The Basic Sequence of Injury in Acute Skin GVHD

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Clinical History

A 65-year-old man underwent allogeneic-related matched peripheral blood stem cell transplant for high-grade myelodysplastic syndrome 35 days ago. His conditioning regimen included fludarabine and melphalan; he received cyclosporine for GVHD prophylaxis. He developed a spreading, mildly pruritic, diffuse erythematous skin rash involving the scalp, trunk, and bilateral lower extremities (Fig. 4.1). A biopsy of the skin rash was taken (Figs. 4.1 and 4.2). He was treated with prednisone and showed improvement of the rash within 1 week.

Diagnosis

aGVHD of the skin

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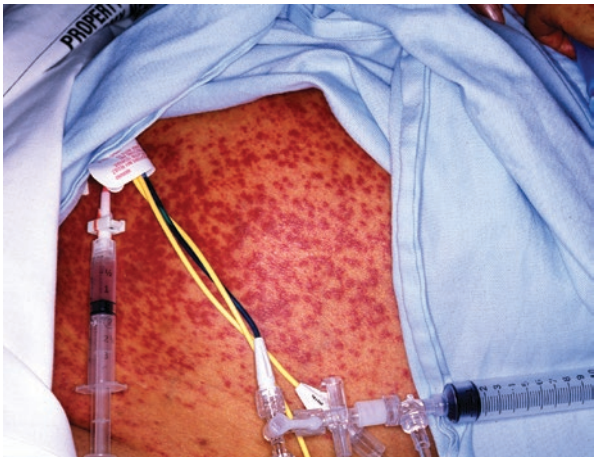

Fig. 4.1 Hyper-aGVHD on day 12 presents with an intense maculopapular rash superimposed onto an erythematous background, similar in appearance to that of our patient

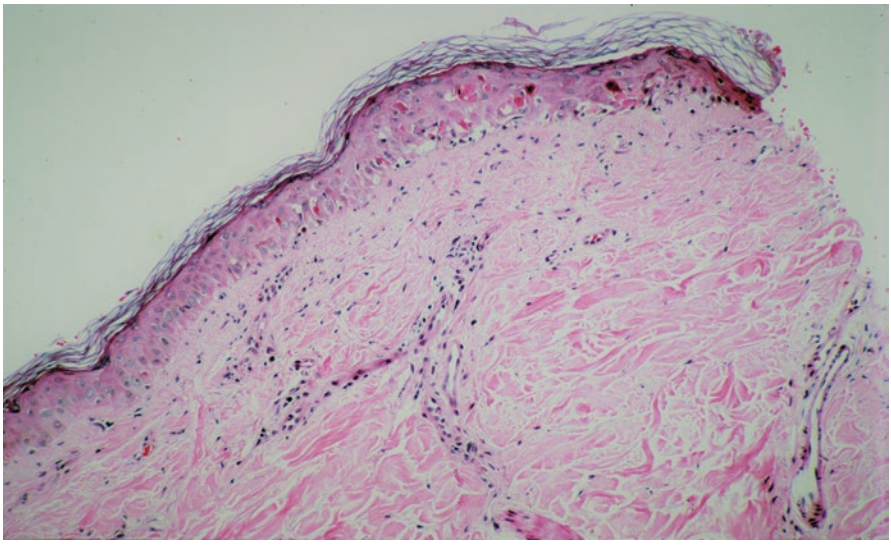

Fig. 4.2 Histology of Fig. 4.1 demonstrates aGVHD with numerous apoptotic keratinocytes, lymphocytic exocytosis, and vacuolar changes in the epidermis

Key Pathology Features

- Apoptotic keratinocytes in the basal epidermis, outer root sheath and hair bulge of follicular unit, or acrosyringium of sweat ducts.
- Basal epidermal vacuolar change.
- Interface dermatitis and perivascular lymphocytic infiltrate.
- Lymphocytes may surround apoptotic keratinocytes (lymphocyte satellitosis).

Differential Discussion

Skin biopsy obtained for histologic evaluation of aGVHD is often initiated when a patient develops a maculopapular rash following HSCT. The differential diagnosis in the case described above includes drug eruption from medications such as antibiotics, toxicity from chemotherapy and transfusion reactions. The presence of five or more apoptotic keratinocytes in association with apoptotic changes in adnexal structures within an inflammatory background of predominantly lymphocytes can help distinguish aGVHD [1]. Although the presence of eosinophils in the dermis in a non-transplant setting is commonly assumed to suggest a drug reaction, some eosinophils do occur with acute and cGVHD and should not exclude this diagnosis [2]. In the early posttransplant period, engraftment syndrome can occur in the period of granulocyte recovery and characteristically includes fever, skin rash, pulmonary edema, and organ dysfunction [3]. Of note, institutions which have used cord blood for the source of donor stem cells with T cell depletion without giving posttransplant methotrexate have reported engraftment syndrome; other institutions using similar transplant protocols but giving posttransplant methotrexate did not [4]. An inflammatory pattern of interface dermatitis with only rare apoptotic keratinocytes raises a broad differential and includes allergic contact dermatitis. Viral exanthem can also present with a similar rash.

There are multiple factors that need to be considered in the interpretation of skin biopsies used to diagnose GVHD. These include the timing of the biopsy, treatment schedules, concomitant use of immunosuppression (IS), and distribution of the rash, as well as the appearance of the skin at the site of biopsy. The timing of the skin biopsy and the severity of GVHD will influence the differential diagnosis. As there are no absolutely specific histopathologic findings in acute skin GVHD, biopsies must be appropriately correlated with posttransplantation timeline and clinical history. If the histologic findings are equivocal, empiric treatment may be given in suspected cases.

Grading of GVHD in the Skin

The histologic grading system for skin aGVHD was first proposed by Lerner et al. in 1974. It assigned the sequential histologic stages with grades as well as defining the minimal histologic criteria for skin aGVHD. In grade I GVHD, a superficial perivascular dermatitis with vacuolization of the epidermal basal region is seen, nonspecific features. Grade II GVHD encompasses an interface dermatitis with occasional dyskeratotic or apoptotic keratinocytes in the basilar or lower spinosum layers and may display lymphocytic satellitosis. Grade III GVHD is represented by extensive apoptotic keratinocytes with reticular degeneration, destruction of the basal layer, and supra-basilar bulla formation. Grade IV GVHD shows full-thickness destruction and ulceration of the epidermis. Grade II changes were proposed as minimal diagnostic criteria for distinguishing GVHD [5]. Current practice recognizes that histologic features are not always definitive for a

specific diagnosis with the NIH consensus pathology recommending using the terms “not GVHD,” “possible GVHD,” and “likely GVHD” as categories of final diagnoses [6].

Differential Diagnosis of Grade I/II GVHD

In practical terms, most skin biopsies taken from post-HSCT patients with aGVHD typically have grade II changes with infrequent apoptotic keratinocytes and only mild inflammatory infiltrates; therefore, review of multiple serial sections is beneficial. The differential diagnosis for low-grade GVHD of the skin includes drug reaction, eruption of lymphocyte recovery, infection, and other preexisting skin conditions (Chap. 3) [7]. Features that favor a diagnosis of GVHD are apoptotic keratinocytes along the outer root sheath of hair follicles and in the basilar epidermis and rete ridges. Eccrine units with architectural disarray and apoptosis are also supportive of GVHD.

Adverse drug reaction is a frequent consideration in HSCT patients, particularly when a rash presents with a distribution or pattern that is somewhat atypical for GVHD. Histologically, spongiosis with a prominent perivascular lymphocytic infiltrate and rare or no apoptotic keratinocytes suggests drug eruption rather than GVHD. Nonspecific features include edema and vascular dilation. Dermal eosinophils can be present in both entities and should not be considered specific to drug reactions. The causative medication may not always be identified due to polypharmacy use in HSCT patients, but antibiotics are a frequent cause.

Eruption of lymphocyte recovery is classically characterized as a maculopapular rash occurring 14–21 days after cytotoxic therapy, which coincides with recovery of peripheral blood lymphocytes. Skin biopsy at this time shows a scant perivascular lymphocytic infiltrate and dilation of vessels with rare or no apoptotic keratinocytes. Sweet’s syndrome, also known as acute febrile neutrophilic dermatosis, is another rash for diagnostic consideration, though the histology of neutrophilic dermatosis is quite different from that of GVHD.

In the subset of HSCT patients who have received busulfan as part of their conditioning regimen, biopsies can show severe keratinocyte dysplasia (SKD) in up to 92% of patients [8]. SKD is characterized by enlarged keratinocytes with bizarrely shaped or enlarged nuclei, prominent nucleoli, mitotic figures, and/or loss of polarity, which can resemble dysplasia of a precancerous epidermal lesion [9] (see Fig. 3.9 in Chap. 3). SKD and GVHD can coexist in the same biopsy, but there is no association between the two entities.

Clinical Characteristics

Histologic findings from skin biopsies do not always correlate well with the severity of rash seen clinically. Normal-appearing skin in a post HSCT patient can

show histologic alterations of aGVHD with scattered apoptotic keratinocytes without significant inflammation (Fig. 4.3). aGVHD typically presents as a maculopapular rash, which typically occurs within the first 100 days after HCT and affects 30–50% of transplant patients. With progression, the rash can become confluent with epidermal exfoliation (Figs. 4.4 and 4.5) or bulbous lesions. Histologically, apoptotic keratinocytes become more numerous, and basal vacuolization and interface dermatitis become more diffuse (Fig. 4.6). Severe cases can eventually resemble toxic epidermal necrolysis (TEN) with full-thickness involvement, subepidermal clefting, and complete dermal-epidermal separation and can be fatal (Figs. 4.7 and 4.8).

Recurrent or new cases with classic features of aGVHD occurring at >100 days can follow withdrawal of IS and are now termed "late acute" GVHD based on NIH criteria [10, 11]. The cumulative incidence of late aGVHD is 10% with a nonrelapse mortality of 23%, indicating the need for continued consideration of aGVHD in later posttransplant evaluation [12].

"Classic cGVHD" refers to cGVHD manifestations occurring without diagnostic features of aGVHD: an "overlap syndrome" is defined by concurrent features

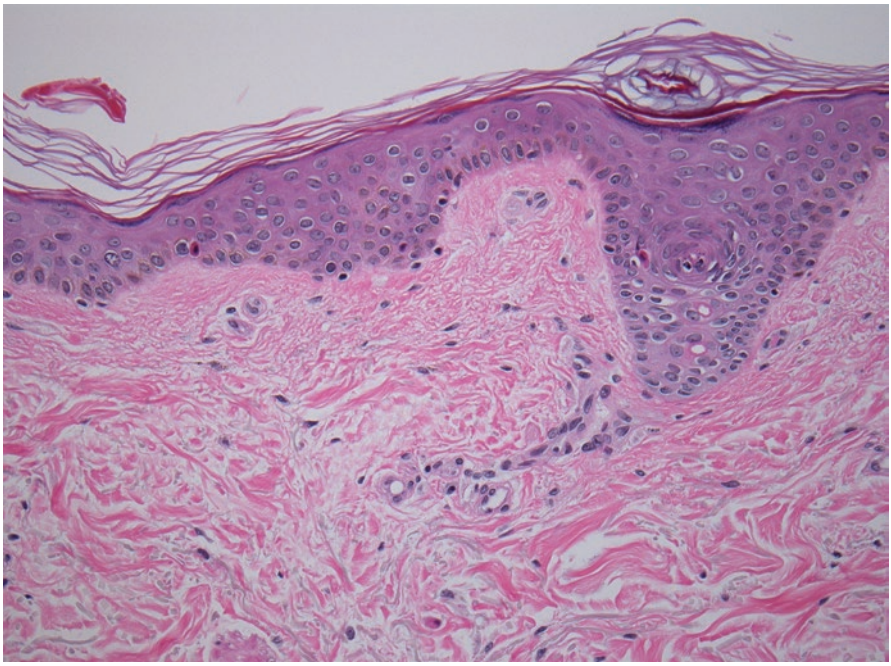

Fig. 4.3 Normal-appearing skin demonstrating GVHD of mild histologic activity with occasional scattered apoptotic keratinocytes and minimal inflammation

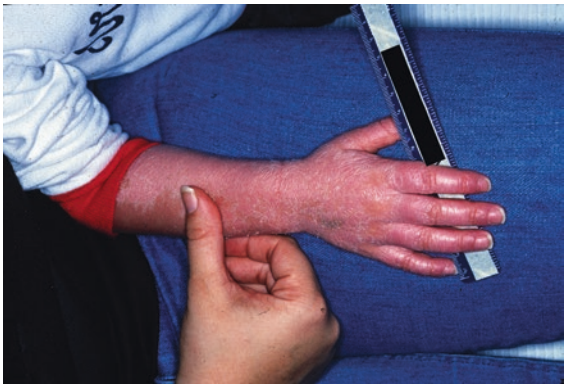

Fig. 4.4 Upper extremity of patient with diffuse rash and severe aGVHD

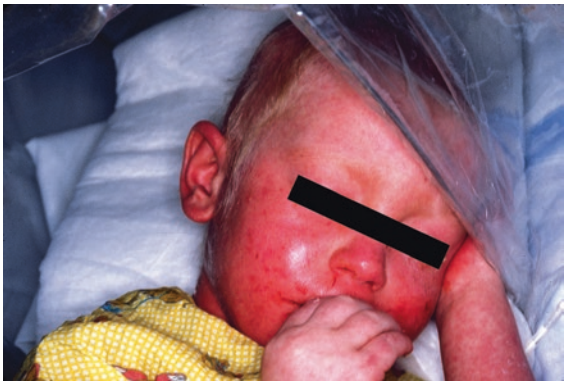

Fig. 4.5 aGVHD with diffuse edematous and erythematous rash

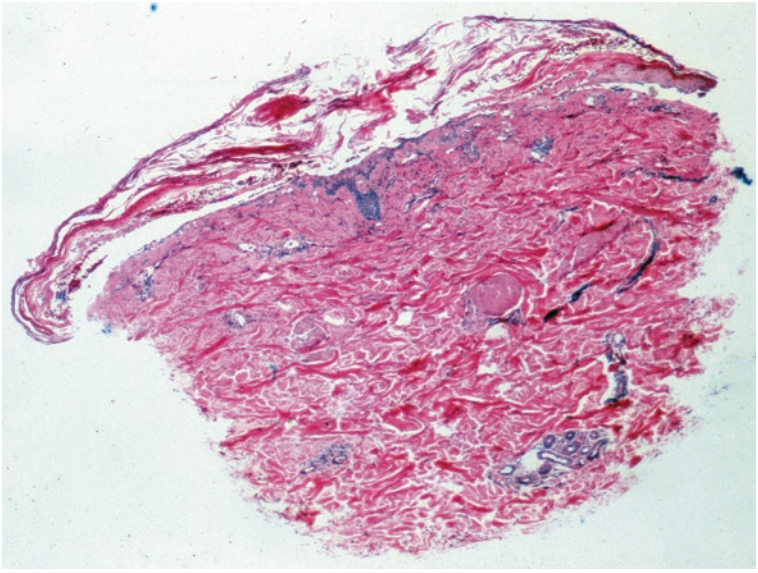

Fig. 4.6 Severe (Lerner grade IV) GVHD has necrosis and separation of the epidermis from the underlying dermis

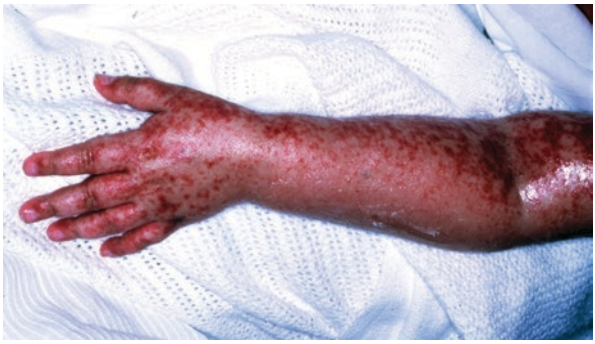

Fig. 4.7 Upper extremity of patient with TEN-like skin changes of severe aGVHD

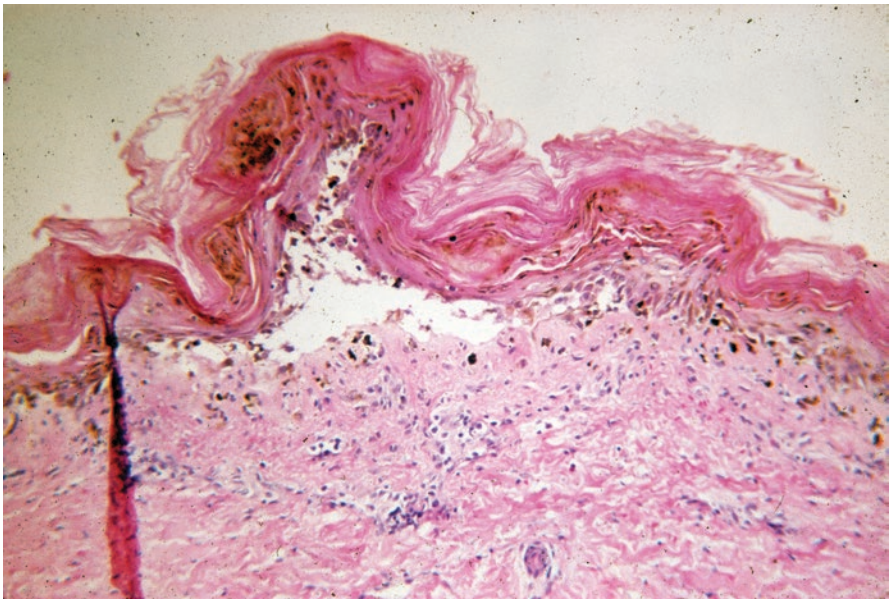

Fig. 4.8 Skin biopsy from patient with TEN-like skin changes demonstrating subepidermal clefting and full-thickness epidermal necrosis

with both chronic and aGVHD. Overlap syndrome features most often involve the skin or gastrointestinal tract and less commonly a cholestatic liver disorder. A prospective study by Pidala et al. in 2012 demonstrated the importance of recognizing the overlap syndrome as significantly higher functional impairment and subsequent adverse prognosis were observed in these patients compared to those with classic cGVHD [13].

Differential Diagnosis of Grade III/IV GVHD

Grade III/IV GVHD is characterized by extensive keratinocyte apoptosis, reticular degeneration, destruction of the basal layer, bulla formation, and eventual full-thickness epidermal destruction and ulceration. The differential diagnosis for this spectrum of histologic findings includes erythema multiforme, Stevens-Johnson syndrome (SJS), and TEN, but the specific entity cannot be distinguished based solely on histologic features and requires clinical context.

Erythema multiforme presents as acute, self-limited targetoid papules, vesicles, or plaques. Histologic evaluation shows vacuolar interface or lichenoid dermatitis, spongiosis, epidermal apoptosis of single or clustered cells often above the basal region, and clefting of the dermal-epidermal junction. Dermal eosinophils are usually absent or rare. With bullous formation, keratinocyte apoptosis becomes confluent with subepidermal clefting. Severe drug eruption manifesting as life-threatening SJS/TEN shows progression to full-thickness epidermal necrosis and blistering and may involve the oral mucosa and conjunctiva.

Chemotherapy-induced acral erythema is a form of toxic epithelial injury caused by cytoreductive conditioning. Though the acral distribution on the palms and soles is highly suggestive of conditioning toxicity, histologically it is difficult to distinguish from severe GVHD. Therefore, factoring in the type of conditioning regimen, waiting until posttransplant day 20–30 to biopsy skin has been suggested [14]. Similar histologic features of these two entities include keratinocyte atypia, vacuolar damage, dyskeratosis, apoptosis, and interface dermatitis. Current transplant protocols using reduced intensity regimens are much less likely to have such prolonged epidermal changes that overlap with aGVHD. A clinician's decision to observe a rash, treat without biopsy, or wait for biopsy before treatment is influenced by their estimated prevalence of GVHD and the desire to avoid delaying treatment of a potential case of hyperacute aGVHD [15].

Pathogenesis of aGVHD

The pathogenesis of aGVHD involves the interaction of donor T lymphocytes with host major histocompatibility complex (MHC) and/or host minor histocompatibility antigens [16]. Mismatches in MHC class or minor histocompatibility antigens are associated with increased risk of severe aGVHD. However, some degree of mismatch may contribute to the graft vs. leukemia response preventing posttransplant relapse of disease. The inflammatory effector response by donor T cells targets selective host tissues including epithelial cells of skin, intrahepatic bile ducts, and gut. Regulatory T cells (Tregs) are play a role in modulation of GVHD severity [17]. Other factors participating in GVHD include T cell costimulatory pathways, cytotoxic cytokines such as TNF-α, and other cell types including natural killer cells.

Serum biomarkers to predict the risk of GVHD and response to IS are an ongoing area of study. For example, soluble tumorigenicity-2 (ST2) has been associated with therapy resistance, and high levels were correlated with overall survival [18, 19].

Key Teaching Points

- Skin aGVHD occurs in 30–50% of HSCT patients. Factors influencing the incidence include whether the donor and recipient are the same gender, whether the donor is related or unrelated to the recipient, the age of the recipient, and prophylactic post-HSCT IS.
- Findings in early posttransplant period may overlap with the residual effects of conditioning toxicity. The posttransplant cutoff for when skin biopsy for aGVHD is evaluable is empiric but occurs much earlier with modern reduced intensity regimens.
- The clinical decision to obtain a skin biopsy to diagnosis GVHD is influenced by the constellation of clinical findings in other organs suggestive or indicative of GVHD based on the criteria of a panel of experts [20].
- The decision to biopsy an isolated rash reflects the clinical estimate of the prevalence of GVHD and the desire to avoid delaying treatment for potentially severe aGVHD.
- Histologic findings may not correlate well with clinical characteristics of the skin rash; clinically normal-appearing skin can show changes of GVHD on histologic evaluation.
- Progression of damage from mild aGVHD begins with infrequent apoptotic keratinocytes and minimal inflammation, followed by interface dermatitis with basal vacuolization and more frequent apoptotic keratinocytes.
- Severe aGVHD may progress to fulminant lesions resembling TEN.
- Presence of dermal eosinophils occurs in GVHD and, in isolation, does not favor drug reaction.
- Overlap syndrome, defined by simultaneous features of both acute and cGVHD, is significantly associated with higher morbidity and mortality.

Questions

1. Histologic characteristics of aGVHD can include the following except:
   A. Interface dermatitis with apoptotic keratinocytes
   B. Apoptosis along outer root sheath of hair follicle
   C. Acute folliculitis
   D. Perivascular dermatitis with basal epidermal vacuolization

2. The differential diagnosis when considering grade II skin aGVHD includes all of the following except:
   A. Stevens-Johnson syndrome
   B. Drug reaction
   C. Eruption of lymphocyte recovery
   D. Infection

3. Dermal eosinophils are present in which conditions?
   A. Drug eruption
   B. Erythema multiforme
   C. aGVHD
   D. A and C

Answers

1. Answer: C
2. Answer: A
3. Answer: D

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