Radiology

Radiologic Imaging and Intervention for Gastrointestinal and Hepatic Complications of Hematopoietic Stem Cell Transplantation[1]

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Hematopoietic stem cell transplantation (HSCT) is an increasingly available treatment option for patients with various oncologic, hematologic, and immunologic diseases. Although HSCT can be curative for some diseases, complications associated with this treatment limit its success and applicability. Gastrointestinal graft-versus-host disease (GVHD) and hepatic veno-occlusive disease are unique and deadly complications of HSCT. These diseases can mimic other HSCT complications, such as infection, hemorrhage, and hepatotoxicity with cholestasis, but GVHD and veno-occlusive disease require specific treatment. Early treatment improves the probability of treatment success. For these reasons, timely and accurate diagnosis is essential. Abdominal imaging and intervention play an important role in the early, minimally invasive diagnosis and treatment of GVHD and veno-occlusive disease. Imaging findings tend to be nonspecific, but common findings that may guide further management or establish a diagnosis in the clinical setting have been defined. In cases where the diagnosis is unclear and liver biopsy is required, image-guided transvenous liver biopsy may be a safer and more practical option than the transcutaneous approach. Image-guided interventions, including intraarterial steroid-injection therapy in severe, systemic steroid-refractory GVHD and transjugular intrahepatic portosystemic shunt placement in veno-occlusive disease with portal hypertension, have shown some promise in small, uncontrolled series. Larger, controlled studies are needed to define the role of these invasive procedures in this patient population.

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Hematopoietic stem cell transplantation (HSCT) consists of the intravenous infusion of stem cells to reestablish hematopoietic or immune function (1). HSCT follows cytoreductive preparation in which the transplant recipient undergoes chemotherapy or radiation therapy of varying intensity with the aim of eliminating existing tumor cells and limiting the host's immune response to transplanted tissue (1). Because HSCT can fully replenish the immune system, indications for this procedure have been expanded beyond hematologic malignancies and deficiencies to include both solid tumors and autoimmune disorders (1). HSCT can be curative, but its success depends on the type and severity of the underlying disease. Worldwide, more than 45 000 HSCT procedures are performed each year (1).

Essentials

- Gastrointestinal graft-versus-host disease (GVHD) and hepatic veno-occlusive disease (VOD) represent unique and potentially deadly complications that may limit the success and applicability of hematopoietic stem cell transplantation.
- Urgent and accurate diagnosis of these diseases may be life-saving, especially in the acute phase or in clinically ambiguous cases.
- Abdominal plain radiographic, US, and CT imaging generally reveal nonspecific signs of disease, but an understanding of frequencies and radiologic subtleties of findings within the clinical setting may guide management.
- When liver disease remains ambiguous, transvenous biopsy is a relatively safe diagnostic procedure that guides clinical management in a majority of these cases.
- Image-guided interventions—intraarterial steroid-injection therapy in GVHD and transjugular intrahepatic portosystemic shunt in VOD—although as yet unproved, have shown therapeutic promise in small, uncontrolled series.

Fatal complications related to HSCT may occur as a direct result of the toxic cytoreductive preparation or because of immunosuppression (1). Complex immune reactions between donor and host tissues may also be fatal, but the graft-versus-tumor effect may actually amplify the therapeutic benefit of HSCT by decreasing the rates of tumor recurrence (2).

Graft-versus-host disease (GVHD) and hepatic veno-occlusive disease (VOD) represent unique and potentially deadly complications of HSCT. GVHD may affect any organ system, but it most commonly affects the skin, gastrointestinal tract, and liver (3,4). Standard first-line therapy involves systemic immunosuppression with steroids and cyclosporine or tacrolimus; methotrexate is used selectively in some cases (3,4). VOD primarily affects the liver, but may progress to systemic vasculitis (5). Treatment remains primarily supportive and most cases resolve spontaneously (5). Severity classifications have been proposed for GVHD (Table 1) and VOD (Table 2); more severe disease is associated with dramatically increased mortality.

The clinical manifestations of these entities may overlap or resemble other HSCT complications, including infection, hemorrhage, and hepatotoxicity with cholestasis (3–5). Radiologic imaging is particularly important in cases that cannot be diagnosed on the basis of clinical or laboratory findings alone, for example, when primarily gastrointestinal or hepatic disease exists without infection or skin involvement. However, while absence of focal lesions may help rule out fungal infection, abscess, or neoplasm, radiologic evaluation lacks specificity in most cases.

Table 3 lists the important abdominal complications of HSCT that should be considered in the differential diagnoses of GVHD and VOD, along with their respective imaging findings.

In this review, we focus on the major abdominal imaging findings in GVHD and VOD and their expected frequencies of occurrence, with reference to the most commonly used imaging modalities of plain radiography, CT, and US. The role of interventional radiology in the diagnosis and treatment of these diseases is also discussed.

Graft-versus-Host Disease

GVHD, occurring in acute and chronic forms, is a multisystem disease complex resulting from the attack of the donor's immune system against vulnerable recipient tissues (29,30). Classically, acute and chronic GVHD were defined as GVHD within or beyond 100 days after HSCT, respectively. However, in 2005, a National Institutes of Health consensus group modified GVHD criteria for the purposes of clinical trials. Broadly, the National Institutes of Health defined acute GVHD as GVHD without clinical or pathologic features of chronic GVHD and defined chronic GVHD as the presence of these features, with or without overlapping acute GVHD, regardless of the time of onset (31). The risk of GVHD depends on the degree of human leukocyte antigen matching and the genetic relation between the donor and the recipient, type of conditioning, graft type, and donor and recipient characteristics such as age, sex, and parity (3). However, high rates of GVHD can be seen even with good human leukocyte antigen matching and postgraft immunosuppression (32).

Acute GVHD with some form of gastrointestinal involvement, that is, grade II–IV, has been reported in 30%–75% of patients undergoing HSCT (3,6,33) (Table 1). Acute GVHD typically manifests as skin rash and gastrointestinal symptoms that may include nausea and vomiting, abdominal pain, diarrhea, weight loss, liver dysfunction, and cholestatic jaundice; pulmonary symptoms are much less common (3).

Published online
10.1148/radiol.10100025

Radiology 2011; 258:660–671

Abbreviations:
GVHD = graft-versus-host disease
HSCT = hematopoietic stem cell transplantation
TIPS = transjugular intrahepatic portosystemic shunt
VOD = veno-occlusive disease

Authors stated no financial relationship to disclose.

Approximately one-half of patients with acute GVHD develop chronic GVHD (3). The overall long-term risk of developing chronic GVHD after allogeneic bone marrow transplantation is estimated at 40%–45% (34,35). However, the risk is greater after acute GVHD, especially higher-grade acute GVHD, and can reach 70%–85% for some patients (34,35). Chronic GVHD typically manifests with features similar to those of autoimmune disease, such as skin and hair changes, dry eyes, and lichenoid mucosal changes (4). Common gastrointestinal symptoms include dry mouth, esophageal reflux, dysphagia, diarrhea, and bloating, as well as anorexia and weight loss (30,36).

Long-term survival for patients with acute GVHD ranges from less than 5% to more than 80%, depending partly on the response to steroid treatment and grade of disease (3,6,37) (Table 1). In HSCT patients, chronic GVHD is the leading long-term cause of nonrelapse mortality (38,39), causing about 30% of deaths in allogeneic bone marrow transplant recipients (39). Long-term survival in chronic GVHD patients is reported to range from about 12% to 75% (38) and is lowest when chronic GVHD has progressed from nonremitting acute GVHD, as opposed to occurring de novo (40). A majority of these deaths result from infection secondary to immunosuppressive GVHD treatment (3). Immunosuppression also diminishes the graft-versus-tumor effect, increasing the rate of tumor recurrence (2). Thus, GVHD represents a major limiting factor in the success of HSCT.

Table 1

Modified Glucksberg Criteria for Grading Acute GVHD

	Minimal Extent of Organ Involvement Needed to Meet Respective Grade Criteria				
Grade	Skin	Liver	Gut	Frequency among HSCT Patients (%)	Day 100 Mortality (%)
I	Rash ≤50% of skin	None	None	12–36	10–22
II	Rash >50% of skin or	Bilirubin 2–3 mg/dL or	Diarrhea >500 mL/d or persistent nausea	12–25	8–37
III	…	Bilirubin 3–15 mg/dL or	Diarrhea >1000 mL or severe abdominal pain	10–24	38–71
IV	Generalized erythroderma with bullae	Bilirubin >15 mg/dL	…	5–16	75–77

Source.—Reference 6.

Table 2

McDonald Criteria for Grading the Severity of VOD

Variable	All VOD	Mild	Moderate	Severe
Weight gain by day 20 (% increase ± standard deviation)	10.9 ± 7.1	7.0 ± 3.5	10.1 ± 5.3	15.5 ± 9.2
Maximum total serum bilirubin level by day 20 (mg/dL ± standard deviation)	12.3 ± 12.8	4.7 ± 2.9	7.9 ± 6.6	26.0 ± 15.2
Liver enlargement or tenderness (%)	92	93	97	81
Ascites (%)	23	5	16	48
Peripheral edema (%)	63	23	70	85
Frequency among VOD patients (%)	100	23	48	28
Day 100 mortality (%)	39	9	23	98

Source.—Reference 7.

Intestinal GVHD

GVHD can affect any part of the gastrointestinal tract, from the esophagus to the rectum. Signs and symptoms may include anorexia, dyspepsia, nausea, vomiting, abdominal pain and tenderness, and secretory diarrhea, with or without hemorrhage (41). The percentage of HSCT patients undergoing endoscopic evaluation or rectal biopsy has greatly increased over the past 2 decades. This increase in the number of diagnostic procedures is thought to be responsible for the dramatic increase in the diagnosis of grade II–IV acute GVHD after HSCT with human leukocyte antigen-identical sibling donors, from 25% to 45% before 1990 to as much as 75% in later series (33). Early upper gastrointestinal GVHD, including persistent nausea without diarrhea, represents the bulk of this increase in diagnosis (33). Concurrently, it became evident that histologically confirmed early intestinal GVHD may occur without skin involvement in as many as 20% of these cases (33). Therefore, suspicion must remain high, even in patients with atypical presentation. In patients with chronic GVHD, intestinal symptoms are most often manifestations of persistent acute GVHD-related intestinal disease. Biopsy has revealed purely chronic GVHD-related intestinal disease in 14% or less of symptomatic patients (36).

Histologically, intestinal acute GVHD is marked by apoptosis of crypt cells, with or without cryptitis (Fig 1); chronic GVHD has the added features of fibrosis and marked mucosal crypt distortion and loss (36). These features, along with underlying capillary bed engorgement and inflammation, are detected at endoscopy as mucosal atrophy or sloughing, bleeding, and hyperemia (Fig 2). Radiologic assessment is particularly important in acute GVHD, where the timing of diagnosis and treatment affects prognosis (42), but imaging findings may be similar regardless of the timing of onset (43,44).

Table 3

Differential Diagnosis of Gastrointestinal and Hepatic Complications of HSCT (Excluding GVHD, VOD, Neoplasia, and Fungal Infection) with Their Respective Imaging Findings

Days from HSCT Within Which Entity May Arise (8)/Disease Entity	Underlying Disease	Imaging Features	Imaging Features That May Help Rule Out GVHD or VOD Alone	Further Diagnostic or Confirmatory Tests
0–30 (pretransplant and early posttransplant period)				
Typhlitis	Necrotizing, hemorrhagic transmural inflammation (9)	Moderate bowel wall thickening, small bowel dilatation, increased ileocecal wall vascularity (ultrasonography [US]), increased mucosal enhancement, target sign (computed tomography [CT]), adjacent fat stranding (CT) (8,10)	Bowel wall thickening limited to ileocecal region, ascending colon; bowel perforation may occur in advanced cases, showing free intraperitoneal air or fluid; ascites is usually mild (8,10–13)	Usually a diagnosis of exclusion (10)
C difficile colitis	Exudative, fibrinous mucosal plaques overlying dilated crypts; inflammation limited to mucosa, submucosa (13,14)	Marked colonic wall thickening in segmental (early) or diffuse (late) fashion, heterogeneous medium-echogenic submucosal edema (US), increased mucosal enhancement, target sign (CT) (13,15–17)	Bowel wall thickening limited to the colon, nodular; characteristic accordion sign at CT: trapping of oral contrast material between thickened low-attenuation haustral folds (10,15)	Fecal testing for *C difficile* toxins or antigens usually sufficient; endoscopy with biopsy in some cases (18)
31–100 (early posttransplant period)				
Viral (mainly cytomegalovirus) gastroenteritis or hepatitis	Intranuclear inclusions (cytomegalovirus), mucosal inflammation and ulceration; in hepatitis, biliary involvement may lead to cholestasis (19–21)	Moderate ileocecal and ascending colonic wall thickening with or without small intestinal involvement, increased mucosal enhancement, target sign (unless hemorrhagic) (CT) adjacent fat stranding (CT), ascites (13), nonspecific signs of hepatobiliary disease, nonobstructive acalculous cholecystitis (22)	Bowel perforation may occur in advanced cases, showing free intraperitoneal air or fluid (12,23)	Virology; gastrointestinal or hepatic histopathologic examination is often necessary in HSCT patients (20,22)
Pneumatosis (cystoides) intestinalis	Mucosal compromise, dissection of intraluminal gas into submucosa or subserosa (8)	Features of typhlitis or acute or chronic GVHD may be present (8,24)	Air bubbles, typically in a cystic fashion; pneumoperitoneum may exist (24)	Not applicable
Thrombotic microangiopathy	Microthrombi leading to ischemic enterocolitis	May coexist with and be indistinguishable from GVHD (8)	Not applicable	Laboratory evidence of hemolysis; endoscopy and biopsy are often required (25)
>100 (late posttransplant period)				
Posttransplantation lymphoproliferative disease	Donor infected with Epstein-Barr virus, B- (or T-) cell proliferation toward lymphoid hyperplasia or malignant lymphoma (26,27)	Lymphadenopathy, hepatosplenomegaly, bowel wall thickening, ascites (8,26)	Extensive mesenteric lymphadenopathy, may be infiltrative (8,26)	Biopsy (28)

Note.—No imaging finding is 100% specific for respective disease entity; various entities may coexist in the same patient.

Imaging Findings

Plain radiographic, CT, and US studies may reveal common findings, with the primary pathologic finding being bowel wall thickening and abnormal mucosal enhancement (Table 4) (44,46). The accuracy of any radiologic finding has yet to be determined, and imaging is generally considered nonspecific. Nevertheless, certain imaging findings may help to distinguish GVHD from other gastrointestinal complications of HSCT, in which immunosuppression is contraindicated. Morphologic and functional signs seen at abdominal radiography, CT, and US along with their reported frequencies in patients with HSCT are listed in Table 4 and illustrated in Figures 3–5.

Findings of plain abdominal radiography are abnormal in 95% of acute GVHD cases, demonstrating separation of bowel loops indicative of wall thickening, air fluid levels, decreased luminal gas, and small bowel dilatation (Fig 3) (49). Small and large intestinal wall thickening, mainly submucosal in origin (48), is seen at US (Fig 4) and CT (Fig 5) in the majority of patients with acute GVHD and may lead to luminal narrowing or separation of bowel loops (50). Bowel wall thickening per se is not specific for GVHD, as it also occurs frequently in other patients with HSCT (47) and those with neutropenia (10). However, intestinal thickening in acute GVHD is typically moderate at less than 5.5–8 mm (10,44,45,47,48), whereas more severe thickening at CT may suggest infection with *Clostridium difficile*, cytomegalovirus, or neutropenic enterocolitis, also known as typhlitis (10). When bowel wall thickening is caused by GVHD, the small intestine is involved in 75%–100% of cases (44,45,47,48), serving to virtually exclude neutropenia-related *C difficile* colitis (10). Like acute GVHD, typhlitis may affect both small and large bowel (10). Where concurrent small and large bowel involvement is seen, two additional findings may help to distinguish acute GVHD from typhlitis: first, a discontinuous distribution of bowel involvement is seen in 41%–54% of patients with acute GVHD (44,45), but is less common in typhlitis (51); second, strictly right colonic involvement is uncommon in acute GVHD (10,44,45,47,48), whereas selective involvement of the right colon or cecum is present in 75%–100% of typhlitis cases (10,51).

Abnormal mucosal enhancement at CT following administration of intravenous contrast material (Fig 5) is seen in nearly 80% of patients with acute GVHD (10,44,45) and is significantly more common in acute GVHD than in other neutropenic causes of bowel disease (10). Mucosal enhancement is limited to thickened bowel segments (44,45). Replacement of mucosa by highly vascular granulation tissue has been shown to be the underlying disease (46). This finding is best appreciated when intravenous contrast material is used in conjunction with negative oral contrast material (8,46). Indeed, Kalantari et al (45) speculated that their relatively low rate of visualized mucosal enhancement (53%) may have been due to the concomitant use of intravenous and positive oral contrast material in their patients. Others have reported 89% enhancement rates when oral contrast material was not used (44). Gastrointestinal symptoms may limit the use of oral or rectal contrast material in GVHD patients (11). When barium is used, severe mucosal ulceration may facilitate intramural infiltration of contrast material, leading to persistent submucosal attenuation

Figure 1

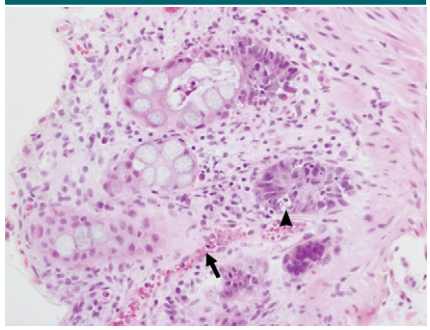

Figure 1: Histopathologic examination of grade I–II gastrointestinal acute GVHD. Photomicrograph shows capillary congestion (arrow) and colonic crypt cell apoptosis (arrowhead). (Hematoxylin-eosin stain; original magnification, ×10.)

Figure 2

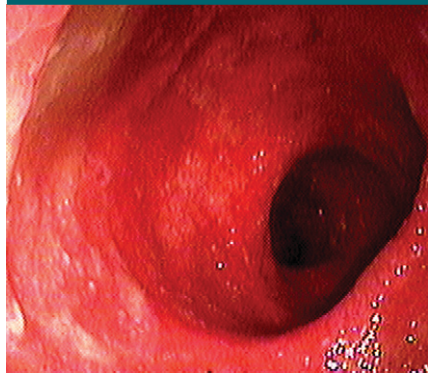

Figure 2: Acute intestinal GVHD. Endoscopic image shows generalized mucosal atrophy, ulceration, and hyperemia.

Table 4

CT and US Findings in Patients with Gastrointestinal Acute GVHD

Variable	CT (%)	US (%)
Bowel wall thickening*	86–100 (10,44,45)	86–100 (47,48)
Mucosal enhancement	54–89 (10,44,45)	Not applicable
Bowel dilatation†	23–86 (10,44,45)	100 (47)
Excessive small intestinal fluid filling	94 (44)	Not assessed
Biliary tract abnormality	41–74 (44,45)	Not assessed
Mesenteric infiltration	29–73 (10,44,45)	0 (47)
Ascites	29–45 (10,44,45)	71 (47)
Blood vessel or flow abnormality	40–90 (engorgement of vasa recta, or comb sign) (44,45)	66 with increased or normal SMA flow (48), 33 with decreased SMA flow (48)‡

* Bowel wall thickening is typically moderate at less than 6–8 mm.

† Small intestinal diameter greater than 2.5 to 3.5 cm, large intestinal diameter greater than 4 to 8 cm.

‡Patients with ischemic bowel, as demonstrated by decreased superior mesenteric artery (SMA) flow, were the only ones in whom therapy failed and who died of gastrointestinal acute GVHD.

Figure 3

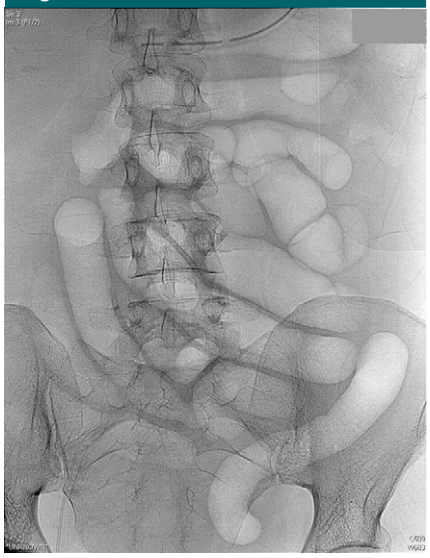

Figure 3: Plain abdominal anteroposterior radiograph in a 34-year-old woman with acute gastrointestinal GVHD shows multiple dilated bowel loops and bowel wall thickening.

Figure 4

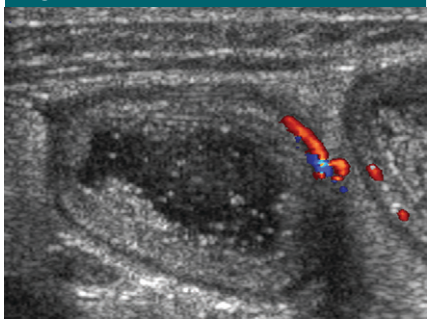

Figure 4: Abdominal high-resolution color Doppler US scan (linear 12-mHz transducer, IUS 22; Philips Healthcare, Eindhoven, the Netherlands) in a 7-year-old boy with gastrointestinal acute GVHD shows small bowel wall thickening.

that can last for weeks after contrast material administration (50,52).

Bowel dilatation, when defined as large intestinal diameter greater than 8 cm or small intestinal diameter greater than 2.5–3 cm, was seen at CT in about 42% of acute GVHD patients (10,44,45). However, when defined as a minimal large intestinal diameter of 4 cm or small intestinal diameter of 3.5 cm, bowel dilatation was seen at US in 100% of cases (47). This apparent discrepancy between imaging modalities may be related to patient selection bias in various published reports or differing definitions of dilatation. Dilatation occurs at a significantly higher rate in acute GVHD than in other neutropenic (10) or HSCT patients (47). It is limited to bowel that is proximal to thickened wall segments (45). Although this sign appears early in the course of clinical manifestations, its persistence seems unrelated to the clinical course (47).

Figure 5

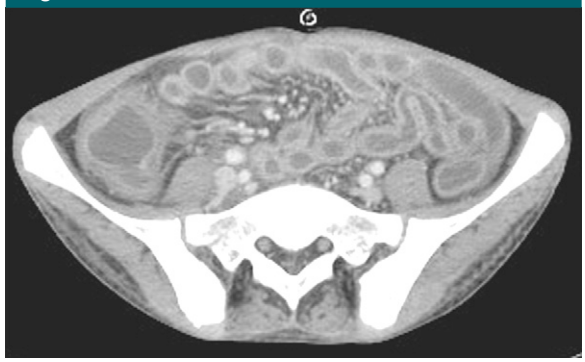

Figure 5: Abdominal CT scan (2-mm section thickness, 1-mm increment, 250 mAs, and 120 kVP) in a 14-year-old boy shows cecal and small bowel wall thickening, mucosal enhancement, and engorgement of the vasa recta. CT was performed with negative oral contrast material (1500 mL of 5% mannitol solution) and 100 mL of intravenous iodinated contrast agent containing 300 mg iodine per milliliter.

At CT, engorgement of the vasa recta, or the comb sign (Fig 5), was seen in about 60% of acute GVHD patients (44,45) and may be more pronounced near thickened bowel wall segments (45). Approximately one-third of patients may have increased blood flow in the superior mesenteric artery, seen at color Doppler US, and one-third may have decreased superior mesenteric artery flow in association with ischemic bowel (47). Importantly, the patients with ischemic bowel and decreased superior mesenteric artery flow showed no response to steroid treatment and died of GVHD (47).

CT signs of mesenteric inflammation, including fat stranding, also known as misty mesentery, have been reported in about 44% of acute GVHD patients (10,44,45) and are more pronounced near thickened bowel wall segments (45). In GVHD, this finding exists without mesenteric lymphadenopathy (45), helping to distinguish GVHD in the late posttransplant period from posttransplant lymphoproliferative disorder, which is associated with extensive lymphadenopathy, hepatobiliary disease, bowel wall thickening, and ascites (26).

Since high-grade acute GVHD is associated with significantly increased mortality (37), the radiologic grading of GVHD can have important implications for prognosis, treatment, and monitoring of response to therapy. Brodoefel et al (44) recently suggested grading criteria based on six CT findings, each correlating with overall clinical, gastrointestinal, and/or pathologic grading of acute GVHD(Fig 6).

Findings in chronic GVHD of the gut, while generally similar to those in acute GVHD, may be less frequent (11,13). Gastrointestinal GVHD and its treatment, together with associated superinfection, act to impair mucosal integrity and immunity (53), leading to imaging signs such as bowel wall thickening. These signs may be related to GVHD or have other etiologies (11). Chronic GVHD may also demonstrate strictures of the esophagus or, less commonly, of the small or large bowel (54).

HSCT-related Hepatic GVHD and VOD

Hepatic complications afflict 80% of allogeneic HSCT patients and have an overall

Figure 6

Abdominal CT variable
Mucosal attenuation on unenhanced scan (≤40 HU; >40 HU) [a, b, c]
Maximal wall thickness (≤3 mm; >3 to ≤6 mm; >6 mm) [a, b, c]
Total number of bowel segments involved (≤3; >3 to ≤6; >6 to ≤9) [a, b]
Ascites [a, b]
Engorgement of vasa recta ("Comb sign") [b]
Mesenteric inflammation ("Misty mesentery sign") [b]

Figure 6: Brodoefel CT grading criteria for acute GVHD (44). Overall clinical grade was determined by combining organ grade from modified Glucksberg grading system (6) with the Eastern Cooperative Oncology Group Performance Scale. Organ (gut) grading was based on modified Glucksberg grading system (6). Histopathologic severity was assessed in terms of crypt atrophy by using a four-point scale (53). *a* = Correlates with overall clinical grading, *b* = correlates with gut grading, and *c* = correlates with pathologic grading.

mortality rate of 37% (55). The most likely differential diagnoses are drug toxicity and drug-induced cholestasis, GVHD, VOD, and infection, including recurrent viral hepatitis. Clinical, laboratory, and radiologic findings usually suffice for diagnosing drug-induced cholestasis and infection (11). In GVHD and VOD, however, findings may be nonspecific and liver biopsy may be required (22,56).

Hepatic GVHD

Hepatic GVHD is primarily a disease of the biliary system, marked histologically by progressive atypical degeneration of small bile ducts (Fig 7). Occurring in half of acute GVHD patients (57), hepatic GVHD typically manifests as cholestatic jaundice, with liver failure and encephalopathy occurring only rarely. Chronic GVHD of the liver affects 40%–73% of human leukocyte antigen-matched bone marrow transplant patients (4). Chronic hepatic GVHD may progress from cholestasis to aggressive

Figure 7

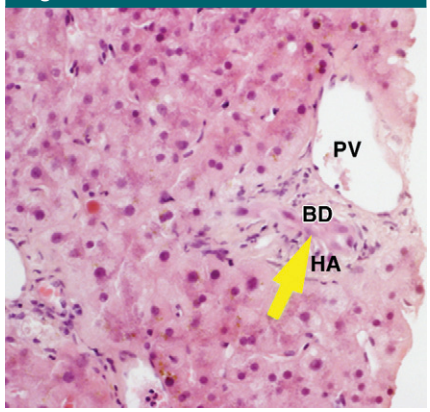

Figure 7: Photomicrograph in a patient with chronic hepatic GVHD disease: the portal triad. Arrow = bile duct, which shows early degenerative changes, *BD* = bile ductule, *HA* = hepatic arteriole, *PV* = portal venule. (Hematoxylin-eosin stain; original magnification, ×20.)

hepatitis and cirrhosis or may manifest as acute hepatitis (58).

Biliary tract abnormalities, including enhancement of the biliary tract, gallbladder wall thickening, dilatation of the common bile duct, pericholecystic fluid, and biliary sludge, are common coexisting extraintestinal CT findings in acute gastrointestinal GVHD and occur in about 61% of cases (Table 4) (44,45). In addition, Ketelsen et al (59) recently reported a significantly greater rate of common bile duct dilatation in patients with gastrointestinal acute GVHD (67%, n = 27) than in HSCT patients without acute GVHD (12%, n = 25). A majority of acute GVHD patients also showed common bile duct and gallbladder wall enhancement, compared with no patients in the control group. Moreover, in 96% of acute GVHD patients, bilirubin concentration correlated significantly with common bile duct diameter (59).

Evidence of biliary tract disease may be seen in other high-mortality HSCT-related diseases, including acalculous cholecystitis and VOD (60), and to our knowledge, no truly reliable GVHD-specific imaging findings exist in the liver. Therefore, given that GVHD of the liver usually coexists with GVHD of the gut, radiologic evaluation of patients with liver disease must include full abdominal scanning, if such investigation is to be diagnostically meaningful. In particular, Erturk et al (61) found that small bowel wall thickening as seen at CT is much more indicative of GVHD than VOD.

Veno-occlusive Disease

VOD, also known as sinusoidal obstruction syndrome, is thought to result directly from chemotherapy- or radiation-induced destruction of hepatic microvasculature during cytoreductive HSCT conditioning. VOD represents the most common cause of liver disease during the first 20 days after HSCT, affecting 10%–60% of HSCT patients (7,62,63), with dramatically increased risk after myeloablative or increased-intensity conditioning (62). In most cases, VOD develops within 1 week before to 3 weeks after cell transplantation and manifests clinically as a specific triad of weight gain due to portal hypertension and fluid retention, jaundice, and painful hepatomegaly (7). Over the long term, VOD may progress to panvasculitis and multiorgan failure. Progression may be related to decreased circulating levels of anticoagulation factors, increased levels of procoagulant proteins, and increased levels of inflammatory mediators (5,64,65). VOD-associated death may result from hepatic, renal, cardiovascular, or respiratory complications. Mortality rates at 100 days range from 9% in mild cases to nearly 100% in patients with more severe presentation, with the latter representing 28% of all VOD cases (7). Overt manifestations of VOD in the form of the clinical triad may lag relative to biologic and radiologic findings (28,66). A high index of clinical suspicion early in the HSCT process therefore may be crucial, especially since timely medical treatment may potentially curb the progression to severe VOD and decrease mortality (67,68).

Centrilobular hemorrhagic necrosis, with venular obliteration, sinusoidal congestion, and fibrosis represents the underlying pathologic basis for the deranged blood flow in VOD (65). The obliteration of venous microvasculature leads to decreased outflow from the liver, with consequent portal hypertension similar to that seen in Budd-Chiari

syndrome (65). Since morphologic and blood flow changes of the liver can exist in patients even before undergoing HSCT preparation (28,69–72), baseline and serial US assessments have been recommended by some authors (28,69–71). Radiologic evaluation in VOD may reveal morphologic changes, including hepatomegaly, splenomegaly, gallbladder wall thickening, increased hepatic echotexture, ascites, and periportal cuffing, as well as signs of blood flow abnormality in the hepatic arterial or portal venous systems (28,43,69–72).

In prospective studies of HSCT patients by Herbetko et al and Hommeyer et al, no gray-scale US finding was strongly associated with VOD (70,71). Stronger associations have been reported with some Doppler findings, but there is inconsistency between studies. In the study by Herbetko et al, a hepatic arterial resistive index of 0.75 or greater was the best indicator of VOD, occurring in 95% of VOD patients. In HSCT patients without VOD, including those with GVHD and hepatitis, the resistive index values always remained below 0.70 (70). Although elevation of the index was not correlated with the severity of VOD, return to baseline resistive index values corresponded with resolution of hepatic dysfunction in most patients (70). It is worth noting that the resistive index could theoretically decrease to normal levels in the presence of hepatofugal flow, as a consequence of hepatic arterial diversion to the portal vein via the sinusoids (72).

Portal venous flow abnormalities, including to-and-fro and hepatofugal flow, are considered more specific for VOD, but they typically occur very late in the disease (69). These findings occur in only 18% of patients and may represent more severe VOD; thus, their diagnostic importance in early or clinically ambiguous liver disease is questionable (69–72).

Lassau et al (28) studied the accuracy of US in diagnosing VOD in a large population of HSCT patients. By using a 14-point scoring system based on seven gray-scale and seven Doppler US findings, with one point per abnormal finding, a total score of 6 was most accurate, with sensitivity of 83% and specificity of 87%. In adults, a total score of 8 or more along with a serum bilirubin level greater than 80 μmol/L was found to be an earlier predictor of mortality than was bilirubin level alone. A Doppler score of 3 or more correlated with portal hypertension, defined as a corrected hepatic sinusoidal pressure of 10 mm Hg or above (28). It should be noted, however, that most data concerning US imaging of VOD were published more than a decade ago, with many conflicting findings that have not been reproduced in later studies. More recently, McCarville et al (73) found in a prospective study that clinical criteria were superior to either gray-scale or Doppler US parameters for the diagnosis of VOD.

If the clinical presentation is ambiguous, CT and US can sometimes be useful in helping to distinguish between hepatic GVHD and VOD. Gray-scale US findings that occur more frequently in VOD are splenomegaly, gallbladder wall thickness greater than 6 mm, hepatic vein diameter of less than 3 mm, ascites, and visualization of paraumbilical veins (28). Doppler findings that occur more frequently in VOD are flow demodulation in the portal vein, decrease in spectral density, decrease in velocity to less than 10 cm/sec or reversal of flow in the main portal vein, hepatic artery resistive index 0.75 or greater, monophasic flow in the hepatic vein, and flow in the paraumbilical vein (28).

CT findings favoring a diagnosis of VOD are periportal edema and ascites (61). A right hepatic vein diameter of less than 0.45 cm at CT is highly suggestive of VOD (61). The rates of occurrence of hepatomegaly and increased portal vein diameter were comparable in VOD and GVHD at both CT and US (28,61).

Transjugular Liver Biopsy

Infectious and cholestatic causes of post-HSCT liver disease are usually identifiable with clinical, laboratory, and radiologic work-up. However, the diagnosis of GVHD and VOD may be more challenging. Typically, VOD manifests with the clinical triad described above, and GVHD manifests with skin as well as gastrointestinal manifestations at the time of clinical hepatic involvement. When patients present with isolated liver disease and the clinical presentation and work-up do not enable a definitive diagnosis, liver biopsy may be needed. Liver histologic examination in these immunosuppressed patients may be evaluated not only for GVHD and VOD, but also for drug toxicity, as well as bacterial, viral, and fungal infection. To our knowledge, data regarding liver biopsy rates in this population have not been published. At our institution, approximately 10% of HSCT patients undergo liver biopsy. Kalantari et al stated that liver biopsy must be performed in most cases to differentiate between hepatic GVHD and VOD (45). Other authors have reported that transjugular liver biopsy is part of a standard approach in the assessment of HSCT patients with liver dysfunction (22).

In some cases, US-guided percutaneous biopsy is performed. However, many HSCT patients are at risk for bleeding secondary to thrombocytopenia or coagulopathy (74). Ascites, which may exist in both GVHD and VOD, presents a technical obstacle to the percutaneous approach. The transjugular approach is considered safe in these patients (22,75–77) and has a major complication risk of about 1% (75). Transvenous access allows sampling from multiple sites, a potential advantage in the diagnosis of VOD, where even severe disease may cause centrilobular necrosis in only 10%–30% of the liver parenchyma (78). Transvenous liver biopsy provides clinically useful information in a majority of cases (75–77,79–81) and influences treatment decisions in about 90% of these patients (75,81).

The transvenous approach also facilitates direct and indirect measurement of hepatic and portal venous pressures, aiding in the diagnosis and management of VOD with secondary portal hypertension. A corrected hepatic sinusoidal pressure greater than 10 mmHg is 52% sensitive and 91% specific for VOD (81), and the prognosis is especially poor when pressure exceeds 20 mmHg (81). Concurrent hepatic venogram may demonstrate small-caliber main hepatic veins, occlusion

Figure 8

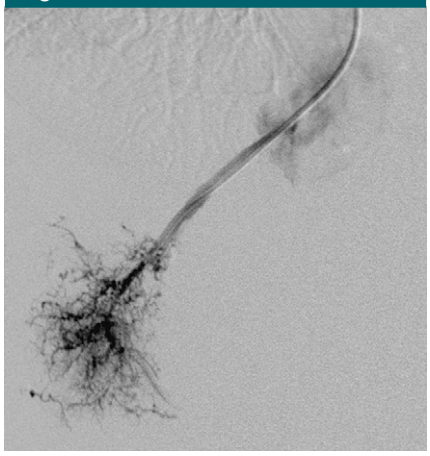

Figure 8: Hepatic venogram in a patient with VOD shows a small-caliber right hepatic vein with a distal spiderweb pattern, mimicking Budd-Chiari syndrome.

of terminal hepatic vein branches, and the so-called spider web pattern, which is classically seen in Budd-Chiari syndrome (Fig 8).

Image-guided Interventional Therapies in GVHD and VOD

Aside from transvenous liver biopsy, some radiologic interventions may be important in the management of HSCT-related complications, specifically, intraarterial steroid-injection therapy in intestinal and hepatic GVHD, and transjugular intrahepatic portosystemic shunt (TIPS) placement in VOD.

Intraarterial Steroid-injection Therapy in GVHD: Rationale and Results

Intraarterial steroid-injection therapy represents adjuvant therapy in patients with systemic steroid-refractory acute GVHD, typically those with grade III or IV disease. GVHD is characterized by both a reduction in the number of steroid receptors in diseased tissue and a decrease in the receptors' affinity for steroids (82,83). Salvage regimens consisting of mega-dose systemic therapy have failed to adequately improve signs and symptoms of acute GVHD and cause profound immunosuppression (84–86), thereby increasing risk of infection (87) and tumor recurrence (88). Since intraarterial steroid-injection therapy delivers treatment directly to the "end-organ" diseased tissue via respective arterial channels, high concentrations of steroids can be applied locally, thereby overcoming the underlying unresponsiveness without further depressing the already incompetent immune system in these patients.

Initial reports in the recent literature suggest that intraarterial steroid-injection therapy is safe and effective in severe acute GVHD, especially if performed early (89–94). Shapira et al (92) and Nakai et al (90) described their experience in 17 patients with grade III–IV gastrointestinal and/or hepatic acute GVHD. Organ response, either partial or complete, was defined as amelioration of abdominal pain or diarrhea volume in gastrointestinal GVHD and a decrease in serum bilirubin level in hepatic GVHD. At least partial gastrointestinal or hepatic response occurred in 92% and 63% of patients, respectively, and complete gastrointestinal or hepatic response occurred in 83% and 38%, respectively. In those with gastrointestinal disease but no hepatic involvement, long-term survival was 50%, but 75% of survivors developed mild chronic GVHD a mean of 1 year after intraarterial steroid-injection therapy. One of four patients with purely hepatic disease survived, with normal bilirubin and only mildly elevated liver enzymes at 1 year. Among patients who died with isolated gastrointestinal or hepatic involvement, GVHD progression was the cause of death in less than 30%. When gastrointestinal and hepatic diseases coexisted, long-term survival was 0%, and GVHD progression was the cause of death in 80%.

Weintraub et al (94) recently presented their experience with intraarterial steroid-injection therapy in 11 patients with treatment-resistant isolated gastrointestinal acute GVHD. Even with a somewhat stricter definition of response to treatment than previously reported, at least partial response was seen in 72%, with complete response in 36%. Survival at 1.5 years was 27%.

By reducing the magnitude of systemic immunosuppression and limiting the extent of disease at the time of treatment, early intraarterial steroid-injection therapy may further improve outcomes and survival (90,92). However, large, controlled studies will be needed before definitive conclusions can be drawn regarding the efficacy of intraarterial steroid-injection therapy in treating GVHD.

Intestinal intraarterial steroid-injection therapy is accomplished via the superior mesenteric, inferior mesenteric, and internal iliac arteries, with or without gastroduodenal artery injection (92). The angiogram may appear normal or show nonspecific early arterial phase mucosal enhancement, resembling changes of inflammatory bowel disease. Hepatic GVHD is effectively a disease of the biliary tree, thus treatment is most appropriately delivered via the hepatic artery. The angiogram usually appears normal.

TIPS in VOD: Rationale and Results

As the hepatic venous system becomes occluded in VOD, increasing portal pressure may ultimately limit hepatic perfusion, leading to hepatocellular or gastrointestinal tissue necrosis and patient death. The finding of stagnant or reversed flow in the main portal vein or its branches at duplex US is an indication for shunt placement (78). Diversion of portal flow with TIPS relieves portal pressure and can potentially improve hepatic and splanchnic perfusion. In a subset of patients, TIPS may allow more time for spontaneous recovery or liver transplantation (65).

Only three small, uncontrolled series, with a total population of 19 patients, have reported the efficacy of TIPS in VOD (78,95,96). No clinical or biologic improvement was noted in any patient who died within 10 days of TIPS placement. Of the 13 patients (68%) surviving for more than 10 days, 11 (58%) improved clinically, with decreased ascites and/or relief from abdominal pain. Decreased alanine aminotransferase and improved prothrombin time were seen in about half of patients, and some improvement of renal function was noted in about 40% overall. These parameters typically improved within about 1 week of TIPS. However, improvement of bilirubin levels was uncommon. TIPS placement was reported to control portal hypertension in all

patients in these small series. Zenz et al (78) reported a 21%–30% decrease in the hepatic arterial resistive index and normalization of portal vein flow velocity, which indicates increased hepatic arterial flow, improved hepatocyte perfusion, and restored splanchnic outflow.

The optimal timing of TIPS placement is uncertain and may depend on post-HSCT survival probability (97). Early TIPS placement may be best. Reported survival 14 days after TIPS placement was 47% in these patients, decreasing to only about 11% at 6 months (78,95,96). Unfortunately, mortality from multiorgan failure remains high. Even after resolution of VOD, most patients die of nonhepatic complications, especially renal or cardiopulmonary failure or sepsis (65,78). Because of the high mortality from nonhepatic complications, HSCT-related VOD was not established as an indication for TIPS placement in recent guidelines by the American Association for the Study of Liver Diseases (98). Controlled studies will be needed to clarify the role of TIPS in patients with VOD.

Summary

Gastrointestinal GVHD and hepatic VOD are two unique and potentially deadly complications of HSCT, in which abdominal imaging helps to gauge disease severity, guide urgent management, and improve patient outcomes; emerging image-guided interventions, although as yet unproved, have shown therapeutic promise in small, uncontrolled series. Early diagnosis improves outcome in GVHD, and new treatment options may offer better outcomes in VOD if the disease is recognized early. CT and US findings can help reveal changes from baseline evaluation, point to the diagnosis, gauge severity of disease, and guide further treatment in GVHD and VOD. Intravenous contrast material administration may improve the accuracy of CT imaging, particularly when used in combination with negative oral contrast material, enabling improved appreciation of bowel wall abnormalities. In cases of liver involvement requiring liver histologic examination for diagnosis, transvenous biopsy is a safer and more practical option than percutaneous biopsy in many patients, although complications may still occur. The transvenous approach also allows measurement of the corrected hepatic sinusoidal pressure, an important prognosticator in VOD. Minimally invasive procedures have shown early promise, but larger, controlled studies are needed to determine their true efficacy. In systemic steroid-refractory severe acute GVHD, intraarterial steroid-injection therapy has been reported in several case series to be a safe and potentially curative adjuvant therapy, especially in cases of gastrointestinal disease without liver involvement. In the few published cases of TIPS placement for VOD, TIPS was reported to reduce symptoms, decrease portal pressure, and improve liver function in most patients. Although it has not shown a clear survival benefit, TIPS may also buy time for those patients in whom liver transplantation is an option.

Acknowledgment: The authors wish to thank Shifra Fraifeld, MBA, for her editorial assistance in the preparation of this manuscript.

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