AJR FOCUS ON:

Imaging of Abdominal and Pelvic Manifestations of Graft-Versus-Host Disease After Hematopoietic Stem Cell Transplant

Meghan G. Lubner[1]
Christine O. Menias[2]
Michelle Agrons[3]
Kinan Alhalabi[2]
Venkata S. Katabathina[4]
Khaled M. Elsayes[5]
Perry J. Pickhardt[1]

OBJECTIVE. Graft-versus-host disease (GVHD) is a common complication of hematopoietic stem cell transplant (HSCT). GVHD predominantly affects the skin, gastrointestinal system and hepatobiliary systems. Imaging findings in the gastrointestinal tract include bowel wall thickening with mucosal enhancement, mesenteric edema, and vascular engorgement. In the hepatobiliary system, hepatosplenomegaly, periportal edema, bile duct dilatation, and gallbladder and biliary wall thickening are seen. Although the imaging findings of GVHD are nonspecific, with a known history of HSCT, GVHD should be considered.

CONCLUSION. GVHD is a serious complication of HSCT, which involves multiple organ systems, with imaging manifestations most commonly seen in the gastrointestinal tract and hepatobiliary system. Knowledge of the imaging manifestations of GVHD, which alone may be relatively nonspecific, taken in conjunction with clinical history including the timing and type of HSCT, laboratory values, stool studies, and dermatologic findings can increase radiologist confidence in suggesting this diagnosis.

Keywords: gastrointestinal, graft-versus-host disease, hematopoietic stem cell transplant, hepatobiliary

DOI:10.2214/AJR.17.17866

Received January 9, 2017; accepted after revision February 23, 2017.

M. G. Lubner received grant funding from Philips Healthcare and Ethicon. P. J. Pickhardt is cofounder of VirtuoCTC, serves as an advisor to Check-Cap, and owns shares in Cellectar, Elucent, and SHINE.

[1]Department of Radiology, University of Wisconsin School of Medicine & Public Health, 600 Highland Ave, E3/311 Clinical Science Center, Madison, WI 53792-3252. Address correspondence to M. G. Lubner (mlubner@uwhealth.org).

[2]Department of Radiology, Mayo Clinic, Phoenix, AZ.

[3]Department of Radiology, Baylor College of Medicine, Houston, TX.

[4]Department of Radiology, The University of Texas Health Science Center at San Antonio, San Antonio, TX.

[5]Department of Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX.

This article is available for credit.

AJR 2017; 209:33–45

0361–803X/17/2091–33

More than 25,000 allogeneic hematopoietic stem cell transplants (HSCTs) are performed every year in the United States, and this number continues to rise [1]. HSCT is used to treat life-threatening hematologic and genetic diseases including malignancies and to restore hematologic and immunologic competence after chemotherapy and radiation therapy [2]. As stem cell transplant becomes more widespread, radiologists encounter transplant recipients with increasing frequency. Various potentially life-threatening conditions have been reported to complicate HSCT including opportunistic infections and other complications caused by dysfunction of the immune system [3]. Stem cell transplant recipients, particularly allogenic and nonmyeloablative recipients, are at risk for developing graft-versus-host disease (GVHD). GVHD is one of the major and life-threatening complications after HSCT, with an overall incidence of up to 59% after HSCT [4].

GVHD is an immunologic disorder that develops secondary to interaction between functionally competent donor T lymphocytes and epithelial cells of the skin, gastrointestinal tract, and liver in the recipient [1]. The number of GVHD cases, particularly chronic GVHD cases, has increased despite advanced immunosuppressive therapy [5]. An estimated 17% of HSCT recipients are readmitted because of GVHD, and hospitalizations may occur as early as 70 days after HSCT for low-grade GVHD or up to 101 days after transplant for more complicated cases [6]. Acute GVHD accounts for approximately 50% of posttransplant deaths that are not related to relapse of the neoplasm [7]. The goal of HSCT is to improve patient survival and decrease the rate of disease relapse. However, the complication of GVHD can result in high cost both to the patient, with reduced quality of life and survival for HSCT recipients, and to the health care system [6, 8–10]. Imaging studies play an important role in the initial diagnosis, treatment follow-up, and surveillance of GVHD. Although tissue sampling is necessary for definitive diagnosis, there are characteristic imaging findings in the gastrointestinal tract and hepatobiliary system that taken in combination with knowledge of the history and timing of HSCT strongly support the diagnosis of GVHD. It is increasingly important for physicians to be familiar with the clinical and imaging features of GVHD to enable timely diagnosis and reduce associated morbidity and mortality.

This article reviews the pathogenesis and classification of GVHD, illustrates the key

imaging findings of abdominal and pelvic manifestations, and highlights the impact of imaging on the identification and management of GVHD.

Stem Cell Transplant

Conventional HSCT is performed after a conditioning regimen (combination of high-dose chemotherapy and radiation therapy) has ablated the recipient bone marrow. In the current era, advances have expanded available conditioning regimens, sources of cells, and the breadth of the donor pool to increase availability and improve outcomes [11–13]. Pluripotent stem cells harvested from marrow or circulating blood of the patient or a donor are transfused to repopulate the bone marrow. Collection of granulocyte colony-stimulating factor (G-CSF)-mobilized progenitor cells from the peripheral blood has largely replaced bone marrow harvest [11–13]. Autologous HSCT is defined as transfusion of the patient's previously harvested cryopreserved cells, syngeneic stem cells are from a genetically identical donor (i.e., monozygotic twin), and allogeneic stem cells come from a donor who is genetically different but shows sufficient histocompatibility [14].

The course after HSCT is divided into three phases. The preengraftment phase is the period between stem cell transplant and restoration of hematopoiesis, typically lasting 15–30 days. During this period, the immune system is severely compromised and patients are pancytopenic (particularly neutropenic) and at high risk for opportunistic infection. The rapidity of neutrophil recovery varies with the type of graft: Approximate recovery time is 2 weeks with G-CSF–mobilized peripheral blood grafts, 3 weeks with marrow grafts, and 4 weeks with umbilical cord blood grafts [15]. The early posttransplant period begins after resumption of hematopoiesis and spans 30–100 days after transplant. Although neutrophil counts have begun to recover, patients often remain deficient in cellular and humoral immunity because of persistent lymphopenia. The late posttransplant phase begins approximately 100 days after transplant when lymphocyte levels return to normal, and humoral immunity continues to improve over the first year [14]. It is typically during the early and late posttransplant period, as the immune system recovers, that allogeneic transplant recipients develop GVHD. GVHD leads to dysfunctional immunity, which puts patients at risk for bacterial, fungal, and viral infections in addition to the manifestations of GVHD itself.

Older or frail patients may undergo nonmyeloablative allogeneic transplants, with reduced intensity conditioning protocols that suppress the recipients' immunity only enough to allow engraftment. The recipient's marrow is only partially ablated, which prevents pancytopenia, leading to fewer infectious complications in the early posttransplant phase. However, these patients remain at risk for GVHD and other related late complications [14].

Pathogenesis

GVHD is the direct result of one of the most fundamental functions of the immune system—that is, differentiating "self" from "nonself." The term "graft-versus-host disease" was introduced in 1955 by Barnes and Loutit [16] to describe the secondary disease consisting of diarrhea, skin changes, and wasting syndrome seen in irradiated mice that were given allogeneic stem cells. Similar responses were seen in other animal studies and early human allogeneic stem cell transplants [17, 18]. GVHD is now recognized as a clinical syndrome caused by target organ injury to the skin, liver, gastrointestinal tract, and rarely lung due to immune cells from a graft (marrow, organ, transfusion) reacting against the recipient. According to Billingham [19], three requirements must be met for GVHD to develop: The graft or donor tissue must contain immunologically competent cells, the recipient must express tissue antigens that are not present in the donor, and the recipient must not be capable of mounting an immune response to eliminate the donor cells. The immunologically competent donor cells are T cells, which respond to genetically defined proteins on host cells—most importantly, human leukocyte antigen (HLA) proteins [1, 20]. These HLA proteins in the recipient are considered foreign, and the donor T cells react against them. Therefore, the transplant of any tissue containing T cells, such as blood products, bone marrow, and solid organs, into a person who is not able to effectively eliminate them may lead to GVHD [1, 20]. As HLA disparity between the donor and recipient increases, so does the likelihood of developing GVHD and the severity of the reaction [20]. Recipients of mismatched transplants are at greatest risk. The prevalence of acute GVHD is seen in 35–45% of patients with matched sibling donors and 60–80% of patients with unrelated donors and one antigen mismatched [1, 11]. Moderate to severe GVHD is seen in 30–50% of patients receiving matched allogeneic transplants [14, 21, 22].

Ferrara and Deeg [23] suggested a three-phase pathogenesis of acute GVHD [1, 17]. In phase I, the conditioning regimen damages and activates host tissues, including skin, intestinal mucosa, and liver. Activated host cells secrete a variety of cytokines that may upregulate adhesion molecules and major histocompatibility complex (MHC) antigens, promoting recognition of MHC antigens or HLAs by donor T cells after the stem cell transplant [17, 24–27]. In phase II, donor T cells recognize recipient HLA complexes (alloantigens) as "not self" via antigen-specific T-cell receptors and become activated. T-cell activation results in the production of a cascade of cytokines [1, 11, 17, 28–34]. Phase III involves inflammatory cellular effectors, which release additional cytokines that result in necrosis, apoptosis, and amplification of local tissue injury leading to the clinical manifestations of GVHD [17, 35]. Despite the systemic response, only a cluster of targets including skin, gut, and liver are predominantly involved. For the gastrointestinal tract specifically, damage to the mucosa leads to translocation of microbial products (including endotoxin and lipopolysaccharide), which creates a feedback loop of cytokine storm and ongoing tissue injury [11, 17, 20, 36].

In the gastrointestinal tract, a distinctive histologic feature of GVHD is epithelial cell apoptosis, most prominent in the regenerative compartment of the gland or crypt. These apoptotic cells contain vacuoles filled with debris and have been described as "exploding crypt" cells [17, 37]. In more advanced GVHD, cystic dilatation of crypts, crypt abscesses, and frank epithelial necrosis and total sloughing of the mucosa can be seen [17, 38, 39]. In the duodenum and small bowel, crypt blunting is seen; the distribution of gastrointestinal GVHD is often patchy, which may require multisite biopsy and pathologic analysis of multiple sections. The histologic hallmark of acute hepatic GVHD is bile duct injury, with changes in biliary epithelial cells including uneven spacing of nuclei, changes in nuclear size, and cytoplasmic vacuolization with apoptosis and necrosis less commonly seen. Cholestasis is present, and with time, portal fibrosis and bile duct loss are seen [11, 40].

In contradistinction to acute GVHD, chronic GVHD has different underlying histopathology and pathophysiology that re-

main less well understood. The current theories relate chronic GVHD to autoimmune disorders, possibly associated with immune dysregulation [1, 11, 32, 33, 41–43]. Interplay between T cells, macrophages, and B cells results in chronic inflammation and stimulation of fibroblasts, leading to the general sclerosing syndrome seen in chronic GVHD [11]. Pathologic analysis shows mucosal, submucosal, and serosal fibrosis; crypt distortion; mild inflammation; Paneth cell metaplasia; and hyalinization of small venules [11, 44]. In the liver, a sharp demarcation between acute GVHD and chronic GVHD does not exist. With time (often > 90 days), portal fibrosis and bile duct loss become evident; however, these changes can be seen in acute GVHD and can be reversible [11]. These changes need to be irreversible to be considered chronic; therefore, chronic GVHD usually requires correlation with a distinctive feature in another organ system [11, 41]. Chronic GVHD is estimated to affect 30–65% of HSCT patients, with incidence differing by regimen, center, and other risk factors [1, 11, 33, 41, 45].

Classification and Staging

Classic acute GVHD typically develops 10–40 days after transplant (usually < 100 days), although persistent, recurrent, or late-onset acute GVHD can be seen after day 100. Acute GVHD most commonly affects the skin first and then progresses to include the gastrointestinal tract (most commonly, the small intestine) and the liver [1]. It is uncommon to see liver and gastrointestinal manifestations without skin lesions. Later, oral manifestations may be seen, such as severe oral pain, xerostomia, ulcerative lesions, and mucositis [46].

Transplant recipients with acute GVHD often develop chronic GVHD, although the presence of acute GVHD is not necessary to develop chronic GVHD. In patients without acute GVHD, chronic GVHD can occur insidiously. Similar risk factors are seen in chronic GVHD, with unrelated allogeneic transplant recipients at higher risk. Chronic GVHD is typically seen in the late posttransplant period, after 100 days, but can occur almost anytime after HSCT. Chronic GVHD is associated with hyperpigmentation and sclerodermalike skin reaction, hepatic fibrosis, and wasting.

Overall, the acute and chronic forms of GVHD have mutually exclusive features at opposite ends of the spectrum. New classification systems have incorporated the gray area between these two, known as "acute-on-chronic GVHD" or "overlap syndrome," which can have features of both acute GVHD and chronic GVHD [1]. The National Institutes of Health (NIH) classification, which is based on more clinical manifestations, recognizes two main categories of GVHD, each with two subcategories. Acute GVHD can be subdivided into classic acute GVHD or persistent, recurrent, or late-onset acute GVHD (occurring after day 100). Chronic GVHD can be subclassified as classic chronic GVHD or an overlap syndrome for patients with features of both acute GVHD and chronic GVHD (Table 1). In this classification system, characteristic skin, gastrointestinal tract, or liver abnormalities are classified as acute GVHD regardless of the amount of time that passed after transplant. Chronic GVHD requires the presence of at least one diagnostic clinical sign or distinctive clinical manifestation confirmed by biopsy or other relevant test in the same or another organ [17, 41] (Tables 1 and 2).

In acute GVHD, the extent or stage of involvement of each of the three primarily involved organs (skin, gastrointestinal system, and liver) determines the grade (severity) of the disease as grade I (mild), grade II (moderate), grade III (severe), or grade IV (very severe) [20]. The NIH Consensus Development Project has formulated a staging system for chronic GVHD based on specific signs, degree of organ involvement, laboratory data, and histologic confirmation [20, 41].

Clinical and Imaging Findings

Acute Graft-Versus-Host Disease

As we have described, GVHD primarily affects the skin, gastrointestinal tract, and hepatobiliary system; hence, patients often present with the clinical triad of dermatitis, enteritis, and hepatitis [20]. Overwhelmingly, the most common, and often the first, organ to be affected is the skin in up to 81% of patients, followed by the gastrointestinal tract in 54% of patients, and the liver in 50% of patients [1]. The lungs, genital tract, and joints are less commonly affected.

Clinical presentation—Development of acute GVHD is often heralded by the development of a diffuse pruritic maculopapular rash that can be followed by desquamation in severe cases. Typically, involvement of the gastrointestinal tract begins after dermatologic disease is clinically evident. Less commonly, gastrointestinal symptoms can occur without skin findings, seen in up to 20% of cases [47]; however, recently there seems to be an increased incidence of isolated gastrointestinal GVHD [11, 48]. Gastrointestinal symptoms in acute GVHD are usually nonspecific and variable [47]. Be-

TABLE 1: National Institutes of Health Classification System for Graft-Versus-Host Disease (GVHD)[a]

Classification	Time of Onset	Features
Classic acute GVHD	Cases present < 100 days of HSCT	Maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea, ileus, or cholestatic hepatitis
Persistent, recurrent, late-onset acute GVHD	Cases present with features of acute GVHD > 100 days after HSCT	Same features as features of classic acute GVHD without diagnostic and distinctive features of chronic GVHD
Classic chronic GVHD	May present at any time after HSCT	At least one diagnostic or distinctive manifestation of chronic GVHD without features of acute GVHD; manifestations can affect skin, nails, eyes, mouth, lungs, gastrointestinal tract, genitalia, fascia, joints, and muscles (see Table 2)
Overlap syndrome	May present at any time after HSCT	Features of acute and chronic GVHD appear together

Note—HSCT = hematopoietic stem cell transplant.

[a]Modified from [41]: *Biology of Blood and Marrow Transplantation,* Vol. 11/edition no. 12, Filipovich AH, Weisdorf D, Pavletic S, et al., "National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease: I. Diagnosis and Staging Working Group Report," pages 945–956, Copyright 2005, with permission from Elsevier.

TABLE 2: Diagnostic and Distinctive Features of Chronic Graft-Versus-Host Disease (GVHD)[a]

Organ	Diagnostic Feature[b]	Distinctive Feature[c]
Scalp and body hair		• New onset of scarring or nonscarring scalp alopecia
		• Scaling, papulosquamous lesions
Nails		• Dystrophy
		• Longitudinal ridging, splitting or brittle features
		• Onycholysis
		• Pterygium unguis
		• Nail loss (symmetric; affects all nails)
Skin	• Lichen planus–like features	• Depigmentation
	• Lichen sclerosus–like features	
	• Morphealike features	
	• Poikiloderma	
	• Sclerotic features	
Eyes		• New onset of dry, gritty, or painful eyes
		• Cicatricial conjunctivitis
		• Confluent areas of punctate keratopathy
		• Keratoconjunctivitis sicca
Mouth	• Hyperkeratotic plaques	• Mucocele
	• Lichen-type features	• Mucosal atrophy
	• Restriction of mouth opening due to sclerosis	• Pseudomembranes
		• Ulcers
		• Xerostomia
Lung	• Bronchiolitis obliterans diagnosed with lung biopsy	• Bronchiolitis obliterans diagnosed with PFTs and radiology
Gastrointestinal tract	• Esophageal web	
	• Strictures or stenosis in the upper to mid third of the esophagus	
Genitalia	• Lichen planus–like features	• Erosions
	• Vaginal scarring or stenosis	• Fissures
		• Ulcers
Fascia, joints, and muscles	• Fasciitis	• Myositis or polymyositis
	• Joint stiffness of contractures secondary to sclerosis	

Note—PFT = pulmonary function test.

[a]Modified from [41]: *Biology of Blood and Marrow Transplantation,* Vol. 11/edition no. 12, Filipovich AH, Weisdorf D, Pavletic S, et al., "National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-Versus-Host Disease: I. Diagnosis and Staging Working Group Report," pages 945–956, Copyright 2005, with permission from Elsevier.

[b]Sufficient to establish the diagnosis of GVHD.

[c]Seen in chronic GVHD but insufficient alone to establish the diagnosis of chronic GVHD.

cause the small bowel and colon are the most common sites of gastrointestinal GVHD, patients most commonly present with secretory diarrhea in addition to fever and abdominal pain. Epithelial damage can lead to mucosal ulceration, so gastrointestinal bleeding, protein-losing enteropathy, and ileus can be seen in severe cases. Esophageal involvement can manifest as mucositis followed by development of webs or strictures, which can produce symptoms of odynophagia. Gastric GVHD can cause nausea and vomiting [14, 17, 49].

Endoscopic findings in patients with GVHD do not always correlate well with histopathologic findings [17, 50] and can range from normal-appearing mucosa to severe ulceration. Investigators have suggested that visible endoscopic lesions are seen in only a minority of cases (16–32%) [17, 51]. When present, mucosal edema, erythema, and friability are most commonly seen, with erosions and ulcers encountered less frequently [17, 50, 51]. Although there is no agreed-on optimal site for gastrointestinal endoscopic biopsy, rectal biopsy is sometimes performed as a first step because of the clinical advantages. If rectal biopsy is not diagnostic or is negative but gastrointestinal GVHD is still suspected, an upper gastrointestinal site such as the stomach may yield additional diagnos-

tic material; some authors suggest that gastric biopsies may be more sensitive in diagnosing acute GVHD [11, 17, 52–56].

Gastrointestinal imaging findings—The hallmark imaging findings in acute GVHD involving the gastrointestinal tract include bowel wall thickening with abnormal marked mucosal enhancement (Fig. 1) and mural stratification, which can be seen involving any part of the gastrointestinal tract [47, 57] but is most common in the small bowel and colon. The mucosal and serosal surfaces avidly enhance to appear hyperattenuating and form a target sign, with a hypoattenuating middle layer representing intramural or submucosal bowel wall edema [58] (Fig. 2). Bowel loops are often fluid-filled and dilated, and bowel loop separation can be seen [14, 21, 59–61]. In one study, all patients with biopsy-proven intestinal GVHD had small-bowel involvement, whereas 59% had further concomitant large-bowel involvement [62]. In this same study, extraintestinal findings such as engorgement of the vasa recta adjacent to affected bowel (91%) and stranding of the mesenteric fat (73%) were noted [62] (Fig. 3 and Table 3). No mesenteric lymphadenopathy was reported in this series [62]. This collection of findings is nonspecific and can overlap with other causes of enteritis; however, the overall extent of bowel involvement tends to be greater in GVHD, often with involvement of both the small bowel and colon in many cases [14, 59, 63].

In many cases, the main differential diagnosis in these patients may include neutropenic enterocolitis, infectious enterocolitis (pseudomembranous colitis, viral infections, fungi), or radiation enteritis in addition to GVHD [64]. Neutropenic enterocolitis most commonly involves the cecum and ascending colon and occasionally involves the ileum, in contradistinction to GVHD. In GVHD, both the small bowel and colon can be involved, but the small bowel is more prominently affected and often is affected in a diffuse distribution. Pseudomembranous colitis usually manifests as a pancolitis with marked eccentric or circumferential fold thickening; small-bowel involvement is uncommon [59]. During the early posttransplant period, the most common cause of gastrointestinal infectious complications is cytomegalovirus (CMV). CMV colitis has a similar appearance to typhlitis, predominantly affecting the terminal ileum, cecum, and right colon [64]. Small-bowel involvement can be seen with CMV or other viral infections (e.g., herpes simplex virus, rotavirus) but is often segmental rather than diffuse. Although overlap exists between GVHD and other enteritides that arise in patients with HSCT, the location and extent of bowel involvement and the presence and intensity of associated findings may narrow the differential diagnosis. In addition, clinical history is critical, taking into account the timing of the HSCT, type of HSCT, and type and timing of conditioning regimen, as well as laboratory values and stool studies, when trying to make a more specific diagnosis [64]. Finally, in addition to imaging, endoscopic examination and gastrointestinal biopsies are critical in establishing the final diagnosis.

Often these patients are evaluated initially with CT. In terms of protocol considerations, IV contrast material is desirable if possible to identify bowel wall enhancement. Some groups have advocated a biphasic protocol (late arterial and portal venous phases) to make mucosal hyperenhancement more conspicuous [65]. CT enterography protocols, which may use a higher IV contrast injection rate or may be biphasic (mucosal and enteric phases), may also have some utility in subtle cases. In many cases, positive oral contrast agent is not desirable. First, it is often poorly tolerated by patients due to severe nausea and vomiting; therefore, opacification of bowel loops with oral contrast material is often poor as well [21]. Second, administration of a positive oral contrast agent may be undesirable because it impairs evaluation of the mucosa and bowel wall. The fluid within the bowel loops often serves as a natural neutral oral contrast agent. If a positive oral contrast agent is administered, prolonged coating of the bowel with oral contrast material at CT or in barium studies may occur because the epithelial damage and mucosal ulceration of the bowel allow the oral contrast material to be incorporated into the sub-

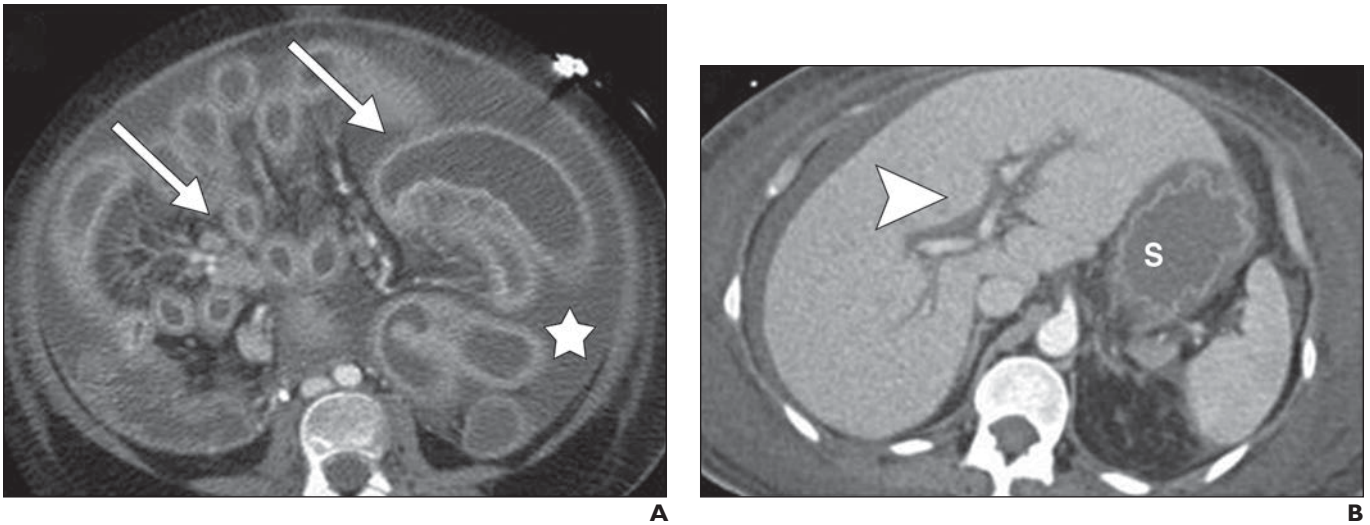

Fig. 1—Two patients with acute graft-versus-host disease (GVHD).
A, 8-year-old girl who presented with abdominal pain and rash 30 days after undergoing hematopoietic stem cell transplant (HSCT) for acute myelogenous leukemia (AML). Axial contrast-enhanced CT image shows diffusely thick-walled small bowel and colon (*arrows*) with marked mucosal enhancement. Many bowel loops are dilated and fluid filled, and mesenteric congestion and ascites (*star*) are seen.
B, 60-year-old woman who presented for imaging follow-up after HSCT for AML. Axial contrast-enhanced CT image shows fluid-filled stomach with mucosal hyperenhancement (S) and periportal edema (*arrowhead*) and ascites.

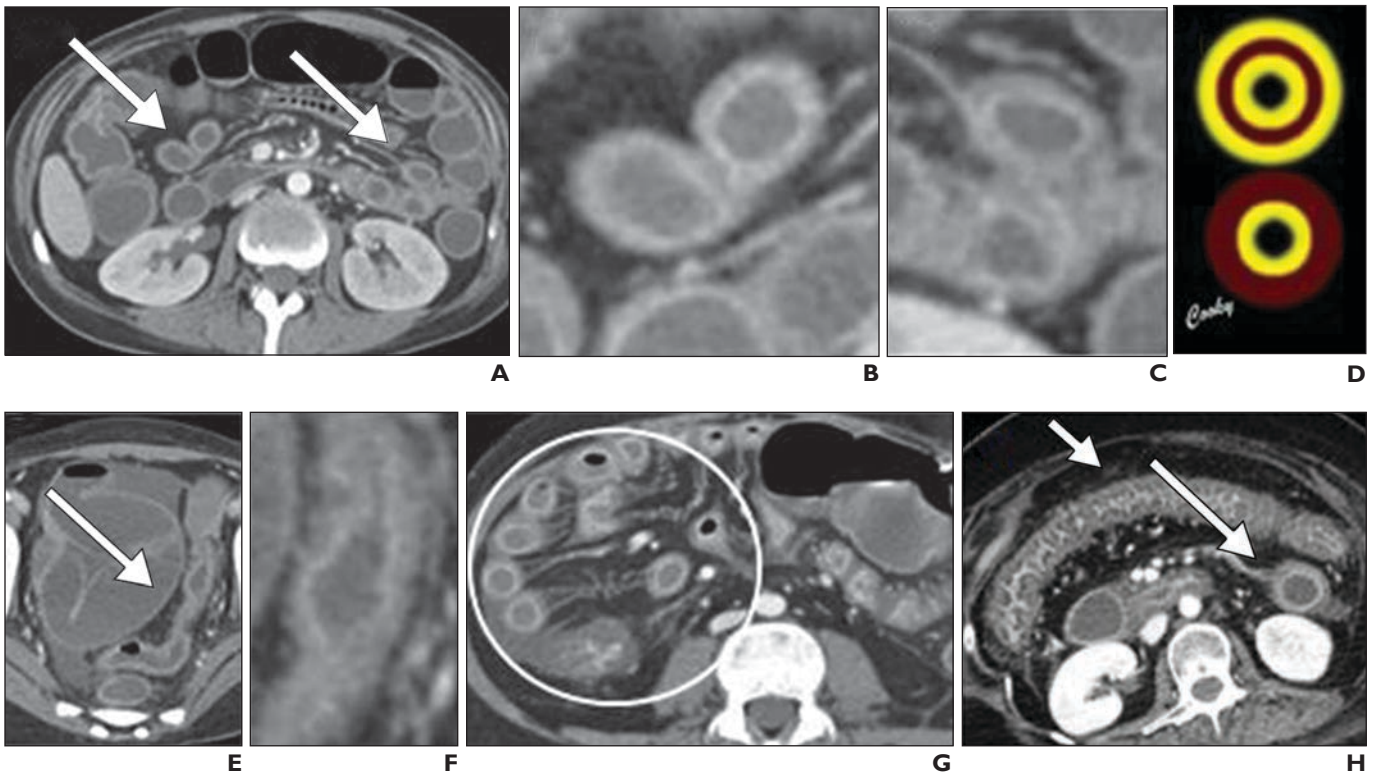

Fig. 2—Target sign seen in three patients with acute graft-versus-host disease (GVHD).
A–C, 23-year-old woman with B-cell acute lymphoblastic leukemia who underwent imaging 30 days after hematopoietic stem cell transplant (HSCT). Axial contrast-enhanced CT (CECT) image (**A**) and magnified views of **A** (**B** and **C**) show small-bowel loops (*arrows*, **A**) that exhibit marked mucosal enhancement with low-attenuation edema in submucosal region.
D, Stylized drawings. Upper drawing shows mucosal and serosal enhancement with submucosal low atttenuation in targetoid fashion. Lower drawing shows halo sign with mucosal hyperenhancement and submucosal edema without associated serosal enhancement. (Drawings by Menias CO)
E and **F,** Axial CECT image of pelvis of same patient shown in **A–C** (**E**) and magnified view of **E** (**F**) depict thick-walled loop of colon with mucosal enhancement and ulceration (*arrow*, **E**).
G, Patient who presented for imaging after undergoing HSCT. Axial CECT image shows multiple thick-walled loops of bowel with targetoid mural stratification, mesenteric edema, and ascites (*circle*).
H, 30-year-old woman who presented with stage 4 grade IV acute GVHD 70 days after undergoing HSCT for sarcoma. Axial CECT image shows extensive wall thickening and mural stratification from duodenum (*long arrow*) through colon (*short arrow*). This involvement of both small bowel and large bowel, nearly in its complete extent, may be more suggestive of GVHD than other enteridities, and diffuse small-bowel involvement is associated with poorer prognosis.

mucosal layer through mucosal ulcers (Figs. 2F and 4). MR enterography could be used in these patients, but this examination requires longer breath-holding and longer table time without motion. This can be challenging for these patients who are often quite nauseated and ill. In theory, glucagon could be used but would likely exacerbate nausea and may not improve the images because these patients often already have dilated fluid-filled loops. Again, a neutral contrast agent, likely an oral contrast barium preparation (VoLumen, E-Z-EM) could be used but is often poorly tolerated and may exacerbate nausea and diarrhea. The fluid-filled loops often have natural oral contrast, and additional agents make the examination more challenging for the patient.

In addition to using CT to diagnose acute GVHD, CT can also be used to grade the severity of GVHD and provide prognostic information about acute gastrointestinal GVHD. One group found that diffuse small-bowel involvement and any colonic involvement were associated with severe clinical presentation [66]. Diffuse small-bowel involvement was also associated with a poorer prognosis and a decreased likelihood of responding to therapy [66].

Hepatobiliary imaging findings—Isolated hepatic involvement is rare because liver involvement is usually seen concomitant with disease involving the skin, gastrointestinal tract, or both [11, 67]. Half of patients with acute GVHD have hepatic involvement, which is primarily a biliary system disease, with progressive atypical degeneration of the small bile ducts. This form of GVHD presents as cholestatic jaundice, which can less commonly progress to liver failure and hepatic encephalopathy [62]. Imaging findings can include hepatosplenomegaly, periportal edema, biliary tract wall thickening and enhancement, gallbladder distention, wall thickening and increased enhancement, and gallbladder sludge (Figs. 5 and 6 and Table 3) [47]. Prominent intramural gallbladder wall edema is sometimes mistaken for "pericholecystic fluid," although perihepatic ascites can be present.

Cholestasis is a common finding after HSCT. While it can be related to hepatobiliary GVHD, cholestasis can also be due to hepatic venoocclusive disease or sinusoidal obstruction syndrome, sepsis, or hepatocellular necrosis caused by infection, ischemia, or medications [68]. Although many of these entities may produce clinical symptoms similar to GVHD, most affect the liver and intrahepatic bile ducts and few would produce extrahepatic biliary ductal dilatation. Ketelsen et

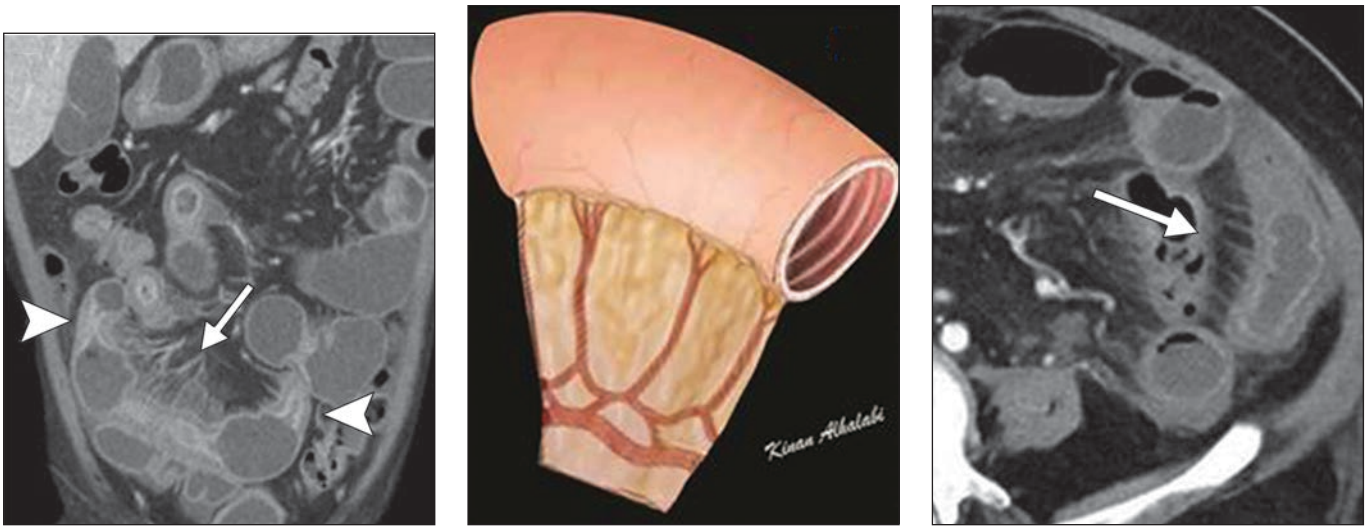

Fig. 3—Extraintestinal findings associated with graft-versus-host disease (GVHD).
A, Coronal contrast-enhanced CT (CECT) image of patient who presented for imaging after undergoing hematopoietic stem cell transplant (HSCT) shows engorgement of vasa recta (*arrow*). Note also bowel wall thickening with mural stratification and dilated fluid-filled loops. This patient may have element of acute-on-chronic disease (overlap syndrome) given that small-bowel strictures (*arrowheads*) are also present.
B, Drawing shows engorgement of vasa recta. (Drawing by Alhalabi K)
C, Axial CECT image of patient who presented for imaging after undergoing HSCT shows engorgement of vasa recta (*arrow*), similar to **A**, with associated mesenteric edema and stranding and thickened fluid-filled bowel loops with marked mucosal enhancement and mural stratification.

TABLE 3: Frequency of Intestinal and Extraintestinal Findings in Acute Graft-Versus-Host Disease (GVHD)[a]

Finding	Percentage of Patients
Intestinal	
Small bowel	
Wall thickening	50
Mucosal enhancement	100
Dilatation	94
Fluid-filled lumen	94
Diffuse involvement	100
Colon	
Wall thickening	19
Mucosal enhancement	100
Dilatation	94
Fluid-filled lumen	100
Diffuse involvement	100
Extraintestinal	
Mesenteric infiltration	73–88
Vasa recta engorgement	91
Hepatomegaly	9–44
Hepatic periportal edema	31–36
Ascites	45–50
Gallbladder wall enhancement	23–100
Gallbladder dilatation	56
Gallbladder wall thickening	9
Pericholecystic fluid	18
Biliary sludge	18
Urinary bladder wall enhancement	88
Splenomegaly	36

[a]Based on data from [21] and [62].

al. [68] looked at the presence and extent of common bile duct dilatation in patients with GVHD and found that they were more likely to have temporary common bile ductal dilatation (compared with control patients without GVHD who also underwent imaging after HSCT) [68]. They defined a pathologic diameter of the common bile duct as greater than 7 mm at CT in patients without cholecystectomy and 8 mm in patients postcholecystectomy and found pathologic diameters in 67% of patients with GVHD compared with 12% of control subjects. Of the patients in the GVHD group, 96% also had cholestatic laboratory values and showed significant positive correlation between bilirubin level and biliary ductal dilatation. In addition, enhancement of the bile duct and gallbladder wall was seen in the GVHD group but not in the control subjects [68]. Involvement of the common bile duct in a patient with cholestasis may be more suggestive of GVHD than of other entities included in the differential diagnosis.

One of the main entities in the differential diagnosis is sinusoidal obstruction syndrome (SOS) (previously known as hepatic venoocclusive disease), and tissue diagnosis is often needed to establish the diagnosis [69]. However, imaging can be helpful in differentiating SOS from GVHD as well. In a series of 18 patients with biopsy-proven hepatic GVHD and SOS at follow-up after HSCT, a right hepatic vein diameter of 0.45 cm or less was found to be highly suggestive of SOS rather than GVHD. For patients who have undergone bone marrow transplant, the CT findings of periportal edema, ascites, and

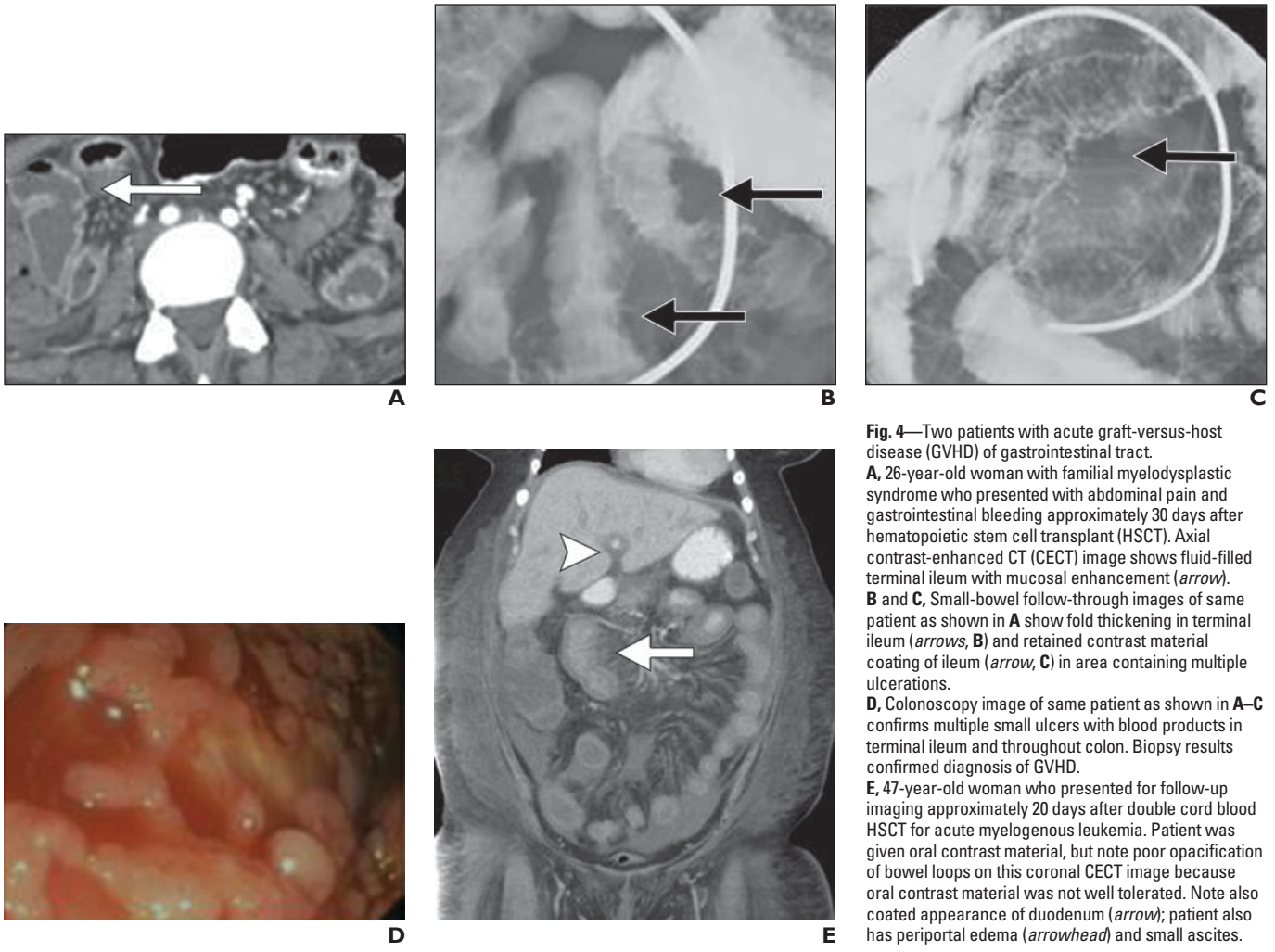

Fig. 4—Two patients with acute graft-versus-host disease (GVHD) of gastrointestinal tract.
A, 26-year-old woman with familial myelodysplastic syndrome who presented with abdominal pain and gastrointestinal bleeding approximately 30 days after hematopoietic stem cell transplant (HSCT). Axial contrast-enhanced CT (CECT) image shows fluid-filled terminal ileum with mucosal enhancement (*arrow*).
B and **C,** Small-bowel follow-through images of same patient as shown in **A** show fold thickening in terminal ileum (*arrows*, **B**) and retained contrast material coating of ileum (*arrow*, **C**) in area containing multiple ulcerations.
D, Colonoscopy image of same patient as shown in **A–C** confirms multiple small ulcers with blood products in terminal ileum and throughout colon. Biopsy results confirmed diagnosis of GVHD.
E, 47-year-old woman who presented for follow-up imaging approximately 20 days after double cord blood HSCT for acute myelogenous leukemia. Patient was given oral contrast material, but note poor opacification of bowel loops on this coronal CECT image because oral contrast material was not well tolerated. Note also coated appearance of duodenum (*arrow*); patient also has periportal edema (*arrowhead*) and small ascites.

right hepatic vein narrowing are more suggestive of SOS, whereas associated small-bowel wall thickening in addition to dilatation of the common bile duct with bile duct wall and gallbladder wall thickening is more suggestive of GVHD [69].

Ultrasound (US) may be a useful modality in imaging hepatobiliary GVHD given its utility in the evaluation of the biliary tree and its portability to image ill patients at the bedside. The Doppler capabilities can be useful for differentiating GVHD from other entities such as SOS. Many of the findings (gallbladder and common bile duct wall thickening, periportal edema, ascites) are well depicted at US. CT also is useful despite the fact that it may be less sensitive for subtle biliary abnormalities because CT still depicts common bile duct dilatation well and may better depict concomitant bowel findings that may raise concern for acute GVHD. As with gastrointestinal evaluation, MRI can be performed and MRCP may be useful for subtle cases of biliary involvement but may not be necessary in some patients and may be less well tolerated.

Using imaging to predict acute graft-versus-host disease—Some groups have also looked at the ability of CT to predict who will develop severe acute GVHD, allowing more aggressive and individualized GVHD prophylaxis. One group performed CT prospectively between days 7 and 14 after transplant [65]. A variety of CT findings including the presence of vasa recta engorgement, gallbladder fossa edema, mesenteric edema, gallbladder or biliary enhancement, and bowel wall thickening or enhancement and the number of bowel loops involved were scored and used to create an image-based risk prediction model. A score of 5 or more showed sensitivity, specificity, and accuracy of 100%, 81%, and 85%, respectively, in predicting development of grade III or IV acute GVHD. However, an even more simplified model that looked at only the presence of mesenteric edema and the number of involved loops was still able to predict the development of GVHD with a sensitivity of 75% and specificity of 95% and correctly classified 90% of patients [65].

Chronic Graft-Versus-Host Disease

Symptoms of chronic GVHD usually present within 3 years of allogeneic HSCT [41]. Chronic GVHD is the leading cause of nonrelapse patient mortality more than 2 years after allogenic HSCT [70]. Although chronic GVHD often follows acute disease, one-third of patients are reported to develop chronic GVHD de novo [1, 11, 33, 41, 71]. The deleterious effects of chronic GVHD often parallel a beneficial graft-versus-tumor effect with lower relapse rates seen in patients with chronic GVHD [1, 11, 33, 41, 45, 70, 71]. The increased use of mobilized peripheral RBCs as the stem cell source and the fact that more patients are surviving the early posttransplant period have resulted in increasing numbers of patients developing chronic GVHD [70].

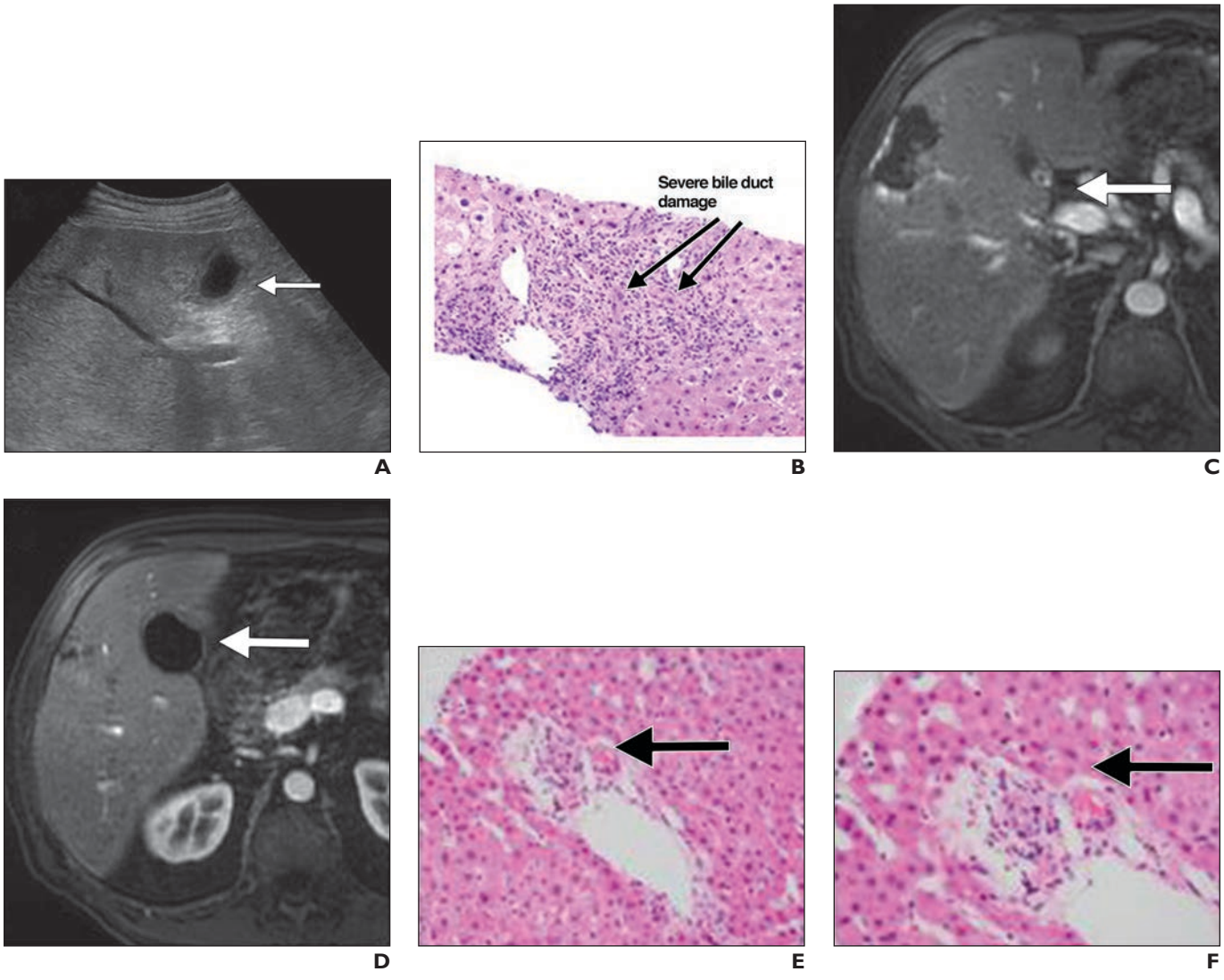

Fig. 5—Acute graft-versus-host disease (GVHD) involving liver in 62-year-old man with elevated liver function test (LFT) results 45 days after hematopoietic stem cell transplant (HSCT) for acute lymphoblastic leukemia.
A, Gray-scale ultrasound image shows gallbladder wall thickening (*arrow*). Given elevation of LFT values, patient underwent liver biopsy.
B, Photomicrograph (H and E, ≈ x200) of surgical pathologic specimen shows severe bile duct damage (*arrows*).
C and **D,** Axial contrast-enhanced T1-weighted MR images show mild gallbladder and cystic duct wall thickening and enhancement (*arrows*).
E and **F,** Photomicrographs (H and E: ×200, **E**; ×400, **F**) of liver biopsy specimen show mild biliary ductal damage (*arrows*).

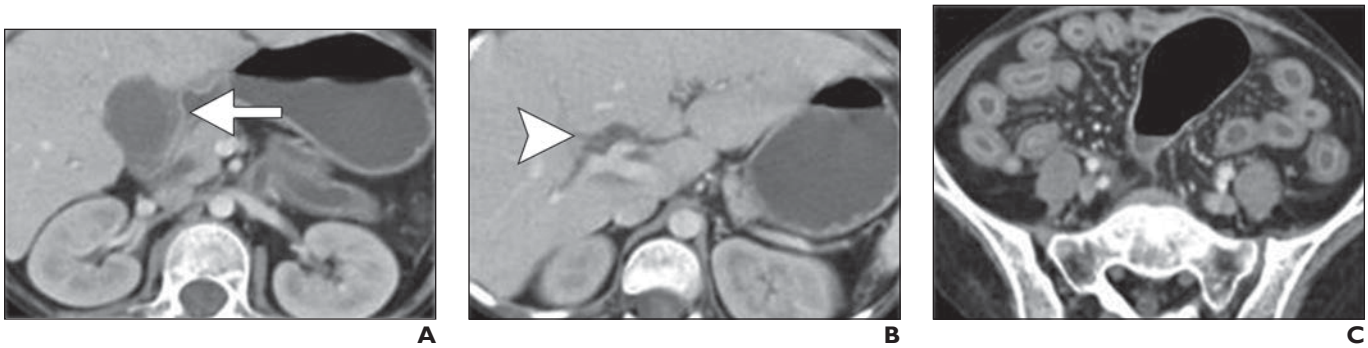

Fig. 6—6-year-old girl who presented with watery diarrhea 3 months after undergoing hematopoietic stem cell transplant (HSCT) for congenital amegakaryocytic thrombocytopenia.
A and **B,** Axial contrast-enhanced CT images show mild distention and wall thickening of gallbladder (*arrow*, **A**) and mild central biliary ductal prominence (*arrowhead*, **B**).
C, Contrast-enhanced axial CT image shows diffuse small- and large-bowel wall thickening with mural stratification. These findings seen in conjunction with findings shown in **A** and **B** raised concern for acute graft-versus-host disease.

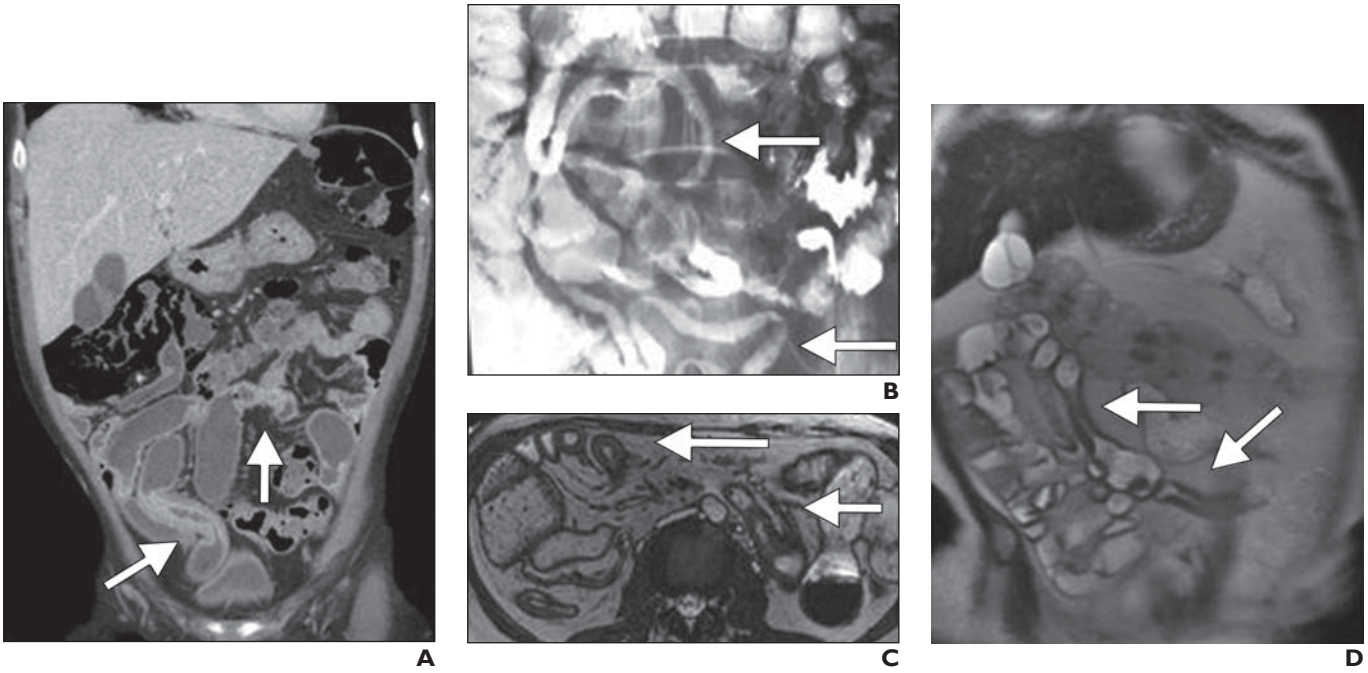

Fig. 7—Chronic graft-versus-host disease (GVHD) in gastrointestinal tract.
A, Patient with chronic GVHD who presented for imaging after undergoing hematopoietic stem cell transplant (HSCT). Coronal contrast-enhanced CT image shows multifocal small-bowel strictures (*arrows*).
B, Patient with chronic GVHD who presented for imaging after undergoing HSCT. Small-bowel follow-through image shows tubular, ribbonlike small bowel (*arrows*) with fold effacement.
C and **D,** Patient with chronic GVHD who presented for imaging after undergoing HSCT. Axial (**C**) and coronal (**D**) T2-weighted images show multifocal small-bowel wall thickening, which appears as low T2 signal intensity, and associated luminal narrowing (*arrows*); these findings are compatible with multifocal small-bowel strictures in setting of chronic GVHD.

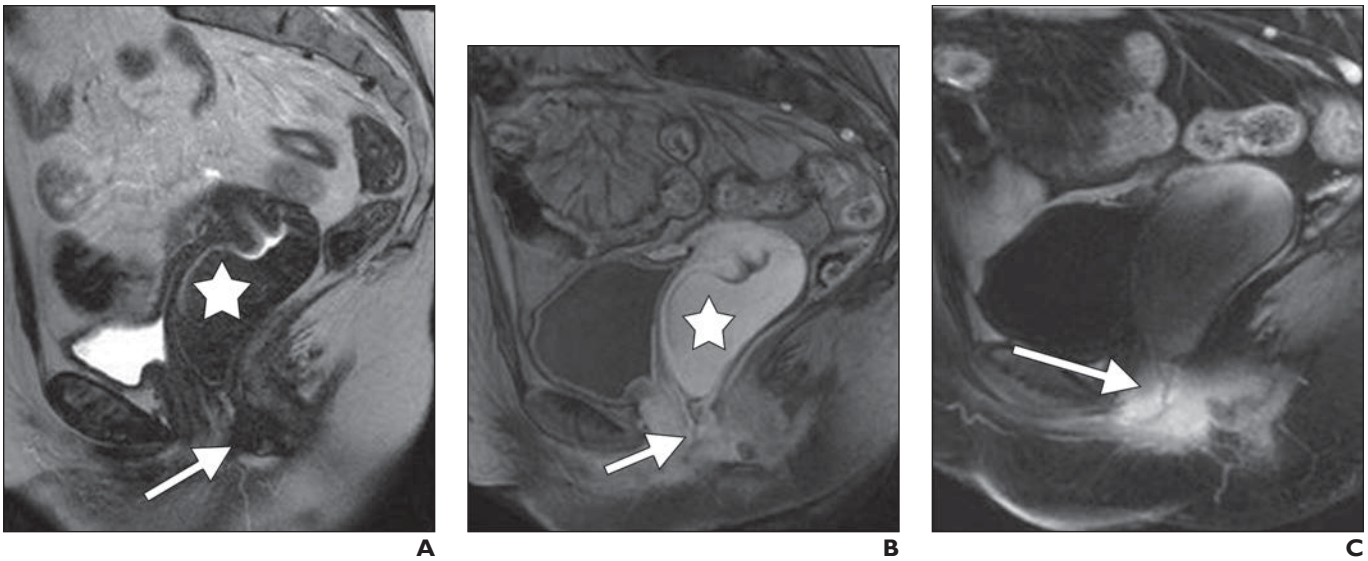

Fig. 8—26-year-old woman who presented with vaginal graft-versus-host disease (GVHD) 8 years after undergoing hematopoietic stem cell transplant for acute myelogenous leukemia.
A–C, Sagittal T2-weighted (**A**), T1-weighted (**B**), and contrast-enhanced T1-weighted (**C**) MR images show hematocolpos (*stars*, **A** and **B**) with vaginal scarring and dense fibrosis (*arrows*) are nearly obliterating distal vaginal cavity.

Clinical presentation—In chronic GVHD, like acute GVHD, the skin is often the first organ to be involved, with a distinct conglomeration of symptoms that is thought to be related to fibrosis of the dermis. These symptoms include poikiloderma, a lichen planus–type reaction (erythematous or violaceous flat-topped papules or plaques with a silvery or shiny appearance on direct light), deep sclerotic features (smooth, waxy, indurated skin), or lichen sclerosis–type lesions (discrete to coalescent gray-to-white moveable papules or plaques, of-

ten with follicular plugs, with a shiny appearance and leathery consistency) [41] (Table 2).

The gastrointestinal symptoms of chronic GVHD are similar to those of acute GVHD, including anorexia, nausea, vomiting, diarrhea, weight loss, and failure to thrive [41]. The chronic intestinal injury can lead to malabsorption and wasting.

Gastrointestinal imaging findings—The imaging findings of chronic gastrointestinal GVHD are associated with chronic bowel wall thickening, which includes esophageal webs or strictures and less commonly segmental small-bowel or colonic strictures. These strictures can be seen throughout the gastrointestinal tract, from the esophagus to the rectum, but are most common in the small bowel and colon [14, 47]. GVHD denudes the gastrointestinal mucosa, which is later replaced by granulation tissue. At CT, this tissue is seen as hyperemic granulation tissue surrounded by lower-attenuation outer bowel wall layers resulting in less mural stratification (mucosal hyperenhancement, submucosal edema, and serosal enhancement) and more of the halo sign (thick mucosal enhancement with surrounding low-attenuation wall [Fig. 7]) [14]. More focal wall thickening with associated luminal narrowing or stricture can be identified and can be multifocal with some areas of upstream dilatation or partial obstruction. In chronic GVHD, "ribbon" bowel is seen, with small-bowel fold effacement and a tubular appearance with associated delayed transit time (Fig. 7). These changes in the bowel and the delayed transit can be seen at barium fluoroscopy studies (Fig. 7). CT remains the mainstay of imaging; however, MRI or MR enterography can be helpful for investigating bowel wall thickening. Although there is often edema (high T2 signal intensity) in the bowel wall in patients with acute GVHD, the bowel wall can become fibrous (low T2 signal intensity) with associated luminal narrowing in patients with chronic GVHD (Fig. 7).

Hepatobiliary imaging findings—Hepatic involvement in chronic GVHD, like in acute GVHD, generally presents as cholestasis with increased bilirubin and alkaline phosphatase levels [41]. Therefore, the distinction between acute and chronic disease cannot be made with liver findings alone, and diagnosis often relies on detection of involvement of other organ systems, as previously described [41]. Again, biliary tract abnormalities, such as enhancement of the biliary tract, gallbladder wall thickening, dilatation of the common bile duct, and gallbladder sludge, are common findings [47].

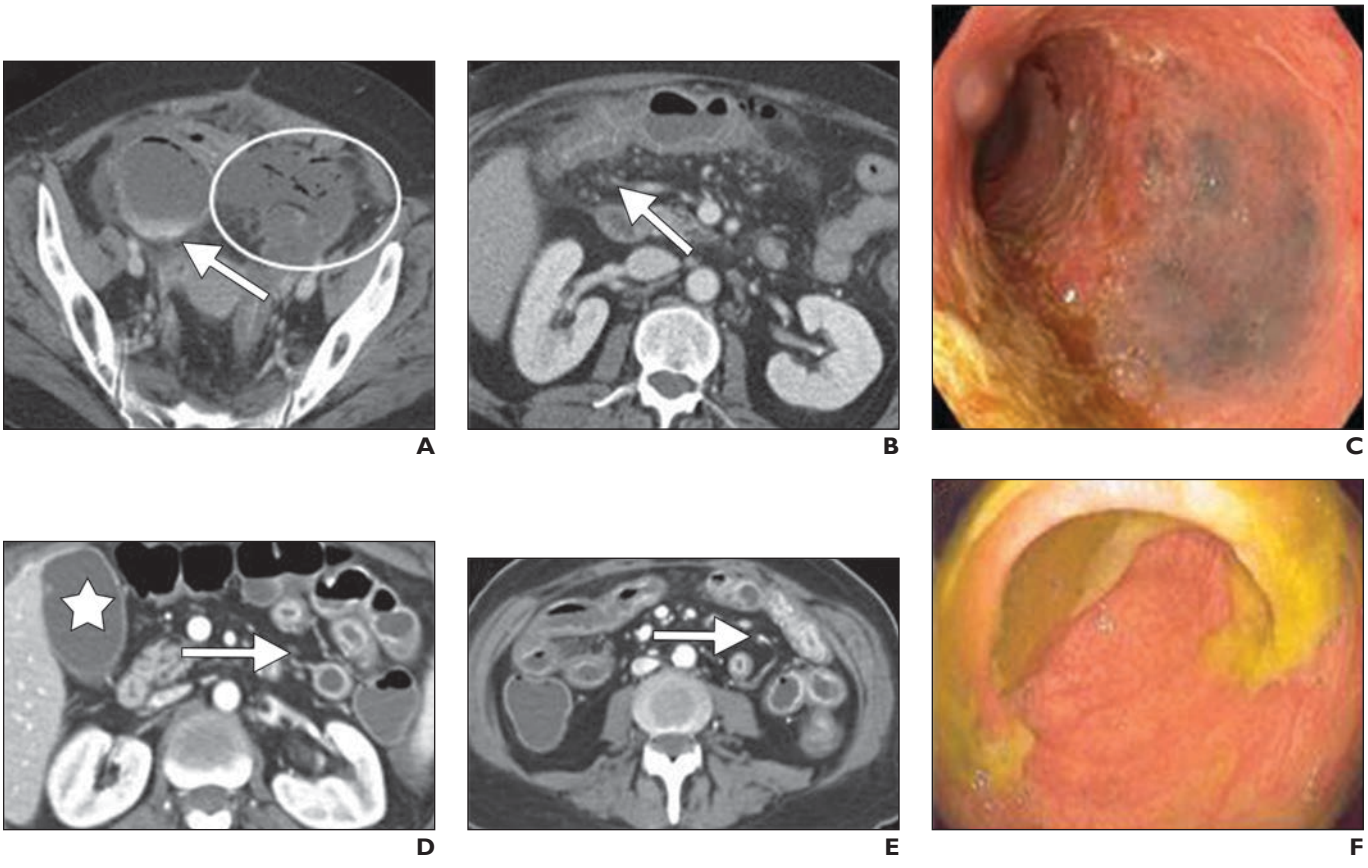

Fig. 9—Chronic graft-versus-host disease (GVHD).
A and **B,** 50-year-old woman with chronic GVHD of bowel who presented with acute abdominal pain approximately 150 days after undergoing hematopoietic stem cell transplant (HSCT) for acute myelogenous leukemia (AML). Axial contrast-enhanced CT (CECT) images show diffuse wall thickening of fluid-filled colon with marked mucosal enhancement and luminal narrowing of proximal transverse colon (*arrow*, **B**). Note collection of fluid and gas in left lower quadrant (*oval*, **A**), adjacent to dilated fluid-filled cecum (*arrow*, **A**). These findings are compatible with cecal perforation, which was confirmed at surgery.
C, Colonoscopic image of same patient shown in **A** and **B** reveals mucosal changes.
D and **E,** 64-year-old man who presented with acute abdominal pain 45 days after undergoing HSCT for AML. Axial CECT images show diffusely thick-walled fluid-filled small bowel and large bowel (*arrows*) with marked mucosal enhancement and mild gallbladder distention (*star*, **D**).
F, Colonoscopic image of same patient shown in **D** and **E** reveals adherent thick pseudomembranous material. These findings are compatible with GVHD with superimposed *Clostridium difficile* infection.

Chronic hepatic GVHD can also result in vanishing bile duct syndrome in which extrahepatic ducts develop strictures similar to those seen in primary sclerosing cholangitis with pruned or diminutive intrahepatic ducts [14, 72, 73]. In these cases, MRCP may be useful in better depicting the intrahepatic involvement.

Genitourniary and gynecologic imaging findings—Involvement of the genitourinary tract, lungs, and joints and fascia is less common. Approximately 25% of long-term female survivors after allogeneic HSCT develop genital chronic GVHD. Genital complications are usually associated with GVHD that involves other organs, with symptoms that range from vaginal or vulvar irritation and ulceration to vaginal stenosis (agglutination). Vaginal symptoms may develop an average of 10 months after bone marrow transplant [74]. These symptoms are unresponsive to systemic or topical estrogens and usually require cyclosporine or surgical lysis [74] (Fig. 8). MRI may be more sensitive in the evaluation of gynecologic manifestations in the pelvis.

In chronic GVHD, the recipient immune system is devastated, with involution of the thymus and depletion of lymphocytes in lymph nodes. In addition, GVHD impairs mucosal lymphoid intestinal immunity by damaging the gut mucosa. Because GVHD is treated with immunosuppressive therapy, patients are also more susceptible to superimposed gastrointestinal infections including *Clostridium difficile*, which can result in severe typhlitis, bowel ischemia, and bowel perforation [14] (Fig. 9).

Treatment

Patients are treated with immunosuppressive prophylaxis early after transplant, usually including a calcineurin inhibitor or methotrexate-based therapy. If acute GVHD develops, steroids remain the mainstay of treatment, with additional or other forms of immunosuppression also applied in refractory cases (including extracorporeal photopheresis) [1, 11, 33, 45]. However, even with treatment, acute GVHD may prove fatal in up to 15% of affected patients [1, 11, 32, 34].

Steroids are the mainstay of treatment of chronic GVHD, like acute GVHD, and are often used in combination with calcineurin inhibitors. There is ongoing research into other novel regimens for the treatment of refractory cases [1, 11, 45].

Conclusion

GVHD is a serious complication of HSCT, which involves multiple organ systems, with imaging manifestations most commonly seen in the gastrointestinal tract and hepatobiliary system. Knowledge of the imaging manifestations of GVHD, which alone may be relatively nonspecific, taken in conjunction with clinical history including the timing and type of HSCT, laboratory values, stool studies, and dermatologic findings can increase radiologist confidence in suggesting this diagnosis.

References

1. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. *Lancet* 2009; 373:1550–1561
2. Levine DS, Navarro OM, Chaudry G, Doyle JJ, Blaser SI. Imaging the complications of bone marrow transplantation in children. *RadioGraphics* 2007; 27:307–324
3. Masouridi-Levrat S, Simonetta F, Chalandon Y. Immunological basis of bone marrow failure after allogeneic hematopoietic stem cell transplantation. *Front Immunol* 2016; 7:362
4. Jagasia M, Arora M, Flowers ME, et al. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. *Blood* 2012; 119:296–307
5. Arai S, Arora M, Wang T, et al.; Graft-vs-Host Disease Working Committee of the CIBMTR. Increasing incidence of chronic graft-versus-host disease in allogeneic transplantation: a report from the Center for International Blood and Marrow Transplant Research. *Biol Blood Marrow Transplant* 2015; 21:266–274
6. Dignan FL, Potter MN, Ethell ME, et al. High readmission rates are associated with a significant economic burden and poor outcome in patients with grade III/IV acute GVHD. *Clin Transplant* 2013; 27:E56–E63
7. Lowsky R, Takahashi T, Liu YP, et al. Protective conditioning for acute graft-versus-host disease. *N Engl J Med* 2005; 353:1321–1331
8. Sun YC, Chai X, Inamoto Y, et al. Impact of ocular chronic graft-versus-host disease on quality of life. *Biol Blood Marrow Transplant* 2015; 21:1687–1691
9. DePalo J, Chai X, Lee SJ, Cutler CS, Treister N. Assessing the relationship between oral chronic graft-versus-host disease and global measures of quality of life. *Oral Oncol* 2015; 51:944–949
10. Boyiadzis M, Arora M, Klein JP, et al. Impact of chronic graft-versus-host disease on late relapse and survival on 7,489 patients after myeloablative allogeneic hematopoietic cell transplantation for leukemia. *Clin Cancer Res* 2015; 21:2020–2028
11. Kambham N, Higgins JP, Sundram U, Troxell ML. Hematopoietic stem cell transplantation: graft versus host disease and pathology of gastrointestinal tract, liver, and lung. *Adv Anat Pathol* 2014; 21:301–320
12. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med* 2006; 354:1813–1826
13. Li HW, Sykes M. Emerging concepts in haematopoietic cell transplantation. *Nat Rev Immunol* 2012; 12:403–416
14. Coy DL, Ormazabal A, Godwin JD, Lalani T. Imaging evaluation of pulmonary and abdominal complications following hematopoietic stem cell transplantation. *RadioGraphics* 2005; 25:305–317; discussion, 318
15. Mackall C, Fry T, Gress R, et al. Background to hematopoietic cell transplantation, including post transplant immune recovery. *Bone Marrow Transplant* 2009; 44:457–462
16. Barnes DW, Loutit JF. *Spleen protection: the cellular hypothesis*. London, UK: Butterworths, 1955
17. Washington K, Jagasia M. Pathology of graft-versus-host disease in the gastrointestinal tract. *Hum Pathol* 2009; 40:909–917
18. Lee F, Dealy JB Jr, Dammin GJ, Brooke MS. The homograft reaction in x-irradiated rabbits treated with homologous bone marrow: a preliminary report. *Ann N Y Acad Sci* 1958; 73:825–833
19. Billingham RE. The biology of graft-versus-host reactions. *Harvey Lect* 1966; 62:21–78
20. Choi SW, Levine JE, Ferrara JL. Pathogenesis and management of graft-versus-host disease. *Immunol Allergy Clin North Am* 2010; 30:75–101
21. Donnelly LF, Morris CL. Acute graft-versus-host disease in children: abdominal CT findings. *Radiology* 1996; 199:265–268
22. Mentzel HJ, Kentouche K, Kosmehl H, et al. US and MRI of gastrointestinal graft-versus-host disease. *Pediatr Radiol* 2002; 32:195–198
23. Ferrara JL, Deeg HJ. Graft-versus-host disease. *N Engl J Med* 1991; 324:667–674
24. Luger TA, Schwarz T. Evidence for an epidermal cytokine network. *J Invest Dermatol* 1990; 95(suppl 6):100S–104S
25. McKenzie RC, Sauder DN. The role of keratinocyte cytokines in inflammation and immunity. *J Invest Dermatol* 1990; 95(suppl 6):105S–107S
26. Xun CQ, Thompson JS, Jennings CD, Brown SA, Widmer MB. Effect of total body irradiation, busulfan-cyclophosphamide, or cyclophosphamide conditioning on inflammatory cytokine release and development of acute and chronic graft-versus-host disease in H-2-incompatible transplanted SCID mice. *Blood* 1994; 83:2360–2367
27. Norton J, Sloane JP. ICAM-1 expression on epidermal keratinocytes in cutaneous graft-versus-host disease. *Transplantation* 1991; 51:1203–1206
28. Unanue ER, Allen PM. The basis for the immunoregulatory role of macrophages and other accessory cells. *Science* 1987; 236:551–557
29. Nishizuka Y. Studies and perspectives of protein kinase C. *Science* 1986; 233:305–312
30. Samelson LE, Patel MD, Weissman AM, Harford JB, Klausner RD. Antigen activation of murine T cells induces tyrosine phosphorylation of a polypeptide associated with the T cell antigen receptor.

Cell 1986; 46:1083–1090
31. Socié G. Chronic GVHD: B cells come of age. *Blood* 2011; 117:2086–2087
32. Garnett C, Apperley JF, Pavlu J. Treatment and management of graft-versus-host disease: improving response and survival. *Ther Adv Hematol* 2013; 4:366–378
33. Blazar BR, Murphy WJ, Abedi M. Advances in graft-versus-host disease biology and therapy. *Nat Rev Immunol* 2012; 12:443–458
34. Socie G, Blazar BR. Acute graft-versus-host disease: from the bench to the bedside. *Blood* 2009; 114:4327–4336
35. Laster SM, Wood JG, Gooding LR. Tumor necrosis factor can induce both apoptic and necrotic forms of cell lysis. *J Immunol* 1988; 141:2629–2634
36. Ferrara JL, Reddy P. Pathophysiology of graft-versus-host disease. *Semin Hematol* 2006; 43:3–10
37. Sale GE, Shulman HM, McDonald GB, Thomas ED. Gastrointestinal graft-versus-host disease in man: a clinicopathologic study of the rectal biopsy. *Am J Surg Pathol* 1979; 3:291–299
38. Bombi JA, Nadal A, Carreras E, et al. Assessment of histopathologic changes in the colonic biopsy in acute graft-versus-host disease. *Am J Clin Pathol* 1995; 103:690–695
39. Lampert IA, Thorpe P, van Noorden S, et al. Selective sparing of enterochromaffin cells in graft versus host disease affecting the colonic mucosa. *Histopathology* 1985; 9:875–886
40. Shulman HM, Sharma P, Amos D, Fenster LF, McDonald GB. A coded histologic study of hepatic graft-versus-host disease after human bone marrow transplantation. *Hepatology* 1988; 8:463–470
41. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant* 2005; 11:945–956
42. Cutler C, Antin JH. Chronic graft-versus-host disease. *Curr Opin Oncol* 2006; 18:126–131
43. Tyndall A, Dazzi F. Chronic GVHD as an autoimmune disease. *Best Pract Res Clin Haematol* 2008; 21:281–289
44. Akpek G, Chinratanalab W, Lee LA, et al. Gastrointestinal involvement in chronic graft-versus-host disease: a clinicopathologic study. *Biol Blood Marrow Transplant* 2003; 9:46–51
45. Baird K, Pavletic SZ. Chronic graft versus host disease. *Curr Opin Hematol* 2006; 13:426–435
46. Eggleston TI, Ziccardi VB, Lumerman H. Graft-versus-host disease: case report and discussion. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 86:692–696
47. Mahgerefteh SY, Sosna J, Bogot N, Shapira MY, Pappo O, Bloom AI. Radiologic imaging and intervention for gastrointestinal and hepatic complications of hematopoietic stem cell transplantation. *Radiology* 2011; 258:660–671
48. Martin PJ, McDonald GB, Sanders JE, et al. Increasingly frequent diagnosis of acute gastrointestinal graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2004; 10:320–327
49. Deeg HJ, Antin JH. The clinical spectrum of acute graft-versus-host disease. *Semin Hematol* 2006; 43:24–31
50. Ross WA, Couriel D. Colonic graft-versus-host disease. *Curr Opin Gastroenterol* 2005; 21:64–69
51. Khan K, Schwarzenberg SJ, Sharp H, et al. Diagnostic endoscopy in children after hematopoietic stem cell transplantation. *Gastrointest Endosc* 2006; 64:379–385; quiz, 389–392
52. Snover DC, Weisdorf SA, Vercellotti GM, Rank B, Hutton S, McGlave P. A histopathologic study of gastric and small intestinal graft-versus-host disease following allogeneic bone marrow transplantation. *Hum Pathol* 1985; 16:387–392
53. Nydegger A, Catto-Smith AG, Tiedemann K, Hardikar W. Diagnosis of gastrointestinal graft-versus-host disease: is rectal biopsy enough? *Pediatr Blood Cancer* 2007; 48:561–566
54. Thompson B, Salzman D, Steinhauer J, Lazenby AJ, Wilcox CM. Prospective endoscopic evaluation for gastrointestinal graft-versus-host disease: determination of the best diagnostic approach. *Bone Marrow Transplant* 2006; 38:371–376
55. Oomori S, Takagi S, Kikuchi T, et al. Significance of colonoscopy in patients with intestinal graft-versus-host disease after hematopoietic stem cell transplantation. *Endoscopy* 2005; 37:346–350
56. Wu D, Hockenberry DM, Brentnall TA, et al. Persistent nausea and anorexia after marrow transplantation: a prospective study of 78 patients. *Transplantation* 1998; 66:1319–1324
57. Jagannathan JP, Ramaiya N, Gill RR, Alyea EP 3rd, Ros P. Imaging of complications of hematopoietic stem cell transplantation. *Radiol Clin North Am* 2008; 46:397–417
58. Pandey T, Maximin S, Bhargava P. Imaging of complications from hematopoietic stem cell transplant. *Indian J Radiol Imaging* 2014; 24:327–338
59. Horton KM, Corl FM, Fishman EK. CT evaluation of the colon: inflammatory disease. *RadioGraphics* 2000; 20:399–418
60. Jones B, Fishman EK, Kramer SS, et al. Computed tomography of gastrointestinal inflammation after bone marrow transplantation. *AJR* 1986; 146:691–695
61. Jabra AA, Fishman EK, Taylor GA. CT findings in inflammatory bowel disease in children. *AJR* 1994; 162:975–979
62. Kalantari BN, Mortele KJ, Cantisani V, et al. CT features with pathologic correlation of acute gastrointestinal graft-versus-host disease after bone marrow transplantation in adults. *AJR* 2003; 181:1621–1625
63. Horton KM, Corl FM, Fishman EK. CT of nonneoplastic diseases of the small bowel: spectrum of disease. *J Comput Assist Tomogr* 1999; 23:417–428
64. Schmit M, Bethge W, Beck R, Faul C, Claussen CD, Horger M. CT of gastrointestinal complications associated with hematopoietic stem cell transplantation. *AJR* 2008; 190:712–719
65. Rashidi A, Lin MF, Cashen AF. Early post-transplant contrast-enhanced abdominopelvic CT scan predicts the risk of subsequent acute GVHD. *Bone Marrow Transplant* 2016; 51:150–152
66. Shimoni A, Rimon U, Hertz M, et al. CT in the clinical and prognostic evaluation of acute graft-vs-host disease of the gastrointestinal tract. *Br J Radiol* 2012; 85:e416–e423
67. Ratanatharathorn V, Nash RA, Przepiorka D, et al. Phase III study comparing methotrexate and tacrolimus (prograf, FK506) with methotrexate and cyclosporine for graft-versus-host disease prophylaxis after HLA-identical sibling bone marrow transplantation. *Blood* 1998; 92:2303–2314
68. Ketelsen D, Vogel W, Bethge W, et al. Enlargement of the common bile duct in patients with acute graft-versus-host disease: what does it mean? *AJR* 2009; 193:[web]W181–W185
69. Erturk SM, Mortele KJ, Binkert CA, et al. CT features of hepatic venoocclusive disease and hepatic graft-versus-host disease in patients after hematopoietic stem cell transplantation. *AJR* 2006; 186:1497–1501
70. Min CK. The pathophysiology of chronic graft-versus-host disease: the unveiling of an enigma. *Korean J Hematol* 2011; 46:80–87
71. Carpenter PA. Late effects of chronic graft-versus-host disease. *Best Pract Res Clin Haematol* 2008; 21:309–331
72. Zelig O, Goldin E, Okon E, et al. Hepatobiliary graft-versus-host disease manifested by common and hepatic biliary duct obstruction. *Digestion* 1997; 58:494–497
73. Geubel AP, Cnudde A, Ferrant A, Latinne D, Rahier J. Diffuse biliary tract involvement mimicking primary sclerosing cholangitis after bone marrow transplantation. *J Hepatol* 1990; 10:23–28
74. Spiryda LB, Laufer MR, Soiffer RJ, Antin JA. Graft-versus-host disease of the vulva and/or vagina: diagnosis and treatment. *Biol Blood Marrow Transplant* 2003; 9:760–765

FOR YOUR INFORMATION

This article is available for CME and Self-Assessment (SA-CME) credit that satisfies Part II requirements for maintenance of certification (MOC). To access the examination for this article, follow the prompts associated with the online version of the article.