Case report

Pseudomembranous and Ulcerative Aspergillus Tracheobronchitis in a Patient with Systemic Lupus Erythematosus and Malignant Lymphoma

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Abstract: We report a case of pseudomembranous and ulcerative Aspergillus tracheobronchitis in a middle-aged female who had been diagnosed with systemic lupus erythematosus (SLE) in her third decade of life and non-Hodgkin lymphoma (NHL) in her sixth decade of life. After undergoing chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone [R-CHOP] for NHL, she received 17.5 mg/day of oral prednisolone and her general condition remained stable. Three months after completion of chemotherapy, she reported chest pain and a cough. Chest CT showed multiple centrilobular nodules with focal cavities. Bronchoscopy showed multiple white pseudomembranes and ulcers in the left second carina and left superior lobar branch. Bronchial washing and biopsies revealed Aspergillus infection. She was treated successfully with oral antifungal drugs. Cases of pseudomembranous and ulcerative Aspergillus tracheobronchitis are rare. Bronchoscopy may be a useful diagnostic tool and predictor of prognosis for invasive pulmonary Aspergillosis.

Key Words: Aspergillus tracheobronchitis, Systemic lupus erythematosus, Malignant lymphoma, Ulcerative tracheobronchitis.

Main document

We report a case of pseudomembranous and ulcerative Aspergillus tracheobronchitis in a middle-aged female. She had been diagnosed with systemic lupus erythematosus (SLE), for which she received 10 mg prednisolone (PSL) once daily, during her third decade of life. In her sixth decade of life,

Received: June 26, 2014. Accepted: July 21, 2015
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she noticed lymph node swelling in her axilla, groin, and anterior chest. Biopsy of the lymph node revealed non-Hodgkin's lymphoma (NHL) (diffuse large B cell lymphoma, Ann Arbor stage ⅣA). She was treated with rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) for 6 months, and complete remission was achieved. After discharge, she received 17.5 mg/day of oral prednisolone and her general condition remained stable. Three months after completion of chemotherapy, she reported pain in the right side of her chest and a cough. Physical examination upon admission (Day 0) revealed slightly anemic conjunctiva and mild pain on the right side of the chest. No deformities, pain, tenderness, swelling, or redness of the trunk or extremities were observed.

Laboratory findings on Day 0 were as follows (Table 1). Hemoglobin level and platelet count were low (10.1 g/dL and 99,000 cells/mm3, respectively). White blood cell count (WBC) was 5800 cells/μL and contained 85.3% neutrophils and 11.8% lymphocytes. Serum C-reactive protein (CRP) and lactate dehydrogenase (LDH) were elevated (3.00 mg/dL and 551 IU/L, respectively), and the (1,3)-β-D-glucan was 11.0 pg/mL. The patient tested negative for QuantiFERON TB3G, Aspergillus antigen (Ag), candida Ag, and cryptococcus Ag.

Chest radiograph obtained on Day 1 showed a 15-mm nodule in the right middle lobe of the lung and small nodules in the left middle and lower lobes of the lung (Fig. 1). Chest computed tomography (CT) obtained on Day 1 showed a 15-mm cavitated nodule on the right middle lobe and multiple small nodules on the left lingual, one of which showed cavitation (Fig. 1).

Bronchoscopy was performed on Day 6 and showed multiple white pseudomembranes and ulcers on the left second carina and left superior lobar branch. Bronchial washing and biopsies revealed

Table 1. Laboratory findings on Day 0

CBC		ALB	2.3 g/dl	ANA	×160	Others	
WBC	8000 /μL	T-Bil	0.45 mg/dl	Homogene	×160	β D glucan	11.0pg/ml
Lymph	14.8 %	BUN	10.1 mg/dl	Speckled	×160	QFT-G 3G	(−)
Neut	82.9 %	Cre	0.46 mg/dl	Anti dsDNA-Ab	(−)	Aspergillus Ag	(−)
Mono	2.1 %	Na	142 mmol/L	Anti RNP-Ab	(−)	Candida Ag	(−)
Eos	0.0 %	K	3.7 mmol/L	Anti SSA-Ab	(−)	Cryptococcus Ag	(−)
Hb	8.5g/dl	Cl	105 mmol/L	Anti SSB-Ab	(−)	C7HRP	1/60200
Ht	26.1 %	CRP	2.59 mg/dl	Anti centromere-Ab	(−)		
Plt	177000 /uL	Ferritin	361 ng/ml	Anti Scl70-Ab	(−)		
Biochemistry		C3	72.9 mg/dl	Anti Jo1-Ab	(−)		
LDH	442 IU/L	C4	19.5 mg/dl	PR3-ANCA	<10EU		
AST	35 IU/L	CH50	40.0 U/ml	MPO-ANCA	<10EU		
ALT	36 IU/L	IgG	620 mg/dl				
ALP	308 IU/L	IgA	127 mg/dl				
TP	4.7 g/dl	IgM	22 mg/dl				

WBC: white blood cell, Hb: hemoglobin, Ht: hematocrit, Plt: platelet, LDH: lactate dehydrogenase, AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, TP: total protein, ALB: albumin, T-Bil: total bilirubin, BUN: blood urea nitrogen, Cre: creatinine, CRP: C-reactive protein, CH50: 50% hemolytic unit of complement, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, ANA: antinuclear antibody, dsDNA: double-stranded DNA, RNP: ribonucleoprotein, PR3-ANCA: proteinase-3 anti-neutrophil cytoplasmic antibody, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, QFT-3G: QuantiFERON-TB-Gold 3G, C7HRP: C7-horseradish peroxidase

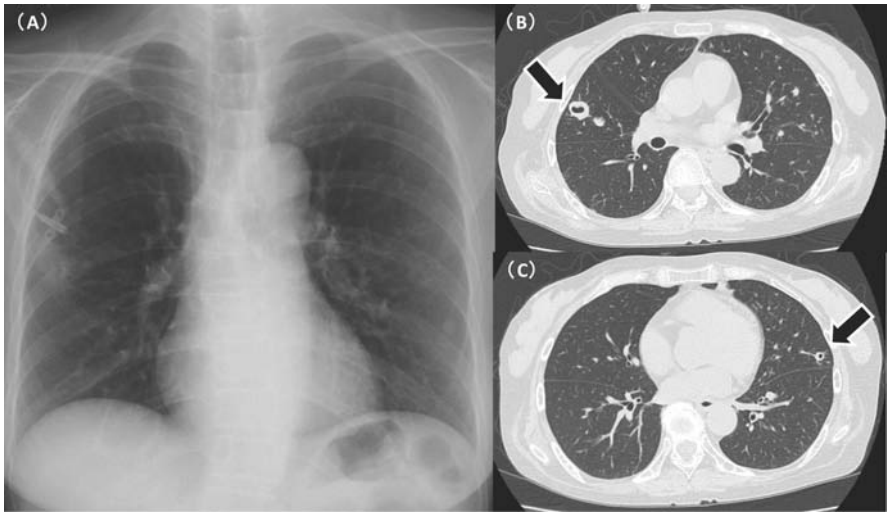

Fig. 1. Radiograph and computed tomography of the chest performed on Day 1 of hospital admission

(A) Chest radiograph shows a 15-mm nodule in the right middle lung and small nodules in the left middle and lower lung.

(B) Chest CT shows a 15-mm cavitated nodule in the right middle lobe (arrow) and multiple small nodules in the left lingula.

(C) One of small nodules in the lingula (arrow) shows cavitation.

Aspergillus fumigatus (Fig. 2), and Aspergillus tracheobronchitis was diagnosed.

Oral voriconazole (VRCZ, 300 mg two times per day), an antifungal medication, was administered initially but was replaced with intravenous micafungin (MCFG, 150 mg daily) due to deterioration of liver function immediately after starting VRCZ. Her symptoms resolved gradually, and MCFG was replaced with oral itraconazole (ITCZ, 200 mg twice daily). Follow-up chest CT showed the cavitated nodule in the right middle lobe had decreased in size and the cavity had disappeared (Fig. 3).

Discussion

Pulmonary Aspergillosis is caused mainly by *Aspergillus fumigatus* and is a major cause of morbidity and mortality in severely immunocompromised patients. Risk factors for Aspergillus infection include severe neutropenia, hematopoietic stem cell and solid organ transplantation, acquired immunodeficiency syndrome (AIDS), and chronic granulomatous disease[1]. SLE and NHL were underlying diseases in this case report, and we identified an Aspergillus infection after the patient had undergone R-CHOP therapy. The mortality rate from invasive Aspergillosis is about 50% for patients with leukemia or lymphoma and about 95% for patients with SLE[2]. Therefore, early diagnosis in severely immunocompromised individuals is essential.

Tracheobronchitis is a rare manifestation of Aspergillus infection, as it occurs in less than 7% of patients with invasive pulmonary Aspergillosis[3]. Cases of Aspergillus tracheobronchitis have been reported after allogeneic bone marrow transplantation[4)5)], and development of pseudomembranous Aspergillus tracheobronchitis after receiving anticancer drugs has been reported[6)7)]. However, cases of pseudomembranous and ulcerative Aspergillus tracheobronchitis in patients with SLE and NHL are

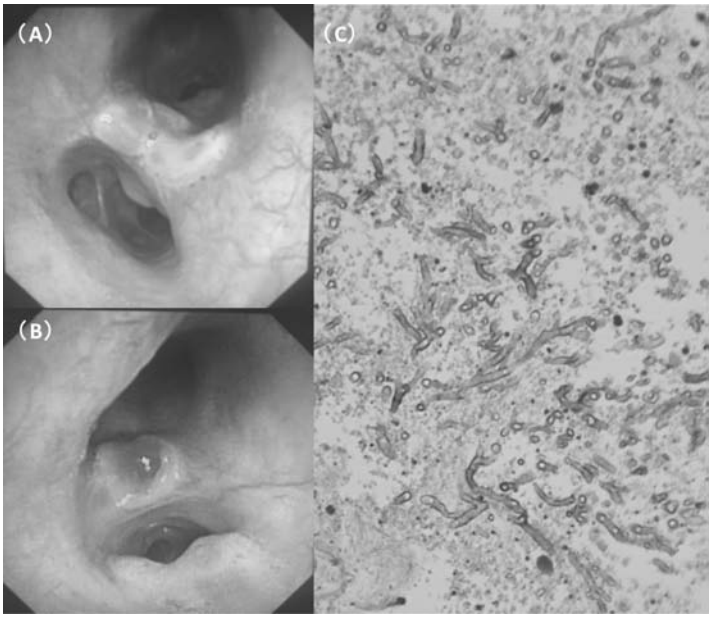

Fig. 2. Bronchoscopy and bronchial biopsy.
(A) and (B) Bronchoscopy shows white multiple pseudomembranes and ulcers in the left second carina and left superior lobar branch.
(C) Bronchial biopsies reveal Aspergillus fumigatus.

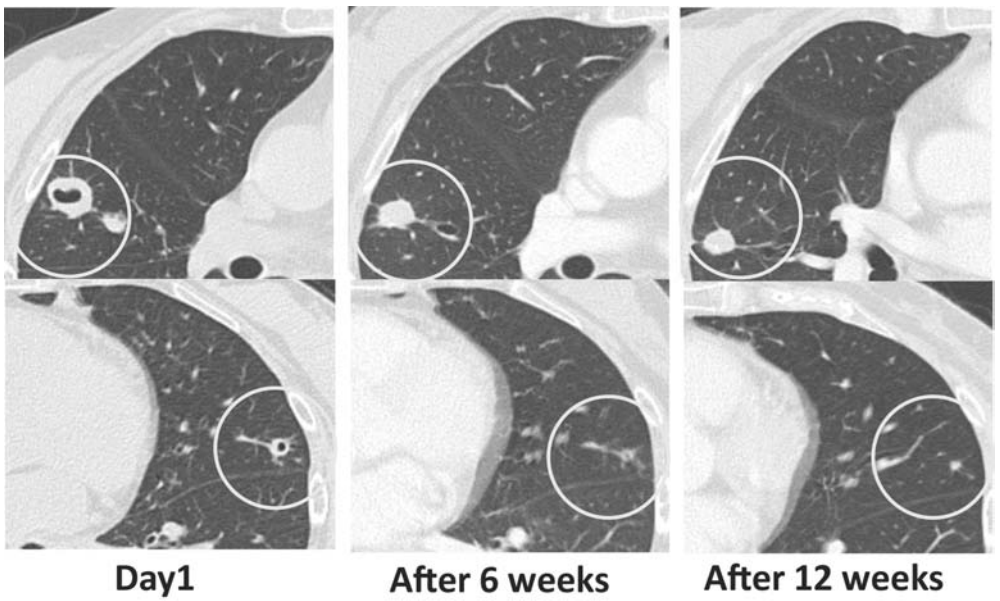

Fig. 3. Chest CT examination after the use of antifungal drugs.
Chest CT shows the contraction of a cavitated nodule after 6 and 12 weeks of antifungal drug administration.

rare[8-10].

In this case, the chest CT showed multiple small nodules in the left lingula and cavitated nodules in the right middle lobe and left lingula. The cavitated nodule in the right middle lobe was 15 mm and partially calcified. Aspergillus grows rapidly in cavitated lesions formed by lung tuberculosis or cystic pulmonary diseases because the normal immune system is not functional within these lesions[11]. Therefore, Aspergillus may have developed and grown rapidly in the cavitated, calcified lesion of the right middle lobe, which may explain the large size (15 mm) of this nodule relative to the others.

A chest CT demonstrating invasive pulmonary Aspergillosis usually shows some nodules or masses surrounded by a halo of ground-glass attenuation or pleura-based, wedge-shaped areas of consolidation[12]. Aspergillus tracheobronchitis, a form of invasive pulmonary Aspergillosis, is characterized by centrilobular nodules and branching linear or nodular areas of increased attenuation that have a tree-in-bud appearance on high-resolution CT[12]. Similarly, multiple nodules were visible on CT in the present case.

One study reported that serology for Aspergillus infection is positive in only 8% of the cases, whereas 50% of bronchial secretions test positive for histologically confirmed Aspergillus infection[13]. Furthermore, this study showed characteristic CT findings of pulmonary Aspergillosis in about 84% of the cases. In our case, the Aspergillus antigen and (1,3)- β-D-glucan were within normal limits. However, we diagnosed the infection early using chest CT and bronchoscopy evaluation, which enabled early therapeutic intervention.

Borna et al. defined three patterns of pulmonary Aspergillus infectioninlung transplant recipients[14]. The first is airway colonization, which involves isolation of Aspergillus species from bronchial specimens in patients without clinical, endoscopic, radiographic, or histologic evidence of invasive disease. The second is isolated tracheobronchitis, which is defined as the isolation of Aspergillus species from endobronchial specimens, the presence of one or more endobronchial lesions without an alternative diagnosis, and no clinical, radiographic, or histologic evidence of invasive parenchymal disease. The third is invasive Aspergillosis, which is defined by radiographic evidence of nodules, infiltrates, cavities, or pleural disease, along with histologic evidence of tissue invasion and isolation of the organism from respiratory specimens with or without evidence of dissemination to other organs. In our case, the chest CT showed multiple small nodules or cavitated nodules in the lung field, and the patient' s report of chest pain suggested that the Aspergillus infection invaded the pleural lesion. Based on these findings, we diagnosed this case as Aspergillus tracheobronchitis, a sub-entity of invasive Aspergillosis.

Four types of isolated invasive Aspergillus tracheobronchitis have been established based on bronchoscopic findings: superficial infiltration type (Type I), full-layer involvement type (Type II), occlusion type (Type III), and mixed type (Type IV)[15]. Briefly, the bronchoscopic features of Type I include inflammatory infiltration, mucosa hyperemia, and superficial ulcers confined to the mucosa and submucosa. By contrast, Type II features include infiltration of tracheobronchial lesions through the matrix layer of the bronchi and Type III is characterized by airway obstruction or constriction to 50% of the original diameter of the involved bronchi. Type IV involves two or more different forms of the bronchoscopic characteristics of the other three types. In our case, bronchoscopy showed multiple white pseudomembranes and ulcers in the left second carina and left superior lobar branch. The patient did not have distinct mucosa hyperemia but she did have white multiple pseudomembranes and ulcers,

suggesting the presence of Type I Aspergillus tracheobronchitis. A previous study showed that patients with isolated invasive Aspergillus tracheobronchitis had a 26.3% incidence of mortality and that patients with Type II or IV have especially poor prognoses, whereas none of the patients with Type I died[15]. Conversely, the mortality of patients with SLE complicated by invasive Aspergillosis is 80-95%[3]. Therefore, even if immunocompromised patients are diagnosed with invasive Aspergillosis with poor prognosis, a superficial finding on bronchoscopy finding, such as that seen in Type I, may be associated with good prognosis as shown in our case.

VRCZ is a first-line drug for the treatment of invasive pulmonary Aspergillosis[16][17]. In this case, VRCZ was initially administered but was discontinued due to deterioration of liver function. We selected MCFG as an alternative therapy because the patient also had low serum potassium and renal dysfunction. After resolution of symptoms, we discontinued the intravenous MCFG and administered oral ITCZ.

In summary, we reported a rare case of pseudomembranous and ulcerative Aspergillus tracheobronchitis in a patient with SLE and NHL. Bronchoscopy is a useful diagnostic tool and may be a predictor of prognosis for patients with invasive pulmonary Aspergillosis.

We have no financial relationships to disclose in this case report.

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〈和文抄録〉

全身性エリテマトーデスおよび悪性リンパ腫の治療中に発症した偽膜を伴う潰瘍性アスペルギルス気管気管支炎

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症例は50歳代の女性．20歳代に全身性エリテマトーデスを発症し，以降ステロイド単独内服で経過観察してきた．50歳代に入り非ホジキンリンパ腫を発症し，R-CHOP：6コース施行後に完全寛解となったため，プレドニゾロン17.5㎎/日内服で経過観察となった．3か月後，突然の咳嗽および胸痛出現し，胸部CT上にて肺野に多発性の空洞形成を伴う結節陰影を認めた．気管支鏡検査にて気管支に偽膜性潰瘍を散見し，同部位の鏡検・培養よりアスペルギルス気管気管支炎と診断．その後，抗真菌薬にて改善を認めた．偽膜を伴う気管支潰瘍を呈する侵襲性肺アスペルギルス症は稀であり，気管支鏡検査による積極的な精査が有用であると考えられた．

キーワード：アスペルギルス気管気管支炎，全身性エリテマトーデス，悪性リンパ腫，潰瘍性気管気管支炎．