Mucosal Biopsy After Bone Marrow Transplantation

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KEYWORDS

• Hematopoietic stem cell transplant • Graft-versus-host disease
• Diarrhea in immunocompromised patient • Apoptosis • Mycophenolate mofetil toxicity
• Cytomegalovirus • Adenovirus • Neutropenic enterocolitis

Key points

- When faced with a gastrointestinal mucosal biopsy from a bone marrow transplant patient, the 3 main things to consider are graft-versus-host disease (GVHD), infection, and drug toxicity.
- The 2015 National Institutes of Health (NIH) guidelines recommend standardized diagnostic language for GVHD.
- Distinction between acute GVHD and chronic GVHD is no longer based on the interval between diagnosis and transplantation; grading criteria and minimal diagnostic features are not established.
- Apoptotic bodies are characteristic of GVHD, but drug effects and viral infections can also cause this finding.

ABSTRACT

Gastrointestinal mucosal biopsies in the hematopoietic stem cell transplantation setting are challenging because histologic features of graft-versus-host disease (GVHD), which is treated by increasing immunosuppression, overlap with those of other conditions, such as infection, which can get worse with GVHD treatment. More than one condition can occur at the same time. It is important to understand the histologic features of GVHD, drug toxicity, infection, and clinical factors surrounding patients, including timing of biopsy in relation to transplantation, medication history, and laboratory data. Rendering a correct diagnosis and generating a pathology report with standard language that can direct clinical management ensure proper management.

OVERVIEW

Graft-versus-host disease (GVHD) is an important complication of hematopoietic stem cell transplantation (HSCT), particularly in the context of allogeneic bone marrow transplantation. It results from donor immune cells that recognize the recipient host as foreign and mediate an immune-mediated attack on host cells. Gastrointestinal involvement occurs in up to 50% of GVHD patients; it is the second most common site involved after skin.[1,2] Optimal endoscopic biopsy protocols evaluating for GVHD have not been determined.[3,4] Sampling of the entire gastrointestinal tract has the highest yield for diagnosing GVHD and ruling out potential mimics. Flexible sigmoidoscopy with rectal biopsy may be considered when patients are unable to tolerate full upper and lower endoscopy.[5]

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GRAFT-VERSUS-HOST DISEASE

CLINICAL FEATURES

Although GVHD classification has been historically based on the interval between HSCT and onset of symptoms, the 2005 National Institutes of Health (NIH) consensus guidelines recommended use of clinical manifestations and test results to classify GVHD rather than an arbitrary time cut-off.[6] Acute GVHD usually occurs within 100 days of transplantation but may persist, recur, or develop beyond that time period and can only be diagnosed in the absence of chronic GVHD. Chronic GVHD may occur with or without features of acute GVHD. Its diagnosis requires at least 1 diagnostic clinical sign or at least 1 distinctive clinical feature with biopsy confirmation. The only clinical features sufficient for diagnosing chronic gastrointestinal GVHD without further investigation are esophageal webs or strictures in the upper esophagus to midesophagus. Biopsies are performed to confirm GVHD when these diagnostic clinical manifestations are not present or other disorders are clinically considered.[7]

PATHOGENESIS OF GRAFT-VERSUS-HOST DISEASE

GVHD has an initiating and an efferent stage. The pretransplant conditioning regimen damages host cells and triggers the initial phase. Antigen-presenting cells are recruited to damaged tissue, where they present host antigens to donor lymphocytes. The donor T cells attack the host, in particular the stem cells in the gut, and delay healing after injury.[8] Loss of mucosal integrity leads to translocation of microbial products into the circulation, promoting cytokine elaboration and propagating tissue injury.

Although GVHD occurs in allogeneic HSCT, a similar syndrome can also occur in autologous HSCT. Autologous HSCT is commonly performed in patients with plasma cell myeloma and involves reinfusion of a patient's own hematopoietic progenitors after chemotherapy.[9–12] Women, in particular those with a history of breast cancer, are more likely to develop GVHD-like syndrome after autologous HSCT.[9] Presumably, loss of self-tolerance results from disruption in these patients. The female preponderance may be parity related; hematopoietic microchimerism may develop from fetal cells persisting in maternal circulation, and GVHD-like syndrome results from the allogeneic fetal immune cells included in the autologous transplantation.[9,13] The histologic features of GVHD in autologous HSCT are identical to those occurring in the allogeneic transplant setting.

MORPHOLOGIC FEATURES OF GRAFT-VERSUS-HOST DISEASE

GVHD causes apoptosis of epithelial cells in the regenerative zones of the gastrointestinal mucosae where stem cells reside: basal epithelium of the esophagus, neck regions of gastric glands, and basolateral aspects of enterocolonic crypts (**Box 1**).[14] Apoptotic cells may have an exploding appearance, contain shrunken cells with

Box 1
Key features of graft-versus-host disease in the modern era

Clinical features

- Interval between transplant and symptoms no longer used to distinguish acute from chronic GVHD
- Esophageal webs and stenoses in upper third to middle third of esophagus are the only diagnostic features of chronic GVHD
- Nausea, vomiting, and anorexia are common in acute and chronic GVHD; require biopsy

Pathologic features

- Apoptotic bodies in stem cell compartment of gastrointestinal epithelium are seen in acute and chronic GVHD
- Chronic GVHD also shows crypt architectural distortion, pyloric metaplasia, or Paneth cell metaplasia
- Severe GVHD showing ulcers and widespread crypt dropout
- Histologic features of gastrointestinal GVHD overlapping with those of other important differential diagnoses