Pathology of Graft vs. Host Disease

A Case Based Teaching Guide

Cecilia C. S. Yeung
Howard M. Shulman
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Foreword: Why Have a Histopathology Primer on Graft-vs-Host Disease (GVHD)?

In 45 years, HSCT has emerged from a last-ditch experimental effort to cure hematologic malignancies into an established treatment with hundreds of transplant centers throughout the world. Despite the numerous technological advances leading to successful outcomes, GVHD with its associated immunodeficiency and infectious vulnerability remains the leading cause of non-relapse mortality.

The advances in the HSCT procedure, along with changes in management of GVHD, have produced an additional set of considerations related to the interpretation of biopsies for diagnosing GVHD and evaluating response to anti-GVHD treatment. These considerations include distinguishing GVHD from pre-transplant conditioning chemo-irradiation toxicities, from coexistent infection, or from adverse post-transplant drug toxicity. There are a number of unresolved or controversial issues: when skin or gut biopsy are indicated, the best endoscopic location for diagnosing GVHD, the minimal diagnostic threshold for a likely or certain diagnosis of GVHD, what histologic activity scoring or grading systems are most useful in guiding clinical decisions that reflect the diagnosis, prognosis, or response to treatment? What "nonclassical" histological alterations are now considered to be part of the spectrum of manifestations of chronic GVHD?

Often these issues and assessment of GVHD are encountered by clinicians and/or pathologists without the expertise or limited exposure to HSCT. Unlike specialty journals and meetings devoted to HSCT, except for the European Germanic GVHD consortium group and the once-per-decade NIH consensus panels, there is a paucity or absence of pathology meetings devoted to sharing information on GVHD. The relevant literature is dispersed among a variety of publications including HSCT specialty journals, general surgical pathology, hematology-related journals, and HSCT textbooks. However, these publications may reflect the institutional practices from a single institution, and textbooks may not include recent developments or expansion of controversial issues.

This book is a primer directed at pathologists and oncologists who confront questions about the surgical pathology related to GVHD that are not necessarily addressed or controversial. We attempt to consolidate the current understanding, along with differing viewpoints from other institutions supplemented by the long years of experience by the authors from the large HSCT program at the Fred Hutchinson Cancer Research Center, where for over 40 years, over 10,000 transplants have been performed. The book format will be short case vignettes. They

cover the gamut of both typical and complex cases of acute and chronic GVHD, and pertinent infectious complications. The vignettes include a clinical case history, associated histologic images, and discussion of relevant questions related to interpretation. The two introductory overview chapters will cover the principles and caveats as related to the pathology of GVHD and a clinical overview of GVHD. The case discussions reflect both the published literature and wisdom from the FHCRC Hematopoietic Cell Transplantation team, the Seattle Cancer Care Alliance Pathology Department, and the University of Washington departments of surgical pathology. For more in-depth details on the clinical diagnosis and treatment of GVHD, please refer to the textbook *Thomas' Hematopoietic Cell Transplantation: Stem Cell Transplantation, 5th Edition*.

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1 The Contributions of Pathology to the Diagnosis and Management of GVHD: Caveats and Lessons Learned

Howard M. Shulman

Histologic descriptions of graft-versus-host disease (GVHD) have contributed significantly the diagnosis and management of GVHD as well as the understanding of its pathobiology. With the increasing complexities of hematopoietic stem cell transplantation (HSCT), making informed interpretations from histologic material—biopsies or autopsies—requires substantial background knowledge. The goal of this publication is to provide updated information for pathologists and clinicians with limited exposure to the HSCT setting and the nuances of histologic interpretations thereof. We illustrate the spectrum of GVHD's histopathology and some of the unresolved debates regarding its interpretation. This book's format includes clinical vignettes of classical GVHD cases as well as complex and challenging case scenarios, supplemented by both gross and histopathologic images of acute (aGVHD) and chronic GVHD (cGVHD). Through these case discussions we present insight from previous studies and experiences, describe the key points derived from the final histologic interpretation, and offer relevant information to elucidate the pathobiology of GVHD.

The classic organs targeted by GVHD are the skin, gastrointestinal (GI) tract, and liver. The principles related to histopathologic interpretation and caveats related to each of the target organs are discussed below and in the respective chapters. The contemporary diagnostic criteria and recommended format for reporting the organs involved with GVHD reflect the insights and applications of newer studies that are summarized in the two NIH histopathology consensus panels published in 2006 [1] and 2015 [2] (Table 1.1).

The cardinal feature of GVHD is apoptosis of the targeted epithelia. Criteria for defining an apoptotic epithelial cell in the skin and gut are discussed in Chaps. 3 and 8,

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Table 1.1 Criteria of the minimal and specific criteria for aGVHD and cGVHD in the organs or systems most often affected by GVHD, according to the NIH histopathology consensus panel's 2015 publication [2]

Organ or system	Minimal criteria for acute/active GVHD[a]	Specific criteria for Chronic GVHD[b]
Liver	Global assessment of dysmorphic or destroyed small bile ducts ± cholestasis, lobular, and portal inflammation	Ductopenia, portal fibrosis, and chronic cholestasis reflect chronicity but are not specific for chronic GVHD
Gastrointestinal	Variable apoptotic criteria (≥1/piece) in crypts	Destruction of glands, ulceration, or submucosal fibrosis may reflect severe or long-standing disease but are not specific for chronic GVHD
Skin, in general	Apoptosis in epidermal basal layer or lower Malpighian layer or infundibulum / outer root sheath of hair follicle or acrosyringium / sweat ducts ± lichenoid inflammation ± vacuolar change ± lymphocytic satellitosis	
Skin lichen planus-like		Combination of epidermal ortho-hyperkeratosis, hypergranulosis and acanthosis resembling lichen planus ± lichenoid inflammation and / or vacuolar changes of eccrine units
Skin morphic (localized or diffuse)		Localized thickening and homogenization of collagen bundles throughout reticular dermis or pandermal sclerosis with overlying interface changes ± thickening and homogenization of subcutaneous septa
Skin lichen sclerosus-like		Homogenization ± sclerosis of papillary dermal collagen with overlying interface changes including melanophages in the papillary dermis and sparse lymphocytic infiltrate
Skin fasciitis		Thickening of fascial septa with adjacent inflammation ± sclerosis of subcutis
Oral/ oropharyngeal mucosa and conjunctiva	Lichenoid interface lymphocytes with infiltration of mucosa (exocytosis) and variable apoptosis[c]	
Minor salivary or lacrimal gland		Periductal lymphocytic infiltrate with infiltration and damaged intralobular ducts, fibroplasia in periductal stroma, mixed lymphocytic and plasmacytic inflammation with destruction of acinar tissue[d]

(continued)

Table 1.1 (continued)

Organ or system	Minimal criteria for acute/active GVHD[a]	Specific criteria for Chronic GVHD[b]
Lung		Constrictive bronchiolitis obliterans: dense eosinophilic scarring beneath the respiratory epithelium, resulting in luminal narrowing or complete fibrous obliteration. May be preceded by lymphocytic bronchiolitis without intraluminal fibrosis[e]
Kidney		Membranous nephropathy, Minimal Change Disease
Lesions of Uncertain Pathogenesis	Central nervous system	
Lung	Cryptogenic organizing pneumonia	
Skeletal Muscle	Myositis	

[a]Conditions that result in lesser degrees of change include immunosuppressive treatment, biopsy very soon after onset of signs, suboptimal or small tissue sample, insufficient serial sectioning, confounding infection, drug reaction, or inflammatory conditions

[b]Once the diagnosis of chronic GVHD has been established or following immunosuppressive treatment, the histological manifestations of active disease may meet only minimal diagnostic criteria for activity. Different manifestations of cutaneous chronic GVHD may all be present together in one biopsy or in separate but concurrent biopsies

[c]Inflammation of the oral mucosa and within the minor salivary glands may persist from prior chemo-irradiation or prior inflammation. The distinction between acute and chronic GVHD requires the addition of distinctive oral manifestations [3]

[d]The distinction of past acinar destruction and fibrosis from ongoing chronic GVHD activity can be difficult and relies on assessing lobules that are not completely fibrotic. Acinar and periductal inflammation with features of damage to ducts, such as vacuolar change, lymphocytic exocytosis, nuclear dropout, dyspolarity or apoptosis, and resultant fibroplasia indicate chronic GVHD activity

[e]Constrictive bronchiolitis obliterans (CBO) should be distinguished from cryptogenic organizing pneumonia, which is also associated with GVHD but has a different clinicopathologic presentation and a more favorable outcome

respectively. A variety of factors are responsible for both false-negative and false-positive interpretations of GVHD. For example, skin and liver biopsies taken at the onset of clinical signs and symptoms of clinically-proven GVHD may not display the diagnostic histologic changes. Prior exposure to corticosteroids may markedly reduce the inflammatory component with variable effects on the degree of epithelia injury. The pathologist and clinician must be aware of these caveats when integrating pathologic findings disparate from clinical assessments.

Skin

Acute GVHD The basic tools needed to interpret skin biopsies include formalin-fixed tissue biopsies stained with H&E. The biopsy should ideally include some hair follicles since the progenitor regions of the follicular unit are targeted by GVHD. The histologic changes, if mild, may be infrequent or spotty. At least 4 and up to 8 serial sections should be evaluated if the tissue block permits. In routine practice, applying immunohistochemistry (IHC) staining to define the cellular phenotypes has not been shown to be a useful adjunct, except when identifying leukemia cutis (Chap. 5). The infiltrates are often sparse, and the discriminating diagnostic antibodies for T-cell subsets require research applications. In fact, Austrian investigators using research techniques to isolate and define both functional and phenotypic T cell profiles from different cutaneous GVHD lesions—acute, lichenoid, or sclerotic—have demonstrated that the different lesions display different T-cell subset patterns and that their cytokine profiles can predict the development of GVHD [4]. Of note, two studies have demonstrated that dermal macrophages may comprise the largest cellular infiltrate in aGVHD and have some correlation with steroid refractoriness [5, 6]. If malignancy is a consideration, appropriate IHC stains should be done (Chap. 5). Most skin biopsies evaluated for aGVHD consist of a 3 mm or 4 mm punch biopsy. The diagnosis of early skin GVHD is discussed in Chap. 3. The different opinions for when a skin biopsy is needed to establish aGVHD are discussed in Chap. 2. Chapter 4 describes the spectrum of cutaneous aGVHD and the differential diagnosis. Most aGVHD of the skin resolves with treatment, albeit with some residual pigmentary and atrophic changes. It should be noted that there is no clear histologic distinction between aGVHD that arises in the first several months or as a late-onset occurrence. However, the clinical implications for the latter are often severe (Chap. 6).

Chronic GVHD Cutaneous cGVHD has a complex biphasic pandermal histology with an early lichen planus-like inflammatory phase (Chap. 6) followed by a pan-sclerotic or morpheic phase that involves the superficial and deep layers of the skin (Chap. 7). It is important that biopsies are full thickness so the dermal adnexa and subcutaneous fat and fascia are included to aid in the evaluation. The majority of the skin biopsies from non-sclerotic skin are done with a punch biopsy. The current consensus recommendation by a panel of clinicians (82%) does not recommend performing a skin biopsy for patients with suspected cGVHD unless there are no other diagnostic features as defined in the NIH consensus' 2014 publication [7]. However, a study from a large tertiary referral treatment center for cGVHD found that 7% of their referral patients lacked confirmation of cGVHD when biopsied [8]. A European consensus panel of dermatologists, clinicians, and pathologists recommended a scalpel biopsy for sclerotic or deep fasciitis GVHD [9], though this recommendation is not uniformly followed in practice because of patients' additional discomfort, slower healing, and need for sutures. The trichrome stain may be useful in judging the degree and location of dermal sclerosis, especially when evaluating