View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

HOSTED BY

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

Radiology of Infectious Diseases 1 (2014) 37–41

www.elsevier.com/locate/jrid

Review

Imaging pulmonary infectious diseases in immunocompromised patients

Xiangpeng Zheng [a,b,*], Guozhen Zhang [a,c]

[a] *Pulmonary Nodule Center, Fudan University Huadong Hospital, 200040 Shanghai, China*
[b] *Department of Radiation Oncology, Fudan University Huadong Hospital, 200040 Shanghai, China*
[c] *Department of Radiology, Fudan University Huadong Hospital, 200040 Shanghai, China*

Received 19 October 2014; accepted 4 November 2014
Available online 12 November 2014

Abstract

Immunocompromised patients are subject to a variety of infectious pathogens involving lungs. Imaging examination of pulmonary conditions could provide valuable information for differentiation diagnosis, treatment assessment as well as prognostic prediction. Imaging manifestations of immunocompromise-related pulmonary diseases could be either pathogen-specific or -non-specific. It is particularly fundamental to recognize these imaging characteristics at suspicion of opportunistic infections in such patients. In this article, we attempt to present a review to refresh and update our knowledge of imaging features of pulmonary infectious diseases in immunocompromised patients.
© 2014 Beijing You'an Hospital affiliated to Capital Medical University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

Keywords: Immunocompromise; Infectious diseases; Imaging; *Pneumocystis jiroveci* pneumonia

The immunocompromised conditions can be attributed to various disorders impairing human immune systems, including human immunodeficiency virus (HIV) infection, primary immune deficiency, and immunosuppression-related medical treatment, such as high-dose corticosteroid use, chemotherapy or transplantation therapy [1]. Among them, HIV infections and consequent AIDS are the most notorious. Since first recognized in 1981, HIV infection has became a global healthcare challenge, being responsible for the death of over 25 million patients. Currently around 33.3 million people are suffering from HIV infection and its associated complications [2]. Clinical complications in immunocompromised patients vary from severe opportunistic infections to unusual malignancies affecting major organs. Fig. 1 outlines the major classes of immunocompromised conditions and associated infections.

Most of imaging modalities available today have certain roles in the evaluation of the pulmonary complications occurring in immunocompromised patients. For example, ultrasound can be used for quantitation of pleural effusion and guiding thoracentesis, if necessary. There have been interests in the roles of MRI in evaluating immunocompromised patients – many are young and there is concern about frequent imaging using ionizing radiation. Still, chest radiograph and CT or high-resolution CT (HRCT) remain the most useful tools. Particularly, cross sectional images from CT or sometimes HRCT, enables better precise characterization of the extent, activity and pattern of pulmonary lesions, guides tissue biopsy whenever necessary, and monitors treatment response. A normal CT may allow exclusion of certain infections, for example pneumocystis, but certain pathogen-related pulmonary infection could be negative in imaging at the initial developing phase of the disease, for example fungal infections. Thus, imaging examination should always be interpreted in the context of the patient's clinical presentation. Table 1 lists the common imaging patterns seen in HRCT examination and frequently underlying infections. In this

* Corresponding author. Department of Radiation Oncology, Fudan University Huadong Hospital, 221 West Yan'an Road, 200040 Shanghai, China.
E-mail address: zhengxp@fudan.edu.cn (X. Zheng).
Peer review under responsibility of Beijing You'an Hospital affiliated to Capital Medical University.

http://dx.doi.org/10.1016/j.jrid.2014.11.001
2352-6211/© 2014 Beijing You'an Hospital affiliated to Capital Medical University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

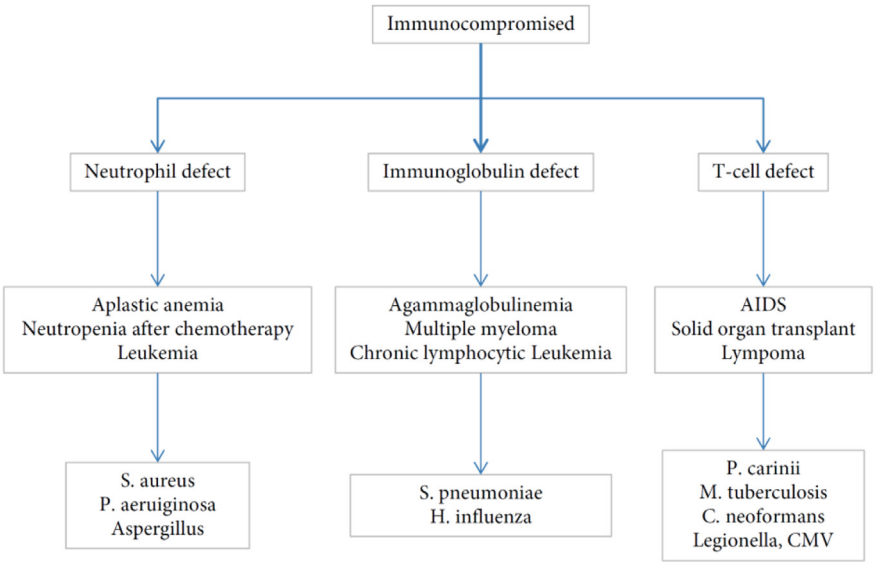

Fig. 1. Major classes of immunocompromised conditions, related clinical entities and infections most commonly associated with each class (Baughman RP [3]).

article, we attempt to present an overview of imaging characteristics of pulmonary infectious diseases in this particular patient population.

1. Bacterial pneumonia

Mycobacterial infection, including both tuberculosis (TB) and non-tuberculous mycobacterial infection, is an important cause of morbidity and mortality in immunocompromised patients, particularly in AIDS patients. According to a report from the World Health Organization in 2009, among the 9.27 million cases of TB, approximately 14.8% occurred in HIV-positive patients with about half of million deaths from HIV-infected TB patients. Fatality rate among HIV-infected TB cases remains 13–14% against less than 4% in HIV negative TB cases [4]. The most common HRCT findings in active TB are centrilobular or linear structures, tree-in-bud appearance and macro-nodules. Consolidation, lymphadenopathy, pleural effusion, ground glass opacity and cavitation also can be observed [5]. In smear-negative AIDS patients with pulmonary TB, specific CT findings have predictive values for accurate diagnosis. These findings include miliary nodules, necrotic lymph nodes, lobular consolidation and tree-in-bud [6]. Of note, unusual radiographic manifestations of TB are more common in immunocompromised patients than in immunocompetent populations.

Table 1
Common HRCT imaging patterns with frequent immunocompromise-related infections.

Imaging patterns		Associated infections
Ground-glass opacity		• Pneumocystis • Cytomegalovirus
Nodules	<1 cm diameter	• Viral pneumonia
	>1 cm diameter	• Invasive aspergillosis • Septic embolism
	"Halo sign"	• Invasive aspergillosis • Candidiasis • Cytomegalovirus pneumonia
	Cavitated nodules	• Septic embolism • Invasive aspergillosis
Tree-in-bud pattern		• Infectious bronchiolitis
Consolidation	Lobar	• Pneumococcus • Klebsiella
	Rounded	• Pneumococcus • Legionella
	Bronchopneumonia	• Gram-negative bacteria • Staphylococcus

The most common non-tuberculous mycobacteria involving lungs is mycobacterium avium complex (MAC). According to a study by the Centers of Disease Control of United States from 1991 through 1992, MAC dominated M. tuberculosis as the leading mycobacterium isolated from immunocompromised patients, particularly since pneumocystis prophylaxis was widely given [7]. It has been reported that MAC infection developed in 33.4% of HIV-infected patients, with predisposition of developing disseminated diseases, involving extrapulmonary organs, such as kidney and liver [8]. However, incidence of MAC infection is quite low in non-HIV immunocompromised patients. Localized pulmonary disease is rare, only seen in less than 5% of patients. Radiographic findings dramatically vary, ranging from normal to mediastinal lymphadenopathy, lobar infiltrates, diffuse or patchy nodular or alveolar infiltrates, without specific imaging patterns associated with MAC infection [9]. Clinically, low CD4 counts less than 50 cells/mm^3 could be indicative of this disease when non-specific pulmonary involvement exists.

According to the Pulmonary Complications of HIV Infection Study, increased incidence of community-acquired bacterial pneumonia (CAP) was associated with HIV infection with 5.5 episodes of pneumonia per hundred person years in HIV-infected patients in comparison with 0.9 episodes in the non-HIV group [10]. However, with the development of antiretroviral treatment, the incidence of CAP in

immunocompromised patients has declined. *Streptococcus pneumoniae* and *Haemophilus pneumonia* are the common pathogens.

Radiographically, lobar or multi-lobar consolidation is the major imaging finding, observed in 45–66% of patients with pyogenic infections [11]. Certainly, HRCT has higher sensitivity in detecting abnormalities in the absence of any conventional radiographic change. HRCT findings include bronchiectasis and evidence of small-airway disease, with ill-defined centrilobular micro-nodules and branching structures or tree-in-bud appearance secondary to mucus impaction [12]. Other imaging characteristics, such as mosaic attenuation due to air trapping, diffuse alveolar involvement and interstitial infiltrates may be seen. Regardless of antiretroviral treatment, no significant differences in the findings of CAP were found in HIV-infected patients [13].

Occurring predominantly in immunosuppressed patients, nocardosis is uncommon but frequently fatal, with a related mortality of up to 80%. The most frequent risk factor is high-dose corticosteroid use in solid organ transplantation, especially lung transplant [14]. Husain et al. reported an incidence of nocardial infection of 2.1% in lung transplant recipients [15]. Radiographic findings of pulmonary nocardiosis include air-space consolidation (with a reported frequency of 64%), variable-sized nodules (57%), masses (21%), pleural effusion (28%), mediastinal and hilar lymphadenopathy (15%) [16]. Pulmonary lesions do not exhibit specific anatomic distribution and cavitation could be seen. In certain cases, differentiating diagnosis is impossible between nocardia and TB infections in lungs.

Other uncommon bacterial pathogens, such as *Pseudomonas aeruginosa*, *Legionella pneumophila*, and *Rhodococcus equi* could cause severe pulmonary lesions in immunocompromised populations. Generally, consolidation, sometimes with progression to cavitation, is the most frequent radiographic finding [17]. Definitive diagnosis needs multidisciplinary efforts, blood test, sputum examination, imaging, and even biopsy.

2. Fungal infection

The incidence of invasive fungal infections has dramatically increased in the past two decades, in parallel to the growing population of immunocompromised patients. *Pneumocystis jiroveci* pneumonia (PJP) is the most common infection in HIV-positive patients. *P. jiroveci*, previously known as *Pneumocystis carinii* causing *P. carinii* pneumonia (PCP), has been classified as a fungus. Abnormal chest radiographs have been reported in up to 90% of patients with suspected PJP. The typical findings include diffuse bilateral symmetrical interstitial infiltrates, most marked in a perihilar distribution [11]. However, the widespread use of prophylaxis therapy has reduced the incidence and severity of classic imaging findings. Unusual presentations include unilateral disease, focal consolidation, and linear densities. CT findings include ground-glass opacity and interlobular septal thickening – sometimes combining to form a 'crazy paving pattern'. Less common manifestations include consolidation and thin-walled cysts or pneumatoceles. Cysts may develop during treatment for pneumocystis as well as at presentation of the initial disease, seen in up to 10% of the cases and mainly located in the upper lobe. The presence of cysts and crazy paving patterns could be helpful to differentiating PJP from hypersensitivity pneumonitis. Pleural effusions and lymphadenopathy are uncommon. HRCT has a high sensitivity and specificity for PJP, 100% and 89%, respectively [18]. The hallmark HRCT findings include diffuse or widespread ground glass attenuation seen in over 90% of cases and mosaic distribution due to alveolar accumulation of fibrin and debris. In addition, history of immunosuppression, especially AIDS, favors the diagnosis of PJP.

Immunocompromised patients, particularly neutropenic patients, are at high risk of developing invasive aspergillosis, involving lungs and extrapulmonary organs. To facilitate the diagnosis of invasive pulmonary aspergillosis for prompt institution of specific therapy and reducing disease dissemination, the European Organisation for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) proposed a classification based on host, clinical, and microbiologic factors [19]. The pulmonary manifestations of aspergillosis can be divided into three categories: (1) semi-invasive (chronic necrotizing) aspergillosis, (2) angioinvasive aspergillosis, and (3) airway invasive aspergillosis (aspergillus bronchopneumonia). Each category has relatively distinct imaging characteristics. In semi-invasive aspergillosis, the characteristic CT findings consist of unilateral or bilateral segmental areas of consolidation or multiple nodular opacities or both, which make reactivation tuberculosis a differentiating diagnosis [20]. The most common manifestations in angioinvasive aspergillosis include Halo sign (i.e. nodules surrounded by a halo of ground-glass attenuation) or pleural based wedge-shaped areas of consolidation, reflecting hemorrhagic infarcts [21]. Airway invasive aspergillosis could have various imaging manifestations ranging from normal appearance to consolidative pneumonia, depending on the extent and severity of involved airway. HRCT enables better characterization of small airway diseases. Common findings include centrilobular nodules and branching linear or nodular opacities, i.e. tree-in-bud pattern. Consolidation could be in peribronchial distribution [22].

Other opportunistic fungal infections include cryptococcal pneumonia, histoplasmosis and candidiasis. Cryptococcus neoformans can infect immunocompromised patient usually when CD4 count is less than 100 cells/mm^3. Central nervous system is the commonest affected organ. The most common radiographic abnormalities of cryptococcal pneumonia consist of a reticular or reticulonodular interstitial pattern, suggestive of interstitial infiltration, while ground-glass attenuation, air-space consolidation, and miliary nodules are less frequently seen [23]. CT pattern in immunocompromised non-AIDS patients seems to differ from that in AIDS patients by the presence of nodules and the absence of reticular or reticulonodular interstitial infiltrates [24]. Histoplasmosis occurs in approximately 2% of AIDS patients, the majority of which

Table 2
Imaging findings of pneumonia caused by fungi and virus in immunocompromised patients.

	Common radiographic findings	Common CT findings
Pneumocystis pneumonia	• Bilateral symmetric ground-glass opacities or fine reticulonodular pattern, mainly involving perihilar regions. • May be diffuse or involve mainly the lower or upper lung zones	• Bilateral symmetric ground-glass opacities • May be patchy or diffuse • May have "crazy paving" pattern
Pulmonary candidiasis	• Unilateral or bilateral areas of consolidation • Poorly defined nodules	• Multiple bilateral nodules • CT halo sign • Patchy or confluent consolidation
Angioinvasive pulmonary aspergillosis	• Bilateral poorly defined nodules • Single or multiple foci of consolidation	• Multiple nodules, 1–3 cm diameter • CT halo sign • Wedge-shaped areas of consolidation • Cavitation, with or without air-crescent sign
Pulmonary histoplasmosis	• Single or multiple nodules • Unilateral or bilateral areas of consolidation • Cavitation is rare	• Diffuse nodular opacities 3 mm or less in diameter • Nodules greater than 3 mm in diameter • Small linear opacities • Focal or patchy areas of consolidation cavitation is rare
Viral pulmonary infections	• Bilateral reticulonodular pattern • Patchy bilateral areas of consolidation	• Multiple small centrilobular nodules • Unilateral or bilateral • Patchy areas of consolidation • Ground-glass opacities

live in temperate regions. Disseminated forms of histoplasmosis may present initially with normal chest radiograph (up to 40% of infected patients), but as the disease progresses, nodular infiltrates and focal or patchy consolidation manifest, mimicking the appearances of tuberculosis [25]. Cavitation rarely occurs in histoplasmosis. Pulmonary candidiasis is relatively uncommon and liver transplant recipients are susceptible to invasive candidiasis. With the widespread prophylactic use of fluconazole and antibiotics, more non-albicans candidiasis occurs with dread mortality. Thus, prophylaxis therapy with extreme caution is necessary and should be restricted to patients with high risks of complicated infections [26]. Chest radiographic abnormalities consist of patchy areas of consolidation, focal cavitation, and multiple pulmonary nodules.

3. Viral infections

Cytomegalovirus (CMV) remains the most common pathogen and responsible for up to 50% of immunocompression-related viral pneumonia [27]. In comparison to immunocompetent population, immunocompromised patients are more prone to viral infections, particularly for those with T-cell defect. However, the range of radiological signs of CMV pneumonia is not subject to the host immune status. Common imaging features include unilateral or bilateral interstitial infiltrates, alveolar consolidation, ground-glass opacities and nodular opacities. Some of signs overlap with infections with pneumocystis, although pleural effusions are more common in CMV pneumonia [28].

During the past decade, respiratory viruses, including rhinovirus, adenovirus, influenza, parainfluenza and respiratory syncytial virus, have been more frequently detected as pathogens of deadly infections in immunocompromised patients with thanks to development of sophisticated molecular diagnostic tools. Additionally, herpes simplex virus may possibly cause a pneumonitis or a focal pneumonia in immunosuppressed. Changes on the chest radiography may be secondary to coexisting bacterial infection as well as due to the primary effect of the virus itself and include bibasal airspace consolidation, peripheral reticular/alveolar infiltrates, and perihilar infiltrates [17].

Table 2 summarizes major imaging findings of fungal and viral pneumonia commonly encountered in immunocompromised patients.

4. Perspective

Past three decades witness great advancement in the medical management of immunocompromised patients, which dramatically improve patients' quality of life and influence clinical courses to some extent. However, pulmonary infections remain leading causes of morbidity and mortality in immunocompromised patients. Classic clinical manifestations of pulmonary diseases become less common, while non-specific and intertwined symptoms and complications are increasingly encountered with heterogeneous imaging features, demanding more multidisciplinary collaboration for accurate management decision making than ever. Despite that imaging findings overlaps and specific characteristics lack for most of infectious diseases, imaging examinations, especially CT and HRCT, play critical roles in providing enormous information regarding pulmonary conditions, etiological differentiation and treatment response. Advancement in imaging techniques will further improve diagnosis accuracy and timely management, thereby reducing the mortality and morbidity from respiratory diseases.

References

[1] Beigelman-Aubry C, Godet C, Caumes E. Lung infections: the radiologist's perspective. Diagn Interv Imaging 2012 Jun;93(6):431–40.
[2] UNAIDS report on the global AIDS epidemic. 2010. p. 7.
[3] Baughman RP. The lung in the immunocompromised patient. Infectious complications part 1. Respiration 1999;66(2):95–109.

[4] World Health Organization (WHO). Chapter 1, Epidemiology. Document WHO/HTM/TB/2009.411. Global tuberculosis control: surveillance, planning, financing—WHO report. 2009. p. 3.
[5] Atwal SS, Puranik S, Madhav RK, et al. High resolution computed tomography lung spectrum in symptomatic adult HIV-positive patients in South-East Asian Nation. J Clin Diagn Res 2014 Jun;8(6):RC12−6.
[6] Feng F, Shi YX, Xia GL, et al. Computed tomography in predicting smear-negative pulmonary tuberculosis in AIDS patients. Chin Med J 2013;126(17):3228−33.
[7] Diagnosis and treatment of disease caused by nontuberculous mycobacteria. This official statement of the American Thoracic Society was approved by the Board of Directors, March 1997. Medical section of the American Lung Association. Am J Respir Crit Care Med 1997;156(2 Pt 2):S1−25.
[8] Hoover DR, Saah AJ, Bacellar H, et al. Clinical manifestations of AIDS in the era of pneumocystis prophylaxis. Multicenter AIDS Cohort Study. N Engl J Med 1993 Dec 23;329(26):1922−6.
[9] Washington L, Miller Jr WT. Mycobacterial infection in immunocompromised patients. J Thorac Imaging 1998 Oct;13(4):271−81.
[10] Hirschtick R, Glossroth J, Jordan M, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary complications of HIV Infection Study Group. N Engl J Med 1995;333:845−51.
[11] Boiselle PM, Tocino I, Hooley RJ, et al. Chest radiograph diagnosis of *Pneumocystis carinii* pneumonia, bacterial pneumonia and pulmonary tuberculosis in HIV-positive patients: accuracy, distinguishing features and mimics. J Thorac Imaging 1997;12:47−53.
[12] Allen CM, AL-Jahdali HH, Irion KL, et al. Imaging lung manifestations of HIV/AIDS. Ann Thorac Med 2010;5(4):201−16.
[13] Shah R, Gupta S, Angeid-Backman E, et al. Pneumococcal pneumonia in patients requiring hospitalization: effects of bacteremia and HIV seropositivity on radiographic appearance. Am J Roentgenol 2000;175:1533−6.
[14] Minero MV, Marin M, Cercenado E, et al. Nocardiosis at the turn of the century. Medicine (Baltimore) 2009;88:250−61.
[15] Husain S, McCurry K, Dauber J, et al. Nocardia infection in lung transplant recipients. J Heart Lung Transplant 2002;21:354−9.
[16] Bargehr J, Flors L, Leiva-Salinas C, et al. Nocardiosis in solid-organ transplant recipients: spectrum of imaging findings. Clin Radiol 2013 May;68(5):e266−71.
[17] Reynolds JH, Banerjee AK. Imaging pneumonia in immunocompetent and immunocompromised individuals. Curr Opin Pulm Med 2012 May;18(3):194−201.
[18] Benito N, Moreno A, Miro J, et al. Pulmonary infections in HIV-infected patients: an update in the 21st century. Eur Respir J 2012;39(3):730−45.
[19] Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002;34:7−14.
[20] Franquet T, Giménez A, Hidalgo A. Imaging of opportunistic fungal infections in immunocompromised patient. Eur J Radiol 2004 Aug;51(2):130−8.
[21] Kuhlman JE, Fishman EK, Siegelman SS. Invasive pulmonary aspergillosis in acute leukemia: characteristic findings on CT, the CT halo sign, and the role of CT in early diagnosis. Radiology 1985;157:611−4.
[22] Logan PM, Primack SL, Miller RR, et al. Invasive aspergillosis of the airways: radiographic, CT and pathologic findings. Radiology 1994;193:383−8.
[23] Cameron ML, Barlett JA, Gallis HA, et al. Manifestations of pulmonary cryptococcosis in patients with acquired immunodeficiency syndrome. Rev Infect Dis 1991;13:64−7.
[24] Zinck SE, Leung AN, Frost M, et al. Pulmonary crytococcosis: CT and pathologic findings. J Comput Assist Tomogr 2002;26:330−4.
[25] Conces Jr DJ, Stockberger SM, Tarver RD, et al. Disseminated histoplasmosis in AIDS: findings on chest radiographs. Am J Roentgenol 1993;160:15−9.
[26] Rano A, Agustí C, Sibila O, et al. Pulmonary infections in non-HIV-immunocompromised patients. Curr Opin Pulm Med 2005 May;11(3):213−7.
[27] Goodrich J. A comparison of cytomegalovirus and community respiratory viruses in immunocompromised patients. Am J Med 1997;102:37−41.
[28] Franquet T, Lee KS, Muller NL. Thin-section CT findings in 32 immunocompromised patients with cytomegalovirus pneumonia who do nothave AIDS. Am J Roentgenol 2003;181:1059−63.