CT Findings of Pulmonary Complications after Hematopoietic Stem Cell Transplantation

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Abstract

Pulmonary complications are a major concern after hematopoietic stem cell transplantation and are an important cause of morbidity and mortality. This pictorial essay reviews and illustrates the CT imaging findings of pulmonary complications after HSCT as a function of time of onset after transplantation.

ABBREVIATIONS

HSCT: Hematopoietic Stem Cell Transplantation; GVHD: Graft-Versus-Host-Disease; DAH: Diffuse Alveolar Hemorrhage; ARDS: Acute Respiratory Distress Syndrome; RSV: Respiratory Syncytial Virus; CMV: Cytomegalovirus; HLA: Human Leucocyte Antigen; PCR: Polymerase Chain Reaction; IPS: Idiopathic Pneumonia Syndrome; OP: Organizing Pneumonia; BOOP: Bronchiolitis Obliterans Organizing Pneumonia; COP: Cryptogenic Organizing Pneumonia; PTLD: Post-Transplant Lymphoproliferative Disorder; EBV: Epstein-Barr Virus; PVOD: Pulmonary Veno-Occlusive Disease

INTRODUCTION

HSCT has been used to consolidate standard chemotherapy treatment of malignancies, mainly hematologic malignancies, which include lymphoma, leukemia, myelodysplastic syndrome and multiple myeloma. In minor cases, it’s also a therapeutic option for solid organ malignancies, non-malignant diseases (sickle cell anemia for example) or congenital disorders, in which hematologic and immunological competence is depressed or absent [1-3].

More recently, it’s also been used as a treatment for immunologic disorders, including multiple sclerosis, systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis and juvenile idiopathic arthritis [4].

There are different types of HSCT, using cells from bone marrow, peripheral blood or umbilical cord blood. These cells can be from the patient him- or herself (autologous), from a nonidentical sibling or unrelated individual with a similar human leukocyte antigen-type (allogeneic) or from an identical twin (syngeneic).

After autologous and syngeneic transplantation, patients are less likely to develop GVHD and therefore they have a lower morbidity and mortality in comparison with patients after allogeneic transplantation. However, there’s a higher relapse rate after autologous and syngeneic transplantation because of the lack of graft versus tumor effect [1].

There are three phases in the process of HSCT: (1) the conditioning of the patient, (2) the infusion of hematopoietic stem cells in the patient, and (3) the engraftment. The conditioning of the patient involves treatment with high-dose chemotherapy, usually combined with total body irradiation, to ablate the bone marrow, destroy the malignant cells and to induce immunosuppression to prevent rejection of the donor stem cells in case of allogeneic HSCT [2,5,6].

The engraftment involves the recovery of the neutrophil count and platelet count, which typically occurs three weeks after HSCT [2,5].

However, it takes up to one year before the patient’s immune system is totally recovered [7].

Pulmonary complications occur in 40 to 60% of the patients and contribute to more than 30% of deaths after HSCT [3,6,7].

In general, pulmonary complications can be classified, depending on time of onset after HSCT and so reflecting the immunological status of the patient: (1) the pre-engraftment phase, (2) the early posttransplant phase, and (3) the late phase (Table 1) [3,7,8].

Infectious pulmonary complications are nowadays less common because of the use of broad-spectrum antimicrobial agents for prophylaxis and treatment. However, nowadays, noninfectious complications were a major cause of morbidity and mortality. Infectious complications are more common after allogenic HSCT because of the posttransplant immunosuppressive therapy to prevent or treat GVHD. Noninfectious complications occur with a similar frequency after allogeneic and autologous HSCT [6].

The purpose of this review is to give an overview of the CT imaging findings associated with pulmonary complications after HSCT as a function of time of onset after transplantation.

**Pre-Engraftment Phase**

The pre-engraftment phase, lasting up to 30 days after transplantation, is predominantly characterized by a profound neutropenia and damage to the mucosal membranes, which predispose the patient to bacterial and fungal infections [9].

Non-infectious complications consist of pulmonary edema, drug toxicity, diffuse alveolar damage (DAH) and engraftment syndrome.

**Infections**

Bacteremias are common but because of the use of empiric broad-spectrum antimicrobial agents, bacterial pneumonia is not often seen.

Fungal infections are a common cause of pneumonia, with an incidence of up to 70%. The most common pathogen is Aspergillus, found in about 10% of patients [3,7].

The typical CT finding of an angio-invasive aspergillosis is a nodule surrounded by a halo of ground glass. This is known as the 'CT halo sign' and represents hemorrhage around central infarction caused by the fungal infection. Cavitation of the nodule (‘air-crescent sign’) can be seen in the recovery phase of the infection, when also the neutrophil count is recovering (Figure 1, 2 A/B) [3,8].

In other cases, aspergillus invades the airway and CT findings are peribronchial or peribronchiolar consolidations or centrilobular nodules less than 5 mm in diameter [3,8].

**Pulmonary edema**

Pulmonary edema is a common complication and maybe caused...
by capillary membrane leakage secondary to chemotherapy, radiotherapy and septicemia. It also may be due to infusion of large volumes of fluid, in combination with the cardiotoxic and nephrotoxic effects of chemotherapy and radiotherapy. CT findings are diffuse ground-glass attenuation, interlobular septal thickening, prominent pulmonary vessels and pleural effusion (Figure 3A/B) [3,8].

**Drug toxicity**

Drug toxicity is most commonly related to treatment with chemotherapeutical drugs such as bleomycin, busulfan, bischloronitrosourea and methotrexate, and is seen approximately in 10% of patients after autologous or allogeneic HSCT. Concomitant radiotherapy increases the risk of pulmonary injury with an incidence up to 30% [7,8,10].

Patients usually present with dyspnea and a nonproductive cough with or without fever [11].

CT findings are nonspecific and there is a wide range of radiological patterns. The most common are diffuse alveolar damage, hypersensitivity pneumonitis and organizing pneumonia. CT findings include ground-glass attenuation, a reticular pattern with intra- and interlobular septal thickening ('crazy paving' pattern), centrilobular nodules and consolidation [6,10].

**Diffuse alveolar hemorrhage**

DAH is a life-threatening complication with a reported mortality of 50-100% despite treatment [6,12,13]. It’s caused by injury to the alveolar microcirculation [13] and is diagnosed in 5% to 20% of patients after HSCT [3,5,6,12].

Clinically, patients typically present with cough and dyspnea, with or without fever. Hemoptyisis is not necessarily present [6].

Risk factors for developing DAH after HSCT include older age, total body irradiation, myeloablative conditioning regimens and severe acute GVHD [14].

While Yen et al [5] have suggested a higher incidence of DAH after autologous HSCT, other authors have reported a similar incidence after autologous or allogeneic HSCT [12] or a higher incidence after allogeneic HSCT [10].

CT commonly demonstrates bilateral areas of ground-glass attenuation and patchy consolidation, predominantly perihilar, often with a superimposed reticular pattern. ('crazy paving' pattern) (Figure 4 A/B). There's typically a rapid deterioration in radiographic abnormalities.

Diagnosis can be hardly made with imaging because the imaging findings in DAH are very similar to those in pulmonary edema or ARDS, especially when there’s a predominant...
dependent distribution of the abnormalities. However, in DAH, the heart volume is typically normal and pleural effusions are absent [3,6,7].

Therefore, bronchoalveolar lavage is classically used for the diagnosis, that may show a progressive bloodier return or an increased number of hemosiderine-laden macrophages. When more than 20% hemosiderin-laden macrophages are found, it’s suggestive for DAH [6,7,12].

**Engraftment syndrome (capillary leak syndrome)**

Engraftment syndrome occurs 7-21 days after transplantation and patients present with erythrodermatous skin rash (as seen in acute GVHD) and fever.

It is characterized by diffuse capillary leakage, what results in noncardiogenic pulmonary edema, during the engraftment of hematopoietic stem cells and neutrophil recovery.

It is described as most often following autologous HSCT, with a reported incidence of 7-11%.

The pathogenesis is multifactorial but appears to be related to the release of pro-inflammatory cytokines.

CT findings are nonspecific and include ground-glass attenuation, perihilar or peribronchial consolidation, interlobular septal thickening and pleural effusions (Figure 5 A/B) [6,10,15].

**Early Posttransplant Phase**

In this phase (after engraftment), occurring between 30 days and 100 days after transplantation, there’s a gradual increase in neutrophil count, while the cell-mediated and humoral immunity is still impaired. This leads to a decrease in fungal infections and an increase in the incidence of viral infections [7].

They are mainly caused by CMV and Pneumocystis carinii, but other viruses should be considered too, such as RSV, Herpesvirus, Influenza virus, Parainfluenza virus and adenovirus [16].

**Infections**

* CMV: The risk of posttransplant CMV infection significantly depends on the CMV serostatus of the donor and the recipient, determined before transplantation [17].

  CMV can be transmitted from a seropositive donor to a seronegative recipient and this has a negative impact on the overall survival and increases the transplant-related mortality [17].

  Usually, infection involves reactivation of a latent virus in seropositive patients, or in minor cases, it can be caused by infusion of CMV positive blood products in a CMV seronegative patient [3]. However, nowadays, most patients receive leucocyte-reduced - filtered - blood products, so the risk of this last cause is markedly decreased [17,18].

  CMV-seronegative recipients getting grafts from CMV-seronegative donors have the lowest risk of posttransplant CMV infection.

  A recent study from Ljungman et al [19] showed that CMV-seronegative patients receiving CMV-seropositive grafts from an unrelated donor, had significantly lower overall survival, decreased relapse-free survival and increased transplant-related mortality, compared with CMV-seronegative patients receiving grafts from CMV-seronegative unrelated donors. However, when HLA-identical sibling donors or mismatched family donors are used in CMV-seronegative patients, donor CMV serological status had only a borderline negative effect after HLA-identical sibling donor transplantation and no effect after mismatched family donor transplantation.

  In the same study, donor CMV serological status had no significant effect on overall survival, relapse-free survival and transplant-related mortality in CMV-seropositive patients receiving grafts from HLA-identical sibling donors or mismatched family donors. When CMV-seropositive patients received grafts from CMV-seropositive, unrelated donors, there was no significant effect on overall survival and a significant effect on transplant-related mortality, compared with CMV-seropositive patients receiving grafts from CMV-seronegative, unrelated donors.

  It is important to distinguish between CMV infection and CMV pneumonia.
CMV infection is defined as the detection of the CMV virus or viral proteins in any bodily fluid or tissue specimen [18].

CMV pneumonia is defined as the presence of signs or symptoms of pulmonary disease in combination with the detection of the CMV virus in lung tissue samples [18].

The incidence of CMV infection is similar in autologous and allogeneic transplants, but the risk of CMV pneumonia is higher and there’s often more severe disease after allogeneic transplantation than after autologous transplantation. The reported incidence of CMV pneumonia is 10-30% after allogeneic and 1-9% after autologous transplantation [18].

CMV-seropositive recipients receiving CMV-seronegative grafts are at greatest risk for developing severe CMV pneumonia. During leukopenia, CMV reactivates in the lungs of the recipient and the graft lacks specific CMV-immunity whereby the graft generates an immune response against the infected lung cells [18].

GVHD and its treatment increase the risk of CMV infection and pneumonia [18].

Prophylactic therapy is given to high-risk patients (i.e. CMV-seropositive recipients or CMV-seronegative recipients with a CMV-seropositive graft) and pre-emptive therapy is started when viral replication is detected with PCR or CMV pp65 antigen is detected in leukocytes.

Due to intense antiviral drug use, the prevalence of early CMV (<100 days after HSCT) has declined to 3-6%. However, the prevalence of late CMV-infection has increased up to 18% [20].

CT findings consist of bilateral, multiple micronodules or ill-defined nodules with associated areas of consolidation or ground-glass attenuation (Figure 6A/B) [3,7].

*Pneumocystis jiroveci pneumonia*

Pneumocystis jiroveci pneumonia is rarely seen because of routine antibiotic prophylaxis. Typically, there are areas of ground-glass attenuation at CT, which may be diffuse, predominantly perihilar or patchy (Figure 7 A/B) [7].

**Idiopathic pneumonia syndrome**

IPS is defined as diffuse lung injury after HSCT in the absence of an infectious etiology, and is a diagnosis of exclusion. It’s the most common cause of diffuse radiologic abnormalities between 30 and 180 days after HSCT [10].

The incidence widely varies among different authors, ranging from up to 10% [21] to 5-25% [22].

The pathogenesis of IPS is unclear but may be associated with drug toxicity or GVHD.

The radiologic pattern consists of nonspecific bilateral consolidations with basilar dominance, similar to noncardiogenic pulmonary edema [10,22].

**Late Phase**

The late phase complications occur after 100 days following transplantation. In this phase, most complications are non-infectious. However, opportunistic infections have to be considered too.

**Infection**

Patients with chronic GVHD are treated with immunosuppressive drugs, that may increase the risk of bacterial infections, fungal infections and viral infections, such as CMV, Pneumocystis carinii, RSV and Herpes viruses [23].

**Bronchiolitis obliterans – chronic GVHD**

Bronchiolitis obliterans occurs in up to 10% of the patients after allogeneic HSCT and it rarely occurs after autologous HSCT. Clinically, patients develop a non-reversible, obstructive lung function pattern. The mortality rate is about 40%. The pathogenesis is complex and multifactorial but is probably associated with chronic GVHD.

CT shows bronchial dilatation/bronchiectasis, a mosaic attenuation pattern and air trapping on expiratory scans (Figure: 8 A-D; 9 A/B) [7].

Chronic GVHD is a result of an immune reaction of...
immunocompetent donor cells against immuno-incompetent host cells. It occurs in up to 50% of patients who survive six months or more after transplantation. Patients with pulmonary GVHD often have disease elsewhere, mainly in the skin, liver or gastrointestinal tract [8].

**Organizing pneumonia**

OP was previously known as BOOP. Because the term BOOP may wrongly suggest a major role for bronchiolitis obliterans, an entity that differs from OP, it is replaced by the term OP.

It occurs almost exclusively after allogeneic HSCT and is associated with GVHD. Total body irradiation may also be associated with the development of OP. The incidence of OP after HSCT ranges from 1 to 10% [24].

Once the diagnosis of OP is made, it is necessary to search for an etiologic diagnosis before the diagnosis of COP can be made. Possible causes of OP are infection (by bacteria, viruses, parasites and fungi), drugs (e.g. bleomycin, busulphan, methotrexate), connective tissue disorders (e.g. dermatomyositis/polymyositis, rheumatoid arthritis, Sjögren’s syndrome), transplantation (stem cell transplantation, lung-and liver transplantation) and hematologic malignancies [25].

Histologically, it is characterized by granulation tissue within the alveolar ducts and the alveoli [24].

Treatment with steroids is usual beneficial but OP frequently recurs [24].

The common patterns of CT findings are patchy consolidations or ground-glass attenuation with a peribronchial and/or peripheral distribution. There’s often a lower lobe predominance. Bronchial dilatation and bronchial wall thickening are common (Figure 10 A/B) [3,7,26].

**Other complications**

Other rare complications are PTLD, associated with EBV infection (Figure 11A/B), and PVOD.

PTLD can involve any of the organ systems. Thoracic involvement manifests most commonly as a pulmonary mass or nodule, either solitary or multiple. These lesions have a randomly distribution, are smooth or irregular, and usually have homogeneous soft-tissue attenuation [27].

PVOD may result from endothelial damage, caused by drug toxicity or infection and leads to occlusion or narrowing of pulmonary veins and venules. This, in turn, leads to pulmonary vascular congestion, progressive dyspnea and right ventricular heart failure.
CT findings are dilatation of the main pulmonary artery, right-sided cardiac chamber enlargement, mediastinal lymph node enlargement, centrilobular ground-glass nodules and interlobular septal thickening. When pulmonary edema is associated with PVOD, a CT-scan may show Kerley B lines or pleural effusion.

Patients with PVOD have a worse prognosis and no specific treatment is available [6,7,28].

**CONCLUSION**

Pulmonary complications are common after HSCT and are an important cause of morbidity and mortality. However, most of them have non-specific radiological features.

In this pictorial essay, we tried to review and to illustrate the pulmonary complications after HSCT in function of time of onset after transplantation.

Pulmonary complications can be classified, depending on time of onset after HSCT. Considering the time frame after HSCT can help us with assessing pulmonary complications.

High resolution CT with an expiratory scan phase should be the standard protocol for a chest CT-scan after HSCT because the expiratory scan phase is useful to detect air-trapping, that can be suggestive for bronchiolitis obliterans, related with GVHD.
Figure 10 A 59-year-old man with cough and slowly progressive dyspnea. CT images show patchy consolidations with peribronchial distribution, which can correlate with (cryptogenic) organizing pneumonia. Earlier CT scans (not shown) show that the consolidations are progressive.

Figure 11 A chest radiograph (not shown) was performed in a 46-year-old man with general malaise and inflammatory blood markers. This showed bilateral nodular consolidations and subsequently, there was performed a CT examination. CT images show bilateral nodular consolidations with discrete ground-glass halo. Histopathological examination of bronchial tissue revealed EBV positive PTLD.

REFERENCES

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