Imaging of complications from hematopoietic stem cell transplant

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Abstract

Stem cell transplant has been the focus of clinical research for a long time given its potential to treat several incurable diseases like hematological malignancies, diabetes mellitus, and neuro-degenerative disorders like Parkinson disease. Hematopoietic stem cell transplantation (HSCT) is the oldest and most widely used technique of stem cell transplant. HSCT has not only been used to treat hematological disorders including hematological malignancies, but has also been found useful in treamtent of genetic, immunological, and solid tumors like neuroblastoma, lymphoma, and germ cell tumors. In spite of the rapid advances in stem cell technology, success rate with this technique has not been universal and many complications have also been seen with this form of therapy. The key to a successful HSCT therapy lies in early diagnosis and effective management of complications associated with this treatment. Our article aims to review the role of imaging in diagnosis and management of stem cell transplant complications associated with HSCT.

Key words: Complications; hematopoietic stem cell; imaging; intervention; radiology; stem cell

Stem Cell Types: Definitions and Classification

Stem cells are undifferentiated biological cells that can differentiate into specialized cells and can undergo mitosis to produce more stem cells. A stem cell is characterized by two essential properties: Power of self-renewal through infinite cycles of cell divisions and capacity to differentiate into specialized cells (also called as potency). While all stem cells have a capacity of self-renewal, not all stem cells are equal in terms of potency. Several lineages of stem cells can be found. The embryonic and adult stem cells are totipotent or omnipotent, allowing them to give rise to any mature cell type. This latter property implies that an entire organism can be constructed from these embryonic stem cells. Multipotent cells can differentiate into a number of cell types, but these are closely related family of cells. Oligopotent cells are further limited to differentiate into only a few cell types (e.g. lymphoid or myeloid cells), whereas unipotent cells can only produce one cell line. It is important to note that the property of self-renewal in stem cells is unlimited. This differentiates them from other non-stem cells like progenitor cells that have a limited capacity of self-renewal. Also, while the stem cells maintain the power of self-renewal, non-stem cells can divide only a limited number of times and are "committed" to differentiate into their respective "target cells."

Access this article online	
Quick Response Code:	Website: www.ijri.org
	DOI: 10.4103/0971-3026.143895

Based on their source, stem cells can be classified into two broad categories: Embryonic stem cells, found in the inner mass of the blastocyst, and adult stem cells, found in various mammalian tissues. Figure 1 presents a simplified representation of the stem cells and their lineages in the body.

Stem Cell Transplant: Current Status and Applications

Autologous or allogeneic hematopoietic stem cell transplantation (HSCT) is now a routine procedure and has

been successfully used for treatment of various hematological conditions such as lymphoma, multiple myeloma, leukemia, anemias, and solid tumors like neuroblastoma and germ cell tumors. Also, selected autoimmune conditions like systemic lupus erythematosus have also been treated using stem cells. According to estimates, more than 50,000 autologous or allogenic transplantation procedures are performed every year worldwide.[1]

Continued research in this area has now made it possible to produce a stem cell from almost any other human cell instead of using embryos.[2] This has alleviated some of the ethical concerns and has created more opportunities in the use of stem cells for tissue repair and regeneration.

Recently, stem cells have been successfully used in treatment of non-hematological conditions in humans with successful cartilage regeneration in human knee using autologous adult mesenchymal stem cells.[3] Subsequently, promising results in a human clinical trial in treating type 1 diabetes mellitus has been shown using cord blood-derived multipotent stem cells (CB-SCs).[4]

Complications in HSCT: Basic concepts

A clear understanding of the stem cell immunophysiology is imperative before attempting to study the complications associated with HSCT. The HSCT therapy is intended to completely or partially replace the recipient's existing diseased hematopoietic system. This process necessitates ablation of the recipient's bone marrow and tumor cells, which usually entails use of high-dose chemotherapy and/or total body irradiation. After this "conditioning regimen," stem cells are transfused to restore and repopulate the patient's marrow.

Transplantation of stem cells has been associated with a myriad of systemic complications ranging from infection, graft versus host disease (GVHD), and neoplasia, predominantly due to the immunosuppression associated with stem cell transplantation. These complications follow a predictable pattern in that recipients of allogenic transplant are at risk for developing GVHD and those receiving autologous transplant, though not at risk of GVHD, have more chances of developing infections or relapse of the disease.

After HSCT, the prognosis of the patient (or development of complications) depends on several factors. From the preceding discussion, it is apparent that the type of transplantation, whether allogenic, autologous, or syngeneic, plays a vital role. The potency of the conditioning regimen is another important prognostic factor, wherein it determines how much residual disease is present at the time of transplantation. Other factors include patient's age and the underlying disease condition. In general, prognosis is poorer in adults, those with autologous transplant, and in whom residual disease was present.[5]

Imaging of stem cell transplant complications

Complications can manifest in almost all organ systems of the body and follow a predictable temporal sequence that mirrors the periods of immunosuppression and recovery following transplantation. In general, there are three phases following transplantation: Pre-engraftment phase (0-30 days post-transplant), early post-transplantation phase (30-100 days post-transplant), and late post-transplant phase (>100 days post-transplant).[6] Figure 2 lists the location, relative frequency, and temporal course of complications following HSCT.

Pulmonary complications

Pulmonary complications are the most frequent of all stem cell transplant complications, occurring in approximately 40-60% patients.[7] These complications are best evaluated using high-resolution computed tomography (HRCT) due to its increased sensitivity and specificity in diagnosis and management of both infectious and non-infectious conditions.[8] However, a pattern-based differential

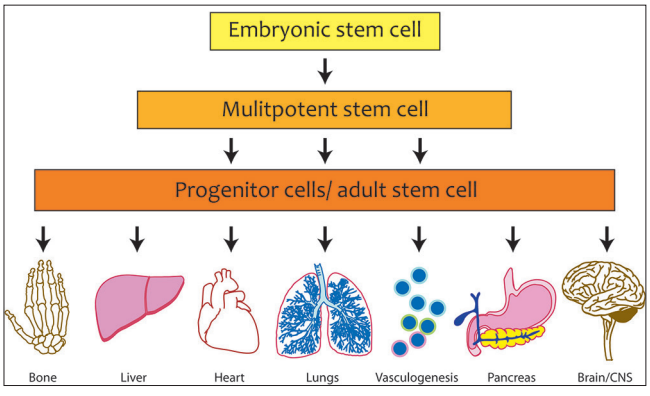

Figure 1: Simplified representation of the stem cells and their lineages in the body

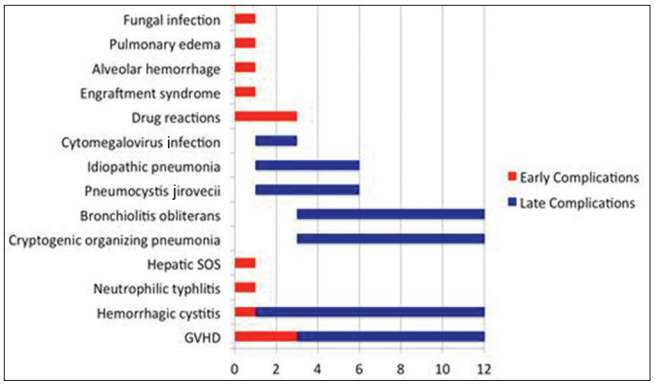

Figure 2: Relative onset and duration of common complications following hematopoietic stem cell transplantation (HSCT). It should be noted that this list is not all inclusive. The *x*-axis plots the timeline since HSCT in months and is divided into early (<1 month) and late (>3 months) phases. Note that a few complications can span both groups

diagnosis is possible based only on chest radiograph findings [Figure 3].

Early complications

Pre-engraftment phase

A variety of complications can occur in the early pre-engraftment phase. Early recognition and prompt treatment is important to prevent morbidity and mortality. However, it should be noted that imaging findings are not specific in many cases, and in the majority of cases, empiric treatment is started based on clinical suspicion. For example, bacterial infection, drug toxicity, and diffuse pulmonary hemorrhage may manifest as consolidation and air-space opacities. In this situation, the role of imaging is twofold. Early detection of the abnormality on CT or radiographs may show abnormality when the clinical abnormalities are nonspecific. The other application of imaging is differentiation of fungal infections from other complications. Most fungal infections produce nodular infiltrates, nodules, or masses. While not definitive, this finding can help in directing appropriate treatment. Developing a pattern approach and knowledge of timeline of complications is most helpful in such situations [Figures 2 and 3].

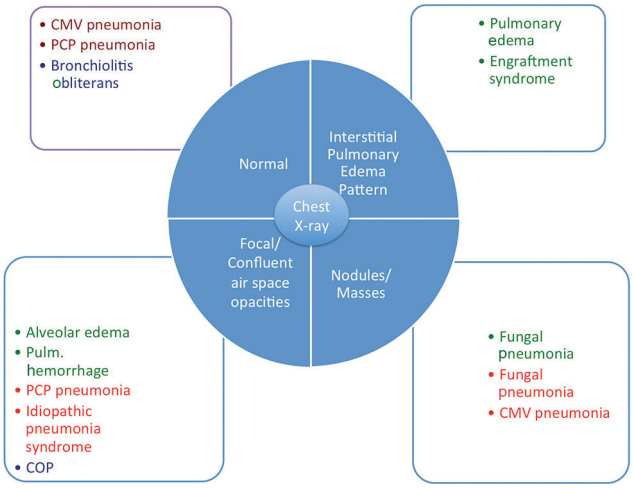

Figure 3: A simplified pattern radiographic approach to evaluate most commonly occurring pulmonary complications on chest radiographs following hematopoietic stem cell transplantation. Within each pattern, the conditions are color coded based on the most likely time of occurrence (green = neutropenic phase, <3 weeks; red = early phase, 3 weeks to 3 months; and blue = late phase, >3 months)

Lung infections

These mostly occur later in the course of the transplant, but are not infrequent early on; approximately 35% of HSCT cases present with lung infection. Overall, there is a trend for non-infectious versus infectious complications, given the widespread use of antibiotics. However, in the pre-engraftment phase, both infectious and non-infectious complications can occur with equal frequency. Fungal infections manifest more often because most patients who are febrile receive empiric antibiotics for assumed bacterial infections, giving mostly negative cultures.[6,9] As much as 50% of all pulmonary infections in the allogenic stem cell transplant setting are fungal in origin.

Fungal pneumonia

Aspergillus fumigatus is the most common fungal agent seen in the setting of HSCT. It is most commonly seen in the early pre-engraftment phase, but can also occur in the post-engraftment and late phases [Figure 4]. Others including *Candida albicans*, *Fusarium*, Zygomycosis (*Mucor* and *Rhizopus*), *Nocardia*, and *Cryptococcus* are less common. The risk factors, prevalence, and key radiological findings of these fungal infections are summarized in Table 1.

Pulmonary edema

This is not uncommon in a post-transplant setting.

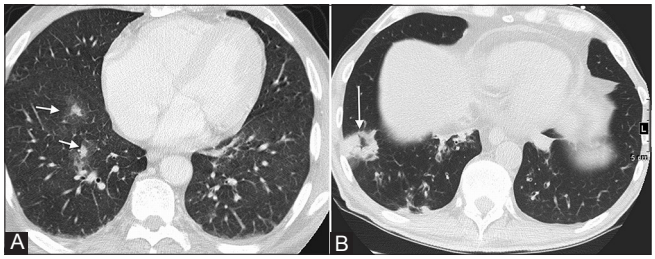

Figure 4 (A and B): *Aspergillus* pneumonia after allogenic transplant on chest CT scan. (A) Classic but nonspecific "halo sign," with nodules surrounded by ground-glass opacity (arrows) (B) Another patient with aspergillus pneumonia post allogenic transplant, demonstrating a cavitary nodule (arrow). [Window Width 1500 HU, Window Level -600 HU]

Table 1: Summary of different fungal infections of the lungs encountered in patients with hematopoietic stem cell transplantation

	Aspergillus	*Candida*	*Zygomycosis*	*Cryptococcus*
Risk factor	Neutropenia, steroid treatment for GVHD	Indwelling venous catheter	Increased use of triazole antifungals for *Asperillus* infections	Neutropenia, steroid treatment for GVHD
Prevalence	10-15%	11%	1-2%	Not known
Radiological findings	Multiple masses, nodules, or air-space opacities; upper lobe; halo sign; tracheobronchial disease	Multiple poorly defined or miliary nodules; halo sign	Angio-invasive disease similar to *Aspergillus*; lung infarction; halo sign; cavitation	Solitary or multiple nodules; cavitation
Course of disease/prognosis	Cavitation, air crescent indicates good prognosis	Rapid-onset clinical disease	Includes *Mucor* and *Rhizopus*; high mortality (80%)	Can be associated with neurological symptoms

GVHD=Graft versus host disease

Other than the routine hydrostatic, cardiac, and renal conditions leading to pulmonary edema, some unique causes relate to drug-induced toxicity, sepsis, transfusion, and intravenous (IV) fluid overload. Pulmonary edema is typically diagnosed based on clinical findings and confirmed radiographically. Engraftment syndrome can be confused with pulmonary edema. This condition is characterized by fever, erythematous rash, and non-cardiogenic pulmonary edema, and usually occurs at the time of neutrophil recovery.[10] Imaging may be normal or show nonspecific findings like ground-glass opacities, hilar/peribronchial air-space consolidations, septal thickening, and effusions that can mimic pulmonary edema, infections, or GVHD.[11]

Diffuse alveolar hemorrhage

Diffuse alveolar hemorrhage (DAH) is a relatively rare complication seen in approximately 2-20% cases. Though rare, it can be life-threatening. Prompt diagnosis and treatment with steroids has shown favorable outcome; hence, awareness of clinical and radiological findings is helpful. In spite of alveolar hemorrhage, gross hemoptysis is rare. The majority of patients with DAH present with tachypnea and dyspnea. It can rapidly progress usually within the first 2 weeks of HSCT. Radiographic findings may precede the development of symptoms by several days, but show nonspecific patchy alveolar infiltrates that become more confluent and show central, mid, and lower lung zone predominance. Diagnosis is established on bronchoalveolar lavage that shows progressive bloodier aliquots of lavage fluid.

Treatment-related toxicity

Lung injury can also result from total body irradiation or chemotherapy with lung toxicity (Carmustine/methotrexate) in the immediate post-transplant period. Chemotherapy and radiation have synergistic risk of producing lung damage.[12] Both imaging and biopsy findings are nonspecific. Imaging may show a pattern similar to acute respiratory distress syndrome (ARDS), hypersensitivity pneumonitis, and organizing pneumonia.[13] Biopsy may show diffuse alveolar damage, histological equivalent of ARDS, type II alveolar epithelial cell atypia and hyperplasia, interstitial pneumonitis, and fibrosis. It is a diagnosis of exclusion.

Early post-transplant phase complications (days 31-100)

Pneumonia remains the most common complication in this period, though less common compared to the pre-engraftment phase. This is due to gradual resolution of severe neutropenia by day 100. Effects of induction chemotherapy and radiation also show healing response during this period. However, due to several factors like T-cell dysfunction, hypogammaglobulinemia, diminished phagocyte function, acute GVHD, and use of immunosuppressant to manage the GVHD, the patient becomes susceptible to multiple infections. Acute GVHD and idiopathic pneumonia are the other non-infectious complications in this period.

Lung infection

Overall, viral [cytomegalovirus (CMV), adenovirus] and fungal infections (*Pneumocystis jiroveci*, *Aspergillus*) are more common than bacterial infections. Due to effective prophylaxis, *P. jiroveci* is rare. Among the bacterial infections, *Staphylococcus* may be seen in patients with indwelling central line. The patients are also prone to infections with encapsulated bacteria like *Streptococcus pneumonia* and *Haemophilus influenzae*.[14]

CMV infection

Most CMV infections result from reactivation of the latent virus in seropositive recipients from the peripheral blood leukocytes or as primary infection from a seropositive donor. CMV infection not only manifests as pneumonia but can also cause hepatitis and colitis. CMV pneumonia carries 15-20% mortality with a high case-fatality rate of 80-90%. Chest radiographs may be normal, but typically show patchy areas of ground glass or consolidation. HRCT may show ground-glass opacities, air-space consolidations, or small (<5 mm) centrilobular nodules[15] [Figure 5]. Other respiratory and enteric viruses (respiratory syncytial virus, RSV and adenovirus) may either produce no radiological findings or may show diffuse ground-glass opacities.

P. jiroveci

It is rare in patients who receive prophylaxis. Chest radiographs can be normal early on or show reticulonodular infiltrates that progress to air-space consolidations. In cases when radiographs are negative, HRCT may show the characteristic ground-glass opacities and/or consolidations, either diffuse or perihilar in distribution. Sparing of the secondary pulmonary lobules has been described on HRCT[16] [Figure 6]. Other features include focal opacities, cavitations/pneumatoceles, or air cysts.

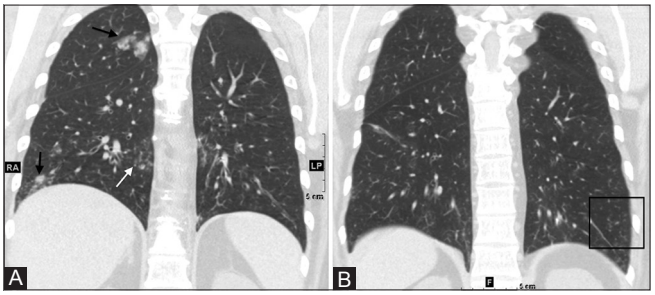

Figure 5 (A and B): CMV pneumonia after allogenic transplant. (A) Coronal CT image shows the nonspecific halo sign (nodules surrounded by ground-glass opacity) as well as centrilobular nodules (arrows) (B) Coronal CT image from another patient demonstrates scattered basilar predominant centrilobular nodules (black box). [Window Width 1500 HU, Window Level -600 HU]

Idiopathic pneumonia syndrome

It is the most common cause of diffuse radiographic abnormalities between 30 and 180 days after transplantation.[17] Idiopathic pneumonia syndrome (IPS) is a group of disorders that show common pathological findings of interstitial pneumonitis and/or diffuse alveolar damage. To make a diagnosis of IPS, two main criteria should be fulfilled. There should be widespread alveolar injury and absence of lower respiratory tract infection.[18]

- Widespread alveolar injury: It is defined as signs and symptoms of pneumonia , multilobar opacities on chest radiograph or CT scan, and evidence of abnormal pulmonary physiology manifested by an increased alveolar-arterial oxygen gradient or the need for supplemental oxygen
- Absence of lower respiratory tract infection, as determined by a negative bronchoalveolar lavage or lung biopsy, ideally followed by a second negative invasive test within 2 weeks.

The etiopathogenesis of IPS is not known, but studies have found an association between increasing incidence of IPS and aggressive preparative chemotherapy and radiation regimen before stem cell transplantation.[19] There is no optimal therapy for IPS. High-dose glucocorticoids have been tried, but overall prognosis is poor with 70-85% mortality.

Radiologically, nonspecific bilateral air-space opacities and consoildations with basilar predominance are seen, similar to non-cardiogenic pulmonary edema.

Late complications

Late post-transplant phase (>100 days after transplant)

This period is characterized by the recovery of host cell mediated and humoral immunity. The main complication during this phase is chronic GVHD, which is a reaction of donor T cells and natural killer (NK) cells to host antigens, treating them as foreign. While rare in autologous HSCT, it can be seen in 40-80% cases of allogenic transplants. Ironically, it needs immunosuppressive medications for both prophylaxis and treatment, halting the recovery of the host immunity. Hence, this phase continues until the stem cell recipient stops all immunosuppressive medications for GVHD, which is approximately 18-36 months post-transplantation. Radiologically, chronic GVHD manifests as bronchiolitis obliterans (BO) and cryptogenic organizing pneumonia.

Figure 6: *Pneumocystis jiroveci* 2 months post stem cell transplant. Axial CT images demonstrate areas of ground-glass opacities (black arrows) with sparing of secondary lobules (white arrows). [Window Width 1500 HU, Window Level -600 HU]

Lung infections

If it were not for the chronic GVHD, infection is unusual in this period. Most infections are localized to the skin, the upper respiratory tract, and the lungs due to loss of skin and mucosal barriers. Viral infections, especially secondary to varicella zoster virus (VZV), are responsible for more than 40% of infections during this phase, bacteria are responsible for approximately 33%, and fungi cause approximately 20% infections.[14] The infections have similar radiological manifestations as discussed previously.

Bronchiolitis obliterans

While mild airflow obstruction and decrements in lung function are common following HSCT, moderate-to-severe airflow obstruction indicates the presence of BO. It has a strong association with chronic GVHD.[20] It can mimic infection and cryptogenic organizing pneumonia during this period; however, absence of fever and lung abnormalities on chest radiographs helps in distinguishing these conditions. The diagnosis of BO is established on pulmonary function tests showing reduced forced expiratory volume in 1 sec (FEV1). HRCT shows expiratory air trapping, mosaic attenuation, and bronchiolectasis. The airflow obstruction is non-reversible and is characterized by intraluminal fibrosis on histology [Figure 7].

Cryptogenic organizing pneumonia

Also called as bronchiolitis obliterans organizing pneumonia or BOOP, it can be due to various causes in post-HSCT setting. Apart from chronic GVHD, it may be related to lung irradiation, following CMV pneumonitis, or may be idiopathic.[21] Histologically, it is characterized by polypoid granulation tissue in the lumina of bronchioles and alveolar ducts, associated with a variable amount of interstitial and air-space mononuclear cell infiltration. HRCT may show bilateral, peripheral, and basilar predominant patchy air-space consolidation, randomly distributed ground-glass opacities, and bronchial wall thickening with dilatation, also described as the open bronchus sign [Figure 8].

Hepatic complications

Acute GVHD of the liver, drug-induced hepatotoxicity, and viral hepatitis are the top three causes of liver disease in HSCT patients. Other notable complications include hepatic sinusoidal obstruction syndrome (SOS) and liver infections.[22]

Acute GVHD of the liver

This is the most common hepatic complication following HSCT. Liver involvement is rarely in isolation, and

is frequently seen with cutaneous and/or acute gastrointestinal (GI) GVHD. Hepatic involvement manifests by rising conjugated bilirubin and alkaline phosphatase that are nonspecific and can be seen in hepatic SOS, viral hepatitis, and drug toxicity. Presence of a rash concurrent with the liver function abnormalities is suggestive of the diagnosis, but liver biopsy is required for confirming damage to the bile canaliculi (bile duct atypia and degeneration, epithelial cell dropout, lymphocytic infiltration of small bile ducts). Imaging findings are not sensitive or specific, but may show temporary dilatation and fluctuation in size of the common bile duct correlating with serum bilirubin concentration.[23]

Liver infections

Viral hepatitis

The impaired cellular immunity post-HSCT can lead to reactivation of latent hepatitis B virus (HBV) that can result in fulminant hepatic failure. This warrants HBV vaccination to those patients who are hepatitis B surface antigen (HBsAg) negative and prophylactic antiviral therapy for those who are HBsAg positive. Unlike HBV, infection with hepatitis C virus (HCV) does not result in acute or fulminant disease. However, in the long term, it is a risk factor for hepatic veno-occlusive disease and GVHD. Imaging does not have much role to play in the diagnosis and management of viral hepatitis other than ruling out other confounding complications like infection or SOS.

Liver abscess

These can be bacterial or fungal in origin. Amongst the fungal infections, hepatosplenic candidiasis is very common. Imaging appearance of fungal infection varies according to the stages of its evolution and presence or absence of neutropenia. During the active phase, the lesion is predominantly hypoechoic on (US) with or without characteristic halo, bull's eye, or wagon wheel appearance. The lesion becomes echogenic in the late phase. On CT and magnetic resonance imaging (MRI), similar phases have been described[24,25] [Figure 9]. It is important to note that fungal lesions may not be visible until the patient recovers from the neutropenic stage. As neutropenia improves, the host mounts a response against the infection, imparting the characteristic halo and enhancement that makes them conspicuous. In a setting of neutropenia, MRI may be more sensitive than CT or US in detecting fungal micro-abscesses, given its increased contrast resolution. In cases when the initial scan is negative and there is a strong clinical suspicion for fungal infection, repeat imaging in 2 weeks may be performed.

Hepatic SOS

This was earlier called hepatic veno-occlusive disease and clinically even mimics Budd-Chiari syndrome. However, it is now known to result from endothelial damage to the hepatic sinusoids causing fibrosis and occlusion of the hepatic outflow. The hepatic veins and inferior vena cava remain patent.[26] SOS is not unique to HSCT and can be induced by the ingestion of pyrrolizidine alkaloids, like herbal tea, high-dose (>30 Gy) radiation therapy to the liver, radio-embolization of liver tumors, and after liver transplantation. It has a prevalence of 14% (5-60%) post-HSCT. No single factor is implicated in its causation. Pre-existing liver disease, aggressive conditioning therapy, young age, and poor baseline performance status of the host are the risk factors for SOS.[27] Diagnostic criteria have been defined that rely on the clinical findings and lab abnormalities. According to

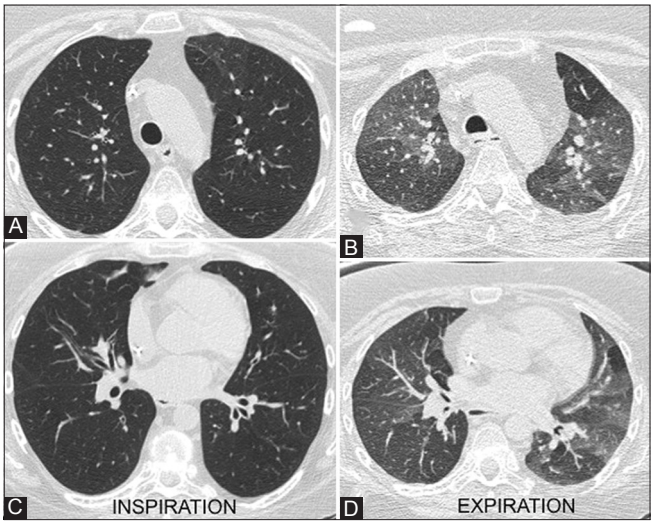

Figure 7 (A-D): Bronchiolitis obliterans 4 months post stem cell transplant. Inspiration and expiration axial CT images at two representative levels demonstrate areas of air trapping (A-D). [Window Width 1500 HU, Window Level -600 HU]

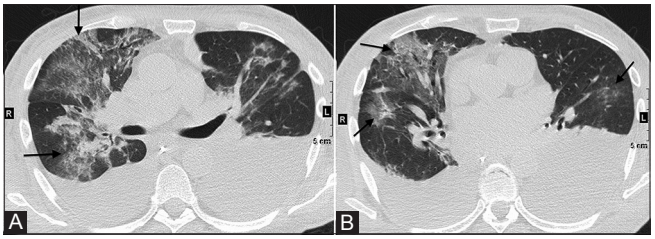

Figure 8 (A and B): Cryptogenic organizing pneumonia 6 months post-transplant. (A and B) Axial CT images demonstrate patchy areas of focal consolidation and ground-glass opacities (arrows). [Window Width 1500 HU, Window Level -600 HU]

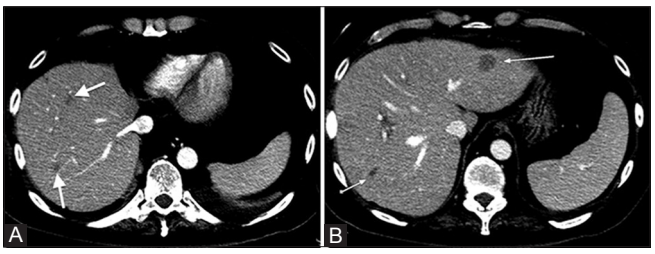

Figure 9 (A and B): Hepatic fungal micro-abscesses 2 months post-transplantation. (A and B) Contrast-enhanced axial CT images demonstrate low attenuation lesions within the liver (arrows)

the modified Seattle criteria, hepatic SOS is diagnosed by occurrence of two or more of the following events within 20 days of HCT: [28]

- Serum total bilirubin >2 mg/dl
- Hepatomegaly or right upper quadrant pain
- Sudden weight gain >2% of baseline body weight (due to fluid accumulation).

US imaging is sensitive in detecting ascites, hepatosplenomegaly, portal vein enlargement, marked gallbladder wall edema, and abnormal Doppler parameters (portal venous pulsatility, hepatofugal portal venous flow, increased hepatic artery resistive index >0.8, and loss of triphasic flow pattern in the hepatic veins) [Figure 10]. However, US findings are nonspecific and similar findings can be seen in patients with absence of SOS. Studies have shown that no US finding is strongly associated with veno-occlusive disease (VOD).[29] Imaging may help in differential diagnosis. For example, the clinical findings of SOS are indistinguishable from those of acute Budd-Chiari syndrome. Doppler ultrasound, CT, or MRI can noninvasively show the thrombosis of hepatic veins and/or intrahepatic or suprahepatic vena cava, differentiating it from SOS where the hepatic venous outflow obstruction is at the level of the sinusoids and terminal hepatic venules. This distinction may be critical as untreated SOS is associated with significant mortality and morbidity. Unlike Budd-Chiari syndrome, anticoagulation with heparin has not proved to be beneficial. Most patients are treated symptomatically with sodium and fluid restriction along with diuretic therapy. Similarly, imaging can be useful to distinguish SOS from hepatic GVHD, another potential mimic in this setting. CT findings of periportal edema, ascites, and narrowed right hepatic vein have been shown to be associated with SOS more than GVHD.[30] It is important to note that this distinction is not entirely reliable and final diagnosis may require biopsy. Table 2 summarizes the salient features of hepatic SOS, GVHD, and Budd-Chiari syndrome.

Bowel complications

Several bowel complications can be seen in the post-HSCT setting like CMV enterocolitis, *Clostridium difficile* infection, or chemoradiation toxicity. However, by far, acute GVHD is the most common complication.

GI tract GVHD

GI tract is one of the most commonly affected target sites of acute GVHD (74%), the other sites being the skin (70%) and liver (44%).[31] GVHD is classified based on clinical features and timing of presentation. The acute and chronic forms of the disease have mutually exclusive features forming opposite ends of the spectrum with an intermediate form having features of both acute and chronic GVHD. Clinically, acute GVHD presents with a maculopapular rash, symptoms of GI upset like nausea, vomiting, diarrhea, and a rising serum bilirubin concentration. In contrast, patients with chronic GVHD commonly demonstrate skin involvement

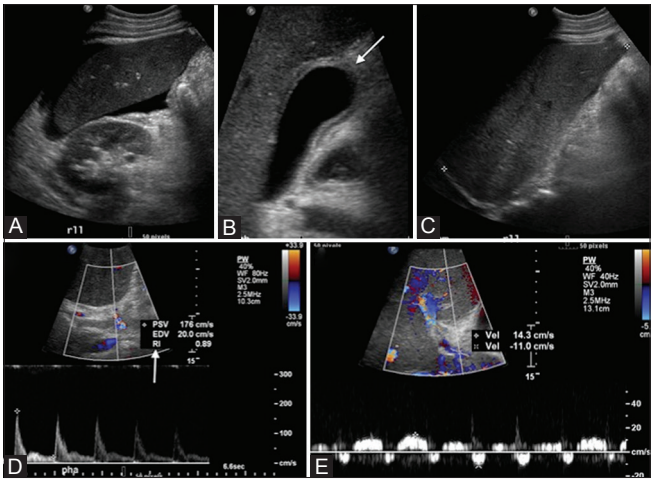

Figure 10 (A-E): Classic findings of hepatic veno-occlusive disease, day 18 post stem cell transplant: (A) perihepatic ascites (B) gallbladder wall thickening (arrow) (C) hepatomegaly (D) hepatic artery with increased resistive index (RI = 0.86) (arrow) (E) pulsatile and bidirectional portal vein flow

Table 2: Summary of salient liver complications after hematopoietic stem cell transplant

	Sinusoidal obstruction syndrome	Budd-Chiari syndrome	Acute GVHD
Risk factors/ etiology	Endothelial injury is the result of conditioning regimen in stem cell transplant	Polycythemia, pregnancy, post-partum, oral contraceptives, HCC	Allogenic stem cell transplant
Pathology	Endothelial damage to the hepatic sinusoids causing fibrosis/occlusion of the hepatic outflow	Intraluminal or extraluminal obstruction of hepatic veins due to thrombus or extrinsic compression	Damage to bile canaliculi with degeneration and lymphocytic infiltration
Clinical features	Weight gain, tender hepatomegaly, increased bilirubin, ascites	Pain, jaundice, hepatomegaly, ascites, liver dysfunction	Rash Liver function abnormal, elevated bilirubin and alkaline phosphatase Associated GI and skin findings
Imaging	US: Ascites, hepatosplenomegaly, PV enlargement, gallbladder wall edema, abnormal Doppler parameters	Thrombus will differentiate from SOS Ascites, hepatosplenomegaly, decreased/absent hepatic vein flow	Temporary fluctuation in size of CBD correlating with changes in serum bilirubin
Treatment	Sodium/fluid restriction, diuretics Anticoagulation of no use	Sodium/fluid restriction, diuretics, anticoagulation Severe cases can be shunted	Steroids

GVHD: Graft versus host disease, SOS: Sinusoidal obstruction syndrome, CBD: Common bile duct, PV: Portal vein, US: Ultrasonography, HCC: Hepatocellular cancer

resembling lichen planus or the cutaneous manifestations of scleroderma; dry oral mucosa with ulcerations and sclerosis of the GI tract. Radiological findings are not diagnostic of GVHD. Upper GI tract involvement is best evaluated on endoscopy and biopsy of the involved mucosa showing mucosal erythema, denudation, and aphthous ulcers. An important caveat is that visually normal mucosa does not rule out GVHD. Hence, histological evaluation is necessary. Lower GI involvement can also be easily established on rectal biopsy with high sensitivity.[32] For noninvasive evaluation of bowel involvement, contrast-enhanced CT with negative oral contrast (water) should be performed to show mucosal hyperemia and "halo sign" [Figure 11]. Fluid-distended bowel loops with thickened walls may be seen. However, these findings are nonspecific and may be seen with infectious enterocolitis, radiation enteritis, and drug-induced or neutropenic collitis (typhlitis).

Other GI complications

Other infectious and non-infectious complications can mimic GVHD. Some CT findings may be helpful in differentiation of these entities. For example, neutropenic enterocolitis commonly involves the ascending colon, especially cecum. There is a higher incidence of pneumatosis, mesenteric stranding, and ascites with neutropenic colitis, compared to acute GVHD. Bowel mucosal enhancement and dilatation are more common in GVHD. Both CMV and *C. difficile* colitis can present with pancolitis with marked colonic wall thickening and nodularity [Figures 12 and 13]. Hence, selective staining of such pathogens should be performed on the biopsy specimens. Occasionally, pneumatosis intestinalis may be seen as air outlining the bowel wall. In many cases, it is benign due to mucosal defects from steroid-induced hypertrophy of the Peyer's patches. The appearance can be dramatic with extensive mesenteric, portal venous gas and frank pneumoperitoneum. This "benign pneumatosis intestinalis" resolves on its own with conservative management; however, it needs to be differentiated from CMV or typhlitis-related pneumatosis where it implies imminent bowel perforation.[33]

Genitourinary complications

Renal functional impairment

It is defined as sustained decrease in glomerular filtration rate below 60 ml/min/1.73 m^2 and can be seen in up to 65% cases in long-term allograft survivors post-HSCT. The etiology of renal functional impairment can be multifactorial, including membranous glomerulopathy and other autoimmune-like diseases of the glomerulus that have been associated with chronic GVHD. No specific imaging findings are seen.

Hemorrhagic cystits

It is a well-known complication of HSCT. It is mostly due to two viruses, adenovirus and BK virus. On CT and US, focal

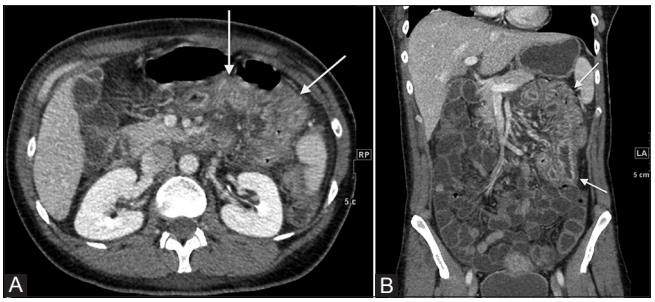

Figure 11 (A and B): Acute GVHD 12 days post allogenic transplant. Axial and coronal contrast-enhanced CT images demonstrate abnormal jejunal wall thickening and mucosal enhancement due to mucositis (arrows)

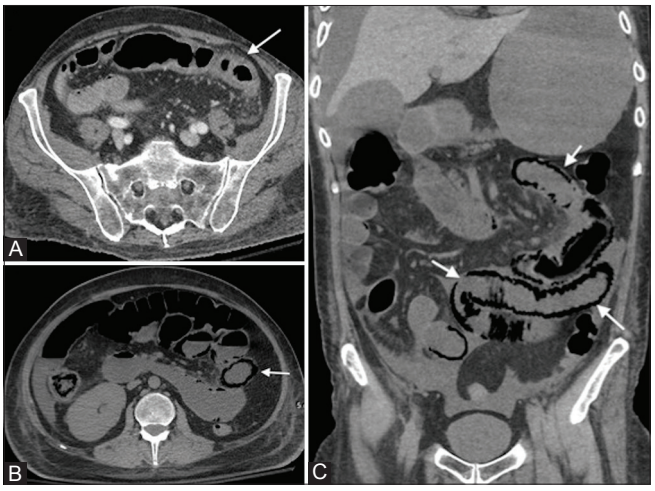

Figure 12 (A-B): CMV enterocolitis in post-transplantation patients. (A) Axial contrast-enhanced CT image through pelvis demonstrates sigmoid wall thickening in a patient with CMV colitis (B and C) Axial and coronal non-contrast CT images in a patient with CMV enteritis demonstrate wall thickening and extensive pneumatosis (arrows); patient expired a few days later

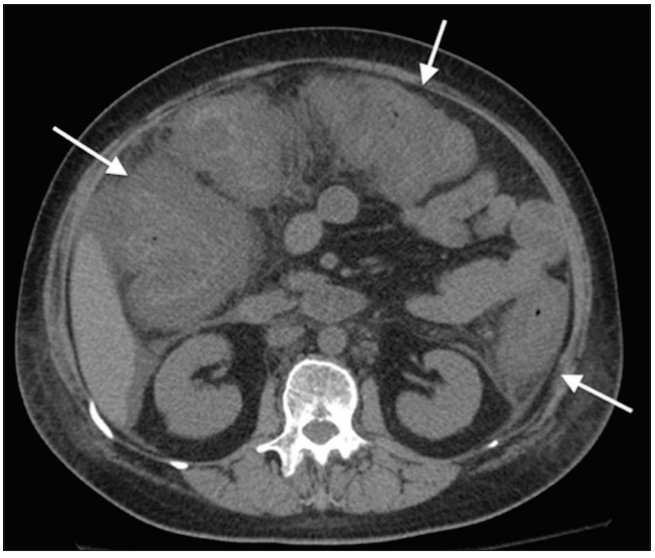

Figure 13: C. *difficile* pancolitis 2 months post-transplantation. Axial contrast-enhanced CT image through the abdomen demonstrates marked colonic wall thickening (arrows)

or diffuse bladder wall thickening may be seen [Figure 14]. There may be intraluminal hematoma or sloughed mucosa.

Two forms of cystitis have been reported. Pre-engraftment cystitis, a milder and transient form, is seen in the first few days of transplantation and responds to supportive therapy, whereas post-engraftment cystitis that occurs 1-2 months following transplantation is protracted, and is associated with severe GVHD and may require surgical intervention.[34]

Renal parenchymal infections

Renal abscesses secondary to bacterial and fungal infections are also common following transplantation. The appearance is similar to infections in other solid organs [Figure 15]. Most infections occur early in the transplant period.

Central nervous system and head-neck complications

CNS infections

Like other systems, the risk of infection and the types of organism that invade the CNS depend on the duration after HSCT and the level of immune impairment. For example, in the early pre-engraftment period, profound neutropenia predisposes to gram-negative bacterial, viral, and fungal pathogens. In the post-engraftment period, CMV, fungal, and gram-positive infections are encountered; in the late post-engraftment period, infections from encapsulated bacteria and herpes zoster virus are common due to impaired humoral immunity. Bacterial infections are rarely manifested due to routine prophylaxis. Amongst the fungal infections, *Mucor* and *Aspergillus* are common, with *Aspergillus* being the overall most common cause of focal infective brain lesion after stem cell transplantation. While bacterial and fungal abscesses are seen as single or multiple focal lesions on CT or MRI, *Mucor* is typically an aggressive infection that occludes vessels and can invade the brain parenchyma [Figure 16]. Herpes also causes an encephalitis pattern, with characteristic temporal lobe involvement.

Other CNS complications

Several other CNS complications can be seen like intra or axial hematomas and infarction that have similar imaging appearance to those seen in the general population. Posterior reversible encephalopathy syndrome (PRES) is a potentially reversible condition thought to result from pre-transplantation conditioning and GVHD prophylaxis. It typically occurs within 1 month of initiation of therapy and is manifested as visual disturbances, cerebellar ataxia, confusion, and seizures. CT and MRI reveal abnormalities in the gray and white matter of occipital, parietal, posterior temporal, and frontal lobes [Figure 17].

Musculoskeletal complications

Osteoporosis and avascular necrosis are the most frequently encountered complications of the musculoskeletal system. Osteoporosis typically occurs early after HSCT, but does show favorable response to bisphosphonate treatment.[35] Avascular necrosis or bone infarction occurs in approximately 5-20% cases following HSCT.[36] The imaging appearance of bone infarction and avascular necrosis is the same as in general population without HSCT. Osteomyelitis is a rare complication following HSCT, but can be lethal and requires aggressive management, frequently with a combination of drugs. Cases of bacterial and fungal osteomyelitis have been reported following HSCT.[37,38]

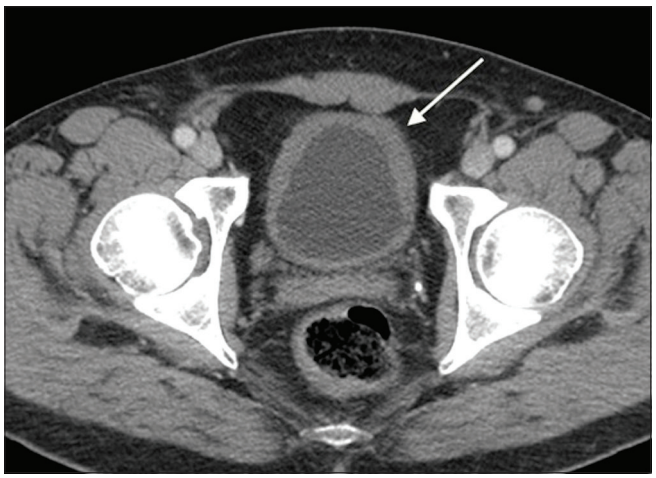

Figure 14: Post-engraftment cystitis in 2 months after transplant. Axial contrast-enhanced CT image demonstrates diffuse urinary bladder wall thickening (arrow)

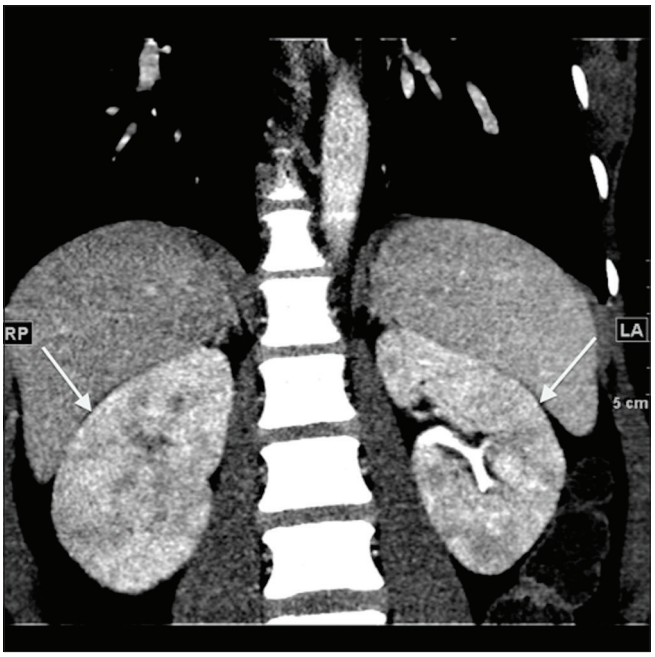

Figure 15: Fungal microabscesses and pyelonephritis 2 weeks after transplant. Coronal contrast-enhanced CT demonstrates bilateral striated nephrogram and discrete small low attenuation foci (arrows)

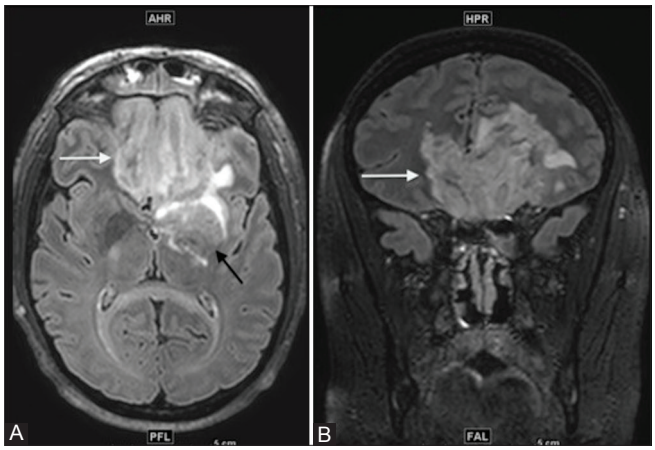

Figure 16 (A and B): Rhinocerebral mucormycosis 2 months post-transplant. (A and B) Axial and coronal T2W FLAIR images demonstrate heterogeneous high signal infiltrative mass involving both inferior frontal lobes (white arrows) and left basal ganglia (black arrow), with adjacent edema

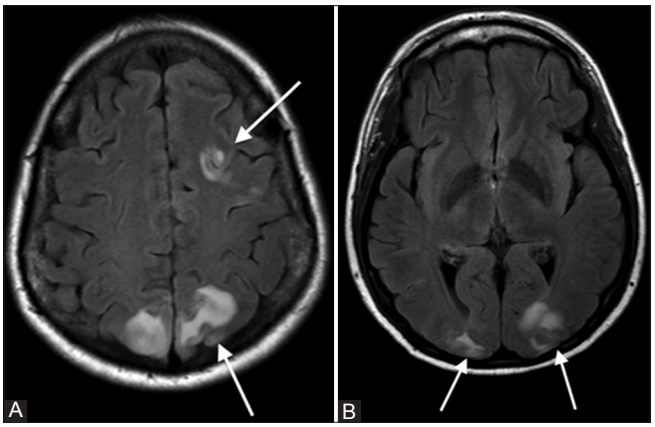

Figure 17 (A and B): Typical findings of posterior reversible encephalopathy syndrome (PRES) 6 weeks after transplantation. (A and B) Axial T2W fluid attenuated inversion recovery (FLAIR) images demonstrate frontoparietal and occipital hyperintensity in the usual distribution of PRES (arrows)

Secondary malignancies

Several secondary malignancies can be seen in patients who have undergone HSCT, occurring at different time periods following transplant. Three different types of malignancies are seen: Solid tumors, hematological malignancies, and post-transplant lymphoproliferative disorder (PTLD). Solid tumors and hematological malignancies typically occur late in the post-transplant course (>3 years), and PTLD usually occurs in the first year after transplantation.[39] This review will focus on PTLD.

Post-transplant lymphoproliferative disease

PTLD is a rare complication of HSCT (prevalance 0.5-1.5%) and in most cases associated with reactivation or primary Epstein-Barr virus (EBV) infection.[40] As stated earlier, most PTLD occurs within the first year post-transpantation, with the risk of development and onset of disease being directly proportional to the degree of immunosupression. Hence, it is not surprising that the lymphoproliferative process may reversed on reduction or withdrawal of immunosupression. This distinguishes PTLD from neoplastic lymphoproliferative disorders in immunocompetent patients. PTLD forms a continum of three lesions: early lesions are non-malignant polyclonal B cell proliferation presenting as infectious mononucleosis-type acute illness, polymorphic PTLD consists of malignant polyclonal or monoclonal lymphoid infiltrates that fall short of all criteria of lymphomas, and monomorphic PTLD consisting of malignant monoclonal lymphoid proliferation meeting all the criteria of B, T, or NK cell lymphomas. PTLD also occurs after solid organ transplantation, but differs from the post-HSCT setting in that it occurs later and is less aggressive.[41] Radiological features include generalized lymphadenopathy and solid organ involvement either diffusely or as focal masses and nodules like pulmonary nodules and liver masses [Figure 18]. Apart from reducing the extent of immunosuppression, it can be managed by using cytotoxic chemotherapy and rituximab. Locoregional treatment like surgery or radiation may also be useful.

Conclusion

Stem cell transplantation is a promising therapy for several chronic degenerative diseases, non-malignant conditions, and malignancies. The traditional approach of stem cell treatment has been the systemic use of hematopoietic stem cells in several hematological conditions like chronic anemias, metabolic conditions, lymphoma, and leukemia. However, such systemic stem cell therapy is limited by several complications in multiple organ systems primarily dependent on the immune status and type of HSCT. Allogenic transplant recipients are at risk for developing GVHD and its related complications, whereas autologous transplant recipients have higher risk of relapse with infections and late transplantation complications being less common. The role of imaging in systemic HSCT is primarily detection and narrowing the differential diagnosis in patients suspected to have post-transplant complications. It is possible to make an accurate diagnosis of HSCT complications on imaging if the radiologist has an understanding of the underlying immune-physiological processes and interprets studies in the light of such information.

Acknowledgement

The authors acknowledge Ms Donna Ashlock for help with Figure 1 in the manuscript.

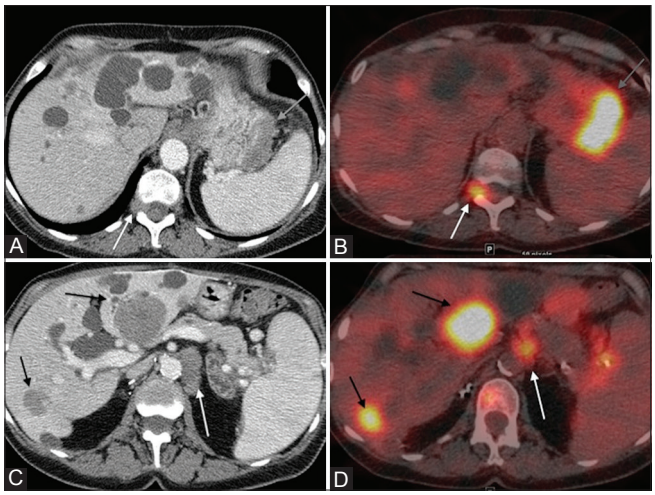

Figure 18 (A-D): Widespread post-transplant lymphoproliferative disorder (PTLD) 4 months post-transplantation. (A and B) Axial contrast-enhanced CT and fluorodeoxyglucose (FDG) positron emission tomography (PET) images demonstrate focal gastric wall involvement (gray arrows) and neural foraminal lesion (white arrows) with abnormal FDG uptake (C and D) Axial contrast-enhanced CT and FDG PET images demonstrate hepatic (black arrows) and nodal disease (white arrows)

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Cite this article as: Pandey T, Maximin S, Bhargava P. Imaging of complications from hematopoietic stem cell transplant. Indian J Radiol Imaging 2014;24:327-38.

Source of Support: Nil, **Conflict of Interest:** None declared.