ELSEVIER

Canadian Association of Radiologists Journal 64 (2013) 200−207

CANADIAN ASSOCIATION OF RADIOLOGISTS JOURNAL

www.carjonline.org

Computed Tomography / Tomodensitométrie

Acute- or Subacute-Onset Lung Complications in Treating Patients With Rheumatoid Arthritis

Reiko Nakajima, MD[a,*], Fumikazu Sakai, MD, PhD[a], Toshihide Mimura, MD, PhD[b], Hitoshi Tokuda, MD, PhD[c], Masahiro Takahashi, MD[a], Fumiko Kimura, MD, PhD[a]

[a]*Department of Diagnostic Radiology, Saitama Medical University, Saitama International Medical Center, Saitama, Japan*
[b]*Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Saitama, Japan*
[c]*Department of Internal Medicine, Social Health Insurance Central Hospital, Tokyo, Japan*

Abstract

Rheumatoid arthritis (RA) is a common systemic disease that manifests as inflammatory arthritis of multiple joints and produces a wide variety of intrathoracic lesions, including pleural diseases, diffuse interstitial pneumonia, rheumatoid nodules, and airway disease. Patients treated for RA can have associated lung disease that commonly manifests as diffuse interstitial pneumonia, drug-induced lung injury, and infection. The purpose of this pictorial review is to illustrate the radiographic and clinical features of lung complications of acute or subacute onset in patients treated for RA and to show the computed tomography features of these complications.

Résumé

La polyarthrite rhumatoïde est une maladie systémique commune qui se manifeste sous forme d'arthrite inflammatoire touchant de multiples articulations et entraîne une grande variété de lésions intrathoraciques, dont des maladies pleurales, la pneumonie interstitielle diffuse, des nodules rhumatoïdes et des maladies des voies respiratoires. Les patients qui reçoivent un traitement contre la polyarthrite rhumatoïde peuvent souffrir d'atteintes pulmonaires associées qui se manifestent communément sous forme de pneumonie interstitielle, de lésions pulmonaires d'origine médicamenteuse et d'infections. Cette revue iconographique vise à illustrer les aspects radiographiques et cliniques des complications pulmonaires aiguës et subaiguës chez les patients qui suivent un traitement contre la polyarthrite rhumatoïde, ainsi qu'à démontrer les aspects tomodensitométriques de ces complications.

Key Words: Rheumatoid arthritis; Lung complications; Acute or subacute onset

Lung complications of acute or subacute onset (within 3 months) in patients treated for rheumatoid arthritis (RA) are divided into 2 major categories: (1) lung complications of the RA itself [1,2] and (2) those related to RA treatment, which include drug-induced lung injury (DLI) and infection. Because clinical and radiographic features of these lesions are similar, the correct diagnosis requires understanding of the combined features. In this article, we illustrate clinical and radiographic features of these conditions.

Lung Complications of RA Itself

Common acute or subacute lung complications of RA include organizing pneumonia (OP) and acute exacerbation (AE) of pre-existing chronic interstitial pneumonia (CIP). Acute interstitial pneumonia (AIP) without pre-existing CIP is rare in patients with RA.

OP

OP is one of the most frequent lung complications of RA. Imaging features are multiple nonsegmental foci of consolidation, which show subpleural or peribronchovascular distribution [3]. Ground-glass opacity (GGO) may be present in the periphery of the consolidation. Traction bronchiectasis may be identified within the consolidation. Differential

* Address for correspondence: Reiko Nakajima, MD, Department of Diagnostic Radiology, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka, Saitama, 350-1298, Japan.
E-mail address: s_reiko@saitama-med.ac.jp (R. Nakajima).

0846-5371/$ - see front matter
http://dx.doi.org/10.1016/j.carj.2011.12.017

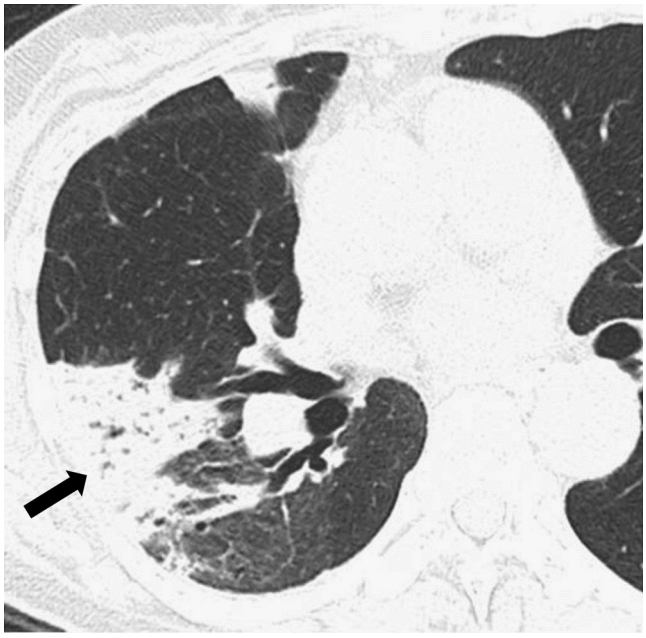

Figure 1. Organizing pneumonia (OP). A 66-year-old woman who underwent salazosulfapyridine therapy for 2 years. High-resolution computed tomography, showing multiple foci of consolidation (arrow) in the subpleural regions. She did not recover completely after administration of broad-spectrum antibiotic drugs, and a new lesion appeared in the right upper lobe. We diagnosed OP based on clinical history and exclusion of infection.

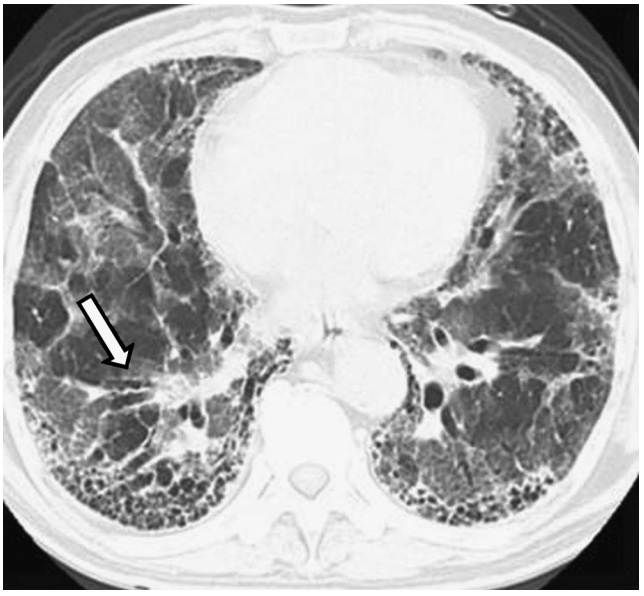

Figure 3. Drug-induced lung injury, acute interstitial pneumonia (AIP)-like pattern. Methotrexate (MTX)-induced lung injury (AIP-like pattern) in a 69-year-old man with pre-existing chronic interstitial pneumonia (CIP) who had been treated with MTX for 4 years. Computed tomography, showing bilateral heterogeneous ground-glass opacity that overlaps pre-existing interstitial pneumonia (IP) of usual (usual IP) pattern in the lower lobes. Traction bronchiectasis (arrow) is evident, which suggests diffuse alveolar damage-like pattern. Because this patient with CIP developed AE whose trigger was thought to be MTX, we diagnosed MTX-induced lung injury.

diagnosis includes bacterial pneumonia, cryptococcus pneumonia, and OP-like DLI (Figure 1 [OP]).

AE of CIP

AE of CIP may develop with RA; symptoms may rapidly progress within 1 month. In patients with RA, AE of CIP may occur with nonspecific interstitial pneumonia (NSIP) but less frequently than AE of CIP with the usual IP (UIP) pattern [2,4]. Imaging features of AE are diffuse or multiple patchy areas of GGO that overlap the features of CIP. Reticular opacity or honeycombing suggests fibrotic changes. Traction bronchiectasis and structural distortion are frequently seen as well. Comparison with previous images is useful for differentiation, and the presence of honeycomb lung suggests AE of CIP caused by AIP (Figure 2 [AE of UIP in RA]).

Complications Related to RA Treatment

Common acute or subacute lung complications include DLI and infection.

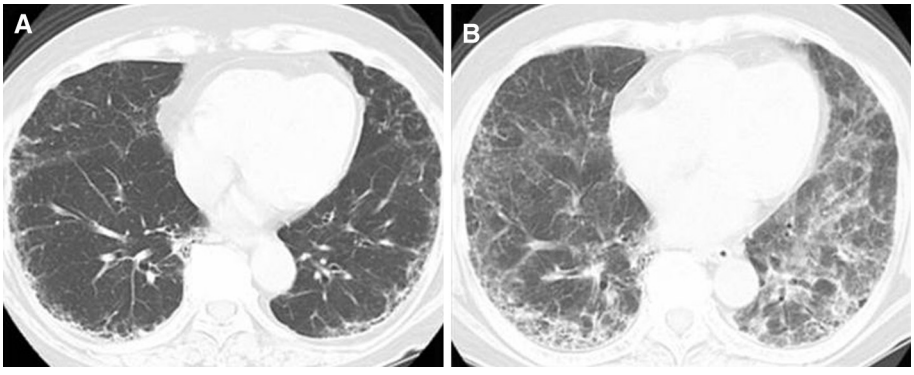

Figure 2. Acute exacerbation of chronic fibrosing interstitial pneumonia (IP). Chronic IP (CIP) of the usual interstitial pattern (usual IP pattern) in a 73-year-old woman with dyspnea for 2 weeks who had undergone therapy with bucillamine and salazosulfapyridine for 6 years. (A) High-resolution computed tomography (HRCT), showing patchy reticular opacity in the subpleural region before the onset of acute exacerbation. (B) HRCT, showing widespread ground-glass opacity that overlaps pre-existing shadow at the onset of lung disease within 1 month. Her rheumatoid arthritis was poorly controlled, and she did not change medicine at the onset of signs. A diagnosis of acute exacerbation of CIP was more likely than drug-induced lung injury.

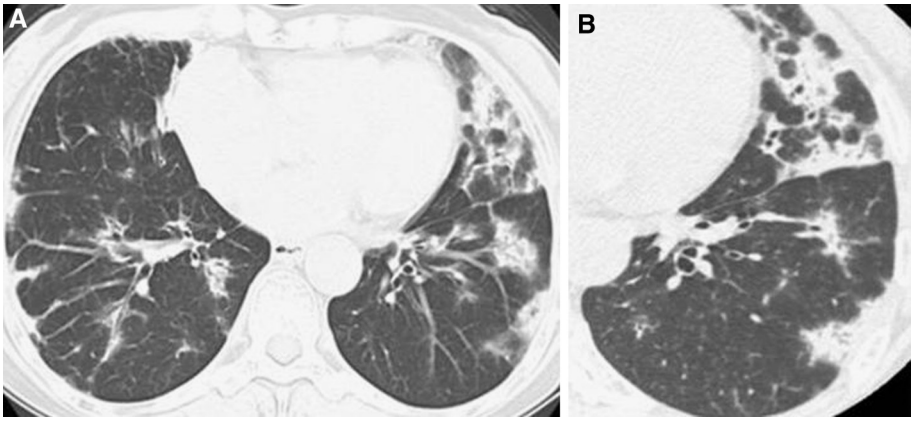

Figure 4. Drug-induced lung injury, organizing pneumonia (OP)-like pattern. Methotrexate (MTX)-induced lung injury (OP-like pattern) in a 73-year-old man with a dry cough and fever who had been treated with MTX for 3 months. (A) Computed tomography (CT) and (B) high-resolution CT, showing multiple foci of consolidation in the subpleural and peribronchovascular regions.

DLI

Although glucocorticoid and many disease-modifying antirheumatic drugs have been used to treat patients with RA, low-dose methotrexate (MTX) is the recent standard treatment [5]; use of anticytokine biologic drugs, such as infliximab, etanercept, and tocilizumab, has also spread rapidly. Because autoimmune mechanisms play an important role in DLI, patients with RA seem more susceptible to DLI.

Clinical Features of DLI

Clinical signs and symptoms of DLI are nonspecific respiratory symptoms, such as dry cough and exertional dyspnea. There are no reliable noninvasive laboratory tests for diagnosing DLI. Accurate diagnosis requires integration of clinical, imaging, and laboratory findings, and includes observation of the temporal relationship between onset of signs and administration of suspicious drugs, the exclusion of infection, and the progression of complications of RA itself. One of the most important roles of imaging diagnosis in the evaluation of DLI is the detection of pre-existing CIP and other destructive diseases, which constitute one of the most important risk factors of DLI.

Imaging Features of DLI

Fundamental imaging features of DLI are patchy or diffuse GGO and/or consolidation that is occasionally accompanied by reticular opacity and interlobular septal thickening. Images of DLI have been classified by similarities to idiopathic forms of lung injury. Based on imaging features, patterns of DLI are classified as AIP-like, OP-like, hypersensitivity pneumonia (HP)-like, eosinophilic pneumonia-like, or NSIP- like pattern, or as unclassifiable [6]. However, because pathologic findings have not been fully evaluated, the application of such imaging classification of DLI is limited. Although DLI caused by a particular drug frequently demonstrates a specific pattern, DLI caused by a single drug may manifest with different pathologic and/or imaging patterns. On computed tomography (CT), the most frequent pattern of MTX-induced DLI is an HP-like pattern; diffuse or widespread patchy GGO that corresponds to pathologic findings of lymphocytic infiltration, with small

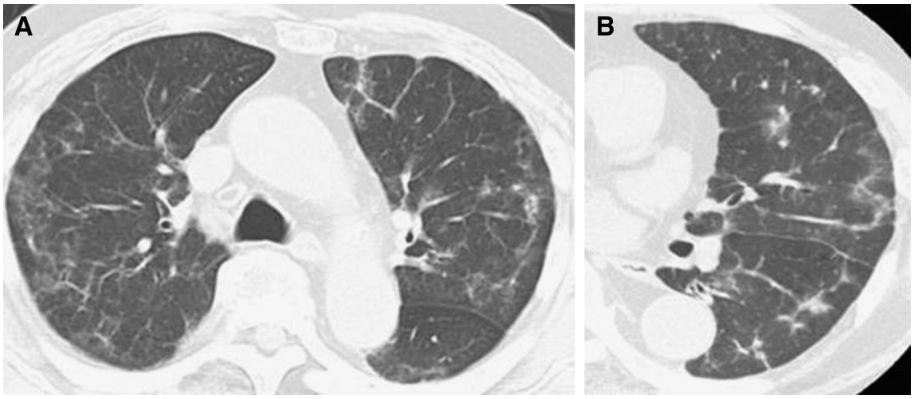

Figure 5. Drug-induced lung injury, nonspecific interstitial pneumonia (NSIP)-like pattern. Bucillamine-induced lung injury (NSIP-like pattern) in a 74-year-old man with dyspnea who had been treated with bucillamine for 2 months. (A) Computed tomography (CT) and (B) high-resolution CT, showing multiple foci of ground-glass opacity along the bronchovascular bundles that mimic NSIP.

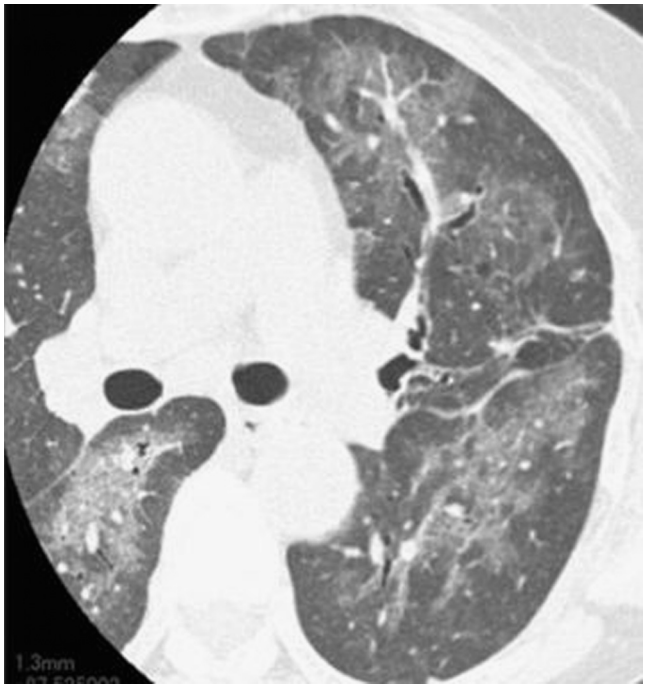

Figure 6. Drug-induced lung injury (DLI), hypersensitivity pneumonia (HP)-like pattern. Methotrexate (MTX)-induced lung injury (HP-like pattern) in a 67-year-old woman with dyspnea who had been treated with MTX for 1 month. High-resolution computed tomography, showing diffuse ground-glass opacity, without structural distortion. The patients discussed in Figures 4–6 changed medications just before the onset of signs. These patients should be considered as DLI after exclusion of infection.

granuloma formation that suggests allergic mechanism [7]. MTX-induced malignant lymphoma may also show acute or subacute onset with generalized symptoms, such as fever (Figure 3 [DLI AIP-like]; Figure 4 [DLI OP-like]; Figure 5 [DLI NSIP-like]; Figure 6 [DLI HP-like MTX]; Figure 7 [MTX-induced malignant lymphoma]).

Infection

The combination of MTX and anticytokine biologic drugs has become a standard therapeutic regimen for RA, but it induces immunodeficiency that may cause opportunistic infection, one of the most serious and frequent complications. In patients with RA, bacterial pneumonia is the most frequent infection, but tuberculosis, fungal infection, *Pneumocystis jiroveci* pneumonia (PcP), and other pneumonia may occur as opportunistic infections. The criterion standard for diagnosing infection is the bacteriologic and/or serologic identification of causative organisms, but other auxiliary tests may be useful.

Bacterial Infection

Bacterial pneumonia is the most frequent infection in patients treated for RA and may be diagnosed with the tests for urine antigens of *Streptococcus* pneumonia and *Legionella pneumophila.* Imaging features of bacterial pneumonia include consolidation from lobular size to lobar distribution (Figure 8 [bacterial pneumonia]).

Mycobacterial Infection

Recently, the wide use of anticytokine biologic drugs has increased the risk of tuberculosis in patients with RA. Prophylactic administration of antituberculous drugs is recommended in patients at high risk for tuberculosis, such as those with pre-existing tuberculosis or diabetes mellitus or those who have undergone glucocorticoid treatment. Standard tests to identify *Mycobacterium tuberculosis* include acid-fast bacillus staining and/or polymerase chain reaction (PCR) for sputum or gastric juice. QuantiFERON (Cellestis Limited, Carnegie, Victoria, Australia) is a more sensitive and specific test to diagnose tuberculosis that can detect *Mycobacterium tuberculosis* infection more accurately than the tuberculin purified protein derivative skin test [8,9].

Imaging features of postprimary tuberculosis include a small, well-circumscribed, nodular opacity approximately 5–10 mm in diameter that typically shows centrilobular distribution. Large cavitary nodule and/or mass shadow or consolidation may be seen. Miliary tuberculosis involves the hematogenous spread of tuberculosis bacilli and appears as

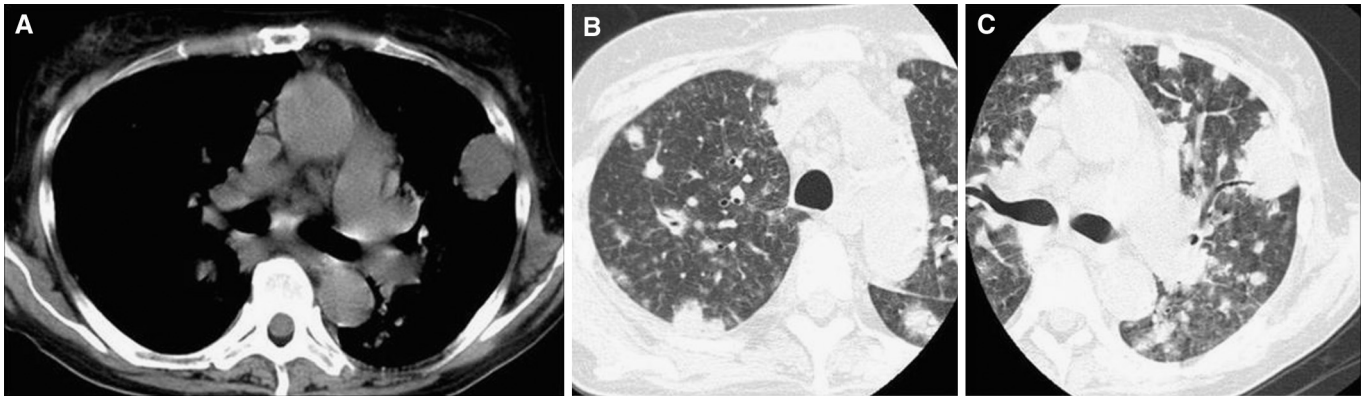

Figure 7. Methotrexate (MTX)-induced malignant lymphoma. MTX-induced malignant lymphoma in a 54-year-old man with fever and cough who was treated with MTX for several years. (A) Computed tomography (CT) and (B, C) high-resolution CT, showing multiple nodular and/or mass opacities, with peribronchovascular distribution. Figure courtesy of M. Ishida, MD, Department of Clinical Medicine, Institute of Tropical Medicine, Nagasaki University, Japan.

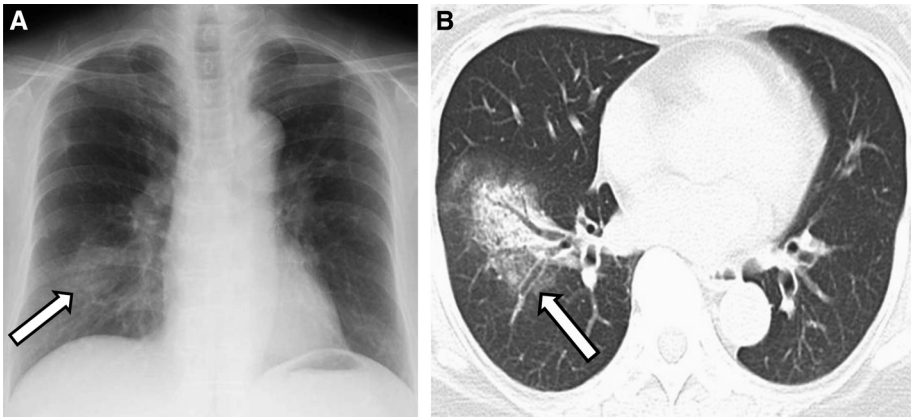

Figure 8. Bacterial pneumonia. Bacterial pneumonia in a 65-year-old woman with fever, cough, and sputum who had received steroid treatment for 1 year. (A) Chest radiograph and (B) computed tomography, showing unilateral and segmental focus of consolidation (arrows). Diagnosis of bacterial pneumonia is based on positive urine *Streptococcus pneumoniae* antigen.

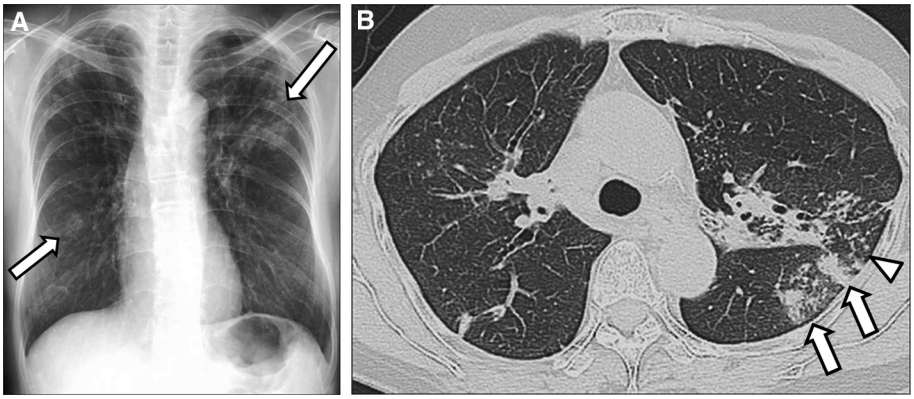

Figure 9. Tuberculosis. Pulmonary tuberculosis in a patient with rheumatoid arthritis treated with tumour necrosis factor inhibitors (infliximab) and methotrexate. (A) Chest radiograph, showing consolidation in bilateral lobes (arrows). (B) High-resolution computed tomography, showing centrilobular foci consolidation (arrow), nodules, and branching opacity (tree-in-bud appearance [arrowhead]) in the left upper lobe. *Mycobacterium tuberculosis* was identified from sputum.

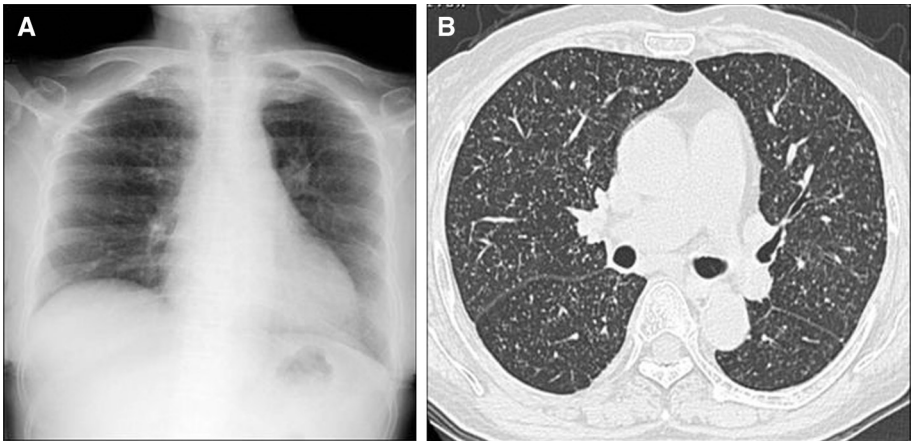

Figure 10. Miliary tuberculosis. Miliary tuberculosis in a 65-year-old woman with cough who had been treated with tocilizumab for 2 years. (A) Chest radiograph and (B) high-resolution computed tomography, showing multiple miliary nodules with random distribution. Diagnosis of miliary tuberculosis is based on bacteriologic detection of *Mycobacterium tuberculosis* from sputum and gastric juice.

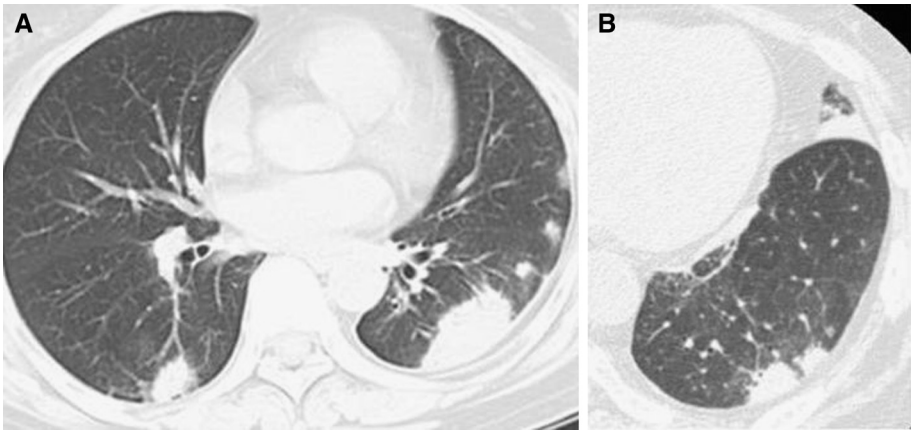

Figure 11. *Cryptococcosis. Cryptococcosis* in a 71-year-old woman with cough who had been treated with bucillamine for 2 years. (A) Computed tomography (CT) and (B) high-resolution CT, showing multiple subpleural nodules and/or consolidation in the lower lobes that mimic cryptogenic organizing pneumonia. The patient's symptoms and radiologic abnormalities resolved after institution of fluconazole therapy.

randomly distributed fine nodular opacities less than 2 mm in diameter (Figure 9 [tuberculosis]; Figure 10 [miliary tuberculosis]). In patients with RA, airway injury and decreased immunity from treatment may cause vulnerability to nontuberculous mycobacteriosis. Imaging features may mimic tuberculosis or present nodular or patchy consolidation predominantly in the right middle lobe and left lingula. Administration of anticytokine biologic drugs may be restricted in cases with nontuberculous mycobacteriosis [10].

Fungal Infection

Fungal infection, such as *Aspergillus* and *Cryptococcus neoformans,* is also seen in patients with RA. Invasive aspergillosis is rare in patients with RA. Structural distortion and decreased immunity from RA may increase the risk of chronic necrotizing aspergillosis (Figure 11 [cryptococcosis]; Figure 12 [chronic necrotizing aspergillosis]).

PcP

One of the most common infections in patients with RA is PcP. The criterion standard for its diagnosis is appropriate staining to identify the organism in respiratory tract secretion. In most PcP in patients treated for RA, sputum shows positive PCR with negative staining of *P jiroveci.* Serum β-D glucan is a useful auxiliary test for PcP; with a cut-off level estimated at 31.1 pg/mL, sensitivity of 92%, and specificity of 86% [11]. Imaging features of PcP include GGO without structural distortion. GGO may show panlobular or multilobular distribution with sharp demarcation [12] (Figure 13 [PcP]).

Diagnosis Pitfall

In patients treated for RA, radiographic features of lung complications of acute or subacute onset often overlap. Especially, diffuse GGO is frequently seen in many diseases. Correct differential diagnosis requires knowledge of and attention to clinical and imaging features and exclusion of infection with laboratory tests (Figures 14–16).

Conclusion

Although lung complications of acute or subacute onset in patients with RA are often difficult to diagnose, knowledge of their combined clinical signs and course, as well as laboratory and radiologic findings, is an important tool in assessing these patients.

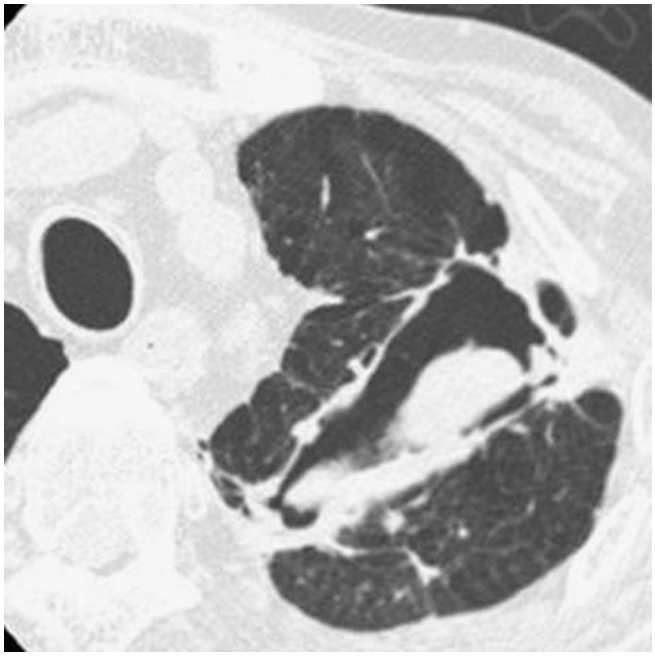

Figure 12. Chronic necrotizing aspergillosis. Chronic necrotizing aspergillosis in a 62-year-old man who had received steroid treatment. High-resolution computed tomography, showing a large cavity lesion that contained a fungus ball in the left upper lobe. *Aspergillus fumigatus* was identified from sputum.

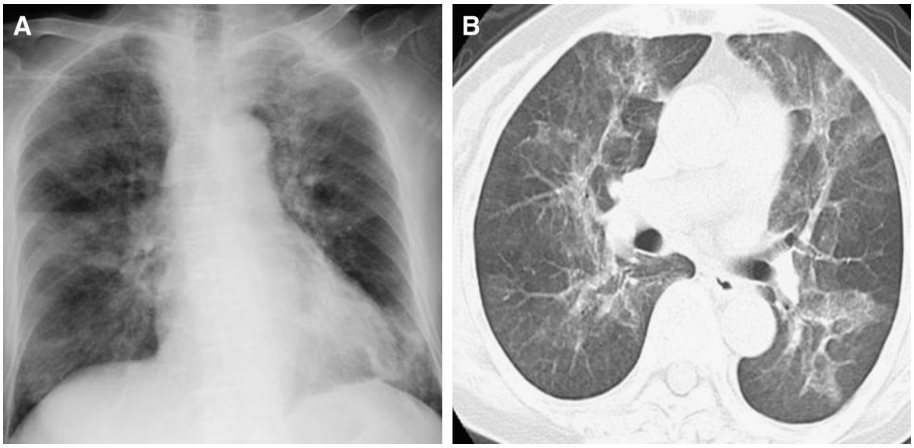

Figure 13. *Pneumocystis jiroveci* pneumonia (PcP). Presumptive PcP in a 74-year-old woman with dyspnea and cough who was treated with a tumour necrosis factor inhibitor (infliximab) for 1 month. (A) Chest radiograph and (B) computed tomography, showing bilateral patchy ground-glass opacity with peripheral sparing. Serum β-D glucan >31.1 pg/mL, bronchoalveolar lavage: positive *Pneumocystis* polymerase chain reaction.

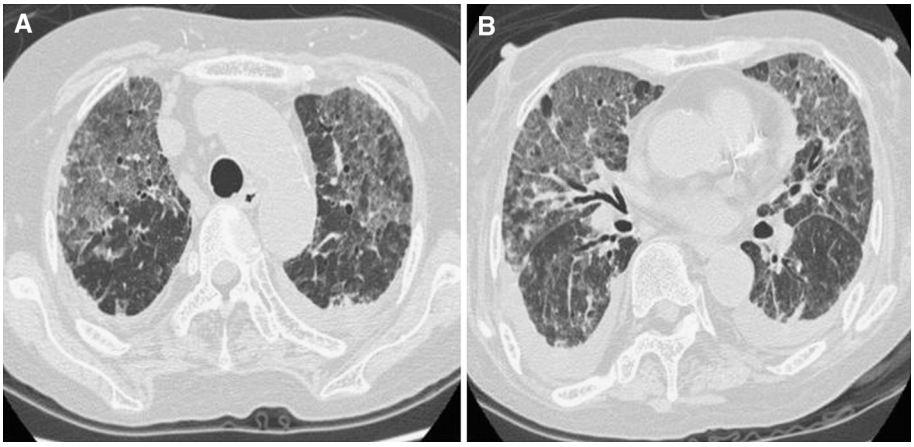

Figure 14. A 65-year-old man with pre-existing chronic interstitial pneumonia (IP) of usual pattern who had been treated with bucillamine for 3 years. (A, B) Computed tomography at onset, showing widespread patchy ground-glass opacity and peripheral sparing. Laboratory data: white blood cell count, 11090/μL (neutrophils, 92.2%); C-reactive protein, 7.99 mg/dL; KL-6, 1880 U/mL; serum β-D glucan, 112 pg/mL. Bronchoalveolar lavage (BAL): positive *Pneumocystis* polymerase chain reaction (PCR), negative Groccot stain of sputum. Diagnosis of *Pneumocystis jiroveci* pneumonia was based on increased serum β-D glucan and positive *Pneumocystis* PCR on BAL.

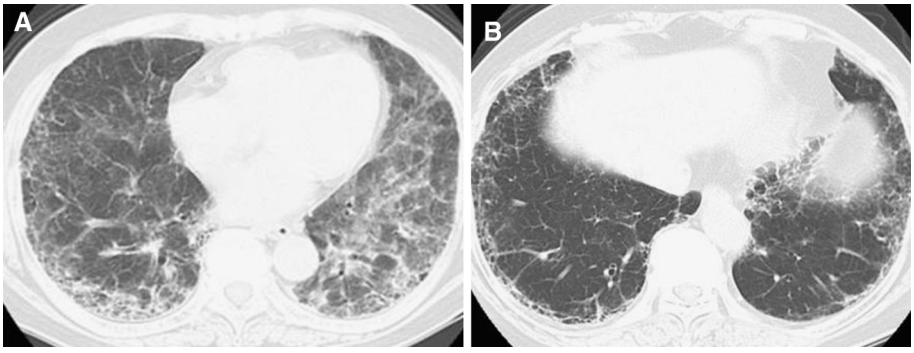

Figure 15. An 87-year-old man with dyspnea who was treated with bucillamine for 2 year. (A) Computed tomography (CT) findings at onset, showing diffuse, patchy ground-glass opacity (GGO) and reticular opacity in the lower lobes. (B) CT findings before onset show patchy reticular opacity in the subpleural region. Laboratory data: KL-6, 2058 U/L; surfactant protein-D, 415.7 ng/mL; Serum β-D glucan, 13.8 pg/mL. Bronchoalveolar lavage: negative Grocott stain; negative *Pneumocystis* polymerase chain reaction. First, we suspected bucillamine-induced lung injury. However, her symptoms and CT abnormalities did not improve despite cessation of bucillamine, so we thought acute exacerbation of usual (usual interstitial pneumonia) pattern was more likely than drug-induced lung injury.

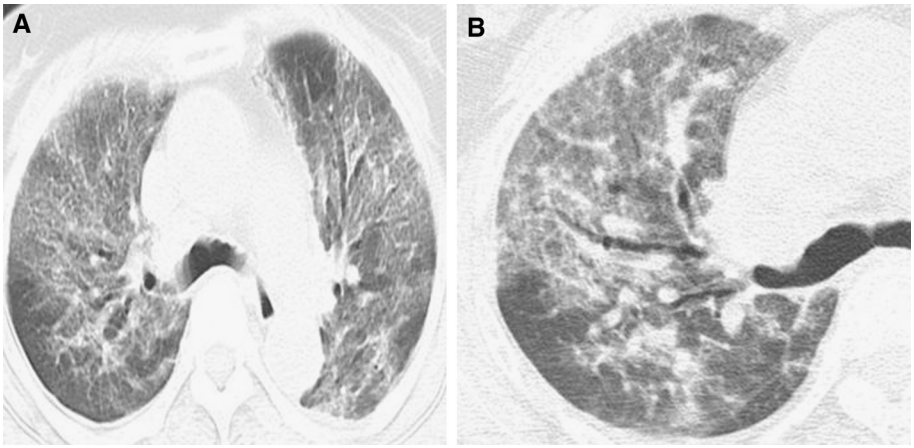

Figure 16. A 75-year-old man with no lung disease who had been treated with methotrexate (MTX) for 4 years. (A) Computed tomography (CT), showing bilateral heterogeneous ground-glass opacity (GGO) and traction bronchiectasis in the lower lobes. (B) High-resolution CT, showing diffuse thickening of the interlobular septa and a scattered area of GGO. Laboratory data: white blood cell count, 19220/μL; (neutrophils: 91.4%); C-reactive protein, 16 mg/dL; KL-6, 1880 U/mL; Serum β-D glucan, <6.0 pg/mL. Bronchoalveolar lavage: negative *Pneumocystis* polymerase chain reaction, and bacteria. Diagnosis of acute drug-induced lung injury caused by MTX was based on exclusion of acute interstitial pneumonia, with no pre-existing chronic interstitial pneumonia; such a diagnosis is rare in patients with rheumatoid arthritis.

Acknowledgements

This study was partly supported by a grant to the Diffuse Lung Disease Research Group from the Ministry of Health, Labour and Welfare, Japan. We thank Drs Minoru Kanazawa, of the Department of Respiratory Medicine, Saitama Medical University Hospital, and Noriko Kamata, of the Department of Radiology, Tokyo Metropolitan Komagome Hospital, for their assistance.

References

[1] Tanaka N, Kim JS, Newell JD, et al. Rheumatoid arthritis–related lung diseases: CT findings. Radiology 2004;232:81–91.

[2] Park IN, Kim DS, Shim TS, et al. Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. Chest 2007;132: 214–20.

[3] Lee JS, Lynch DA, Sharma S, et al. Organizing pneumonia: prognostic implication of high-resolution computed tomography features. J Comput Assist Tomogr 2003;27:260–5.

[4] Kondoh Y, Taniguchi H, Kawabata Y, et al. Acute exacerbation in idiopathic pulmonary fibrosis. Analysis of clinical and pathologic findings in three cases. Chest 1993;103:1808–12.

[5] Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 Recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008;59:762–84.

[6] Rossi SE, Erasmus JJ, McAdams HP, et al. Pulmonary drug toxicity: radiologic and pathologic manifestations. RadioGraphics 2000;20: 1245–59.

[7] Arakawa H, Yamasaki M, Kurihara Y, et al. Methotrate-induced pulmonary injury: serial CT findings. J Thorac Imaging 2003;18: 231–6.

[8] Mori T, Sakatani M, Yamagishi F, et al. Specific detection of tuberculosis infection with an interferon-gamma based assay using new antigens. Am J Respir Crit Care Med 2004;170: 59–64.

[9] Brock I, Weldingh K, Lillebaek T, et al. Comparison of tuberculin skin test and new specific blood test in tuberculosis contacts. Am J Respir Crit Care Med 2004;170:65–9.

[10] Winthrop KL, Chang E, Yamashita S, et al. Nontuberculous mycobacteria infections and anti–tumor necrosis factor-α therapy. Emerg Infect Dis 2009;15:1556–61. Available at: http://www.cdc.gov/eid/content/15/10/pdfs/1556.pdf. Accessed January 18, 2012.

[11] Tasaka S, Hasegawa N, Kobayashi S, et al. Serum indicators for the diagnosis of Pneumocystis pneumonia. Chest 2007;131: 1173–80.

[12] Rettner P, Ward S, Heyneman L, et al. Pneumonia: high-resolution CT findings in 114 patients. Eur Radiol 2003;13:515–21.