration of the disease, and cause considerable morbidity for the patient [16] (Figure 13).

Mucous membranes are affected in approximately 80% of patients with cGVHD [17], resulting in erosions, oral pain, and sicca symptoms that interfere

with nutrition and quality of life. A lacy, white network, Wickham striae, may develop on the buccal mucosa, lips, and palate (Figure 14a). Other mucosal and gingival lesions become atrophic, erythematous, or erosive (Figure 14b) and are indistinguishable from erosive lichen planus. Atrophy of the tongue is associated with shortened or absent lingual papillae [18], although elongation of papillae, geographic tongue, and white nondetachable plaques are also seen (Figure 14c). Chronic mucosal GVHD may predispose to squamous cell carcinoma, and biopsies should be performed if this is suspected [19,20] (Figure 14d). When the salivary glands are a target, xerostomia and dental caries become problems [21]. Because of the disturbance in the epidermal barrier, topical or oral antifungal prophylaxis is advisable, as are antiviral agents.

Genital involvement affects sexuality and overall quality of life [22]. After HSCT, symptoms of inadequate estrogenization occur secondary to premature ovarian failure, and this should be distinguished from early cGVHD. Vaginal GVHD develops an average of 10 months from transplantation and symptoms may include dryness, erosions, ulcerated or thickened mucosa, narrowed or obliterated introitus, frequent vaginal infections, and symptoms of dyspareunia [23]. Similarly, phimosis may occur in men. Mucosal strictures, like those of the esophagus, may require dilatation.

SUMMARY

In this review, we developed a detailed description focusing on lesional morphology of cutaneous cGVHD. We hope this approach will result in the identification of early changes of cGVHD and the development of a common descriptive terminology. In addition to the effort of the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease [1,24,25], we hope to contribute to systematize the classification of cutaneous cGVHD. The polymorphic nature of cutaneous cGVHD is poorly understood and this classification system is a first step in creating different morphologic categories. From here on, we intend to verify any correlation of lesional morphology with outcome and response to therapy, with the hope of optimizing the management of this very complex group of patients.

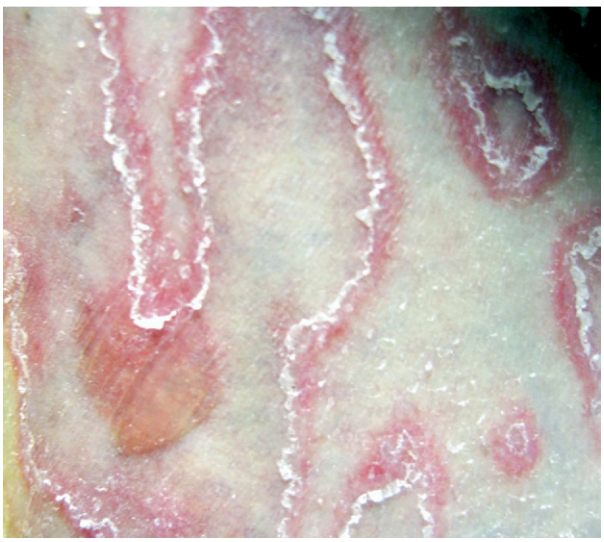

Figure 6. Chronic GVHD presenting as an annular reactive erythema resembling erythema annulare centrifugum. Note the bullous lesion that showed histologic evidence of epidermal necrosis.

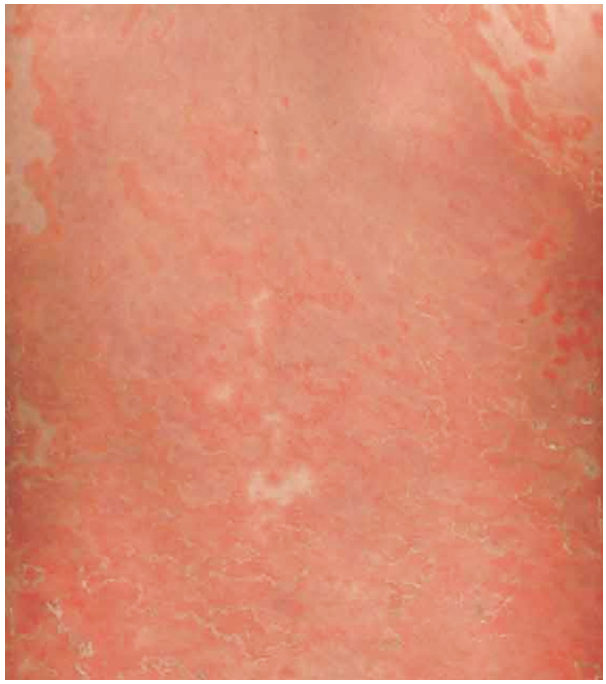

Figure 7. Chronic GVHD presenting as erythroderma (confluent erythematous plaques). The initial lesions, as seen on the periphery, were annular.

REFERENCES

1. Shulman HM, Kleiner D, Lee SJ, et al. Histopathologic diagnosis of chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: II. Pathology Working Group Report. *Biol Blood Marrow Transplant*. 2006; 12:31-47.
2. Beers B, Kalish RS, Kaye VN, Dahl MV. Unilateral linear lichenoid eruption after bone marrow transplantation: an unmasking of tolerance to an abnormal keratinocyte clone? *J Am Acad Dermatol*. 1993;28:888-892.
3. Schauder CS, Hymes SR, Rapini RP, Zipf TF. Vesicular graft-versus-host disease. *Int J Dermatol*. 1992;31:509-510.
4. Aractingi S, Janin A, Devergie A, Bourges M, Socie G, Gluckman E. Histochemical and ultrastructural study of diffuse melanoderma after bone marrow transplantation. *Br J Dermatol*. 1996;134:325-331.

5. Kossard S, Ma DD. Acral keratotic graft versus host disease simulating warts. *Australas J Dermatol*. 1999;40:161-163.
6. Pavletic SZ, Martin P, Lee SJ, et al. Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group Report. *Biol Blood Marrow Transplant*. 2006;12:252-266.
7. Lacour JP, Sirvent N, Monpoux F, et al. Dermatotmal chronic cutaneous graft-versus-host disease at the site of prior herpes zoster. *Br J Dermatol*. 1999;141:587-589.
8. Cohen PR, Hymes SR. Linear and dermatomal cutaneous graft-versus-host disease. *South Med J*. 1994;87:758-761.
9. Penas PF, Jones-Caballero M, Aragues M, Fernandez-Herrera J, Fraga J, Garcia-Diez A. Sclerodermatous graft-vs-host disease: clinical and pathological study of 17 patients. *Arch Dermatol*. 2002;138:924-934.
10. Aractingi S, Socie G, Devergie A, Dubertret L, Gluckman E. Localized scleroderma-like lesions on the legs in bone marrow transplant recipients: association with polyneuropathy in the same distribution. *Br J Dermatol*. 1993;129:201-203.
11. Garnis S, Billick RC, Srolovitz H. Eruptive vascular tumors associated with chronic graft-versus-host disease. *J Am Acad Dermatol*. 1984;10:918-921.
12. Soo JK, Mortimer PS. Eruptive angiomas associated with graft-versus-host disease. *Br J Dermatol*. 2006;154:376-378.
13. Hymes SR, Farmer ER, Burns WH, et al. Bullous sclerodermalike changes in chronic graft-vs-host disease. *Arch Dermatol*. 1985;121:1189-1192.
14. Janin A, Socie G, Devergie A, et al. Fasciitis in chronic graft-versus-host disease. A clinicopathologic study of 14 cases. *Ann Intern Med*. 1994;120:993-998.
15. Gottlober P, Leiter U, Friedrich W, et al. Chronic cutaneous sclerodermoid graft-versus-host disease: evaluation by 20-MHz sonography. *J Eur Acad Dermatol Venereol*. 2003;17:402-407.
16. Sanli H, Arat M, Oskay T, Gurman G. Evaluation of nail involvement in patients with chronic cutaneous graft versus host disease: a single-center study from Turkey. *Int J Dermatol*. 2004;43:176-180.
17. Sullivan KM, Shulman HM, Storb R, et al. Chronic graft-versus-host disease in 52 patients: adverse natural course and successful treatment with combination immunosuppression. *Blood*. 1981;57:267-276.
18. Aractingi S, Chosidow O. Cutaneous graft-versus-host disease. *Arch Dermatol*. 1998;134:602-612.
19. Grundmann-Kollmann M, Martin H, Ludwig R, et al. Narrowband UV-B phototherapy in the treatment of cutaneous graft versus host disease. *Transplantation*. 2002;74:1631-1634.
20. Abdelsayed RA, Sumner T, Allen CM, Treadway A, Ness GM, Penza SL. Oral precancerous and malignant lesions associated with graft-versus-host disease: report of 2 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2002;93:75-80.
21. Nagler RM, Nagler A. Salivary gland involvement in graft-versus-host disease: the underlying mechanism and implicated treatment. *Isr Med Assoc J*. 2004;6:167-172.
22. Spinelli S, Chiodi S, Costantini S, et al. Female genital tract graft-versus-host disease following allogeneic bone marrow transplantation. *Haematologica*. 2003;88:1163-1168.
23. Spiryda LB, Laufer MR, Soiffer RJ, Antin JA. Graft-versus-host disease of the vulva and/or vagina: diagnosis and treatment. *Biol Blood Marrow Transplant*. 2003;9:760-765.
24. Couriel D, Carpenter PA, Cutler C, et al. Ancillary therapy and supportive care of chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: V. Ancillary Therapy and Supportive Care Working Group Report. *Biol Blood Marrow Transplant*. 2006;12:375-396.
25. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2005;11:945-956.

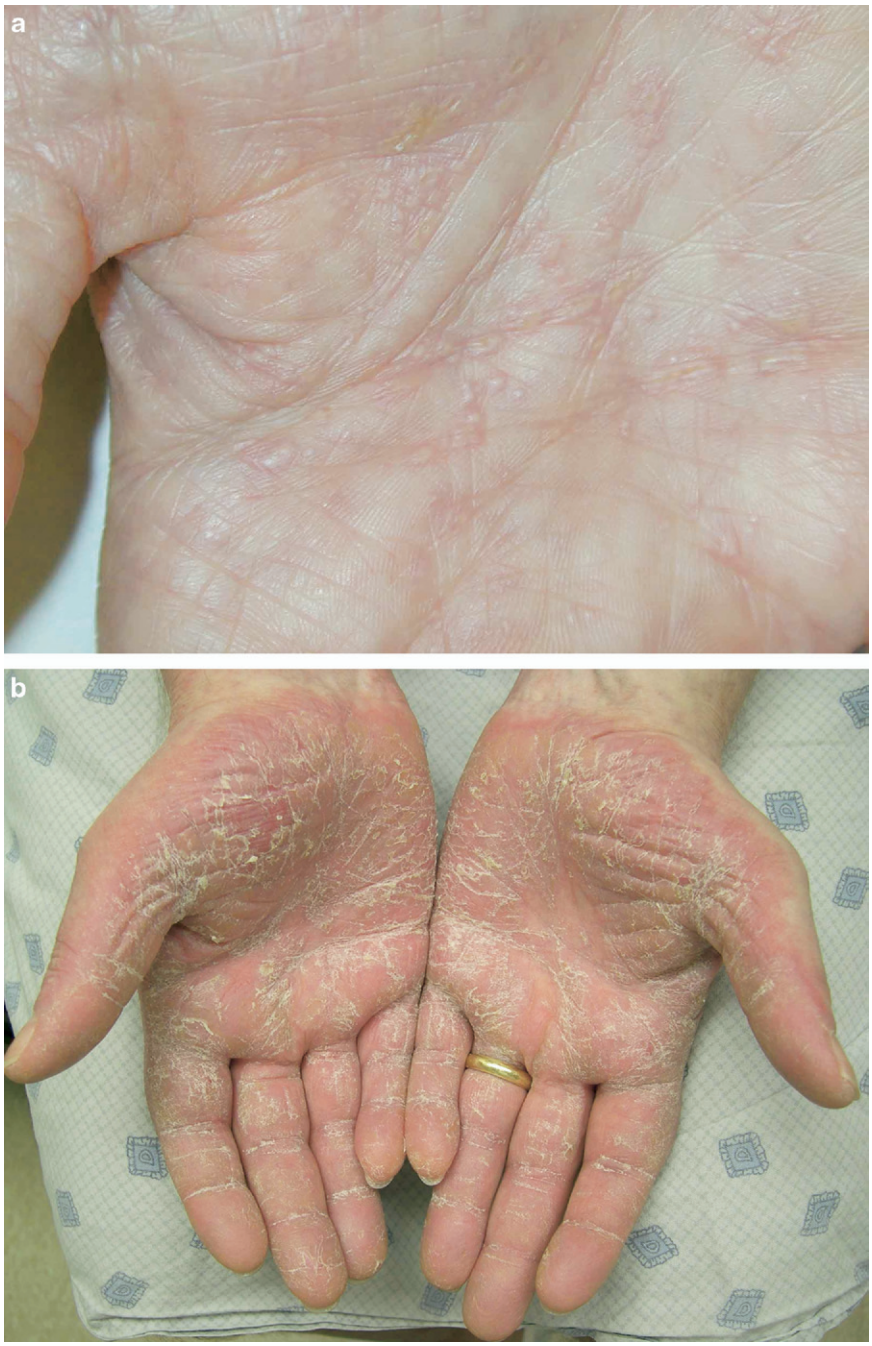

Figure 8. a, Chronic GVHD presenting as acral erythema with deep-seated vesicles. b, Chronic GVHD presenting as painful palmer erythema and edema.

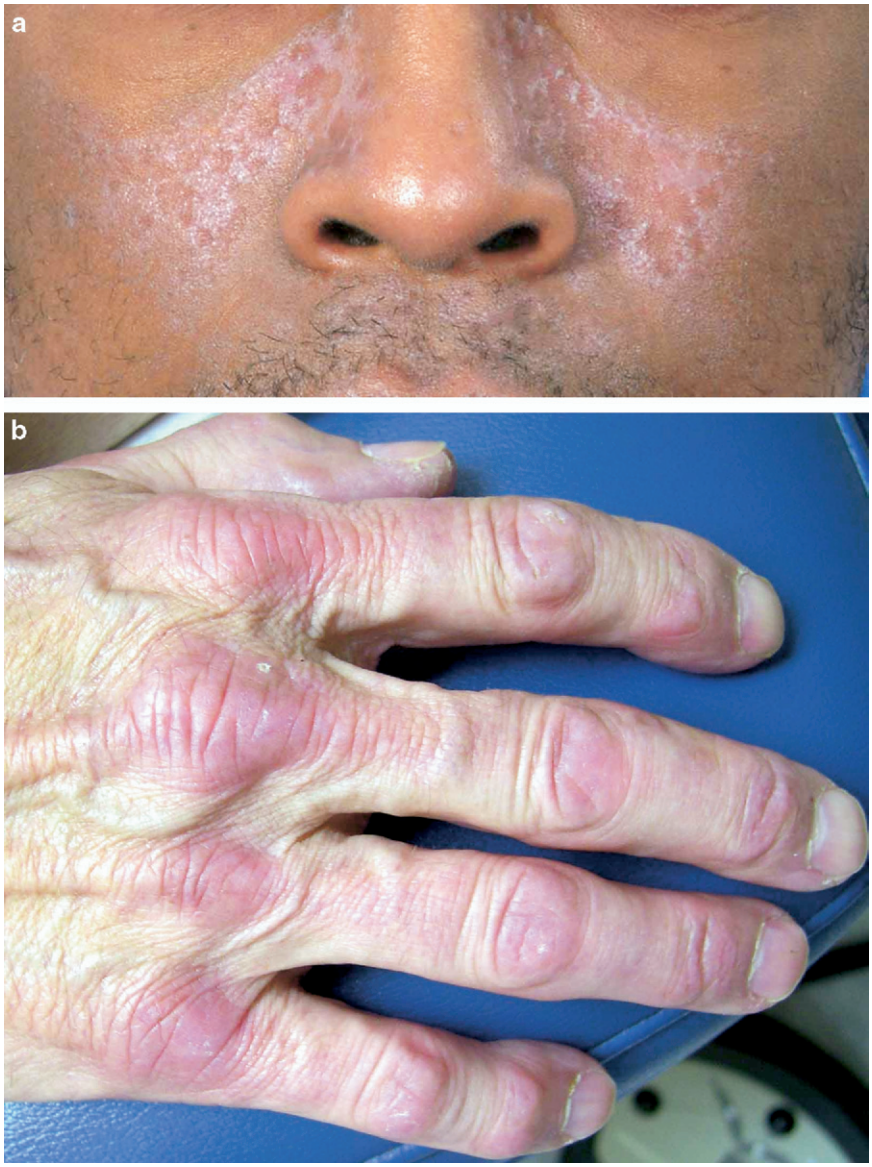

Figure 9. a, Chronic GVHD presenting with a rash in a "butterfly" malar distribution. These lesions are poikilodermatous, showing hyper- and hypopigmentation, atrophy, and telangiectasia. b, Chronic GVHD presenting with erythema over the metacarpal interphalangeal, proximal interphalangeal and distal interphalangeal joints.

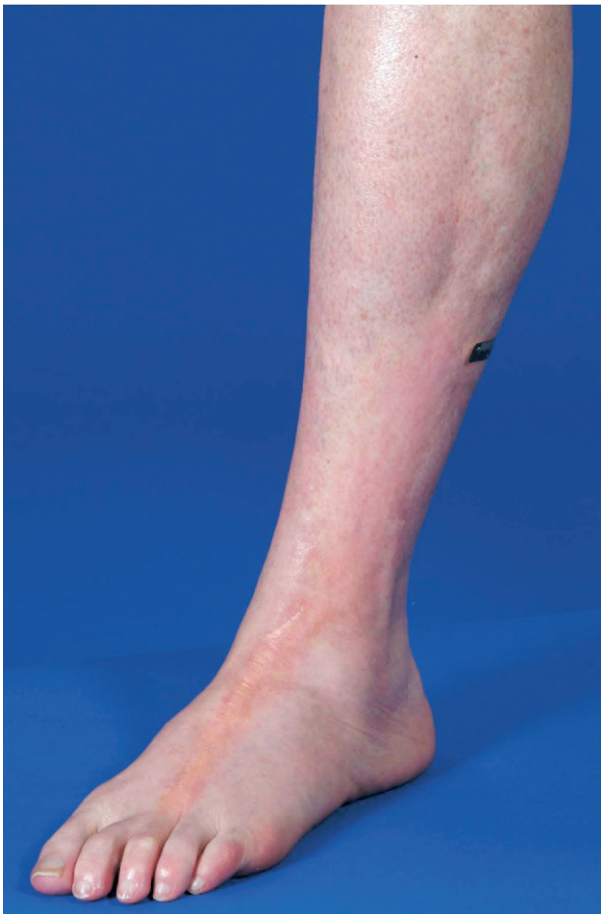

Figure 10. Band-like deep dermal sclerosis presenting in a linear pattern.

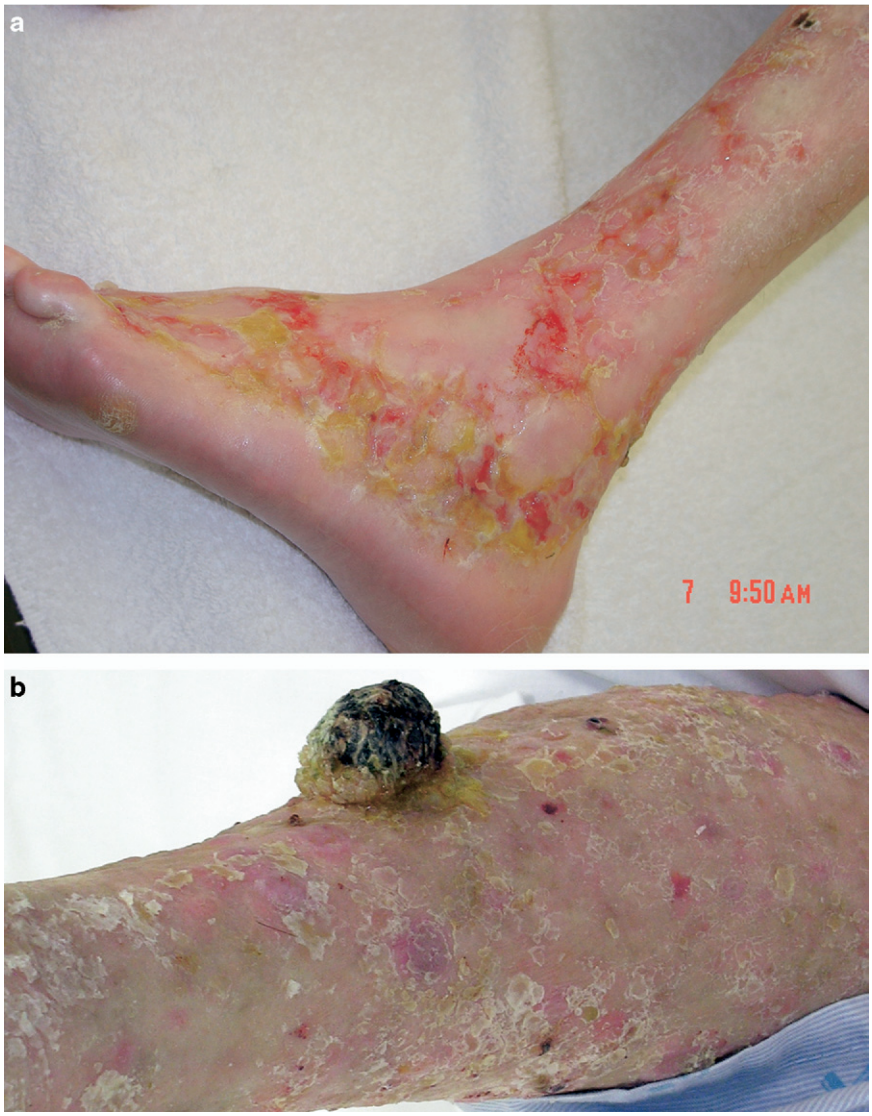

Figure 11. a, Sclerosis of the dermis and subcutaneous tissue producing "pipestem" legs with overlying erosions. b, Benign angiomatous (vascular) lesions appearing as a blue-black nodule in a patient with severe dermal sclerosis and resolving bullous changes with residual crusts. Biopsy may be necessary to establish the diagnosis and rule out a skin cancer. c, "Groove" sign (arrows) produced by fibrosis around tendons. d, Rippling and "cellulite" appearance in the axillae produced by subcutaneous septal fibrosis.

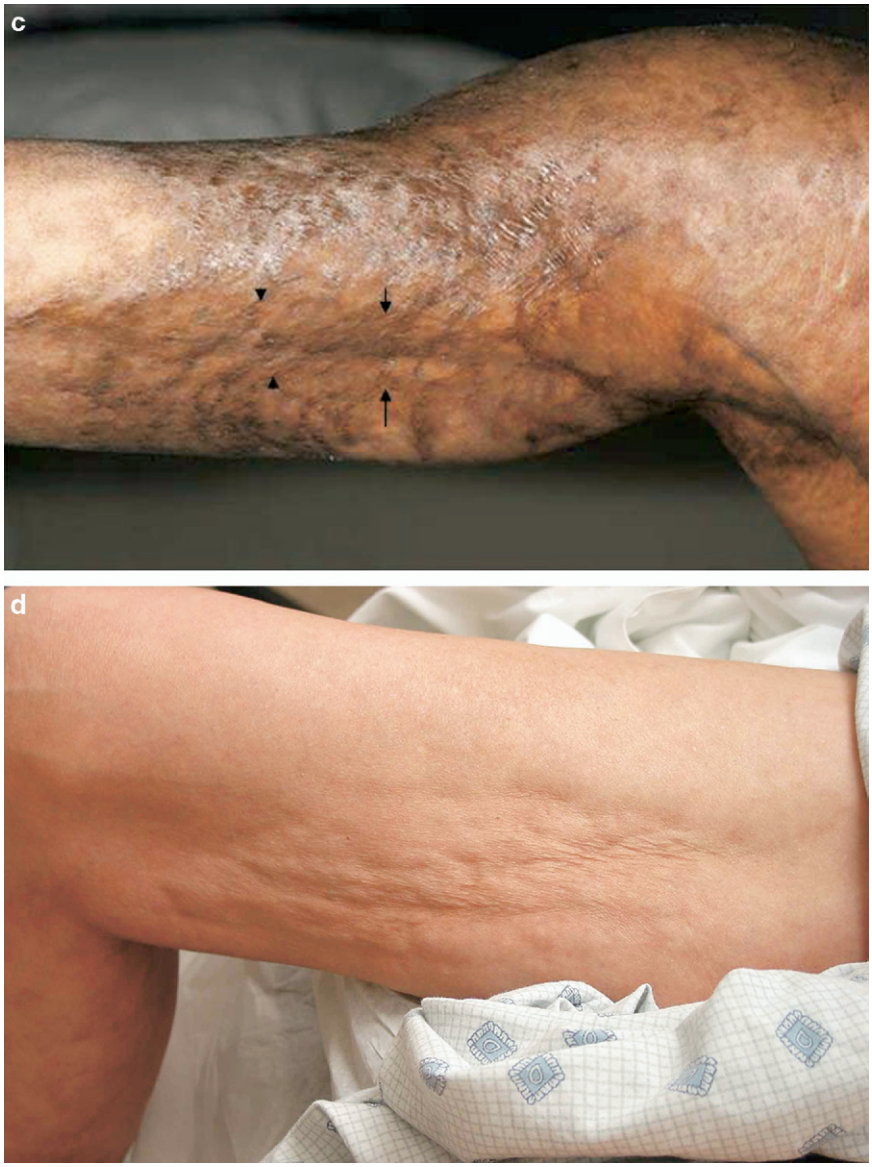

Figure 11. Continued

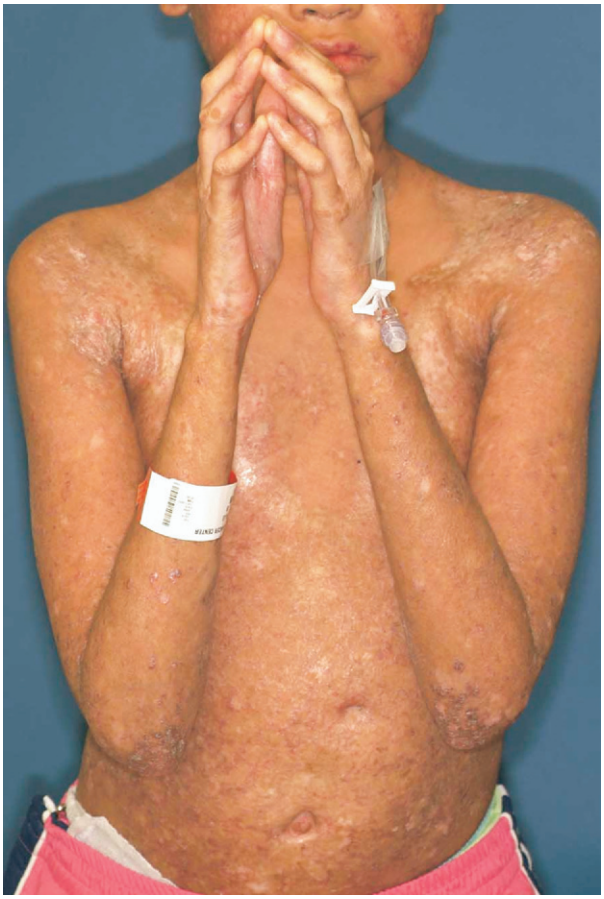

Figure 12. Positive "prayer" sign (acute limitation of wrist dorsiflexion) in a patient with fasciitis. This patient also has dermal sclerosis with dyspigmentation, a facial eruption in a butterfly distribution, and lichen planus-like lesions near the elbow. Her antinuclear antibody was positive at 1:640.

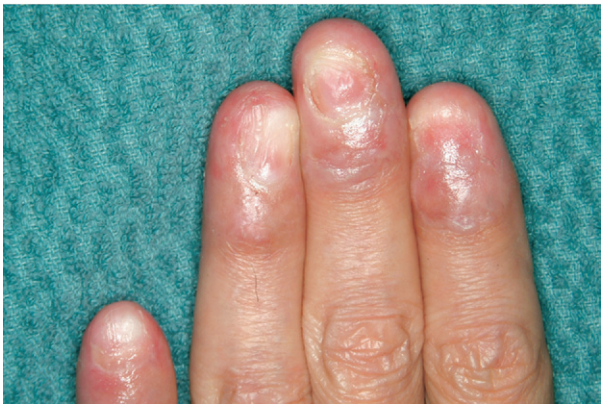

Figure 13. Nail loss in cGVHD, with periungual and nail bed changes.

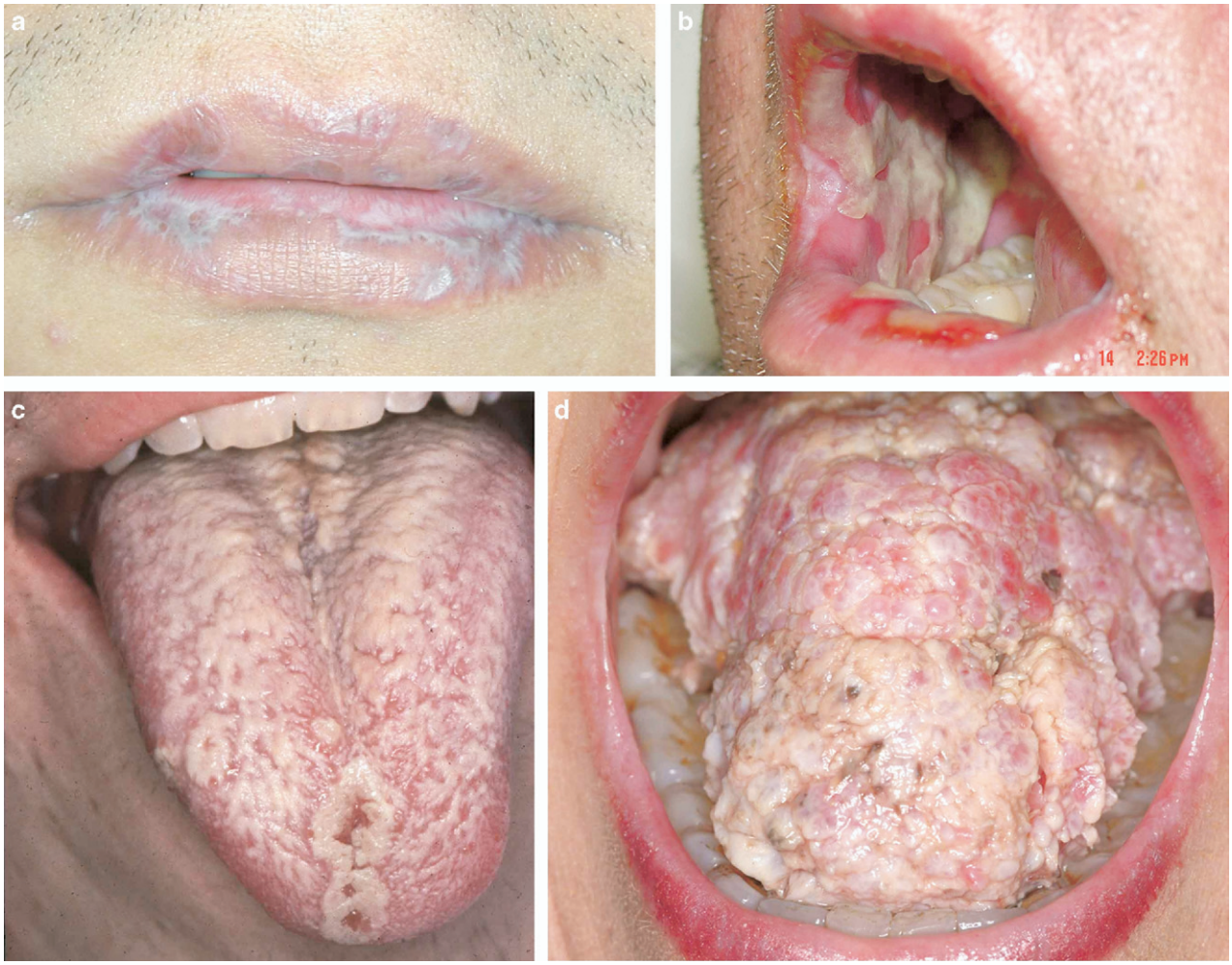

Figure 14. a, Typical Wickham striae, a network of fine lines, are seen on the lips of this patient with cGVHD. b, Erosive mucositis in cGVHD. c, Adherent white nondetachable plaques on the tongue in cGVHD. d, Chronic GVHD of the tongue complicated by documented papilloma virus and biopsy proven squamous cell carcinoma.