Early GVHD with Follicular Rash

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Cecilia C. S. Yeung, Thanh T. Dinh, and Howard M. Shulman

Clinical History

Our patient was a 52-year-old man with high-risk chronic lymphocytic leukemia, (Rai stage III–IV disease, refractory to chemotherapy) with recent transformation in peripheral blood. He received the HSCT from an HLA-matched sibling donor. On day 22, he developed a punctate red rash on both arms and back which progressed to clinical grade III (Figs. 3.1 and 3.2). He received treatment with prednisone. Microscopic photographs of the punctate rash were taken (Figs. 3.3, 3.4, and 3.5). The rash was resolved after treatment with prednisone. No other long-term complications of HSCT were noticed for this patient.

C. C. S. Yeung (✉) · H. M. Shulman
Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

Department of Pathology, University of Washington School of Medicine, Seattle, WA, USA

Pathology Section, Seattle Cancer Care Alliance, Seattle, WA, USA
e-mail: cyeung@fredhutch.org; tigermaya@comcast.net

T. T. Dinh
University of Washington, Seattle, WA, USA

Seattle Institute for Biomedical and Clinical Research, Seattle, WA, USA

Swedish Hospital, Seattle, WA, USA
e-mail: thanhd2@uw.edu

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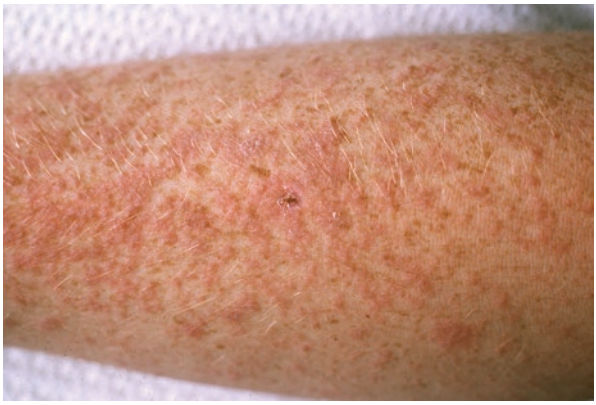

Fig. 3.1 This gross photo of the patient's arm on day 22 has a diffuse rash with small red punctuate lesions

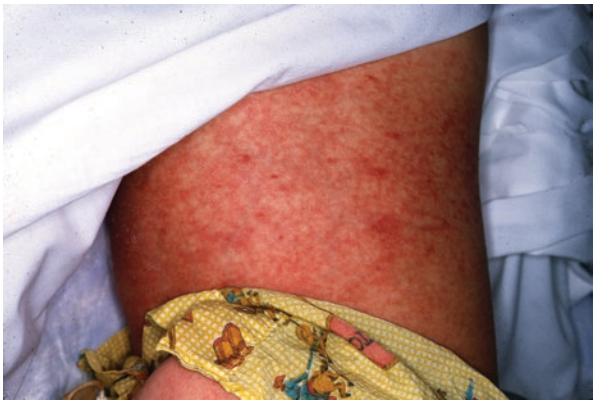

Fig. 3.2 This is a gross photo of a separate patient presenting with an early confluent erythematous macular rash over his torso on day 15, which was diagnosed on skin biopsy as early GVHD. The illustrated rash resembles clinical grade III that our patient developed

Diagnosis

Early onset of acute graft-versus-host disease (aGVHD) of the skin with involvement of the follicular unit

Key Pathology Features

- Variable keratinocyte apoptosis affecting the epidermis, follicular unit, and acrosyringium.

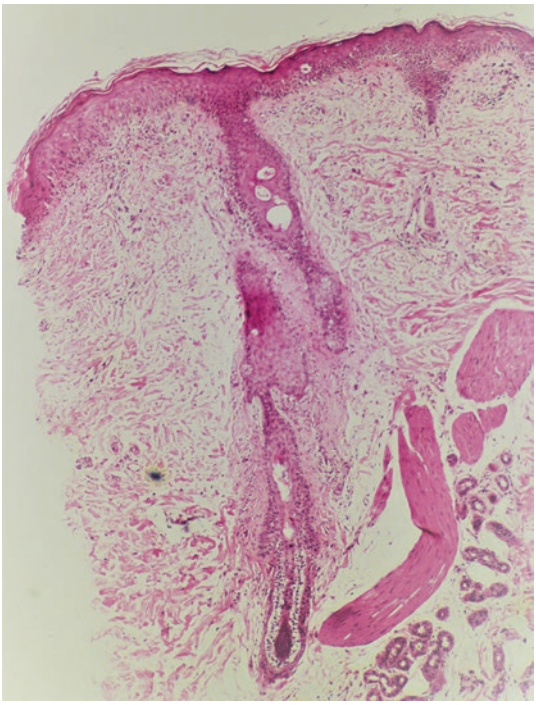

Fig. 3.3 This lower-power image of the entire hair follicle demonstrates an inflammatory reaction surrounding the follicular adventitial dermis

- Regions rich in progenitor cells are preferentially involved, basal keratinocytes, tips of rete ridges, and follicular bulb and bulge.
- Basilar vacuolization, lymphocytic satellitosis of epidermal basilar layer, melanin incontinence in the superficial dermis, and RBC extravasation may be seen.
- Biopsy performed soon after onset of rash may have only nonspecific basilar vacuolization and mild inflammation.
- Heavy lymphocytic inflammation with spongiosis and little or no keratinocyte apoptosis is most consistent with spongiotic dermatitis of non-GVHD origin.
- There is no clear histologic distinction between aGVHD that arises in the first several months or as a late-onset occurrence.

Differential Discussion

Post-transplant skin rashes are very common, especially in the first ~100 days. The histologic spectrum of early GVHD reflects several factors, the degree of allogeneic disparity between the graft donor and host recipient, cytotoxic conditioning, type and length of any prior exposure to IS prophylaxis or treatment, and duration of the rash before biopsy. The use of screening skin biopsies for aGVHD in the early post-transplant period in an asymptomatic patient is not a standard practice. Even if histopathologic criteria for GVHD are present, the biopsy still may not be accepted as GVHD [1]. A biopsy obtained in the early post-HSCT period may demonstrate

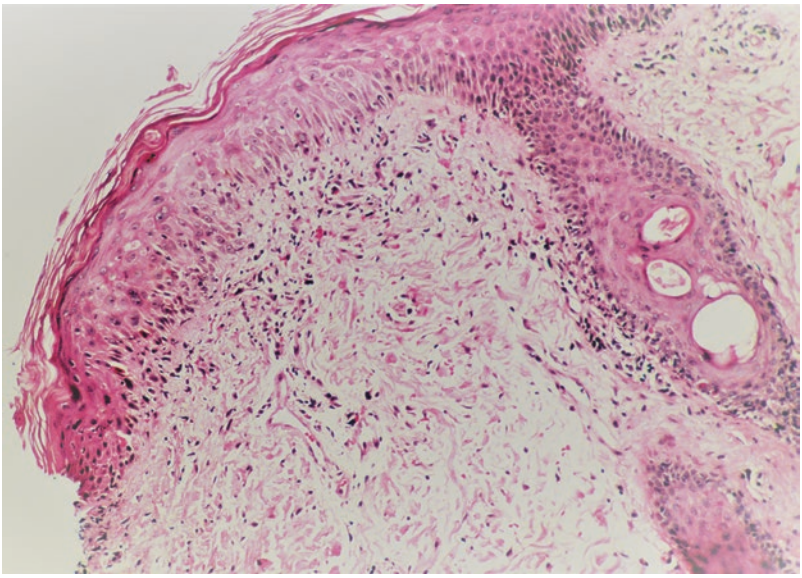

Fig. 3.4 This higher-power image of the same hair follicle and epidermis as in Fig. 3.3 demonstrates an inflammatory reaction comprised dominantly of lymphocytes. There are many apoptotic cells along the basilar portions of the epidermis and hair follicle

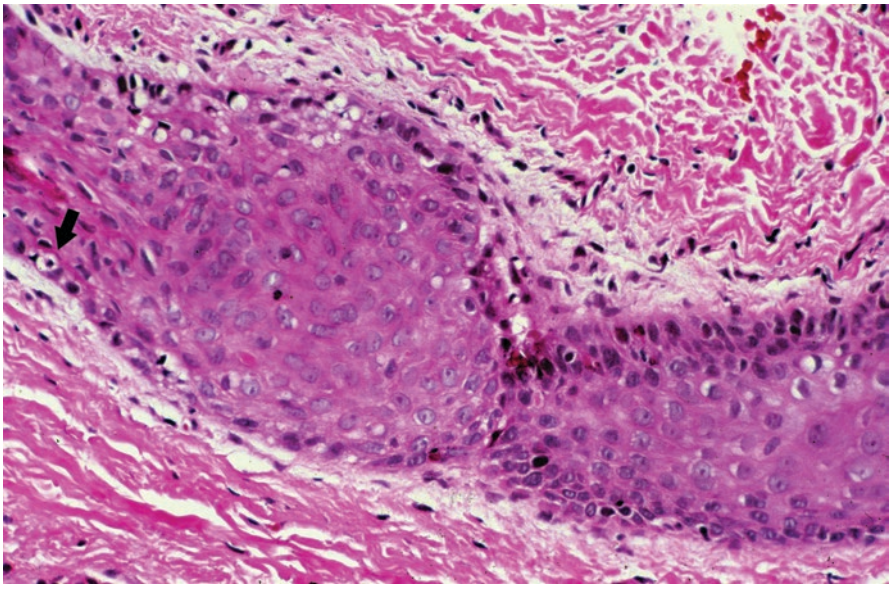

Fig. 3.5 This is a high-power microscopic image of the follicular bulge region (the widened region of the hair follicle where the arrector pili attaches) and a site of progenitor cells demonstrating characteristic GVHD features including inflammation and apoptosis (arrow) along the outer root sheath of the bulge region

nonspecific histologic features and/or overlap with other histologically similar entities. It once was a common practice at our institution to obtain serial biopsies to verify the diagnosis of aGVHD especially in the early post-transplant period. Examination of the serial biopsy would either confirm persisting GVHD or otherwise present further nondiagnostic changes [2]. However, clinicopathologic criteria developed from a 2015 consensus panel have replaced the examination of serial biopsies [3].

Pathobiology

The initial investigations into the pathobiology of GVHD focused predominately on T cell-mediated injury of target epithelia while largely ignoring the contributions of the endothelium [4] in T cell trafficking as well as a major target in solid organ rejection. In 1985, Sale et al. noted squamous epithelial basal cells in the epidermal rete tips were targeted preferentially in aGVHD [5], and Cotsarelis et al. showed that similar cells reside in the bulge region of the hair follicle [6]. Additional studies proved these basal squamous stem cells expressed cytokeratin 15, enabling immunohistochemistry labeling of squamous epithelial progenitors [7]. Subsequent murine studies by Zhan et al. showed that cytokeratin 15-positive progenitors when exposed to cytokines change their apoptotic vulnerability from antiapoptotic to proapoptotic phenotype, thereby becoming preferential epithelial targets in GVHD [8, 9]. Of relevance, some drugs, such as lovastatin, may interfere with the expression of GVHD by blocking T cell adhesion, proliferation, and cytokine production [10]. Pulses of anti-GVHD prophylactic methotrexate given before the skin is biopsied will suppress the lymphocytic inflammatory component [11].

Early GVHD Histologic Features Classic histologic features of GVHD include superficial interface dermatitis with vacuolar change mostly occurring in the basilar layer, sometimes accompanied with lymphocyte satellitosis or a lichenoid pattern of lymphocytic inflammation [1, 12, 13] (Fig. 3.6). The lymphocytic infiltrates are often sparsely scattered within the papillary dermis and around superficial venules. Lymphocyte satellitosis describes intraepithelial lymphocytes which surround apoptotic keratinocytes in the basilar layer and rete ridges. However, this is not a pathgnomonic diagnostic feature of aGVHD because drug reactions can show similar features [14] (Fig. 3.7). Cardinal histologic features that provide stronger support for the diagnosis of GVHD in the skin include apoptosis in the epidermal basilar and lower spinosum layers. A comparative study of aGVHD after T cell depletion vs non-GVHD skin rashes found features more suggestive of aGVHD were diffuse basal vacuolization, extensive keratinocytes apoptosis involving the entire epidermis, and mild rather than dense inflammatory infiltrates [15]. The hallmark of GVHD-induced cell death, apoptosis, is a shrunken hypereosinophilic keratinocyte with a pyknotic nucleus [16] (Figs. 3.3 and 3.5).

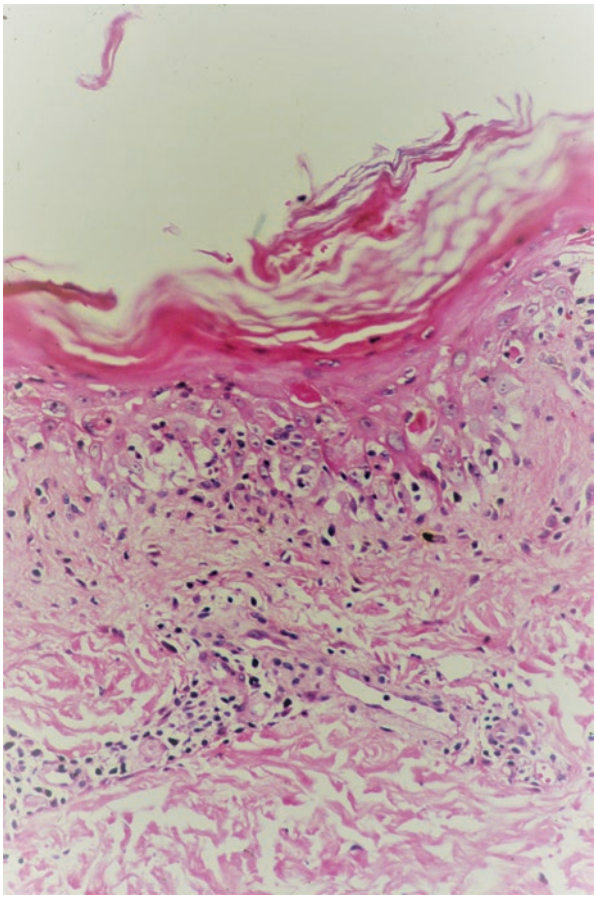

Fig. 3.6 This is the image of severe aGVHD with marked destruction of the cells in the stratum spinosum with reticular degeneration of the basal layer, extensive apoptosis, and lymphocytic inflammation

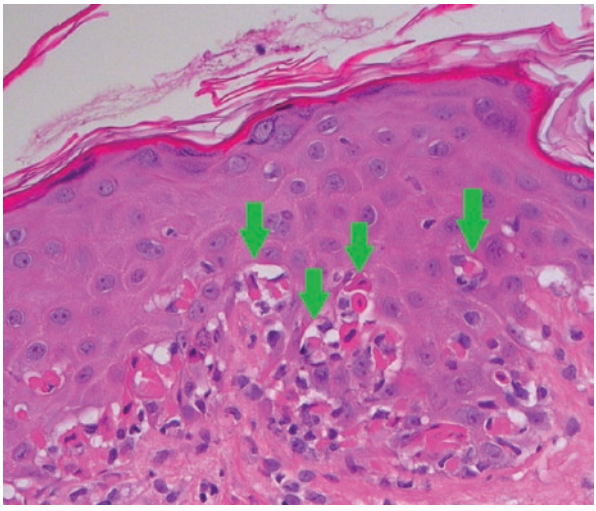

Fig. 3.7 This is a high-power image of a skin involved by aGVHD of severe histologic activity. The green arrows are pointing to a confluence of apoptotic keratinocytes which are surrounded by lymphocytes

Differential Diagnosis

Early post-transplant skin rashes may occur from toxicity to conditioning chemo-irradiation, reactions to drugs or antibiotics, transfusion reaction, infections, engraftment syndrome, or GVHD [17–23]. Presentations of dermatoses such as atopic dermatitis (eczema) can also bare strikingly similar histology to GVHD [24]. Histopathological changes seen in GVHD are often nonspecific. A GVHD diagnosis is aided by the gross appearance of the rash, the clinical context such as timing of engraftment, the number of days post-transplant, and the concurrent treatments, e.g. antibiotics and/or immunosuppressive agents [11]. Kohler et al. studied 16 histologic parameters in 179 skin biopsies (i.e., dyskeratotic keratinocytes, basal vacuolization, satellitosis, and necrotic cells in appendages) in an attempt to discern statistically distinct histological features of GVHD: but no single feature was expressed with greater statistical significance, failing to suggest a reliable single predictor or combination of predictors [25]. An early study by Sale et al. had also recommended avoiding the histologic diagnosis of skin GVHD before day 20 post-transplant because of the similar findings in autografted recipients who received intense myeloablative regimens [2]. The conclusions from these studies cannot be corroborated nor extrapolated to all HSCT centers because of differences in institutional practices, e.g. conditioning regimens, basis for study patient selection, and the uncertainty of how GVHD was clinically defined. Today, with the widespread use of mismatched unrelated allogeneic donors and the use of reduced intensity conditioning regimens, it is no longer tenable to avoid doing skin biopsies until day 20. This conundrum challenges accurate interpretation of skin biopsies in the early post-transplant period. There are different opinions on if and when skin biopsy is needed for diagnosis [26]. In Firoz's classic study on decision analysis for deciding when to do a skin biopsy, clinical estimation of the prevalence of GVHD was less influential than the possibility of not treating early severe GVHD [27].

Distinguishing between aGVHD and drug hypersensitivity reactions (DHR) can be especially challenging because aGVHD and DHR may not be distinguishable based on histologic features [14, 20, 28, 29]. In addition, the presence of eosinophils neither proves a drug reaction nor excludes GVHD [28]. Further complicating the problem are cases where components of both GVHD and DHR are likely. In these cases, having good communication between the pathobiologist and the clinical team over specific initiation of new drugs and onset of rashes as well as a trial of withdrawing the suspected drug may be needed to make a definitive diagnosis. Knowledge of additional clinical features can help narrow the differential, including facial involvement, presence of diarrhea, or hyperbilirubinemia, which are more likely due to GVHD [29]. Atopic dermatitis cannot be reliably distinguished from GVHD, as they have similar microscopic features; the diagnosis of atopic dermatitis relies primarily on the clinical physical exam and history [24]. Keratosis pilaris is a common condition with small, bumpy, hard follicular papules and pustules on the posterolateral upper arms, cheeks, anterior thighs, or buttocks, which are generally flesh colored but on occasion present as erythematous papules. In these latter instances, keratosis pilaris cannot be easily distinguished from GVHD in gross

appearance (Fig. 3.8). Engraftment syndrome may be more prevalent with certain sources of stem cells and conditioning regiments, e.g. T cell depletion with cord blood transplant, particularly if post-HSCT prophylaxis is not utilized.

In the early transplant era, rigorous multi-agent chemo-irradiation conditioning therapy could produce severe epidermal changes that resembled dysplasia, defined by Li et al. as severe keratinocyte dysplasia (SKD) [30]. SKD histological changes include enlarged, aberrantly shaped nuclei, enlarged keratinocytes, prominent nucleoli, possible multi-nucleation, loss of polarity, and mitotic figures in the epidermis which can be seen following conditioning with busulfan and have been reported to persist for months [30] (Fig. 3.9). SKD may be very difficult to distinguish from enlarged dyskeratotic cells found in some precancerous dysplasia. SKD has been reported in up to 92% of HSCT recipients who received a busulfan-conditioning regimen [31] and can occur concurrently with GVHD.

Rashes mimicking GVHD infrequently occur secondary to opportunistic infectious agents such as viruses, bacteria, and/or fungi in an immunocompromised host. Scabies is a contagious skin infestation by the mite called *Sarcoptes scabiei* that causes an intensely pruritic erythematous rash with macules/papules with a predilection for skinfolds and creases [32]. aGVHD has a predilection for palms and soles of the feet and presents in the acute phase with erythematous macules (Fig. 3.2). However, GVHD rashes are typically described as tender, whereas scabies are typically severely itchy (Fig. 3.10).

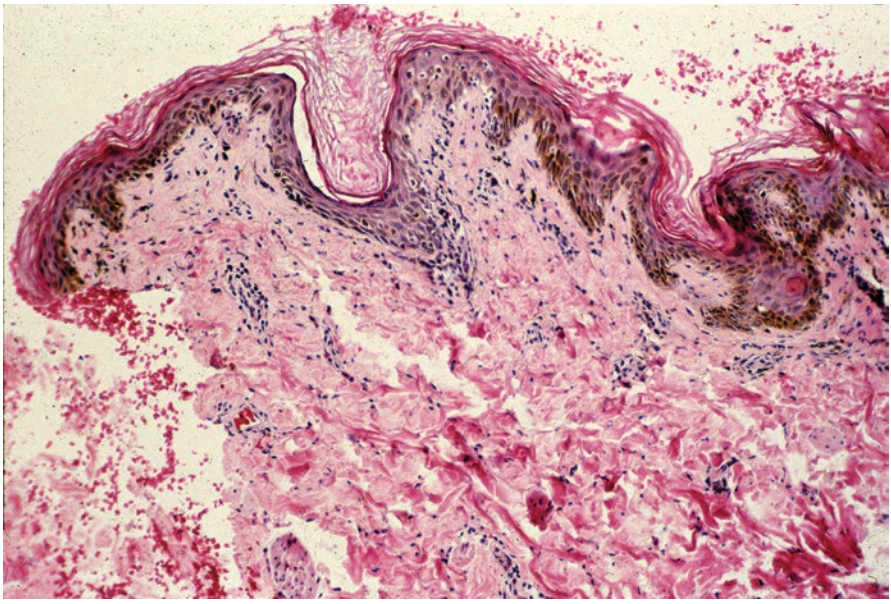

Fig. 3.8 This is a low-power image demonstrating keratinous plugging and lymphocytosis, which may resemble keratosis pilaris at low power

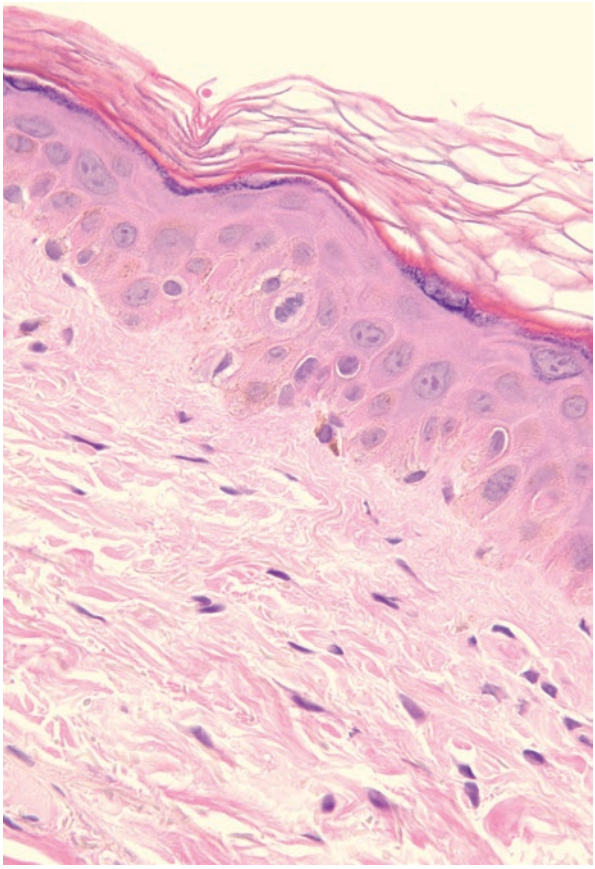

Fig. 3.9 This high-powered microscopic image of an H&E-stained skin shows an epidermis demonstrating severe keratinocyte dysplasia from a patient with AML, who is s/p HSCT day 40. Note the enlarged irregular keratinocytes with prominent nucleoli and the rare mitotic figure

CMV vasculitis is a rare serious complication in immunocompromised patients with high rates of morbidity and mortality [33, 34]. CMV vasculitis involving the cutaneous vessels has a characteristic skin rash with small erythematous papules. The microscopic changes show characteristic enlarged endothelial cells with prominent eosinophilic nuclear inclusions (Fig. 3.11). If the patient is taking prophylactic antiviral medication, these pathognomonic features of CMV can be suppressed, and additional immunohistochemistry will have to be employed to confirm CMV infection.

Uncommon cutaneous infections by both bacterial and fungal organisms have also been described secondary to severe disseminated systemic infectious such as with *Staphylococcus aureus* or various fungal organisms including *Aspergillus*, *Fusarium*, and zygomycetes (Fig. 3.12).

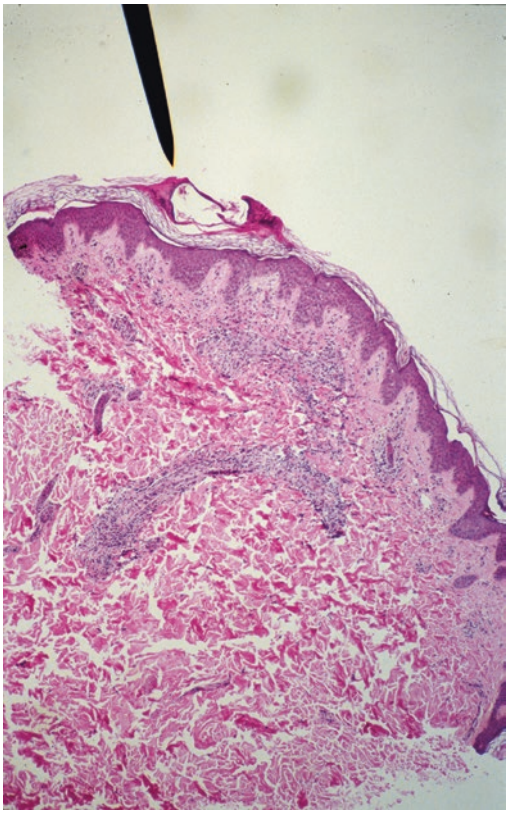

Fig. 3.10 This low-powered microscopic image of H&E-stained skin shows an epidermis with perivascular chronic inflammation associated with a mite, whose cross section is embedded into the stratum corneum (arrow) and clinically confirmed as scabies infection

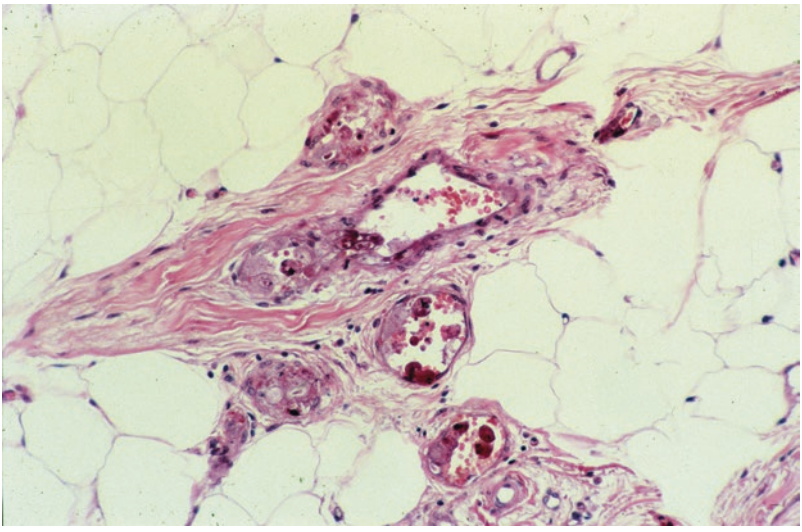

Fig. 3.11 This image is a high-power photo of the deep dermal vessels from a patient with disseminated CMV vasculitis; note the atypical endothelial lining cells with enlarged nuclei

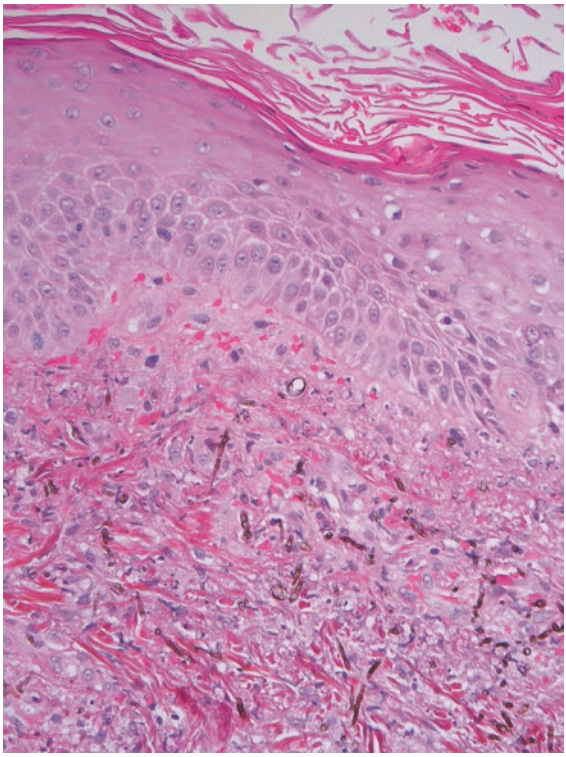

Fig. 3.12 This microscopic image of a skin biopsy stained with methenamine silver demonstrates silver positive fungal organisms in a patient with disseminated scopulariopsis infection

Teaching Points

1. The necessity of obtaining a skin biopsy for aGVHD is shaped by several factors: the associated clinical findings supporting a diagnosis of GVHD, as well as context including the donor-host allogeneic disparities, and avoiding delay for treatment of potential hyperacute aGVHD.
2. The interpretation of aGVHD is the sum of the clinical assessment plus the histologic findings which generally follow the international consensus guidelines [3]. Likewise, the presence of eosinophils neither proves a drug reaction nor excludes GVHD [28].
3. Early GVHD has features of superficial interface dermatitis with vacuolar change and keratinocyte apoptotic in the basilar layer and lymphocytic inflammation, sometimes with lymphocyte satellitosis.
4. Early post-transplant skin rashes are common and may occur from toxicity to conditioning chemo-irradiation, drug or antibiotic reactions, transfusion reaction to blood products, infections, engraftment syndrome, or GVHD.
5. The initial sites of the GVHD attack are in progenitor cell regions, the follicular hair bulb and the bulge region, and the tips of rete ridges.

Questions

1. Is it possible to ascribe different degrees of damage depending on the allogeneic incompatibility?
2. Which of the following are conditions that can mimic GVHD?
   A. Drug hypersensitivity reaction
   B. Atopic dermatitis
   C. Infection
   D. Engraftment syndrome
   E. All of the above
3. A patient develops a markedly itchy diffuse rash over the trunk back and upper arm 37 days post-transplant. A skin biopsy demonstrates lymphocytic infiltration and spongiotic change in the epidermis without apoptosis (Fig. 3.13). The patient described severe clinical excoriation (itchiness), particularly along skin creases. Which of the following diagnoses explains these symptoms?
   F. Early acute GVHD
   G. Follicular GVHD

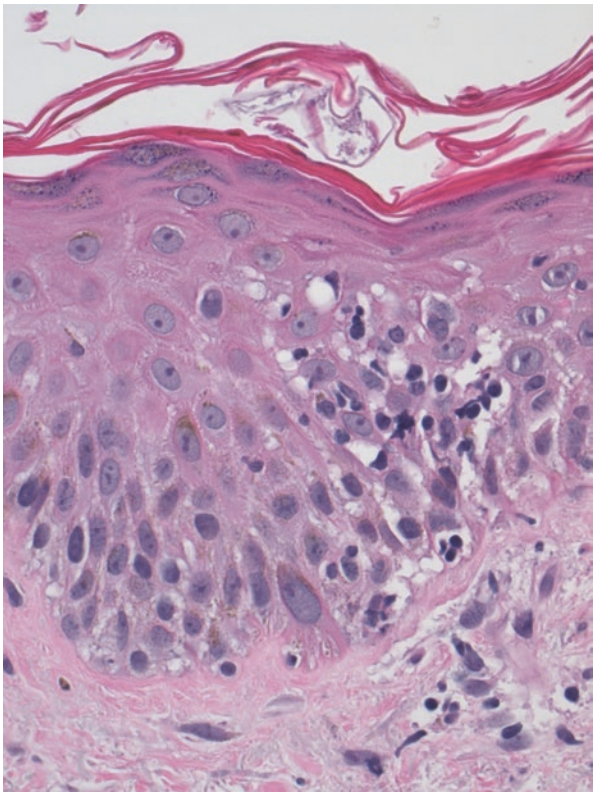

Fig. 3.13 A skin biopsy demonstrating lymphocytic infiltration and spongiotic change in the epidermis without apoptosis. Note the subcorneal structures

H. Scabies infection
I. Drug eruption
J. Contact dermatitis

Answers

1. Answer: No; however the date of onset, the tempo, and prognosis may be influenced.
2. Answer: E
3. Answer: C

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