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Pneumonia in immunocompromised patients: updates in clinical and imaging features

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ABSTRACT

Pulmonary infection is a major cause of mortality in immunocompromised patients. Immunosuppression can be divided into neutropenia, humoral immunodeficiency, and cellular immunodeficiency. Pulmonary infection in these patients typically depends on the type, duration, and degree of immunodeficiency. Pulmonary infection in immunocompromised patients is often nonspecific, both clinically and radiologically, but a certain type of pulmonary infection may provide typical radiological features helpful for definitive diagnosis. Therefore, it is essential to incorporate clinical information into radiological features to narrow down the differential diagnosis and to potentially reduce the morbidity and mortality associated with pulmonary infections in immunocompromised patients.

Keywords: Chest radiography; Computed tomography; Immunocompromised host; Pneumonia

INTRODUCTION

Pneumonia in immunocompromised individuals has been increasing as a result of increased use of immunosuppressive agents for the treatment of advanced cancers, connective tissue and autoimmune disorders, and prevention of rejection or graft-versus-host diseases (GVHD) after solid organ or stem cell transplantation. Acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus (HIV) infection is also a major cause of immunodeficiency, particularly in developing countries [1,2].

Pneumonia accounts for approximately 75% of all pulmonary complications in immunocompromised patients, and therefore, early and accurate diagnosis is crucial because of its high morbidity and mortality rate [3]. Chest radiography is still a mainstay of screening and initial diagnosis of suspected pulmonary infection in immunocompromised patients, and is commonly performed to monitor therapeutic responses and identify suspected complications. However, it is difficult to distinguish pulmonary diseases from pleural diseases using chest radiography. It is also difficult to determine the causative pathogen of these diseases. Computed tomography (CT) may overcome some limitations of chest radiography through its improved

resolution, but its ability to determine the causative pathogen is limited because there are substantial overlaps in CT features among different infections [4]. Therefore, it is essential to combine clinical information with radiological features in order to accurately diagnose pulmonary infection in immunocompromised patients. Knowledge of mechanism of immunodeficiency, environmental exposure, and duration and severity of immunodeficiency is fundamental for the accurate differential diagnosis of the cause of pulmonary infection in these patients [5].

The aim of this review was to update the information on pneumonia in immunocompromised patients. We particularly focused on imaging features and new therapeutic agents used for the diagnosis and treatment of pneumonia in the era of personalized medicine.

TYPE OF IMMUNE DEFECTS

Immune defects can cause pulmonary infections of varying severity, and can be categorized into primary (congenital) and secondary (acquired) immune defects. Secondary immune defects are responsible for recurrent pulmonary infection in adults. Secondary immune defects occur when the immune system is disrupted due to underlying diseases, medications, or medical conditions. Chemotherapy, radiation therapy, chronic illness, and malignancies can cause secondary immune defects. HIV infection results in a secondary immunodeficiency known as AIDS. Hematologic malignancies such as leukemia or myeloma produce cancerous immune cells, which replace normal stem cells in the bone marrow. This reduces the number and activity of B-cells, and leads to hypogammaglobinemia. There are five major types of immune defects, which are commonly associated with specific kinds of pulmonary infections (Table 1) [6].

HEMATOLOGIC MALIGNANCY AND HEMATOPOIETIC STEM CELL TRANSPLANTATION

Pulmonary infection is one of the most common causes of morbidity and mortality in patients with hematologic malignancy and patients who undergo hematopoietic stem cell transplantation (HSCT). In HSCT recipients, specific infections are more likely to occur during specific time periods after HSCT because of the evolutionary changes in immunity (Table 2) [7,8].

Table 1. **Types of immunological defects, predisposing factors, and common pathogens which cause pulmonary infections**

Defects	Bacteria	Fungi	Viruses	Parasites
Phagocytes	*Staphylococcus aureus* *Pseudomonas aeruginosa* *Klebsiella pneumoniae* *Escherichia coli*	*Aspergillus* spp. *Candida* spp.		
B-cell	*Streptococcus pneumoniae* *S. aureus* *Haemophilus influenzae* *P. aeruginosa*			
T-cell	*Legionella* spp. *Nocardia* spp. *Mycobacteria* spp.	*Pneumocystis jirovecii* *Cryptococcus neoformans* *Histoplasma capsulatum* *Coccidioides immitis* *Candida* spp.	Cytomegalovirus Varicella-zoster virus Herpes simplex virus	*Toxoplasma gondii* *Strongyloides stercoralis*
Splenectomy	*S. pneumoniae* *S. aureus* *H. influenzae*			
Steroid therapy	*S. aureus* *Legionella* spp. *Nocardia* spp. *Mycobacteria* spp. *P. aeruginosa* Other gram-negative bacteria	*Aspergillus* spp. *Candida* spp. *C. neoformans* *H. capsulatum* *C. immitis*	Cytomegalovirus Varicella-zoster virus Herpes simplex virus	*T. gondii* *S. stercoralis*

Pre-engraftment period (day 0 to 30)

Neutropenia (<500 cells/μL) occurs immediately following HSCT and increases the risk for fungal infection. Fungal pneumonia in the pre-engraftment period accounts for approximately 25% to 50% of all pneumonia in allogenic HSCT recipients. The *Aspergillus* species are the most common fungal pathogens, and typically present as either angioinvasive (Fig. 1) or airway invasive forms (Fig. 2). Unlike diseases caused by other pathogens, aspergillosis is likely to occur during any period after HSCT. Bacterial pneumonia in this period is usually uncommon, probably due to the empiric use of broad-spectrum antibiotics during the initial stage when an infection is suspected [9,10].

Early post-transplantation period (day 31 to 100)

Aspergillosis and cytomegalovirus (CMV) pneumonia are the most common pulmonary infections during this period (Fig. 3). The incidence of CMV pneumonia is much higher in allo-

Table 2. Pulmonary infection after hematopoietic stem cell transplantation

Pre-engraftment (day 0–30)	Post-engraftment (day 31–100)	Late engraftment (day >100)
Neutropenia	Defect in CMI & humoral immunity	Community-acquired infection
Aspiration	CMV	*Streptococcus*
G (–) bacilli	*Pneumocystis jirovecii*	*Staphylococcus*
Aspergillus	Idiopathic pneumonitis GVHD	Varicella GVHD Bronchiolitis obliterans BOOP

CMI, cell-mediated immunity; CMV, cytomegalovirus; GVHD, graft-versus-host disease; BOOP, bronchiolitis obliterans organizing pneumonia.

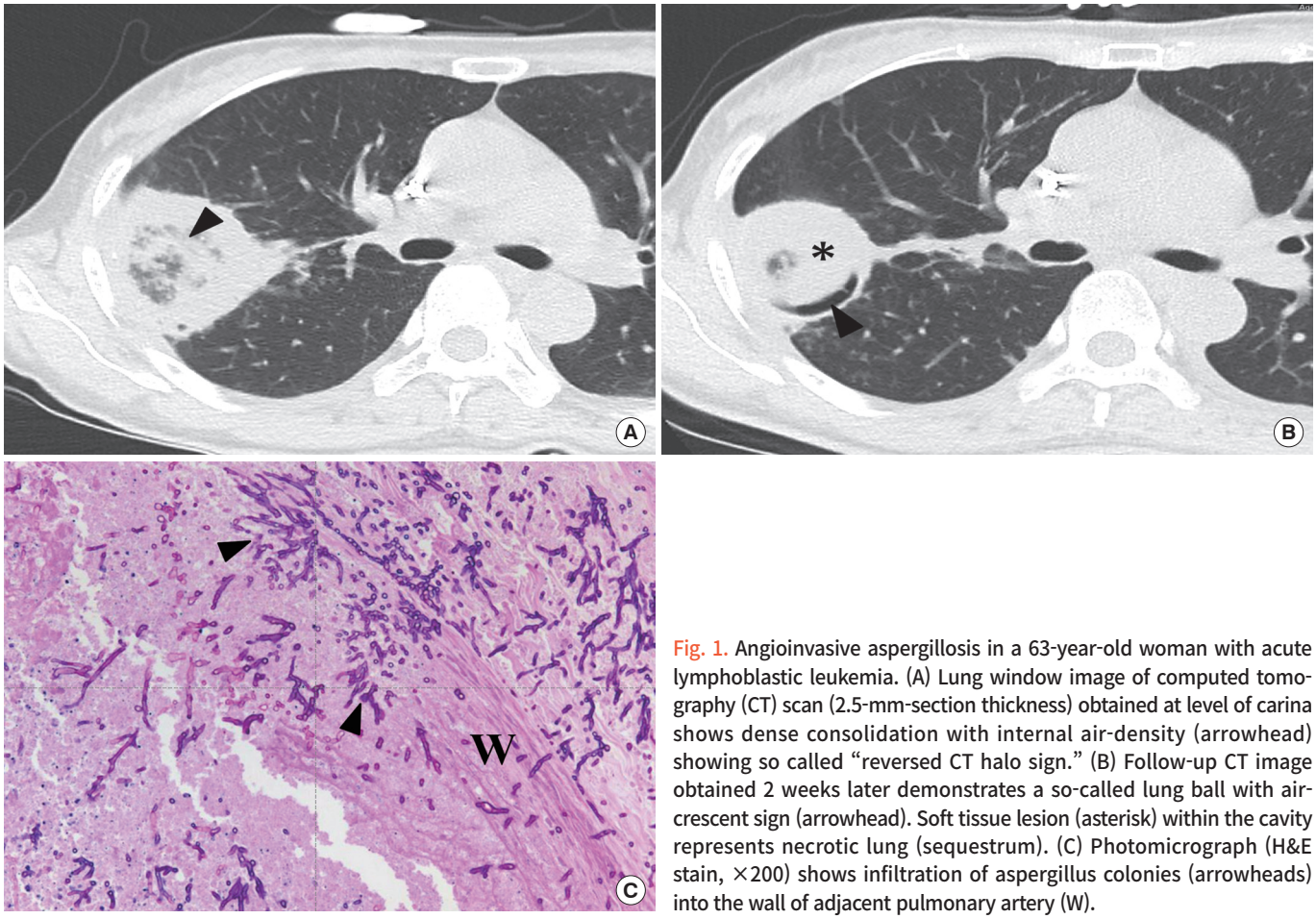

Fig. 1. Angioinvasive aspergillosis in a 63-year-old woman with acute lymphoblastic leukemia. (A) Lung window image of computed tomography (CT) scan (2.5-mm-section thickness) obtained at level of carina shows dense consolidation with internal air-density (arrowhead) showing so called "reversed CT halo sign." (B) Follow-up CT image obtained 2 weeks later demonstrates a so-called lung ball with air-crescent sign (arrowhead). Soft tissue lesion (asterisk) within the cavity represents necrotic lung (sequestrum). (C) Photomicrograph (H&E stain, ×200) shows infiltration of aspergillus colonies (arrowheads) into the wall of adjacent pulmonary artery (W).

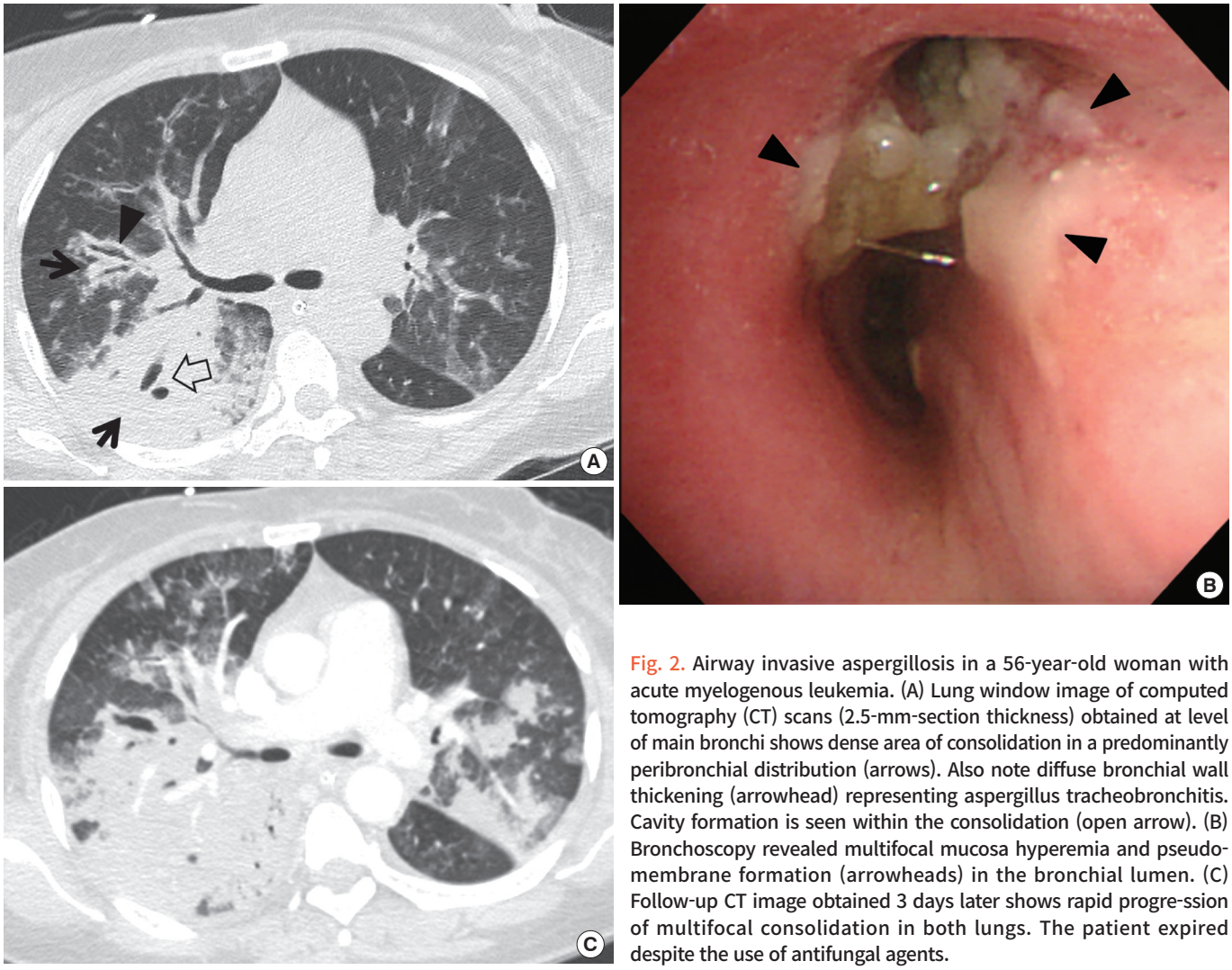

Fig. 2. Airway invasive aspergillosis in a 56-year-old woman with acute myelogenous leukemia. (A) Lung window image of computed tomography (CT) scans (2.5-mm-section thickness) obtained at level of main bronchi shows dense area of consolidation in a predominantly peribronchial distribution (arrows). Also note diffuse bronchial wall thickening (arrowhead) representing aspergillus tracheobronchitis. Cavity formation is seen within the consolidation (open arrow). (B) Bronchoscopy revealed multifocal mucosa hyperemia and pseudomembrane formation (arrowheads) in the bronchial lumen. (C) Follow-up CT image obtained 3 days later shows rapid progre-ssion of multifocal consolidation in both lungs. The patient expired despite the use of antifungal agents.

genic HSCT recipients (10% to 40%) than in autologous HSCT recipients (2%). CMV infection is caused by the reactivation of a latent virus during immunosuppression or by the infusion of CMV-seropositive blood or marrow products into seronegative recipients [11-13]. After the implementation of preemptive strategies to prevent CMV diseases, the incidence of CMV pneumonia has decreased. *Pneumocystis jirovecii* pneumonia (PJP) is rare in HSCT recipients because of the effective prophylaxis.

Idiopathic pneumonia syndrome is a diagnosis of exclusion and is thought to be the result of pulmonary toxicity in chemotherapy, sequelae of undiagnosed pulmonary infection, or GVHD. It is characterized by diffuse alveolar damage without evidence of lower respiratory tract infection. The prognosis of idiopathic pneumonia syndrome is very poor and the 1-year survival rate is only 15% [14].

Late post-transplantation period (after day 100)

After day 100, humoral and cell-mediated immunity gradually return to the normal state in autologous HSCT recipients, but GVHD often occurs in allogenic HSCT recipients. Patients with GVHD are at risk for pneumonia because of direct inhibition of immune function or the use of immune-suppressive drugs to treat GVHD. Aspergillosis and mucormycosis are the most common fungal infections, and adenovirus, Respiratory syncytial virus (RSV), varicella-zoster virus, and parainfluenza virus are common viral pathogens [15].

HIV INFECTION

Since AIDS was first reported in the 1980s, it has been associated with enhanced susceptibility to opportunistic infection, which is the main cause of morbidity and mortality in these patients. With the introduction of highly active antiretroviral

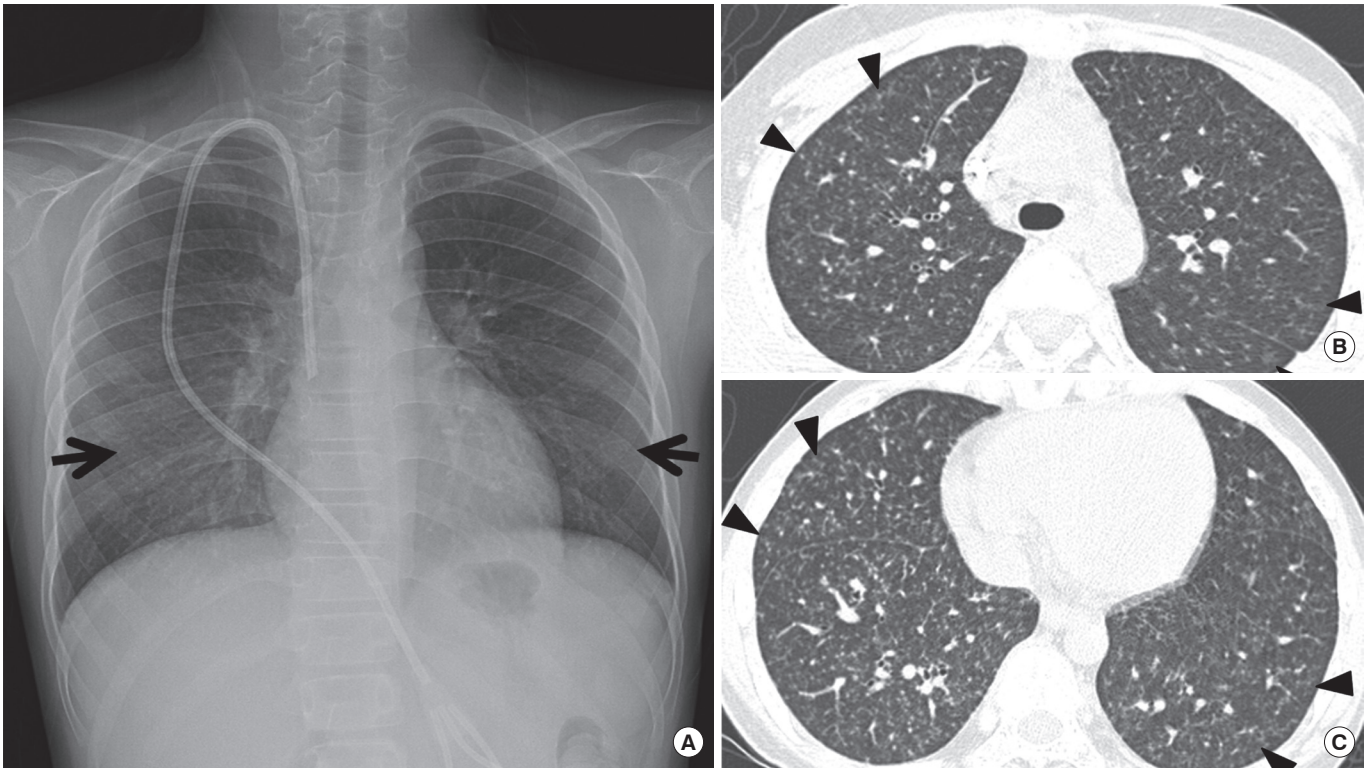

Fig. 3. Cytomegalovirus pneumonia in in a 14-year-old male who underwent allogenic hematopoietic stem cell transplantation 2 months ago. (A) Chest radiograph shows diffuse ill-defined ground-glass opacities in both lower lung zones (arrows). (B, C) Lung window images of computed tomography scans (2.5-mm-section thickness) obtained at levels of aortic arch (B) and left ventricle (C), respectively, depict diffuse and poorly-defined ground-glass opacity nodules (arrowheads) in both lungs.

Table 3. Pulmonary infection in AIDS

CD4 >200 cells/μL	CD4 between 50 and 200 cells/μL	CD4 <50 cells/μL
Bacterial pneumonia	Bacterial pneumonia	Bacterial pneumonia
TB (reinfection)	Primary TB	Atypical appearances of TB
	Pneumocystis jirovecii	*P. jirovecii*
	Fungal infection	Fungal infection
		MAC
		CMV

AIDS, acquired immunodeficiency syndrome; CD4, cluster of differentiation 4; TB, tuberculosis; MAC, *Mycobacterium avium* complex; CMV, cytomegalovirus.

therapy (HAART) in 1996, opportunistic infection in AIDS patients dramatically decreased, and therefore HIV has become a chronic disease in industrialized countries but still remains a major cause of mortality in developing countries (Table 3) [16].

Bacterial pneumonia

The incidence of bacterial pneumonia in HIV-infected patients is 25-fold higher than that in the general population [17]. The most common pathogen is *Streptococcus pneumoniae*, followed by *Haemophilus influenza, Staphylococcus aureus*, and *Pseudomonas*. The incidence of bacterial pneumonia increases as the number of cluster of differentiation 4+ (CD4+) T lymphocytes decreases.

P. jirovecii pneumonia

One of the most common opportunistic infections in HIV-infected patients is PJP (Fig. 4). Originally known as *Pneumocystis carinii*, but now renamed as *P. jirovecii*, this organism was first classified as a protozoan but has now been classified as a fungus [18]. PJP typically occurs when the CD4+

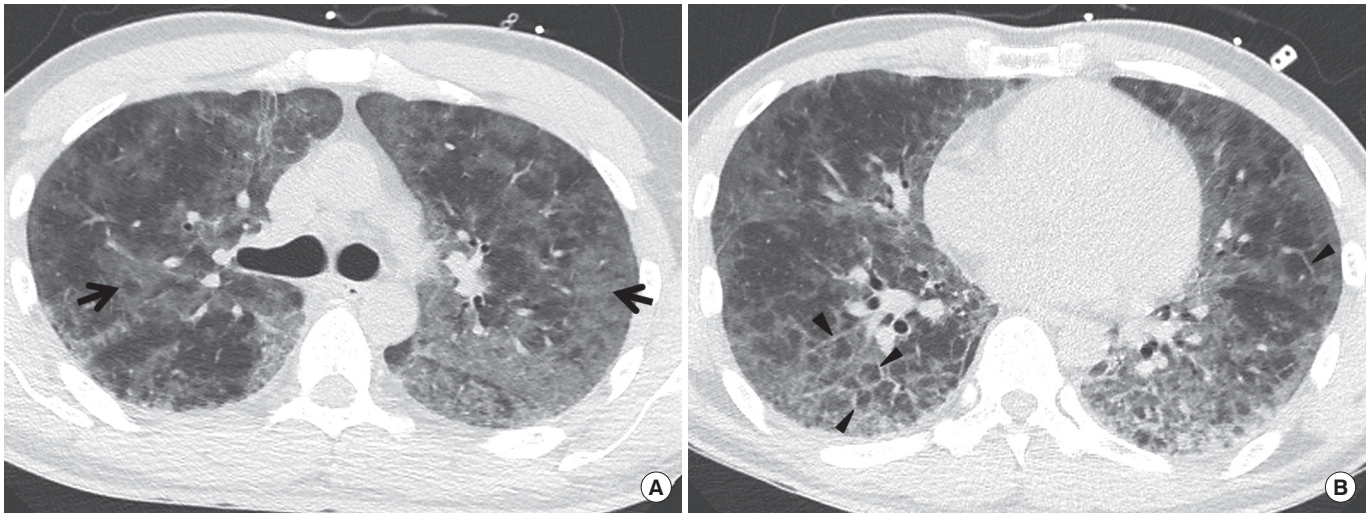

Fig. 4. Pneumocystis pneumonia in a 37-year-old man with acquired immunodeficiency syndrome (AIDS) (cluster of differentiation 4+ [CD4+] count, 75 cells/μL). (A, B) Lung window image of computed tomography scan (2.5-mm-section thickness) obtained at levels of carina and lung base, respectively, demonstrate diffuse ground-glass opacity with geographic pattern (arrows). Also note smooth interlobular septal thickening showing crazy-paving appearance (arrowheads).

T-cell count falls below 200 cells/μL [2]. As with other pathogens in HIV-infected individuals, the incidence of PJP declines following the widespread use of HAART and prophylaxis. However, PJP is still the most common opportunistic pulmonary infection in HIV-infected patients, being responsible for approximately 25% of cases of pneumonia during HIV infection [2,16]. PJP presents with an insidious onset of fever, dry cough, and worsening dyspnea, which are typically present for about 1 month prior to the diagnosis, in contrast with the more acute presentation seen in other opportunistic infections. The diagnosis of PJP is confirmed by the detection of organisms or the amplification of the DNA of specimens obtained by bronchoalveolar lavage (BAL) or induced sputum using polymerase chain reaction (PCR) [19]. Trimethoprim-sulfamethoxazole, which acts by inhibiting folic acid synthesis, is the drug of choice for the treatment of PJP and prophylaxis.

Mycobacterium tuberculosis/nontuberculous mycobacterial infection

Tuberculosis has re-emerged as a global health problem because of AIDS. It is estimated that one-third of HIV-infected patients were co-infected with tuberculosis [20]. It has been suggested that HIV-infected individuals have a 50- to 200-fold greater risk for tuberculosis than the general population [21]. Tuberculosis can occur at any stage of HIV infection [22]. Reactivated tuberculosis is often the most common manifestation of HIV infection. Radiological manifestations are mainly dependent on the immune-status (CD4+ count) of the patients. When the CD4+ count is greater than 200 cells/μL, the imaging features are typically those of postprimary tuberculosis. In patients with CD4+ count less than 200 cells/μL, findings are typically those of primary tuberculosis, including lymphadenopathy, airspace consolidation, and pleural effusion (Fig. 5). A CD4+ count less than 200 cells/μL increases the risk of disseminated infection.

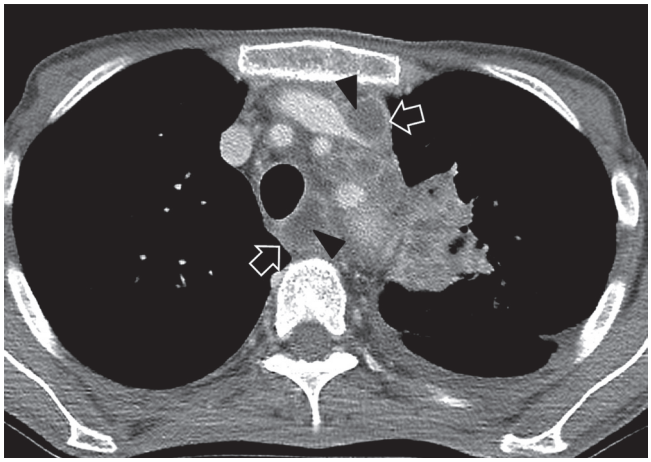

Fig. 5. Tuberculous mediastinal lymphadenopathy in a 56-year-old man with acquired immunodeficiency syndrome (AIDS) (cluster of differentiation 4+ [CD4+] count, 56 cells/μL). Mediastinal window image of computed tomography scan (2.5-mm-section thickness) obtained at level of aortic arch vessels shows multiple necrotic lymph nodes enlargement having enhancing wall (open arrows) and internal low-attenuation (arrowheads).

Fungal infection other than PJP

Cryptococcus neoformans may present as a disseminated disease in HIV-infected individuals with CD4+ T-cell count less than 100 cells/μL. Meningitis is the most common manifestation and the lung is the second most affected organ [23,24]. Cryptococcal pulmonary infection usually manifests as a more severe disease in HIV-infected individuals compared with other hosts with normal immunity. Invasive pulmonary aspergillosis (IPA) is uncommon in patients with AIDS mainly because of the relatively spared neutrophil and granulocyte functions. IPA usually occurs in AIDS patients with CD4+ T-cell count less than 100 cells/μL [25].

Viral infections

Immunocompromised hosts are particularly susceptible to pneumonias caused by the CMV and herpes viruses. CMV is the most common viral pathogen in AIDS patients [26]. Retinitis and gastrointestinal involvement are the most common presentation of CMV in patients with AIDS, but pneumonia is uncommon. Although CMV may produce serious sequelae and death among organ transplant recipients, its significance as a pulmonary pathogen in HIV-infected patients is often unclear [27]. HAART has reduced the incidence of CMV infection in AIDS patients. When present, CMV pneumonitis typically affects patients with advanced level of immune-suppression (CD4+ T-cell less than 100 cells/μL). Co-infection with PJP is not uncommon and is a poor prognostic sign [28,29].

RADIOLOGICAL MANIFESTATIONS ACCORDING TO SPECIFIC PATHOGENS

Aspergillosis

Pulmonary manifestations of aspergillosis in immunocompromised hosts can be classified as either airway invasive or angioinvasive aspergillosis.

Angioinvasive aspergillosis

Angioinvasive aspergillosis is one of the most dreadful opportunistic infections in severely immune-compromised patients such as patients with hematologic malignancies, blood stem cell recipients, and patients with AIDS. *Aspergillus* invades blood vessels, leading to hemorrhagic necrosis and pulmonary infarctions [30]. Proteolytic enzymes from the recruited neutrophils may cause separation of necrotic tissue from the adjacent lung, resulting in intracavitary sequestrum, the so-called lung ball (Fig. 1B).

Radiographic findings consist of poorly defined solitary or multiple nodules and consolidations. The characteristic CT findings include solitary or multiple nodules surrounded by ground-glass opacity (CT halo sign) and peripheral wedge-shaped areas of consolidation (Fig. 1A). The former corresponds to pathologic changes in central necrosis surrounded by hemorrhagic parenchyma while the latter is caused by intralobular hemorrhage and parenchymal infarction. Nodule or consolidation may undergo cavitation (air-crescent sign) (Fig. 1B) when the neutrophil count recovers, which indicates a favorable prognosis.

Airway-invasive aspergillosis

Airway-invasive aspergillosis is histologically characterized by the presence of *Aspergillus* organisms deep in the airway basement membrane [31]. Radiographic findings of airway-invasive aspergillosis consist of bronchial wall thickening, ill-defined nodules, or consolidations. During CT, centrilobular nodules and branching linear opacities or tree-in-bud appearance may be seen in patients with bronchiolitis. Consolidation may be seen in bronchopneumonia during peribronchial distribution. Diffuse and dense bronchial and/or tracheal wall thickening may be seen in *Aspergillus* tracheobronchitis, which would suggest pathological invasion of the airway basement membrane (Fig. 2) [32].

Mucormycosis

Zygomycetes (which include *Rhizopus* and *Mucor*) are the most common pathogens. Pulmonary infarction by vascular invasion is the characteristic pathologic finding. Mucormycosis is common in patients with diabetes mellitus, especially in cases complicated by ketoacidosis as well as in patients with hematologic malignancies or severe burn. Mucormycosis is a fatal disease with a mortality rate up to 80% if not treated aggressively during the early stage. Pulmonary mucormycosis most frequently presents as consolidation or nodule/mass with a halo sign at CT (Fig. 6). Morphologic changes into the reversed halo sign, central necrotic cavity, or air-crescent sign occur with treatment and recovery of absolute neutrophil count (Fig. 6) [33].

CANDIDIASIS

Candidiasis is a rare opportunistic infection mainly caused by *Candida albicans*. *Candida* is a ubiquitous saprophyte normally present in the gastrointestinal tract, oropharynx, vagina, and skin. Pulmonary candidiasis may occur by either hematogenous spread from the gastrointestinal tract or aspiration from the oropharynx. The former presents as multiple

bilateral nodules often associated with areas of consolidation while the latter manifests as aspiration pneumonia in dependent lungs (Fig. 7). CT halo sign may occur in approximately 30% of cases [34,35].

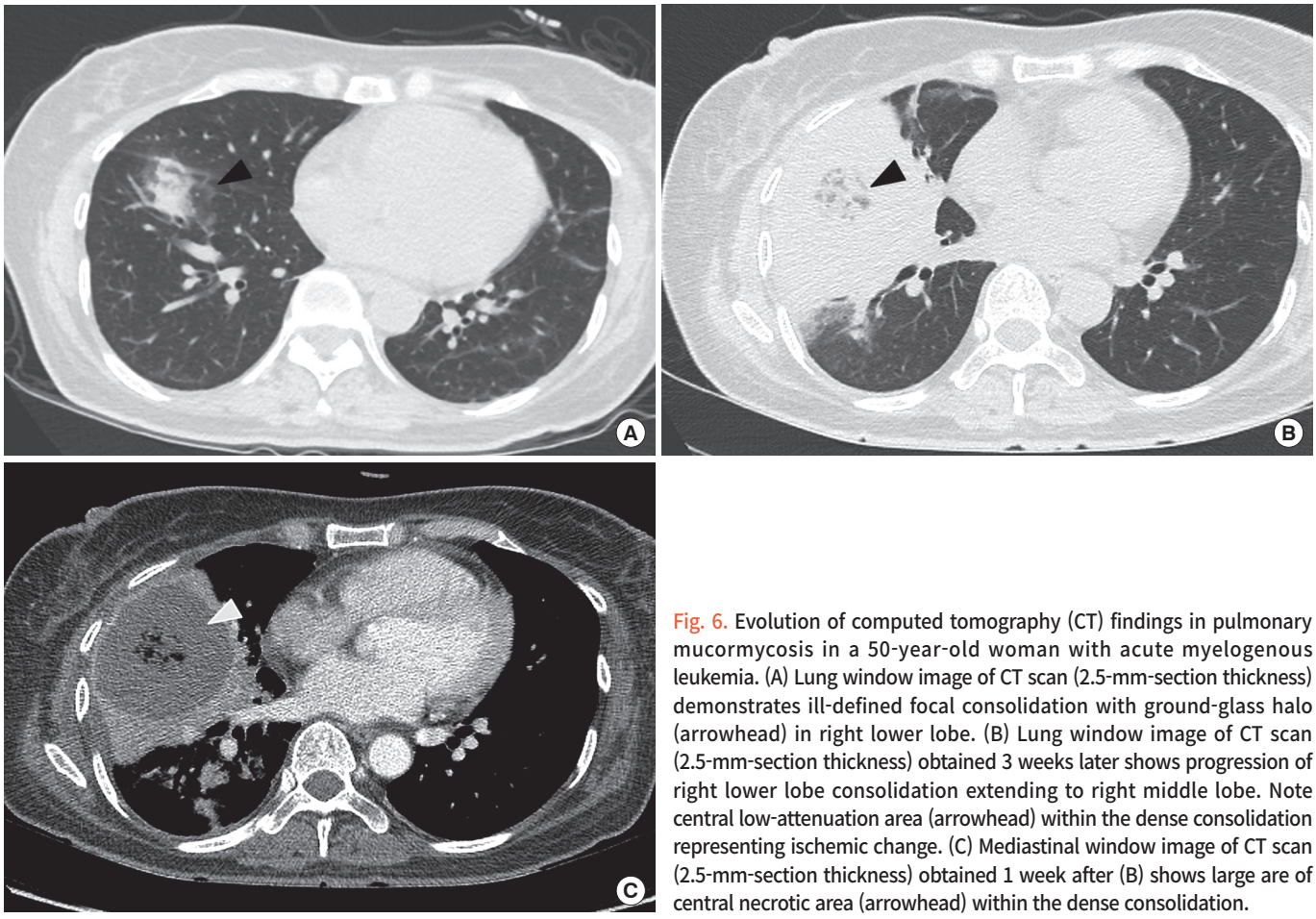

Fig. 6. Evolution of computed tomography (CT) findings in pulmonary mucormycosis in a 50-year-old woman with acute myelogenous leukemia. (A) Lung window image of CT scan (2.5-mm-section thickness) demonstrates ill-defined focal consolidation with ground-glass halo (arrowhead) in right lower lobe. (B) Lung window image of CT scan (2.5-mm-section thickness) obtained 3 weeks later shows progression of right lower lobe consolidation extending to right middle lobe. Note central low-attenuation area (arrowhead) within the dense consolidation representing ischemic change. (C) Mediastinal window image of CT scan (2.5-mm-section thickness) obtained 1 week after (B) shows large are of central necrotic area (arrowhead) within the dense consolidation.

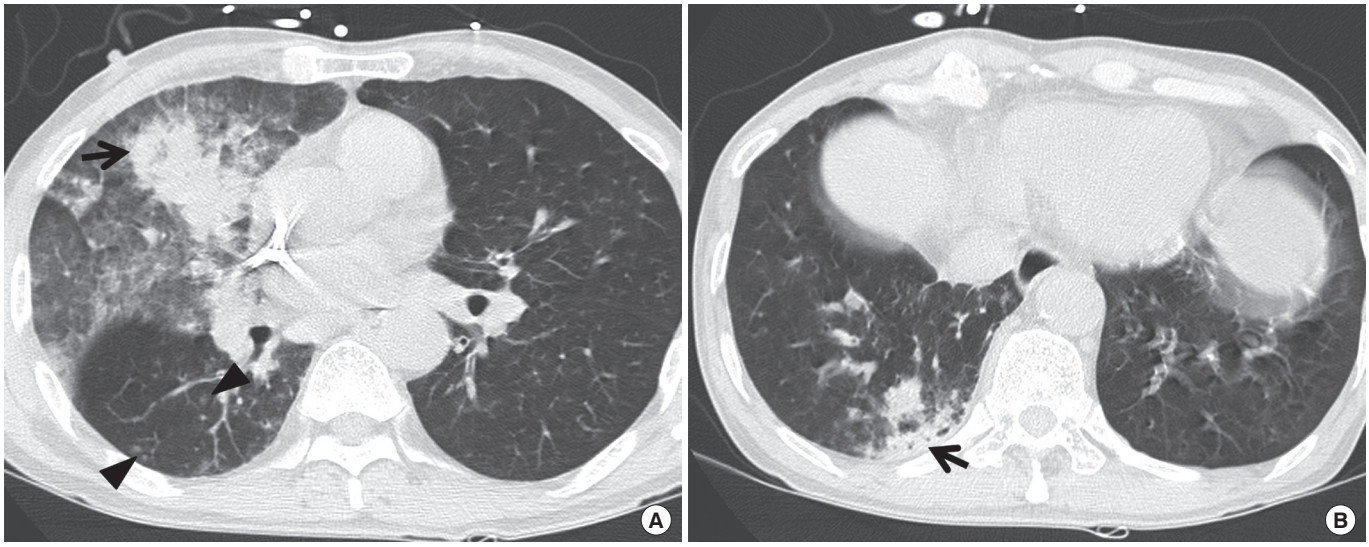

Fig. 7. Candida aspiration pneumonia in a 67-year-old man with acute myelogenous leukemia. (A, B) Lung window images of computed tomography scans (2.5-mm-section thickness) obtained at levels of left atrium (A) and liver dome (B), respectively, demonstrate multifocal consolidation (arrows) and small poorly-defined nodules (arrowheads) in right lung.

Cryptococcosis

Cryptococcosis is caused by inhalation of cryptococcal particles, which are found worldwide. Cryptococcosis predominantly occurs in immunocompetent patients as an indolent infection, but may also be seen in immunocompromised hosts. Serum cryptococcal antigen levels are helpful in the diagnosis of cryptococcosis. The most common CT finding of pulmonary cryptococcosis in immunocompetent hosts is a single or multiple nodules with varied margins (Fig. 8) [36]. In immunocompromised hosts, cavitation within nodules and parenchymal consolidation are more common and the extent of involvement is larger [37].

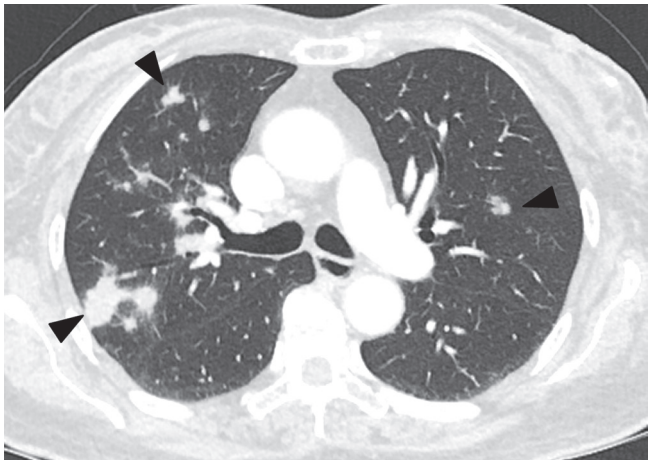

Fig. 8. Cryptococcosis in a 70-year-old woman with uncontrolled diabetes mellitus. Lung window images of computed tomography scans (2.5-mm-section thickness) obtained at level of right main bronchus depicts multifocal nodular consolidation with variable size (arrowheads) in both lungs.

P. jirovecii pneumonia

Typical radiographic findings of PJP include bilateral perihilar or diffuse ground-glass opacities, which may progress into airspace consolidation in untreated patients [38]. A nor-

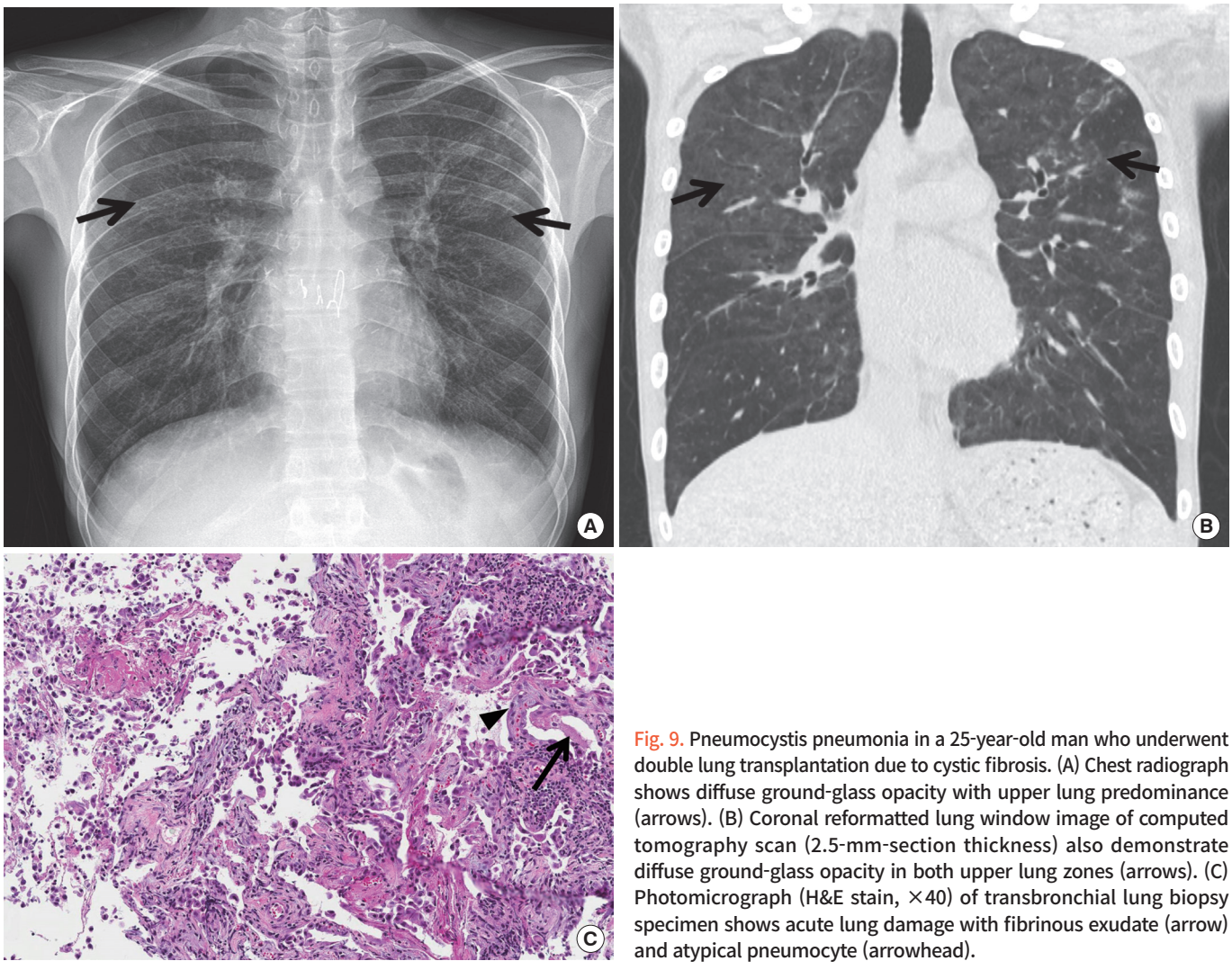

Fig. 9. Pneumocystis pneumonia in a 25-year-old man who underwent double lung transplantation due to cystic fibrosis. (A) Chest radiograph shows diffuse ground-glass opacity with upper lung predominance (arrows). (B) Coronal reformatted lung window image of computed tomography scan (2.5-mm-section thickness) also demonstrate diffuse ground-glass opacity in both upper lung zones (arrows). (C) Photomicrograph (H&E stain, ×40) of transbronchial lung biopsy specimen shows acute lung damage with fibrinous exudate (arrow) and atypical pneumocyte (arrowhead).

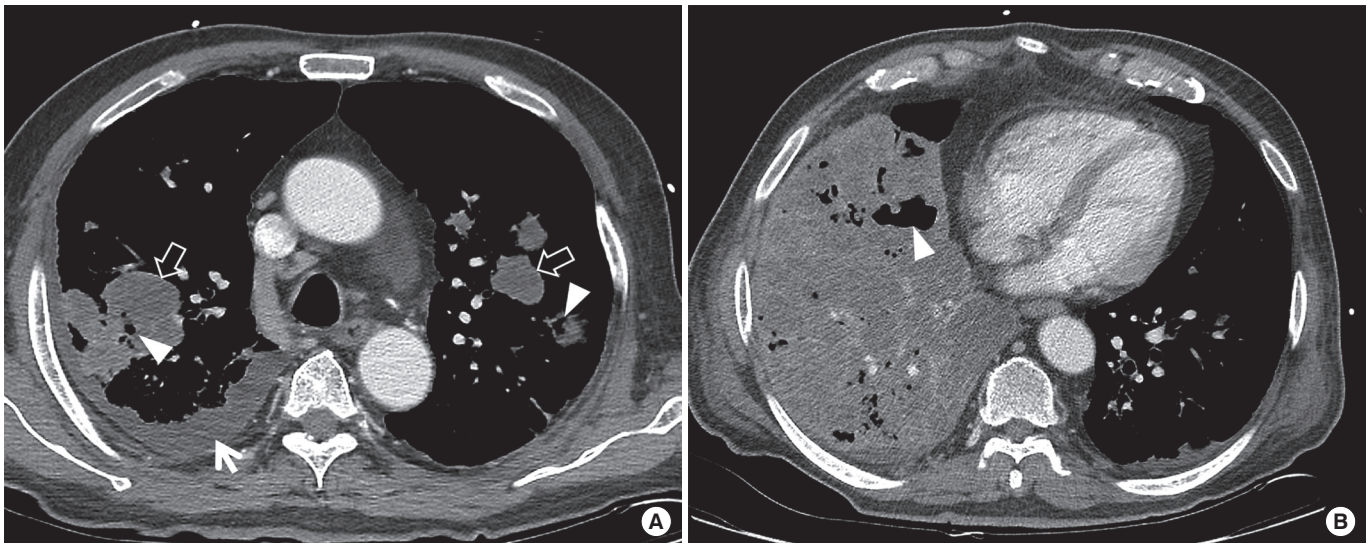

Fig. 10. Pulmonary nocardiosis in a 69-year-old man with uncontrolled diabetes mellitus. (A, B) Mediastinal window images of computed tomography scan (2.5-mm-section thickness) obtained at level of azygos arch (A) and left ventricle (B), respectively, demonstrate multifocal necrotic consolidations (open arrows) with internal cavitary change (arrowheads). Also note right pleural effusion (arrow).

mal chest radiograph has been reported in up to 39% of patients, especially in severely immunocompromised patients, and therefore does not exclude the possibility of PJP [39].

The classic CT finding of PJP is widespread ground-glass opacities, which correspond to areas of alveolar exudate (Fig. 9). The ground-glass opacities may be patchy or geographic in distribution, which typically has upper lobe and perihilar predominance. Sometimes, interlobular septal thickening overlapped by ground-glass opacities produce a so-called crazy paging appearance. Cyst formation (i.e., pneumotocele), seen in one-third of patients, is thought to be related to the infiltration of organisms into the parenchyma with subsequent necrosis and cavitation. The cysts may be variable in shape, but usually measure 5 mm to 3 cm in diameter with thin walls and upper lobe predominance [39-41].

Nocardiosis

Nocardia is a gram-positive aerobic bacillus with microscopic appearance of branching hyphae, which is found in the soil and distributed throughout the world. Nocardiosis typically occurs in immune-compromised hosts, particularly patients with lymphoma, organ transplant, chronic renal disease, or AIDS, although infection may occasionally develop in immunocompetent patients as well [42]. Typical radiographic findings of nocardiosis include nonsegmental airspace consolidation, which usually abuts the pleura. Cavitation is commonly seen in approximately one-third of patients. Pleural effusion is common, and empyema may also occur (Fig. 10A). Common CT findings include multifocal consolidation with central low-attenuation, rim enhancement, and cavitation (Fig. 10). CT may provide information on the extent of disease and may help to obtain necessary materials for a definitive diagnosis [43]. Similar to pulmonary tuberculosis or actinomycosis, nocardiosis can extend into the chest wall and form an abscess or phlegmon [44].

Viral pneumonia

The radiographic findings of CMV pneumonia include bilateral areas of ground-glass opacities and/or minimal consolidation associated with multiple pulmonary nodules typically less than 5 mm in size. The most common CT findings are bilateral ground-glass opacities, minimal areas of consolidation, and nodules less than 10 mm in size (Fig. 3) [45]. Nodules tend to show random distribution and are sometimes associated with ground-glass halo (CT halo sign). The imaging differential diagnosis for PJP or other forms of viral pneumonia is difficult, but PJP may contain small pulmonary cysts and may have a more apical distribution and more homogeneous ground-glass opacities [46].

NEW ANTIBIOTIC AGENTS FOR PNEUMONIA IN IMMUNOCOMPROMISED PATIENTS

The diagnosis of pathogens is more important for individualized management because etiologic pathogens are more di-

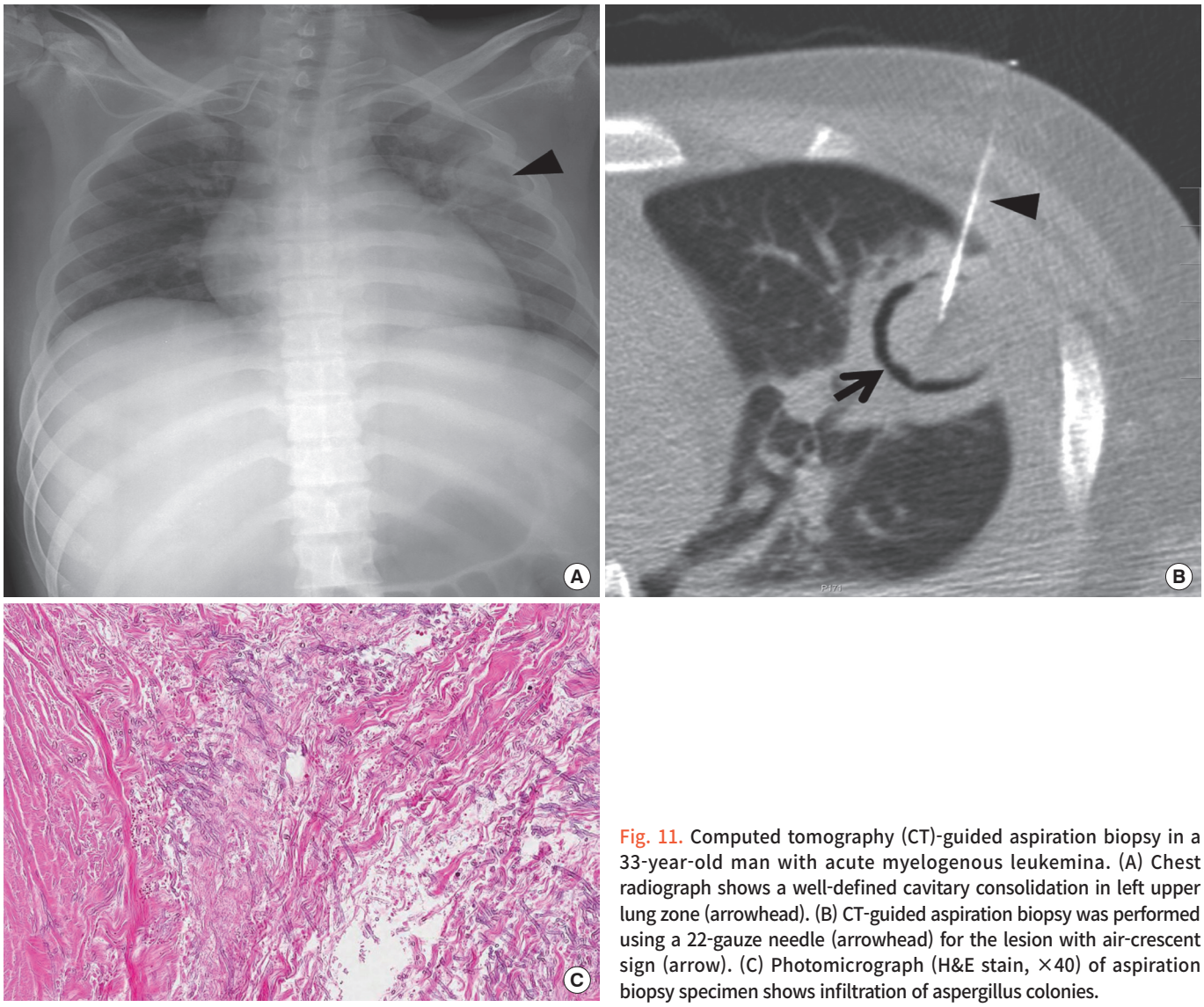

Fig. 11. Computed tomography (CT)-guided aspiration biopsy in a 33-year-old man with acute myelogenous leukemina. (A) Chest radiograph shows a well-defined cavitary consolidation in left upper lung zone (arrowhead). (B) CT-guided aspiration biopsy was performed using a 22-gauze needle (arrowhead) for the lesion with air-crescent sign (arrow). (C) Photomicrograph (H&E stain, ×40) of aspiration biopsy specimen shows infiltration of aspergillus colonies.

verse in immunocompromised patients [47]. Non-culture-based diagnostic methods based on molecular techniques and antigen detection (*Aspergillus* galactomannan antigen, β-D-glucan, and cryptococcal antigen) could be selectively used according to clinical presentations and imaging findings. Invasive diagnostic procedures including transbronchial lung biopsy, BAL, and percutaneous needle aspiration/biopsy are often needed for definite diagnosis in patients with atypical presentations [48]. Aspiration or biopsy specimens should be requested for cultures (bacterial, mycobacterial, and fungal culture) as well as pathology (Fig. 11). For the treatment of pneumonia in immunocompromised patients, it is necessary to decrease the use of immunosuppressants as much as possible, because immune restoration is important. The treatment of bacterial pneumonia will not be reviewed here because the principle is similar to treatment in immunocompetent patients.

Newer antifungal agents which are more effective against fungal infections have become available over the past 10 to 15 years. Among triazole agents, voriconazole is recommended as the primary medication for treating invasive aspergillosis [49]. Isavuconazole, in combination with liposomal amphotericin B, can be used as an alternative treatment, while posaconazole can also be used for salvage therapy. For mucormycosis, the first-line therapy involves the use of liposomal amphotericin B [50]. While voriconazole is not effective against mucormycosis, isavuconazole and posaconazole have antifungal activity against mucormycosis. When using triazoles, drug-drug interactions should be considered. *Candida* isolates from respiratory specimens should be cautiously evaluated as etiologic pathogens because *Candida* spp. are

commonly found in the oropharynx, and *Candida* pneumonia is rare. Echinocandins including caspofungin, anidulafungin, and micafungin have fungicidal activities against *Candida* spp. They are considered similarly effective when used as the primary medication for treating invasive candidiasis although metabolism, drug interactions, and clinical indications are somewhat different among echinocandins [51]. Fluconazole or voriconazole can be used as an alternative agent or step-down therapy if the isolates are susceptible. The duration of therapy for fungal pneumonia is usually determined by clinical and radiographic improvements of lesions [49].

The treatment of choice for PCP is trimethoprim/sulfamethoxazole. When trimethoprim/sulfamethoxazole fails, a combination of primaquine and clindamycin may be used. This is more effective as a secondary agent compared to others [52].

Ganciclovir is the first-line therapy for CMV pneumonia [53]. In cases that involve ganciclovir resistance, foscarnet can be used alternatively. Common respiratory viruses can cause severe pneumonia in immunocompromised patients [47]. A multiplex PCR assay for influenza, RSV, and adenovirus would be helpful for the diagnosis of viral infection. Oseltamivir or peramivir should be used if clinical suspicion of influenza is high. Based on the success reported in the use of aerosolized ribavirin, it is recommended as a treatment for patients with RSV infection [54]. Intravenous and oral ribavirin have been used successfully in some cases [55]. Palivizumab, a humanized monoclonal antibody against RSV, is effective for preventing RSV illness in children. However, there is insufficient data on its use as a treatment for established RSV pneumonia [56].

CONCLUSION

Pulmonary infection is a common cause of morbidity and mortality in immunocompromised patients. A variety of organisms can cause pulmonary infections in these patients, and the radiological findings are usually nonspecific. However, some specific organisms are more likely to cause specific types of infections during the course of immunosuppression. Therefore, it is essential to combine all clinical information on symptoms, laboratory findings, nature of underlying immune defects, and duration and severity of immunodeficiency with radiological findings. Integration of these clinical features and radiological findings can provide a more accurate differential diagnosis, and potentially reduce the morbidity and mortality associated with pulmonary infections in immunocompromised patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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