Evolutions in the Clinical Management of GVHD

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Introduction

More than 40 years have passed since the first classic clinical and pathologic descriptions of acute graft-versus-host disease (GVHD) following allogeneic hematopoietic stem cell transplantation (HSCT) [1]. In that era, only a small proportion of patients survived long term. Most patients died within a few weeks or months from transplant-related complications including multi-organ acute GVHD (aGVHD), infection, interstitial pneumonia, or relapse. A few long-lived survivors of allogeneic HSCT developed a polymorphic syndrome, different from aGVHD, and resembling several autoimmune diseases that became known as chronic GVHD (cGVHD). Over the ensuing decades, the management of patients post-HSCT has improved significantly with refined strategies and algorithms based on GVHD risk stratification. These strategies have enabled us to tailor immunosuppressive regimens, to use lower drug doses or shorter treatment duration for patients with low-risk disease, and to implement earlier more intensive therapy for high-risk patients.

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C. C. S. Yeung, H. M. Shulman (eds.), *Pathology of Graft vs. Host Disease*,
https://doi.org/10.1007/978-3-319-42099-8_2

Academic sources to address the broad range of clinical and pathologic issues related to the evaluation, diagnosis, and management of acute and chronic GVHD include two journals devoted exclusively to HSCT (*Biology of Blood and Marrow Transplantation* (BBMT) and *Bone Marrow Transplantation* (BMT)) and two NIH consensus conferences. These efforts have comprehensively and reproducibly characterized various subjects concerning GVHD etiology, progression, clinical and histopathological presentation, differential diagnosis, and treatment. However, transplant physicians recognize the challenges of inter-institutional variability in the diagnosis and grading of GVHD, and, thus, recent efforts have implemented internationally standardized guidelines for managing transplant patients. The current definitions and criteria for acute and chronic GVHD were developed by consensus of expert panels [2–5] (Table 2.1). Prior to the second NIH consensus meeting, a survey of expert clinicians delineated areas of agreement and controversy regarding what clinical and histologic features were diagnostic, distinctive, or not acceptable as evidence of cGVHD [15].

Over 10,000 allogeneic and autologous HSCT were carried out in 2016 alone for a variety of hematologic malignancies, marrow failure, inherited syndromes,

Table 2.1 Adapted table based on the 2014 Recommended cGVHD-specific core measures for assessing responses in cGVHD trials [5]

Measure	Organ system	Clinician assessed	Patient reported
Signs and symptoms	Integument	NIH skin score (0–3) [6]	Skin itching (0–10)
	Ocular	NIH eye score[a] (0–3) [3, 7]	Chief eye complaint (0–10)
	Oropharyngeal	Modified oral mucositis scale (0–12) [8, 9]	Mouth sensitivity (0–10)
	Hepatobiliary	Total bilirubin (mg/dL), ALT (U/L)	
	Pulmonary	FEV-1 (liters, % predicted)	Lee symptom scale 6 (0–100) [10]
		NIH lung symptom score (0–3) [11]	
	Musculoskeletal	NIH joint score (0–3) [12]	
		Photographic range of motion (4–25)	
	Gastrointestinal (GI)	Esophagus, upper GI, lower GI response (0–3) [5]	
Global rating		None-mild-moderate-severe (0–3) [10]	None-mild-moderate-severe (0–3) [10]
		0–10 severity scale (0–10) [13]	0–10 severity scale (0–10) [13]
		7-point change scale (−3 to +3) [14]	7-point change scale (−3 to +3) [14]

ALT alanine transaminase; *FEV-1* forced expiratory volume, first second; *NIH* National Institutes of Health

[a]Components include both signs and symptoms

immunologic disorders, and assorted cancers. The increasing use of HSCT to treat multiple disorders is possible because of numerous technological advances and biological insights. Included among such advancements are less toxic conditioning regimens (reduced intensity conditioning), the use of allogeneic donor stem cells derived from peripheral blood or umbilical cord blood, more effective anti-GVHD immunosuppressive regimens for both prophylaxis and treatment, and a wider availability of donors (both related and unrelated), with more precise immunogenetic donor/recipient matching for histocompatibility antigens (HLA) and refined methods of identifying infectious agents. Furthermore, the availability and prophylactic application of new antiviral, antibacterial, and antifungal agents has markedly reduced the incidence of life-threatening infections. However, the expanded use of unrelated individuals or HLA-haploidentical family members and other partially matched individuals as stem cell donors, in addition to the inclusion of older patients as allogeneic recipients, has been associated with an increase in the incidence of acute and chronic GVHD.

Many of the original descriptions of GVHD were based on observations in patients with undertreated or refractory aGVHD. Subsequently, the histologic interpretation of biopsy tissue was affected by numerous modifications in the HSCT procedure. In the initial era of HSCT, certain cytotoxic changes in the skin and gut, presumably related to high-dose pre-transplant conditioning with chemo-radiotherapy, were found to mimic GVHD and persist for up to 3 weeks [16]. A reliable histologic diagnosis of GVHD was understandably challenging. However, many modern conditioning regimens using reduced intensity conditioning lessen or eliminate confounding cytotoxic changes; thus, censoring interpretation of any biopsy taken during this early period may no longer be necessary. Differing degrees of HLA incompatibility between stem cell donors (related or unrelated) and patients can also lead to earlier onset of aGVHD. In the setting of such a patient with high risk for the development of early and severe GVHD, the first day post-transplant that a skin biopsy may be considered informative relies on clinical judgment. However, several confounding differentials can mimic GVHD in its early stages, such as preexisting conditions, reactions to drug toxicity, engraftment syndrome, or infection. Different sources of hematopoietic stem cells, e.g. marrow versus peripheral blood or cord blood and a variety of new immunosuppressive (IS) agents, all may affect the manifestations of early acute, chronic, and late-onset acute GVHD.

How to Use This Book

The classic target organs of aGVHD are the skin, gastrointestinal tract, and liver. The clinical approaches to deciding when pathological interpretation would be most helpful and from which site a biopsy should be obtained are outlined in the remainder of this chapter. Details of the pathologic features and the associated differentials are discussed in the ensuing chapters.

AGVHD presents most frequently in the gastrointestinal (GI) tract, followed by the skin and then by the liver. Some 30–50% of patients experience

symptoms or exhibit histopathological changes in multiple organs. Historically, cGVHD occurred in 30–70% of patients as a polymorphous multi-organ syndrome with features similar to various autoimmune disorders (Chaps. 6, 7, 12, 17, 18, 19, and 20). Results of ongoing investigations incorporating antithymocyte globulin (ATG) in conditioning regimens and administering cyclophosphamide after donor cell infusion suggest that the current incidence of cGVHD is closer to 35%. Among the most prominent manifestations is the pleiotropic biphasic skin involvement with both a lichenoid inflammatory and a later fibrotic sclerodermatous phase. Other histologic manifestations of cGVHD include a generalized sicca syndrome with oral, lacrimal, and diffuse mucosal involvement (Chap. 17), bronchiolitis obliterans syndrome (Chap. 18), immune mediated cytopenias, ductopenic cholestatic liver disease, polymyositis, and various kidney disorders [17]. Some patients with cGVHD manifest an overlap with aGVHD in the skin and gut, so distinction between acute and chronic GVHD can be difficult around day 100 post-transplant. Furthermore, neither the liver nor the gut exhibits histologic changes specific for acute or chronic GVHD. The findings of esophageal webs and muscularis mucosae fibrosis are an exception to this exclusionary rule (Chap. 12). A multivariate analysis comparing the risk factors for acute and chronic GVHD identified differences in the mechanisms of development of acute and chronic GVHD. A recent review of the immunopathogenetic relationship between acute and chronic GVHD suggests that reconstitution of the immune repertoire following stem cell infusion plays a critical role in GVHD development (Chap. 20) [18, 19]. The current NIH indications for an open lung biopsy to rule out the bronchiolitis obliterans syndrome are provided in Chap. 18. Recent studies show that cGVHD patients have antibodies which cross-react with surface membrane antigens on the tissues of infected organs [20].

Skin

Erythematous maculopapular rashes from cutaneous aGVHD in the early post-transplant period are related to allogeneic lymphocytic attack and cytokine release [21–24]. The differential diagnosis of early skin rashes includes conditioning-associated cytotoxicity drug reactions (especially those caused by antibiotics), reaction to blood products, and viral infection (Chap. 4). The histology of early skin GVHD, even in the hyperacute presentation, is not pathognomonic even when keratinocyte apoptosis occurs. Thus, there is a lack of consensus regarding the necessity of obtaining a skin biopsy for suspected aGVHD in the early post-transplant period. In a hypothetical analysis study, the decision of whether a skin biopsy was necessary to confirm suspected aGVHD was influenced by the estimated prevalence of GVHD and the value of potential outcomes, e.g. the need to treat potentially aggressive GVHD immediately [25]. In a study aimed at determining the best time point for biopsy and workup of cutaneous GVHD, 88% of European pathologists, dermatologists, and transplant physicians believed a skin biopsy was necessary when *chronic* GVHD was suspected. However, only 62% believed a skin biopsy was needed when

aGVHD was suspected and no other organ showed features of aGVHD [26]. The results of this study, especially the lack of consensus regarding the necessity of a biopsy in aGVHD, are not entirely surprising. Because the need for performing a biopsy is a prevailing issue [27], it has prompted the development of established guidelines for diagnosis. A large, international multicenter panel of experts has developed guidelines for the standardization of the clinical and histological data used for diagnosing and staging of aGVHD with the goal of improving uniformity and reproducibility of the diagnosis of GVHD in clinical trials [4].

Chronic GVHD in Skin and Genitalia

Both the severity and prevalence of cGVHD have increased in the past decade due to increased use of mobilized peripheral blood stem cells for transplantation, improved survival in the post-transplant period, and increased rate of transplantation in older patients [28–30]. The current NIH consensus recommendations, which are followed by most clinicians (82%), do *not* recommend skin biopsies for patients with suspected genital/vulvar cGVHD unless there are no other diagnostic features as defined in NIH 2014 [31]. However, a study from a large tertiary treatment center for cGVHD showed that in 7% of referred patients, GVHD was not confirmed when biopsied [32]. Assessment of morphic and sclerodermatous cGVHD typically relies on visual and physical evaluation as a biopsy of sclerotic skin may not be able to distinguish active changes from static preexisting changes [33].

Liver

Liver dysfunction is common after transplantation and occurs with varied severity due to a wide range of etiologies. At the onset of liver dysfunction, the following variables must be considered to deduce differentials of liver dysfunction: time and type of recent treatments, any preexisting conditions, specific parameters of the transplant regimen, and the constellation of laboratory tests.

The incidence of liver GVHD has decreased over the last few decades from a reported incidence of around 70% in the 1970s to less than 20% during this past decade [34, 35]. Liver GVHD can present as multisystem GVHD, with an acute hepatitic onset (see Chap. 16) requiring treatment, or it can present as a slowly progressive cholestatic disorder with elevated serum liver enzyme levels and jaundice, sometimes without other manifestations of GVHD (Chap. 14).

Aside from GVHD, sources of liver dysfunction can be categorized into those that occur early (generally before full engraftment) (Chap. 13), those which occur in the immediate post-transplant period, and those that occur late (beyond day 100) after transplantation (Chap. 16). Sources of early liver dysfunction include veno-occlusive disease/(sinusoidal obstruction syndrome, (VOD/SOS), infections, drug toxicity, sepsis, and congestive hepatopathy from cardiac decompensation [36] (Chaps. 13 and 14). Late liver dysfunction may have similar etiologies as early

dysfunction, such as infection with viral or fungal organisms, drug toxicity, and preexisting conditions (e.g., nonalcoholic steatohepatitis). All of these are potential comorbidities that can complicate GVHD cases (Chaps. 15 and 16).

The decision to obtain a liver biopsy is based on the urgency to identify the likely cause of elevated liver function tests that are not clearly identifiable by the clinical context. This applies especially to the identification of causes such as infections or a malignant process. Thin-gauge needles should be avoided for biopsies since they distort the tissue architecture and complicate interpretation of the biliary structures—the cardinal target of liver GVHD. A transvenous approach with a needle or forceps biopsy should include measurement of the manometric intrahepatic pressure gradient to aid in the diagnosis of VOD/SOS. Workup of any liver biopsy, if suggested by the clinical history, should consider markers of viral infection, and potentially hepatotoxic drugs, the timing of administration of IS, the pattern and level of elevated liver function tests, information on GVHD in other organs, and any previous liver biopsies. Of note, though CMV commonly involves the liver when there is a systemic infection in the gut or lungs, it is not a cause of marked liver dysfunction in the early or later periods [37, 38].

Gastrointestinal (GI)

GVHD of the GI tract is common with incidence rates of over 50% [39, 40] to as low as 15% in a recent study restricted to reduced intensity conditioning transplants [41]. Gut GVHD will typically present after day 20 post-transplant. It is clinically categorized either as a milder upper tract syndrome with primarily gastric symptoms of anorexia, nausea, and vomiting or as a more severe lower gut syndrome with abdominal pain, diarrhea, and hematochezia. Other ancillary laboratory studies that may help in narrowing the differential diagnosis, if the patient's GVHD involves the lower or upper gut, include diarrhea volume, increased protein in diarrhea fluid (protein-losing enteropathy), and declining serum albumin levels [40, 42]. Due to the patchy nature of the mucosal changes in GI GVHD, histopathology (which is based on tiny, usually millimeter, and fragments) should be assessed simultaneously with the gross appearance of the gut by endoscopy to render a more accurate diagnosis. Histology should be considered complementary to the clinical picture and macroscopic endoscopy findings. Discrepancies between clinical signs, endoscopic findings, and histology are not uncommon and should be reviewed together with the clinical teams [43–45].

While histologic features of GVHD overlap with other diagnostic entities (e.g. engraftment syndrome, drug reactions, other autoimmune diseases, and infections), they can inform the clinician in several ways: First, according to the 2015 WHO consensus criteria, a pathologist can inform the clinician of a likely GVHD diagnosis and the need to initiate or continue treatment. Quantifying the apoptotic activity or particular location of the gut histology can aid in stratifying risk and advise the need for treatment (Chap. 10). Histology can be an effective parameter for assessing efficacy of treatment when serial biopsies can be obtained. A post-treatment biopsy

can be used to gauge repair and response to therapy and rule out infections such as *C. difficile* enteritis (Chap. 14). Treatment decisions, which are based on the severity of the symptoms, range from observation and follow-up evaluation, to systemic steroids, to alternative second-line therapy options such as anti-thymocyte globulin (ATG), ruxolitinib, mesenchymal stem cells, phototherapy, lithium and alpha-1-antitrypsin, or ibrutinib (an inhibitor of Bruton tyrosine kinase) [46].

Histologic features associated with poor prognosis include GVHD in the lower gut [47], the lack of re-epithelialization after a fortnight of systemic steroid administration, and the loss of intestinal Paneth cells [48]. Late-onset acute GVHD superimposed on cGVHD also has a poor prognosis [49]. Other factors associated with increased mortality include steroid-resistant disease, older age (>18 years), increased serum bilirubin, and GI bleeding [44].

Specific biomarkers may facilitate early identification of high-risk patients. Serum proteins such as TIM3, sTNFR1, ST2, IL-6, and Reg3a have been positively correlated with more severe GVHD [48, 50–54]. Markers of vascular injury and ensuing endothelial activation, such as loss of thrombomodulin, increased blood levels of angiopoietin-2 [55, 56], and other alterations of circulating angiogenic factors have been associated with risk of GVHD or GVHD responsiveness to steroid treatment [4, 52, 57, 58].

Additional Reading

This chapter is meant to be a brief introduction and a clinical overview of GVHD. More extensive and detailed information is provided in the following references [59–61]. For a comprehensive review of the immunobiology and recent treatments for acute and chronic GVHD, please refer to the review articles by Zeizer and Blazar [62, 63]. Good review articles on new therapeutic options for cGVHD are also available [46, 64].

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