

Pulmonary Infections - High-Resolution Computed Tomography (HRCT) Patterns in Bone Marrow Transplant Patients

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Abstract

Background: To study the high-resolution computed tomography (HRCT) findings in bone marrow transplant patients with pulmonary infection and to determine distinguishing features among the different types of infections.

Methods: This study included 109 bone marrow transplant recipients with documented pulmonary infection. High-resolution CT (HRCT) of the chest were performed, and diagnosis was proven soon after onset of symptoms. Diagnosis was confirmed by bronchoalveolar lavage, sputum cytology, response to therapy, biopsy and autopsy.

Results: Out of 109 patients 40 were having pulmonary infections due to fungi, 38 bacteria, 18 viral- cytomegalovirus (CMV), 9 pneumocystis jiroveci pneumonia (PJP) and 4 mycobacterium tuberculosis. Large nodules more than 1cm in diameter were seen in 28 out of 40 patients with fungal pneumonia (70%), 5 of total 38 patients with bacterial pneumonia (13.1%), 3 of 18 patients with viral infection (16.6%). The halo sign was present in 23 out of 28 patients having large nodules with fungal pneumonia (82.1%), 3 of 31 patients with nodular opacities in bacterial pneumonia (9.6%), 2 patients (11.1%) with viral and none with pneumocystis jiroveci pneumonia. There was no significant difference in the prevalence of the other HRCT patterns including small nodules, ground-glass attenuation, and air-space consolidation among viral, bacterial, and fungal infections.

Conclusion: The HRCT pattern of large peripheral nodules, nodules with cavitation, visualization of halo sign and peripheral wedge shaped opacities are most suggestive of fungal infection. In our study, large peripheral nodules and the halo sign were statistically more common in patients with fungal infections. Other HRCT patterns are not specific and thus not helpful in differentiating among the various types of pulmonary infections seen in bone marrow transplant patients.

Key Words: Pulmonary infections, High resolution computed tomography (HRCT). Bone marrow transplant.

Introduction

Variety of pulmonary infections occur in bone marrow transplant patients and these are a major cause of morbidity and mortality. Despite the fact that routine prophylaxis for common pathogenic organisms and empiric therapy of febrile episodes during the early neutropenic period are given, these infections do occur. The neutropenic period includes the first 30 days after marrow transplant, when the transplanted marrow is not yet functioning and the patient remains neutropenic. The frequency of infectious and noninfectious pulmonary complications is similar during neutropenic period. Pulmonary infections are a common cause of morbidity and mortality after bone marrow transplantation.^{1,2} During the neutropenic phase bacterial and fungal infections may occur. During early phase (i.e. 2-3 weeks to 100 days) pneumocystis jiroveci pneumonia (PJP), Cytomegalovirus and other viral pneumonias are the common complications.³ Early and accurate diagnosis of these complications is important because of the high morbidity and mortality associated with infection and because of the frequent complications. Infection is most common cause of pulmonary complications after bone marrow transplantation.⁴ These complications are best evaluated using high-resolution computed tomography (HRCT) due to its increased sensitivity and specificity. Pulmonary complications are the most frequent of all stem cell transplant complications, occurring in approximately 40-60% patients.¹ Even though the initial imaging diagnostic tool for Haematopoietic stem cell transplant recipients with pulmonary impairment remains the chest radiograph, it is normal in 15% of symptomatic patients with proven infiltrative lung diseases.⁵ HRCT may show pulmonary abnormalities in patients with normal findings on radiographs and is superior to

radiography in depicting the pattern and extent of abnormalities.

Patients and Methods

This cross sectional study included 109 patients who after bone marrow transplantation had proven pulmonary infection (n=109) and in whom HRCT was done soon after the onset of symptoms. The patients were selected by reviewing medical records who underwent bone marrow transplantation from Jan 2014 till Jan 2016 at Armed forces bone marrow transplant centre Rawalpindi Pakistan. Symptoms were identified. The symptoms included fever, cough, dyspnea and chest pain. The study group included 44 females and 65 males who ranged in age from 1 to 58 years. The transplantation was performed for the treatment of chronic myelogenous leukemia, severe aplastic anemia, acute nonlymphocytic leukemia, myelodysplastic syndrome, acute lymphocytic leukemia, and Hodgkin's disease. The pathogens responsible for the pulmonary infections were confirmed by the following means: bronchoalveolar lavage, sputum culture, response to specific therapy, biopsy, and autopsy. Fungal infection was diagnosed by culture, histologic evidence of tissue invasion, response to antifungal therapy and radiological evidence of decrease in size and number of nodules. The diagnosis of CMV was based on detection of the characteristic inclusion bodies in material obtained at bronchoalveolar lavage, autopsy, or lung biopsy and positive polymerase chain reaction test results of blood. One of the patients, a young boy was given diagnosis of pneumocystis jiroveci pneumonia (PJP) based on radiological findings but was latter confirmed to be CMV on autopsy after death of the patient. Diagnosis of bacterial infection was based on a positive culture of sputum or bronchoscopic aspirate in majority of cases combined with positive blood or pleural fluid cultures and complete blood picture. Mycobacterium tuberculosis infection was diagnosed on Montoux test, sputum culture and mycobacterium tuberculosis PCR.

CT images were obtained at end-inspiration using a 2-mm collimation at 10-mm intervals and were reconstructed with a high-spatial-frequency algorithm and photographed. CT scans were analyzed by 2 radiologists and final diagnosis were made regarding the findings by consensus. HRCT findings evaluated were pattern of the pulmonary abnormalities (nodules, halo sign, ground-glass haze, air space shadowing), distribution of the lesions (peripheral or central; and upper, middle, or lower zones; unilateral or bilateral), bronchial wall thickening, pleural effusions. The

nodules larger than 1 cm in diameter were classified as large and less than 1 cm in diameter as small.

Ground-glass haze in radiology appears as hazy area of increased attenuation of the lung with preserved bronchial and vascular markings; air-space consolidation, as homogeneous increase in parenchymal density with obscuration of the margins of vessels and airway walls and may exhibit air bronchograms. Large nodule, as a round opacity equal to or more than 1cm in diameter; small nodule, as round opacity less than 1 cm in diameter; tree-in-bud pattern, centrilobular nodules with linear branching pattern that resemble a budding tree; bronchial wall thickening, also referred as peribronchial cuffing is described as thickness of the bronchial wall more than 1/6th of the bronchial diameter; and lymph node enlargement, as lymph nodes with short-axis diameter more than 1cm. The ground-glass opacities was classified as diffuse, focal, or patchy. The distribution of air-space consolidation was classified as patchy or focal. Criteria for these findings were those defined in the Fleischner Society's glossary of terms.⁶

Results

Wide range of pulmonary parenchymal abnormalities was observed on HRCT. Out of 40 cases of fungal pneumonias 30 were caused by Aspergillus organisms, 3 by Candida albicans, and 7 by both organisms (Figure 1&2). Nodules were the most common finding seen in these patients. Large nodules mostly peripherally distributed were noted in 28 of 40 patients (70%); in 23 of these 28 patients (82.1%) with large nodules, most of the nodules showed CT halo sign (nodules surrounded by ground glass opacity). Small nodules in a predominantly centrilobular distribution were seen in 6 cases (38%). Cavitating nodules were seen in 21 out of total 40 patients with fungal pneumonia (52.5%). Large peripheral wedge shaped pleural based opacities with halo of ground glass attenuation in 18 out of 40 patients (45%) and tree-in-bud pattern was seen in 4 patients (10%). In 18 out of 40 cases, the nodules were associated with air-space consolidation, with ground-glass opacities and peripheral wedge shaped opacities. Eleven out of 40 patients (27.5%) had areas of air-space consolidation, involving both lungs in asymmetric fashion. 5 patients (12.5%) had bilateral asymmetrical areas of ground-glass attenuation.

Thirty eight patients developed bacterial pneumonia (34.8%). Nodular opacities, ground-glass attenuation, cavitation and air-space consolidation were commonest findings in patients with bacterial pneumonia. The consolidation was involving both

lungs asymmetrically (Table 1; Figure 1). Sixteen patients had areas of ground-glass attenuation (42.1%). The patterns of ground glass opacity were diffuse, patchy and focal. The ground-glass opacities were bilateral symmetrical in 10 patients and asymmetrical in 6 patients. Pleural effusion was noted in 11 of total 38 patients with bacterial pneumonia (28.9%). The bacterial pneumonias were due to Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Enterococcus faecalis.

Four out of total 109 patients (3.6%) were diagnosed to have mycobacterium tuberculosis. Tree bud appearance, air space consolidation, small nodular opacities and ground glass opacities were common findings in tuberculosis. All patients with CMV pneumonia showed abnormal findings on HRCT scans. Bilaterally symmetrical ground glass opacities (non segmental), and air space consolidation were common findings in these patients.

In Pneumocystis jiroveci pneumonia (PJP), formerly known as pneumocystis carinii pneumonia (PCP), chest xray may be normal during early course of disease or may show reticulonodular shadowing that progresses to air space consolidations. Ground glass opacities and cysts were commonest findings on HRCT.



Figure 5 .Pneumocystis jiroveci pneumonia, Bilateral symmetrical ground glass haze.

Table 1: Various HRCT findings in pulmonary infections in bone marrow transplant patients

HRCT Findings	Fungal Pneumonia (n= 40)	Bacterial Pneumonia (n= 31)	CMV Pneumonia (n= 16)	PJP Pneumonia (n= 9)	Tuberculosis n=4
Large Nodules	70%	16.1%	16.6%	-	-
Small Nodules	38%	83.8%	55.5%	11.1%	50%
Halo Sign.	82.1%	9.6%	11.1%	-	-
Ground Glass Haze	12.5%	42.1%	61.1%	55.5%	25%
Consolidation	27.5%	71%	50%	44.47%	75%
Tree in bud appearance	10%	19.2%	-	-	50%

Discussion

Bone marrow transplantation is currently the treatment of choice for many hematologic malignancies and severe congenital or acquired disorders of the hematopoietic and immune systems.⁶ Infective complications are a serious cause of morbidity and mortality following hematopoietic stem cell transplant (HSCT) and the lung is a particular target organ post-transplant.⁷ Type of infection depends upon the course of immunosuppression and recovery. Hematopoietic Stem cell transplant (HSCT) recipients have severe impairment in cell-mediated immunity as result of the conditioning regimen, immunosuppressive therapy and graft-versus-host disease (GVHD).⁸ These predispose to fungal, bacterial, and viral pneumonias.^{9,10} In the pre engraftment period (0-30 days), profound neutropenia and damaged mucosal membranes are the predominant defects in host defense, which predispose the patient to bacterial and fungal infections.¹¹ During the period after engraftment (31-100 days), there is impairment of both cellular and humoral immunity that predisposes the patient to mainly CMV infection.¹² The most common organism of fungal pneumonia is Aspergillus species, being responsible for 90% of such infections.¹³ Candida species, usually Candida albicans, is the second most frequent fungal organism



Figure 1: Invasive Aspergillosis, Cavitating nodules with retracted necrotic tissue and ground glass halo.



Figure 2: Large peripheral wedge shaped pleural based opacities with halo fo ground glass attenuation (haemorrhagic edema).



Figure 3 .Bacterial pneumonia-Consolidation right lower lobe with right pleural effusion



Figure 4 .Cytomegalovirus pneumonia, Bilateral patchy ground glass and nodular opacities.

and is seen most commonly in patients with leukemia and lymphoma.¹⁴

Prolonged neutropenia and corticosteroid use are major risk factors for the development of invasive aspergillosis.^{15,16} The lung lesions in invasive pulmonary aspergillosis are characterized by vascular invasion and occlusion of small- to medium-sized pulmonary arteries by fungal hyphae.¹⁷ On chest x-ray this angioinvasion is usually seen as peripheral nodules. . At computed tomography (CT), the pulmonary nodules may be surrounded by hazy ground-glass attenuation, which represents hemorrhage around the central infarction caused by angioinvasion.^{18,19} The CT Halo sign represents surrounding parenchymal hemorrhage and is highly suggestive of invasive aspergillosis in appropriate clinical settings.²⁰ Although the halo sign in neutropenic patients is highly suggestive of invasive aspergillosis, it has also been documented in patients with Candida infection, CMV pneumonia, herpes simplex virus infection, and Kaposi's sarcoma. Cavitation in nodules usually occurs late during resolution phase of angio-invasive aspergillosis.²¹ Pulmonary candidiasis radiological features include consolidation and nodules which mainly involves lower lung lobes.. The characteristic pathologic findings consist of hemorrhagic nodules that usually measure 2-4 mm in diameter and frequently have a necrotic center containing the organisms.²²

In present study most common finding seen in patients with fungal pulmonary infections included large nodules (70%) and CT Halo sign seen in 82.1% patients with large nodules. Peripheral wedge shaped opacities seen in 45% patients. This was in accordance with study done by Ecuissato DL et al.⁴ Bacteremia is a common complication in the pre engraftment period, occurring in 10%-59% of bone marrow transplant recipients.^{11,23} The most common bacteria resulting in pulmonary infection in bone marrow transplant patient in first 0-30 days are in oral and intestinal mucosa. Gram negative bacteria including Klebsiella, as well as Gram positive bacteria, Staphylococcus spp and Streptococcus spp. Because of the early empirical use of broad-spectrum antibiotics during periods of fever, bacterial pneumonia is infrequently diagnosed during the pre-engraftment period.¹⁵

Cytomegalovirus (CMV) remains the most common pathogen and responsible for up to 50% of immunocompression-related viral pneumonia.²⁴ It is caused by reactivation of latent virus at time of severe immunosuppression. Common imaging features include unilateral or bilateral interstitial infiltrates,

alveolar consolidation, ground-glass opacities and nodular opacities.²⁵ CMV diagnosis can be confirmed on radiological findings along with isolation of virus from bronchoalveolar lavage and lung tissue. Mortality is high (80-85%) and uniformly fatal if not treated²⁶

Pneumocystis jiroveci pneumonia (PJP) is one of the commonest cause of interstitial pneumonia in immunocompromised patients that leads to air space disease. In most patients with Pneumocystis jiroveci-induced pneumonia, diffuse alveolar or interstitial opacities can be observed on chest radiographs.²⁷ Dominant HRCT findings in our study were ground glass opacities involving perihilar regions (55.5%), but can be diffuse.

Most reports of TB in HSCT patients were from ASIA reflecting that TB incidence ranging from 0.0014 (USA) to 16% (Pakistan).²⁸ TB in this population of patient is mainly due to reactivation of latent infection.⁸ In immunocompromised host patients, the radiological finding could be mitigated or absent on chest x-ray and on this panel the CT-scan provided additional information to help diagnose pulmonary TB.²⁹

Conclusion

The HRCT pattern of large peripheral nodules, nodules with cavitation, visualization of halo sign and peripheral wedge shaped opacities are most suggestive of fungal infection. HRCT patterns like Ground-glass opacities, air-space consolidation, and small nodules points towards viral, bacterial, tuberculous and fungal pneumonia in bone marrow transplant patients and a considerable overlap of these radiological features can be evident.

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