Abdominal complications affect more than 80% of patients who undergo hematopoietic stem cell transplantation (HSCT) for treatment of benign or malignant hematologic disease and some solid tumors. HSCT can be performed using cells from bone marrow, peripheral blood, or umbilical cord blood. These stem cells may be from the patient him- or herself (autologous transplant), from relatives or nonrelatives with very similar human leukocyte antigen (allogeneic transplant), or from an identical twin (syngeneic transplant). Posttransplantation complications are classified according to the amount of time elapsed between transplantation and onset. Complications that occur during the first 100 days are divided into preengraftment phase complications (≤30 days after transplantation) and early posttransplantation phase complications (31–100 days after transplantation) and include infectious and noninfectious conditions such as hepatic veno-occlusive disease (VOD), hemorrhagic cystitis, neutropenic colitis, benign pneumatosis, and acute graft-versus-host disease (GVHD). Hepatic VOD, neutropenic colitis, and acute hemorrhagic cystitis are associated with the pretransplantation conditioning regimen. After the first 100 days, chronic GVHD and lymphoproliferative disease are the main complications. Computed tomography and ultrasonography are the primary imaging techniques used in HSCT patients and can help make an early diagnosis, grade the severity of impact, and (if necessary) recommend further investigations to confirm the diagnosis.

SA-CME LEARNING OBJECTIVES FOR TEST 3

After completing this journal-based SA-CME activity, participants will be able to:

■ Discuss the pathophysiology of complications of hematopoietic stem cell transplantation.
■ Describe the imaging findings of abdominal complications of hematopoietic stem cell transplantation.
■ Correlate various types of data obtained in patients who undergo hematopoietic stem cell transplantation.

See www.rsna.org/education/search/RG

Introduction

Hematopoietic stem cell transplantation (HSCT), also known as bone marrow transplantation and peripheral blood stem cell transplantation, involves the collection of cells from bone marrow, peripheral blood, or umbilical cord blood. According to the Center for International Blood and Marrow Transplant Research, approximately 55,000–60,000 HSCTs are performed worldwide each year (1).

The most common indications for this type of treatment are the malignant hematologic diseases, which include leukemia (acute myeloid, acute lymphoblastic, and chronic lymphocytic), lymphoma (Hodgkin and non-Hodgkin), myelodysplastic syndrome, and multiple myeloma. HSCT is also used to treat nonmalignant hematologic disorders (eg, aplastic anemia, Fanconi anemia, and Kostmann syndrome) and immunologic disorders (eg, Wiskott-Aldrich syndrome, severe combined immunodeficiency, and chronic granulomatous disease). In children, HSCT is indicated for neuroblastoma, Wilms tumor, retinoblastoma, and sarcoma. Genetic disorders such as mucopolysaccharidosis, adrenoleukodystrophy, and thalassemia are also indications for HSCT (2).
The graft-versus-tumor effect can amplify the therapeutic benefit of HSCT by decreasing tumor recurrence rates.

Mismatched transplantation carries a high risk of graft-versus-host disease (GVHD). Nonrelated umbilical cord blood has much less stringent requirements for HLA matching because of a lower prevalence of GVHD.

Before transplantation, most patients with hematologic malignancy undergo a conditioning regimen known as myeloablation, which involves high-dose chemotherapy or radiation therapy to kill any resident cancer cells, suppress the patient’s immune system, and leave a disease-free environment. Because many patients are unable to withstand myeloablation, the use of reduced-intensity nonmyeloablative regimens with low-dose chemotherapy or radiation therapy prior to transplantation (also called minitransplantation or reduced-intensity transplantation) is possible. In these cases, hematopoiesis from the residual bone marrow prevents pancytopenia, and recipients have fewer complications during the early posttransplantation phase. Tandem transplantation is an autologous procedure in which the patient undergoes two sequential courses of high-dose chemotherapy combined with stem cell transplantation (3).

Engraftment can be detected in the blood 2–4 weeks after infusion of hematopoietic stem cells. Although advances in immunosuppressive therapy and management of infections have improved long-term survival, transplant recipients remain at risk for a multitude of complications. These complications involve various organs and are divided into three phases that are defined in terms of (a) degree of impairment of the patient’s immune system and (b) time to recovery.

The first period, known as the preengraftment phase (≤30 days after transplantation), is characterized by profound pancytopenia, which leaves the patient susceptible to bacterial and fungal infections. Furthermore, the conditioning regimen injures the mucosae and produces toxic pneumonitis, leukoencephalopathy, and hepatic veno-occlusive disease (VOD).

In the second period, known as the early posttransplantation phase (31–100 days after transplantation), successful engraftment of donor stem cells is followed by recovery of neutrophil count, although lymphocyte deficiency persists, with cellular and humoral immunologic impairment and frequent viral and fungal infections. GVHD may also appear.

In the third period, known as the late posttransplantation phase (>100 days after transplantation), the cellular immune system recovers, but humoral immunodeficiency persists, and chronic GVHD and posttransplantation lymphoproliferative

<table>
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<th>Table 1: Abdominal Complications Following HSCT</th>
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<tr>
<td>Neutopenic colitis (typhilitis)</td>
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<td>Infectious enterocolitis</td>
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<td>Benign pneumonitis</td>
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<td>Renal and urinary tract complications</td>
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<td>Renal abscesses and pyelonephritis</td>
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<td>Renal vein thrombosis</td>
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<td>Late posttransplantation complications</td>
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<td>Chronic GVHD</td>
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<td>PTLD</td>
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<td>Secondary tumors</td>
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A stem cell transplant may be autologous (patient’s own stem cells saved before treatment), allogeneic (stem cells donated by relatives or nonrelatives), or syngeneic (stem cells donated by the patient’s identical twin).

Autologous transplantation has a lower risk of complications than the other types of transplantation, although it has higher tumor recurrence rates. Immune-mediated antitumor or graft-versus-tumor effects are absent. Autologous transplantation is typically used to treat lymphoma and multiple myeloma.

Allogeneic transplantation is the most commonly performed type, especially in patients with leukemia or myelodysplastic syndrome. It involves antigens that are similar but not identical to those of the patient. All human beings inherit a double set of six major genes that produce six major corresponding antigens: human leukocyte antigen (HLA)–A, -B, -C, -DP, -DQ, and -DR. The three most important antigens to match when choosing nonself donors for transplantation are HLA-A, -B, and -DR, and as many as 20 varieties exist for each of these HLA-producing genes (up to two allelic differences between donor and recipient are accepted). Matching these antigens helps minimize the chances of graft-versus-host or host-versus-graft attacks.

The graft-versus-tumor effect can amplify the therapeutic benefit of HSCT by decreasing tumor recurrence rates.

Mismatched transplantation carries a high risk of graft-versus-host disease (GVHD). Nonrelated umbilical cord blood has much less stringent requirements for HLA matching because of a lower prevalence of GVHD.

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risk factors, and typical course. These complications have been divided into four groups: hepatobiliary, gastrointestinal tract, renal and urinary tract, and late posttransplantation complications (Table 1).

**Hepatobiliary Complications**

Liver enzyme alteration affects up to 80% of patients undergoing HSCT. Drug toxicity is a common cause of liver dysfunction in the posttransplantation period. In these cases, the role of imaging is not usually relevant, although drug toxicity should always be considered in the differential
diagnosis. In the following sections, we discuss other causes of hepatic dysfunction, including hepatic VOD, acute hepatic GVHD, and infection.

**Hepatic VOD**

Hepatic VOD occurs in approximately 54% of patients undergoing allogeneic transplantation and is slightly less common in autologous transplantation. Children with neuroblastoma have a significantly higher risk of contracting VOD than patients who undergo HSCT for other solid tumors (4). VOD often occurs following a myeloablative conditioning regimen, although its prevalence is lower in reduced-intensity conditioning regimens. It usually appears 2–4 weeks after transplantation.

Potential mechanisms of injury include endothelial damage with obstruction of the hepatic sinusoids, subsequent fibrosis, and portal hypertension secondary to the toxic effect of chemotherapy and radiation therapy (5).

Patients have painful hepatomegaly, jaundice, and unexplained weight gain (Seattle criteria), as well as ascites. However, other conditions may have similar manifestations, making the differential diagnosis more challenging. Clinical suspicion is crucial, and early medical treatment can potentially decrease mortality.

The first diagnostic method used in patients with hepatic VOD is generally ultrasonography (US). The most common findings at B-mode US are gallbladder wall thickening, ascites, and narrowed hepatic veins. Doppler US findings include decreased or hepatofugal portal venous flow, a monophasic flow pattern in the hepatic veins, increased hepatic artery resistance (resistive index >0.8), and paraumbilical circulation.

Splenomegaly and varices have been shown to correlate with disease severity (Fig 1).

The utility of US in the diagnosis of VOD is controversial, and McCarville et al (6) showed that clinical criteria are diagnostically superior to both gray-scale and Doppler US.

Multidetector computed tomography (CT) and magnetic resonance (MR) imaging are useful, especially in ruling out other potential diagnoses. Multidetector CT findings include heterogeneous and hypoattenuating liver parenchyma, periportal and gallbladder wall edema, ascites, and narrowed hepatic veins (eg, right hepatic vein diameter <0.4 cm) (Fig 2) (7). At MR imaging, the liver parenchyma is hypointense on T1-weighted images and hyperintense on T2-weighted images, with heterogeneous enhancement of all hepatic segments and no focal hepatic lesions (Fig 3) (8). The absence of radiologic findings is not uncommon. Transvenous liver biopsy is a relatively safe procedure that allows a definitive diagnosis to be made (9,10).

**Acute Hepatic GVHD**

Between 30% and 50% of allogeneic transplant recipients develop GVHD, regardless of whether the conditioning regimen was myeloablative or nonmyeloablative. Recipients of mismatched transplants are at greatest risk, with approximately 50% having liver involvement (11). The acute form manifests 2–10 weeks after transplantation and is produced by an attack by the donor’s immune system (T lymphocytes) on recipient tissues. The main finding is atypical degenerative changes in biliary epithelium.

The skin, gastrointestinal tract, and liver are most frequently affected in GVHD. A macular erythematous rash on the face, trunk, and extremities is typical in these patients.
Acute GVHD is classified according to severity and number of organs involved as grades I–IV, with grade IV having the highest mortality rate (Table 2) (12). Clinical manifestations include painful hepatomegaly, jaundice, nausea, and vomiting.

No reliable specific imaging findings of GVHD are detected in the liver. US and multidetector CT show gallbladder wall thickening, ascites, and periportal edema (Fig 4) (13). Because acute hepatic GVHD generally coexists with GVHD of the gut, the most common findings are small bowel wall thickening, mucosal enhancement, and bowel dilatation. Ketelsen et al (14) recently reported that common bile duct dilatation and fluctuation in duct diameter
Hepatic GVHD (biopsy proved) in a 42-year-old patient with myelodysplastic syndrome who had undergone mismatched allogeneic HSCT 45 days earlier. Axial contrast-enhanced CT images show minimal periportal edema (a) and thickening of the gallbladder wall (b).

Figure 4.

Alterations may not be detected during the neutropenic phase, and the examination should be repeated if clinical suspicion persists.

The most common fungal infections are those caused by *Candida* and *Aspergillus* species; *Cryptococcus neoformans* infection and mucormycosis are less common. US findings in liver fungal abscesses include multiple hypoechoic “bull’s-eye” or “wheel-in-wheel” lesions (Fig 5) (15). Multidetector CT with intravenously administered contrast material reveals small hypodense lesions with peripheral ring enhancement. CT performed during the arterial and venous phases improves detection of these lesions, up to one-third of which can be viewed exclusively in the arterial phase (Fig 6) (16). A similar pattern of enhancement can be seen at gadolinium-enhanced MR imaging. In the acute phase, the larger lesions are hyperintense on T2-weighted images and iso- or hypointense on T1-weighted images.

Viral hepatitis, mainly that caused by cytomegalovirus (CMV), may occur in the early posttransplantation period and manifests with cholestasis. Nonspecific signs are observed at US and multidetector CT. In some instances, ascites and gallbladder wall edema may also appear. Infection may be confirmed with antigen or polymerase chain reaction assay.

The most commonly found bacteria in positive blood cultures are *Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *S aureus*; these organisms generally cause bacteraemia without identifiable liver lesions (17).

### Table 3: Radiologic Findings of Hepatic VOD and GVHD

<table>
<thead>
<tr>
<th>Finding</th>
<th>VOD</th>
<th>GVHD</th>
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<tbody>
<tr>
<td>Time frame (wks)</td>
<td>1–5</td>
<td>2–10</td>
</tr>
<tr>
<td>Gallbladder wall edema</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Ascites</td>
<td>+++</td>
<td>±</td>
</tr>
<tr>
<td>Narrowed hepatic vein</td>
<td>+++</td>
<td>±</td>
</tr>
<tr>
<td>Small bowel wall thickening</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Doppler criteria</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Bile duct dilatation</td>
<td>-</td>
<td>++</td>
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Note.—Adapted, with permission, from reference 5. – = rarely seen, ± = sometimes seen, ++ = often seen, +++ = very often seen.

Infection

Bacterial and fungal infections in the preengraftment and early posttransplantation phases are common. Painful hepatomegaly and fever are the most typical clinical symptoms.

Gastrointestinal Tract Complications

The gastrointestinal tract is commonly affected by complications of HSCT, which are a major
cause of morbidity and mortality in transplant recipients. The major complications include acute GVHD, pseudomembranous colitis, neutropenic colitis, infectious enterocolitis, benign pneumatosis, and thrombotic microangiopathy.

Because clinical symptoms can be nonspecific, radiologic evaluation is essential for establishing the diagnosis, assessing disease extent, and choosing the most appropriate treatment.

**Acute GVHD**

Acute GVHD appears 2–10 weeks after allogeneic transplantation depending on the grade of histocompatibility between donor and recipient but independent of whether the conditioning regimen was myeloablative or nonmyeloablative. Other risk factors involved in this complication are graft type, patient age and gender, and donor-recipient parity. HSCT performed after a nonmyeloablative conditioning regimen is associated with a considerable delay in the onset of acute GVHD.

GVHD results from damage to the recipient’s gastrointestinal epithelium produced by the donor’s lymphocytes. Histopathologically, the denuded mucosa is replaced by a layer of highly vascularized granulation tissue. Acute GVHD with some form of gastrointestinal involvement has been reported in 30%–70% of patients who undergo HSCT (18–21). Any segment of the digestive tract can be affected, from the esophagus to the rectum.

The clinical course of acute GVHD includes nausea, vomiting, diarrhea, weight loss, abdominal pain, and, sometimes, fever. Skin rash and liver dysfunction are always present (Table 2).
Multidetector CT is the most frequently used diagnostic approach; however, US may be sufficient in pediatric patients. Multidetector CT studies are performed only with intravenous contrast material; most patients cannot tolerate oral contrast material, which can also mask mucosal enhancement. Findings at multidetector CT include diffuse bowel wall thickening, mucosal enhancement with the “halo sign” (mucosal and serosal enhancement), bowel dilatation, mesenteric fat stranding, ingurgitated vessels (“comb sign”), and ascites (Figs 7, 8). The small intestine is involved in 75%–100% of cases. Intestinal thickening is moderate, and discontinuous distribution is observed in one-half of patients. Concomitant small and large bowel involvement is observed in 86% of patients (21,22).

Brodoefel et al (23) recently suggested grading criteria that are based on six CT findings: (a) mucosal attenuation at nonenhanced CT (<40 HU or >40 HU); (b) wall thickness (3, 3–6, or >6 mm); (c) number of segments involved (three, between three and six, or between six and nine); (d) the comb sign; (e) misty mesentery; and (f) ascites. Each of these findings is correlated with clinical, gastrointestinal, and pathologic findings for the grading of acute GVHD.

Bowel wall thickening is not specific to GVHD, and the differential diagnosis must include CMV infection, neutropenic enterocolitis, and other types of enterocolitis. Tissue sampling is often necessary to confirm the diagnosis.

The long-term survival of HSCT patients is highly variable and depends on grade of disease and response to corticosteroids.

Pseudomembranous Colitis
Pseudomembranous colitis is an acute infection caused by toxins that are produced by unopposed overgrowth of Clostridium difficile after broad-spectrum antibiotic therapy during pancytopenia (preengraftment phase). This condition causes severe colonic inflammation, and the disease course includes watery diarrhea, fever, and abdominal pain.

Although pseudomembranous colitis is considered a type of pancolitis, the most frequently damaged segments are the sigmoid colon and the rectum (24). Radiologic findings at intravenous contrast-enhanced multidetector CT (oral and rectal contrast material are unnecessary) include marked thickening of the colonic wall (11–15 mm), low-attenuation haustral folds, mucosal enhancement in the affected segment, and mesenteric fat stranding with a lower grade than in other types of colitis.
Neutropenic colitis (also known as typhlitis) is most common in children undergoing HSCT and rare in adults. The mucosal barrier is damaged by the conditioning regimen, and necrotizing hemorrhagic transmural inflammation of the bowel is observed. Neutropenic colitis appears during the preengraftment phase (≤30 days after transplantation). Its prevalence is increasing due to the greater intensity of chemotherapy regimens.

Patients have fever, vomiting, right lower quadrant pain, and bloody or watery diarrhea.

The most commonly affected areas are the terminal ileum, cecum, and ascending colon, although other colonic segments and small bowel loops may also be affected. Multidetector CT reveals thickening of the wall of the cecum and terminal ileum, mucosal enhancement, and pericolonic fat stranding. Mural air and bowel perforation may also be observed. Ascites is rarely detected (Fig 10) (21,22,26).

The differential diagnosis should include CMV infection, bacterial ileoceitis, pseudomembranous enterocolitis, and appendicitis.

Treatment usually involves bowel rest and antibiotics. Surgery is necessary in advanced cases in which bowel perforation is suspected (27).

**Infectious Enterocolitis**

In the preengraftment and early posttransplantation phases, HSCT patients are at high risk for superinfection from bacteria (e.g., *Pseudomonas*, *Klebsiella*...
Figure 11. *P. aeruginosa* bacteremia in a 52-year-old patient with non-Hodgkin lymphoma who had undergone allogeneic HSCT 22 days earlier. Axial contrast-enhanced CT images show localized small bowel wall thickening (a) with pneumatosis and mesenteric fat stranding (b).

Figure 12. Benign pneumatosis in a 33-year-old patient with AML who had undergone allogeneic HSCT 80 days earlier. Axial contrast-enhanced CT images obtained at different window levels show benign pneumatosis in the wall of the ascending, transverse, and descending colon, along with dilated small bowel. The patient underwent corticosteroid therapy for GVHD.

Symptoms are nonspecific, and in most cases, diarrhea, fever, and abdominal pain are present. The most significant finding in bacterial enterocolitis at multidetector CT, with its high positive predictive value, is marked wall thickening and nodularity of a long segment of the bowel. Pneumatosis can be observed in the intestinal wall, as can fat stranding and bowel perforation with pneumoperitoneum and ascites (Fig 11). The presence of intestinal perforation and the general deterioration of the patient warrant aggressive surgical treatment.

CMV gastroenteritis is a major cause of infection during the early preengraftment phase. Diarrhea with hemorrhage and peritonitis are common. Imaging findings are nonspecific, the most common being bowel wall thickening, ascites, and fat stranding, especially in the ileocecal region (21). CMV infection is confirmed by the presence of CMV antigenemia.

Segmental enteritis with strong mucosal enhancement and perienteric fat stranding is also seen in infection caused by rotavirus, herpes simplex virus, and adenovirus. Infection caused by varicella zoster virus is a possible cause of severe abdominal pain (29,30).

Fungal infections are common in patients with severe and prolonged neutropenia. Aspergillosis is most frequently systemic, although localized
infection of the gastrointestinal tract is possible. *Aspergillus* species has a marked tendency to invade blood vessels and cause hemorrhage and infarction. *A. colitis* may manifest as toxic megacolon (31). Similar findings may be observed in invasive candidiasis and mucormycosis.

**Benign Pneumatosis**

Benign pneumatosis is thought to arise from corticosteroid therapy (most frequently administered to treat GVHD), which induces hypertrophy of Peyer patches, resulting in mucosal defects and dissection of the submucosa or subserosa due to the entry of intraluminal gas. Benign pneumatosis resolves with conservative management (32,33).

Figure 13. Thrombotic microangiopathy in a 30-year-old patient with chronic myeloid leukemia who had undergone allogeneic HSCT 37 days earlier. Axial nonenhanced (a) and contrast-enhanced (b) CT images show increased intraluminal and mucosal attenuation (bleeding), a hypoattenuating submucosal zone, distended small bowel loops, ascites, and mesenteric fat stranding.

Benign pneumatosis appears in the early pregraftment phase. The patient is asymptomatic, and the results of abdominal examination are normal. Multidetector CT shows pneumatosis in the submucosal and subserosal layers of the intestinal wall (Fig 12). Gas can be present in the mesenteric and portal veins, as well as in the abdominal cavity (pneumoperitoneum). Ascites is not observed.

The differential diagnosis should include infectious colitis, although the clinical situation in affected patients is serious and abdominal examination is pathologic (34). The most useful diagnostic key in benign pneumatosis is the asymptomatic status of the patient.

**Thrombotic Microangiopaty**

Thrombotic microangiopathy is an uncommon complication with a high mortality rate that occurs in patients who undergo allogeneic or autologous...
HSCT. It is caused by damage to the microvasculature followed by the formation of microthrombi and ischemia. Risk factors include acute GVHD, cyclosporine A, tacrolimus, and whole-body radiation therapy. The intestinal tract is frequently involved, although severe renal failure, hemolytic anemia, and an elevated serum lactate dehydrogenase level are also common (35).

Thrombotic microangiopathy is usually observed in the early preengraftment phase. Symptoms include intense bloody diarrhea that does not respond to conservative management. Thrombotic microangiopathy can coexist with GVHD, and the two conditions are clinically indistinguishable (36,37).

Multidetector CT should be performed without oral contrast material and both with and without intravenous contrast material. Noncontrast multidetector CT demonstrates high-attenuation areas representing intraluminal and intramucosal hemorrhage. Slight thickening of the wall of the small intestine, mesenteric fat stranding, and bowel dilatation may also be observed (Fig 13).

Laboratory findings such as an elevated serum lactate dehydrogenase level and the presence of fragmented erythrocytes support the diagnosis.

Patients with thrombotic microangiopathy have a poor outcome and a high mortality rate. Plasmapheresis may be effective (38).

**Renal and Urinary Tract Complications**

Hemorrhagic cystitis and renal abscesses are the most common and severe complications in HSCT patients. Other complications, such as renal vein thrombosis, spontaneous subcapsular hemorrhage, and lithiasis, are less common.

**Hemorrhagic Cystitis**

Two different types of hemorrhagic cystitis are distinguished on the basis of severity and time of appearance. The early type appears a few days after transplantation. It is secondary to the conditioning regimen, especially when the patient has received cyclophosphamide, and generally responds to conservative management.

The late type occurs about 80–100 days after transplantation and is generally associated with GVHD. It does not usually respond to immunosuppressive treatment, and surgical intervention is not uncommon (39).

Hemorrhagic cystitis manifests clinically as dysuria and hematuria that is sufficiently intense to require blood transfusions.

Patients can be evaluated with US or multidetector CT, and findings include bladder wall thickening, irregular and sloughed mucosa, and intraluminal clots (11). Intense mucosal enhancement is seen at intravenous contrast-enhanced multidetector CT (Fig 14).

In children, viral infection of the bladder (polyomavirus and adenovirus) is very similar to hemorrhagic cystitis in HSCT (40).

Thickening of the bladder wall can cause ureteral obstruction and make it necessary to perform clearance maneuvers, such as percutaneous nephrostomy catheter placement (41).

**Renal Abscesses and Pyelonephritis**

Although renal and urinary tract infections are common in the preengraftment phase, they can appear at any time during recovery of cellular and humoral immunity. Bacterial and fungal infections such as aspergillosis and candidiasis are common.
Figure 16. Chronic GVHD in a 34-year-old patient with chronic myeloid leukemia who had undergone allogeneic HSCT 100 days earlier. MR enterographic image shows no abnormal findings. However, subsequent biopsy revealed chronic GVHD.

Clinical manifestations include fever, lower urinary tract symptoms, and positive renal fist percussion.

Imaging is not generally performed for lower urinary tract infections, although it is necessary when complicated pyelonephritis or abscess is suspected. Intravenous contrast-enhanced multidetector CT may reveal one or more wedge-shaped areas of lesser enhancement extending from the papilla to the renal cortex in the corticomedullary phase and alternating bands of hypo- and hyperattenuation in the nephrographic phase (Fig 15). The abscesses form hypoattenuating collections with wall enhancement.

Fungal infections may manifest as multiple small, hypoattenuating collections in the renal cortex. Fungus balls (mycetomas) in the collecting system appear as irregularly margined masses that cause obstruction (42).

Late Posttransplantation Complications
Late posttransplantation complications appear after day 100. By this time, recovery of cellular immunity is complete; however, recovery of humoral immunity may take several years. The most common complications during this period are chronic GVHD, PTLD, and secondary tumors and tumor recurrence.

Late effects can also include toxicity from the treatment regimen, infections resulting from immunodeficiency, endocrine disturbances, growth impairment, and psychosocial adjustment disorders (43).

Chronic GVHD
Clinically, chronic GVHD resembles autoimmune collagen disorders, with dry eyes and mucosa; skin hyperpigmentation; and scleroderma-like hepatic, esophageal, and salivary gland changes, as well as anorexia and weight loss.

Nowadays, acute GVHD is defined as GVHD without clinical or pathologic features of chronic GVHD, and chronic GVHD is defined as the presence of these features regardless of the time of onset (44). Chronic GVHD is the most common late complication, affecting about 40%–45% of
patients who undergo allogeneic HSCT. Around 70%–85% of patients with acute GVHD develop the chronic form, although acute GVHD is not an essential requirement for chronic GVHD (9,45,46). Chronic GVHD causes profound immunosuppression (43).

Gastrointestinal GVHD often runs its course without demonstrating imaging findings (Fig 16), although strictures of the esophagus or small or large bowel can be observed. Chronic hepatic GVHD is usually similar to primary sclerosing cholangitis with extrahepatic duct stricture (11). Biopsy must be performed to confirm or rule out the diagnosis.

**Posttransplantation Lymphoproliferative Disorder**

PTLD is secondary to uncontrolled overgrowth of Epstein-Barr virus due to infected donor cells. Epstein-Barr virus–infected B cells proliferate when the recipient’s T cells are depleted as a result of immunosuppressive treatment. The spectrum of abnormal findings includes mononucleosis, polyclonal B-cell hyperplasia, and monoclonal B-cell malignancy.

PTLD affects about 1%–1.5% of all allogeneic transplant recipients. Recent studies suggest a higher prevalence in the pediatric population and in umbilical cord blood recipients. Risk factors for the development of PTLD include HLA mismatching, T-cell depletion, and the use of antilymphocyte antibodies as a conditioning regimen or for treatment of GVHD (47–49).

Clinical manifestations can range from a mononucleosis-like course to fulminant non-Hodgkin lymphoma. Typical signs of Epstein-Barr virus infection include fever, adenopathy, and weight loss.

PTLD should be staged conventionally by obtaining CT images of the chest, abdomen, and pelvis, as well as a serum lactate dehydrogenase level for prognostic purposes. Epstein-Barr virus polymerase chain reaction assay with peripheral blood may be useful at the time of diagnosis and during follow-up as a means of monitoring treatment response (47,48).

Radiologic findings include lymphadenopathy, hepatosplenomegaly, and ascites. In some series, extranodal disease with focal hepatic, splenic, or renal lesions and intestinal masses have been found more often than nodal involvement alone (26,49,50).

When possible, the node, mass, or affected organ should be removed to establish the diagnosis. Determination of the PTLD histologic subtype is decisive for treatment and prognosis. PTLD occurs earlier and behaves more aggressively after HSCT than after solid organ transplantation (Fig 17) (49).

**Secondary Tumors and Tumor Recurrence**

Patients who have undergone HSCT are at a higher risk of developing secondary tumors in the future. In 10-year survivors, the risk increases eightfold and is significant for melanoma, glioblastoma, and connective tissue tumors of the oropharynx, liver, thyroid gland, and bone. The risk factors for secondary tumors are genetic defects, high-dose irradiation in the conditioning regimen, T-cell depletion of the marrow, HLA nonidentity of the donor, and chronic GVHD (43).

Children younger than 10 years of age have been found to have the greatest overall risk of developing posttransplantation malignancy (51).

Recurrence of the primary disease must also be considered, often within 2 years of HSCT and more frequently with autologous HSCT (Figs 18, 19).

The disease course for secondary tumors is no different from that in patients who have not undergone HSCT.
Conclusion

HSCT is one of the key treatments for patients with hematologic diseases, whether malignant or benign; therefore, it is widely used in hematology departments. Knowledge of the pathophysiologic mechanisms that are triggered before and after engraftment is essential when making a firm diagnosis of the many complications that may be seen in these patients. Abdominal and thoracic complications increase morbidity and mortality. Multidetector CT and US findings can help in making an early diagnosis, grading the severity of impact, and, if necessary, recommending further investigations to confirm the diagnosis. In cases of liver involvement, minimally invasive procedures such as transvenous biopsy are recommended. New techniques such as MR elastography will require further evaluation. In combination with radiologic findings, clinical findings associated with the type of transplant, preconditioning regimen, and time elapsed since transplantation will help the radiologist develop a differential diagnosis.

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References


11. Coy DL, Ormazabal A, Godwin JD, Lalani T. Imaging evaluation of pulmonary and abdominal complications following hematopoietic stem cell trans-


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Because acute hepatic GVHD generally coexists with GVHD of the gut, the most common findings are small bowel wall thickening, mucosal enhancement, and bowel dilatation.

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Findings at multidetector CT include diffuse bowel wall thickening, mucosal enhancement with the “halo sign” (mucosal and serosal enhancement), bowel dilatation, mesenteric fat stranding, ingurgitated vessels (“comb sign”), and ascites.

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Wall thickening is more pronounced than in other types of colitis. The swollen hypoattenuating haustra and hyperemic enhanced mucosa form the “accordion sign,” which is highly suggestive of the diagnosis.

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The most useful diagnostic key in benign pneumatosis is the asymptomatic status of the patient.

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Radiologic findings include lymphadenopathy, hepatosplenomegaly, and ascites. In some series, extranodal disease with focal hepatic, splenic, or renal lesions and intestinal masses have been found more often than nodal involvement alone.