Nonfibrotic Hypersensitivity Pneumonitis Complicated by Chronic Progressive Pulmonary Aspergillosis : A Case Report

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Diagnosis of chronic pulmonary aspergillosis in patients with nonfibrotic hypersensitivity pneumonitis is difficult, especially after treatment with systemic corticosteroids has been initiated. Therefore, treatment for chronic progressive pulmonary aspergillosis (CPPA) is often delayed. Although the chief complaint of non-fibrotic hypersensitivity pneumonitis complicated by pulmonary aspergillosis is often fever, the fungus cannot be identified, even after repeated sputum culture tests. Herein, we report a case of pulmonary aspergillosis that developed after initiating treatment with systemic corticosteroids and was difficult to diagnose. The patient had a fever that continued after the introduction of steroids. CPPA was eventually diagnosed based on histopathological examination of a bronchoscopy sample. When CPPA is suspected in patients with hypersensitivity pneumonitis, bronchoscopy may improve their prognosis. *Shinshu Med J 71 : 235—240, 2023*

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Ⅰ Introduction

Hypersensitivity pneumonitis (HP) is a chronic lung disease of variable severity, clinical presentation, and natural history[1]. Based on the presence or absence of fibrosis on imaging or histopathologic examination, HP is classified as nonfibrotic (inflammatory only) or fibrotic (mixed inflammatory and fibrotic or fibrotic only)[2]. In humid environments, fungi, particularly *Penicillium* spp. and *Aspergillus* spp., can cause HP[3]. Not only fungi can cause HP, but fungal growth in the lungs of patients with HP, manifesting as chronic progressive pulmonary aspergillosis (CPPA) is a rare but serious complication[4]. CPPA can occur as a complication in patients with HP and prolonged systemic corticosteroid use[5].

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Herein, we describe the clinical course of a patient with severe nonfibrotic HP complicated by CPPA and the response to treatment including intensive care, systemic corticosteroids, and antifungal drugs.

Ⅱ Case Report

A 78-year-old man was referred to our hospital due to dry cough for 8 months. Apart from the medical history of prostate cancer and postoperative right common iliac artery aneurysm, he was an otherwise healthy non-smoker. He lived in a 40-year-old wooden house, and had built a wooden hut on his property 2 years previously, in which he grew plants. He had no history of keeping birds, and there were no bird nests around his residence. He had no history of drug allergies. Chest computed tomography (CT) revealed faint graund-glass opacities (GGO) in both lungs **(Fig. 1A, B)**. 148 days before this hospitalization, bronchoalveolar lavage (BAL) was performed during bronchoscopy of the right middle lobe of the lung for diagnosis. The lymphocyte percentage in the

BAL fluid (BALF) was 79.0 %, which is consistent with the BALF in HP. The BALF CD4/8 ratio was as high as 14.73, indicating that home-related hypersensitivity pneumonitis was more likely than other types of hypersensitivity pneumonitis, such as summer-type hypersensitivity pneumonitis. Suspecting home-related HP, the mold in his residence was removed. No inhalation antigens associated with summer-type hypersensitivity pneumonitis, bird fancier's lung, or humidifier lung were identified during the patient's interview. Nevertheless, 133 days before this hospitalization, he was temporarily readmitted to our department with suspected worsened HP as his first hospitalization. CT showed worsening GGO in both lungs **(Fig. 1C, D)**. After hospitalisation his nonfibrotic HP improved without treatment, and he was discharged. The hut on his premises intended for growing foliage plants was suspected to be the cause, and his doctor advised him not to use it. Subsequently, 79 days before this hospitalization, he developed a fever and was readmitted to our hospital as his second hospitalization. He was started on prednisolone (PSL) 60 mg/day for flare-ups of nonfibrotic HP. A chest CT scan taken after the initiation of PSL treatment showed improvement of the GGO in both lung fields **(Fig. 1E, F)**. After discharge the PSL dose was tapered to 15 mg/day. Although PSL-based pharmacotherapy temporarily reduced GGO in both lungs, he visited our hospital because of fever and dyspnea, was diagnosed with recurrence of nonfibrotic HP, and was urgently re-admitted to our department (hospital day 1). On admission, his body temperature was 38.6 ° C and his oxygen saturation (SpO_2) was 77 % on room air. Physical examination revealed fine

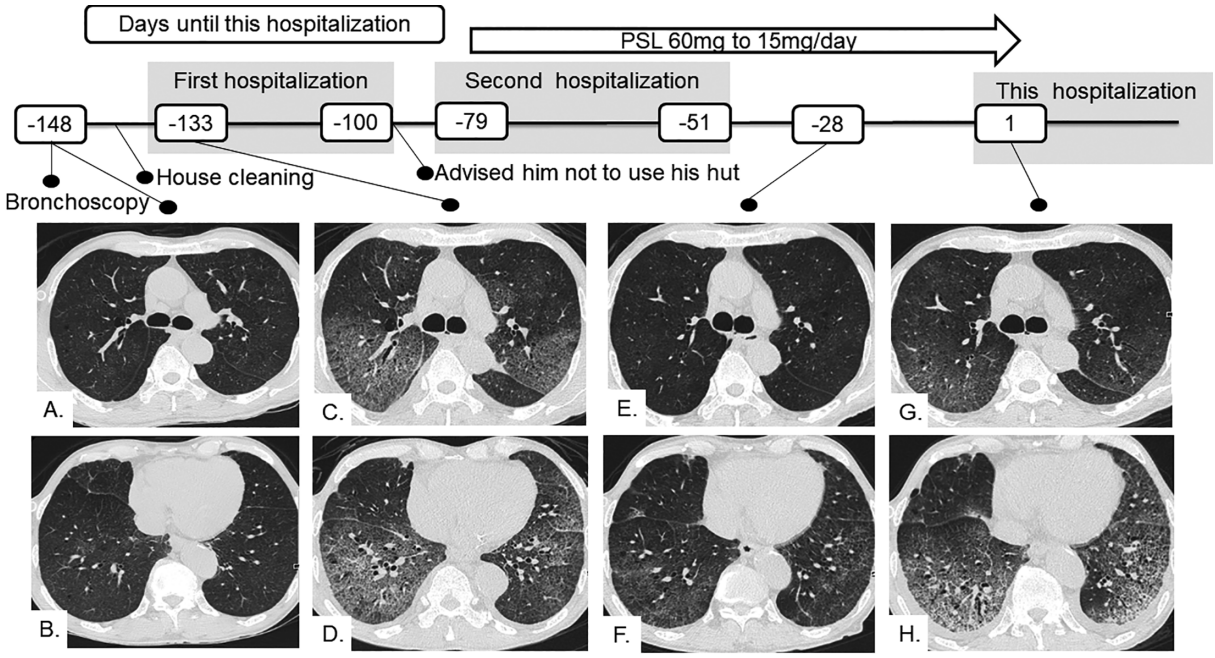

Fig. 1 Chest computed tomography (CT) over the clinical course of the patient's disease. Figures A, C, E and G are cross-sectional CT images at the level of the carina trachea. Figures B, D, F and H are cross-sectional CT images at the level of the diaphragm. Figures A and B are CT images taken on June 3 (148 days prior to the admission). A : CT image showing segmental ground-glass opacities (GGO) in both upper lobes ; B : CT image showing GGO in both lower lobes. Figures C and D are CT images taken on August 11 (79 days prior to the admission). C : CT image showing increased concentrations of GGO in the dorsal upper lobes of both lungs ; D : CT image showing posterior consolidation with air bronchograms in the posterior segments of the lower lobes of both lungs. Figures E and F are CT images taken on October 1 (28 days prior to this admission). E : CT image showing disappearance of the GGO in the upper lobes of both lungs ; F : CT image showing disappearance of the GGO in the lower lobes of both lungs. Figures G and H are CT images taken on October 29 (hospital day 1). G : CT image showing worsening of the GGO in both upper lobes and dorsum of the lungs ; H : CT image showing worsening of the dorsal GGO and the GGO in the lower lobes of the lungs.

Table 1 Laboratory test results on admission

Parameter	Result	Reference Range
Hematology		
White blood cell count (/μL)	4210	3300–8600
Neutrophil count (/μL)	3500	1170–6130
Hemoglobin (g/dL)	13.0	11.6–14.8
Platelet count ($\times 10^4$/μL)	6.4	15.8–34.8
Blood chemistry		
Total protein (g/dL)	5.1	6.6–8.1
Albumin (g/dL)	2.9	4.1–5.1
Blood urea nitrogen (mg/dL)	32.5	8.0–20.0
Creatinine (mg/dL)	1.41	0.65–1.07
AST (U/L)	37	13–30
ALT (U/L)	29	10–42
LDH (U/L)	352	124–222
Total bilirubin (mg/dL)	1.43	0.40–1.50
γ-Glutamyl transferase (U/L)	46	13–64
BNP (pg/mL)	98.0	0–20
C-reactive protein (mg/dL)	5.14	0.00–0.14
KL-6 (U/mL)	4304	105–435
SP-D (ng/mL)	586	
PT-INR	0.99	0.85–1.15
D-dimer (μg/mL)	2.2	0.0–1.0
Serology		
Rheumatoid factor	Negative	
Beta-D-glucan	Negative	
Aspergillus antigen	Negative	
Aspergillus antibody	Negative	
Arterial blood gas (FiO_2 0.5)		
pH	7.445	7.340–7.450
$PaCO_2$ (Torr)	29.3	32.0–45.0
PaO_2 (Torr)	78.0	75.0–100.0
HCO_3^- (mmol/L)	19.8	22.0–28.0
PaO_2/F_iO_2 ratio	156	

ALT, alanine aminotransferase ; AST, aspartate aminotransferase ; BNP, Brain Natriuretic Peptide ; SP-D, surfactant protein D ; FiO_2, inspired oxygen fraction ; KL-6, Krebs von den Lungen-6 ; LDH, lactate dehydrogenase ; $PaCO_2$, partial pressure of arterial carbon dioxide ; PaO_2, partial pressure of arterial oxygen ; PT-INR, prothrombin time-international normalised ratio.

crackles in both lower lungs. Blood tests showed thrombocytopenia (64,000/μL) and elevated levels of blood urea nitrogen (BUN, 32.5 mg/dL), creatinine (1.41 mg/dL), C-reactive protein (CRP, 5.14 mg/dL), Krebs von den Lungen-6 (KL-6, 4304 U/mL), and lactate dehydrogenase (LDH, 352 U/L) **(Table 1)**. *Aspergillus* antigen and antibody tests results were both negative, and his beta-D-glucan level was within the normal range. Chest CT showed further deterioration of the GGO and consolidation **(Fig. 1G, H)**.

Considering the recurrence of nonfibrotic HP, steroid pulse therapy (intravenous methylprednisolone 1,000 mg/day for 3 days), followed by an increase in oral PSL administration to 60 mg/day, was initiated. He required a high-flow nasal system for several days after starting treatment but was able to reduce his oxygen requirements to 2 L/minute by nasal cannula on hospital day 5. Unfortunately, on hospital day 29, he developed sepsis due to *Streptococcus sanginus*, probably due to dental caries, and an intravenous Sul-

bactam / Ampicillin was started. On hospital day 38, a CT scan revealed a new cavitary nodule at the apex of the right lung **(Fig. 2A, B)**. A complex fungal infection was suspected and micafungin was administered intravenously ; however, his fever did not subside. A blood sample on hospital day 60 was positive for *Aspergillus* antigen. On hospital day 77, bronchoscopy was performed because of suspected worsening of his pulmonary aspergillosis, and a transbronchial lung biopsy was obtained from the upper lobe of the right lung. The biopsy specimens showed numerous hyphae, consistent with pulmonary aspergillosis **(Fig. 3)**. A culture with bronchial lavage fluid was negative ; therefore, antifungal drugs were considered effective. Based on the serologic findings of *Aspergillus* antigen conversion and the transbronchial lung biopsy findings, the diagnosis of CPPA was made. After the bronchoscopy, the antifungal drug was changed from intravenous micafungin to oral voriconazole and his fever improved. Intravenous voriconazole was considered as an alternative ; however, we decided to administer oral voriconazole owing to difficulties in establishing intravenous access. A CT scan performed on hospital day 97 showed shrinkage of the right apical cavitary nodule **(Fig. 2C)**. Although his pulmonary aspergillosis improved, his physical strength gradually declined during his long hospital stay, and he was transferred to another hospital for rehabilitation.

Ⅲ Discussion

Herein, we describe a case of pulmonary aspergillosis that worsened after the beginning of systemic corticosteroids treatment for HP. PSL 0.5–1 mg/kg/day corticosteroids have been shown to be effective for nonfibrotic hypersensitivity pneumonitis that recurs despite efforts to avoid inhalation antigens ; this patient was also at risk of respiratory failure and was started on PSL 60 mg/day (1 mg/kg/day)[6)7)]. After the oral administration of PSL was started, PSL was gradually tapered to 15 mg/day at a relatively rapid pace because CT showed rapid improvement in

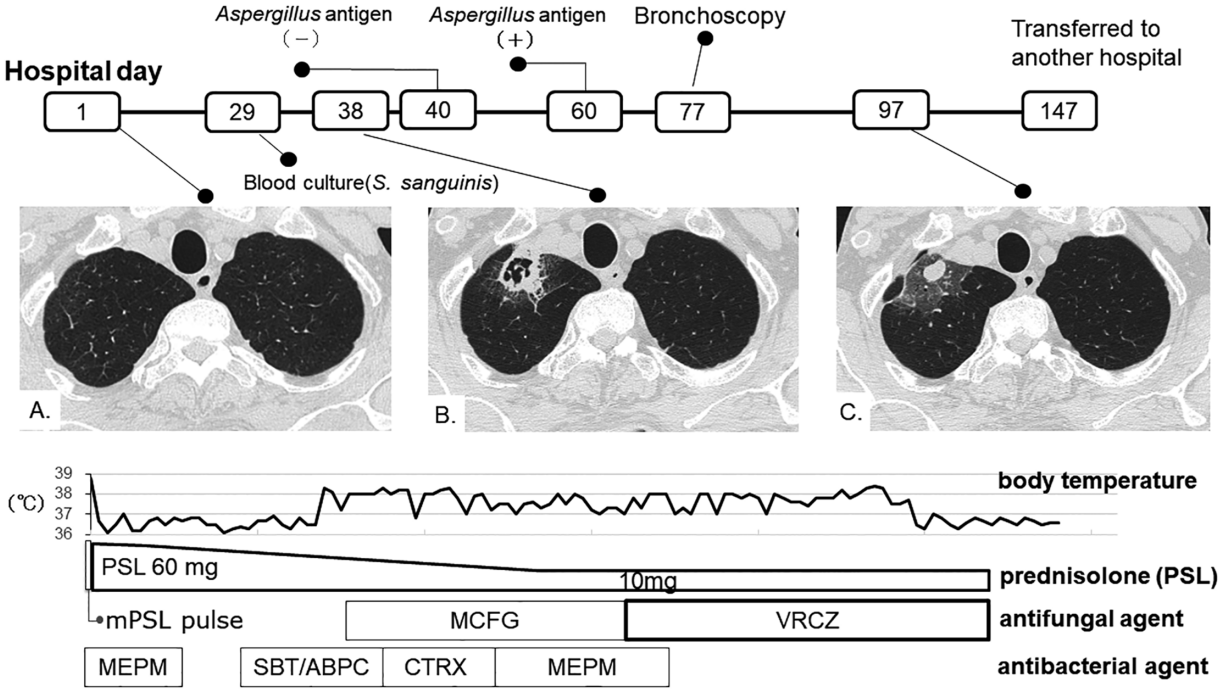

Fig. 2 The clinical course according to the day of hospitalisation. Chest computed tomography (CT) showing progression of ground-glass opacities with cavitation (A, B). CT after starting voriconazole showing a reduction in the size of the abnormal opacities (C).

CTRX, ceftriaxone ; MEPM, meropenem ; MCFG, micafungin ; mPSL, methylprednisolone ; SBT/ABPC, sulbactam, ampicillin ; VRCZ, voriconazole.

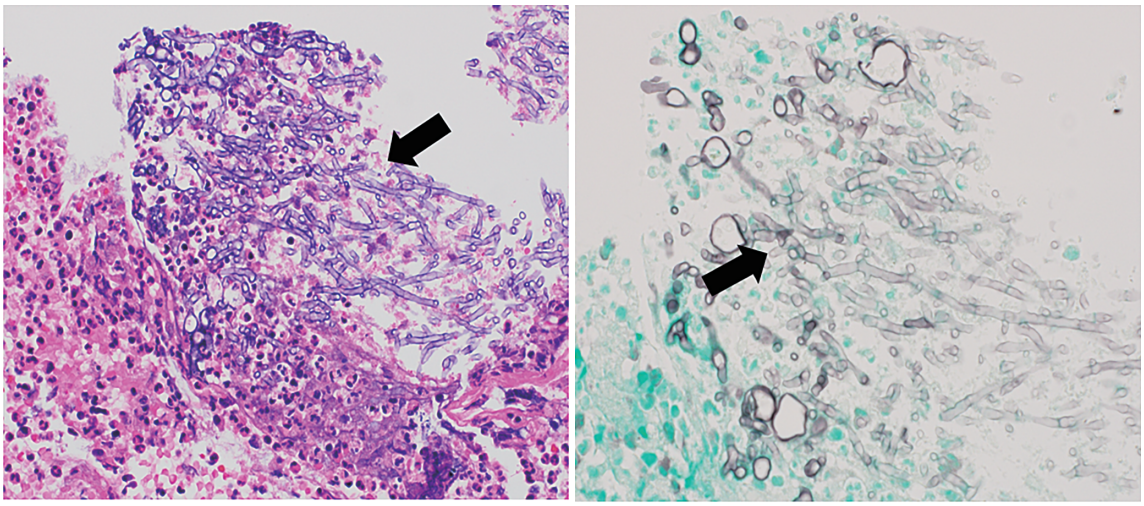

Fig. 3 Histopathology of a bronchoscopy biopsy specimen of the upper lobe of the right lung collected by transbronchial biopsy showing numerous hyphae, consistent with pulmonary aspergillosis. Thin, septate hyphae with regular branching can be seen in each section (arrows). A : Hematoxylin and eosin stain (×40) ; B : Grocott stain (×60).

pulmonary GGO. The patient had repeated exacerbations of HP and developed CPPA after the dose of steroids was increased. Long-term steroid use is a risk factor for pulmonary aspergillosis. Other risk factors include diabetes mellitus, malnutrition, alcoholism, and advanced age[8]. To accomplish steroid dose reduction, it is essential to concentrate on the avoidance of hypersensitivity pneumonitis recurrence. If the causative antigen is presumed to be present in the house or residential environment, as in this case, measures such as relocation or deep cleaning are required to prevent the recurrence of hypersensitivity pneumonitis.

A positive serum *Aspergillus* immunoglobulin G (IgG) antibody test is important for the diagnosis of CPPA[9]. In Japan, *Aspergillus* antigen tests, which are covered by national health insurance, are often used as an alternative to *Aspergillus* IgG antibody tests. However, in this case, the *Aspergillus* antigen and antibody test results on admission were negative. After recognizing that the *Aspergillus* antigen test had changed to positive, a bronchoscopy was performed, and following a confirming diagnosis, the medication was changed from micafungin to voriconazole. This case suggests that retesting for *Aspergillus* antigens to confirm seroconversion is important in determining the appropriate timing of bronchoscopy. When pulmonary aspergillosis is suspected, timely bronchoscopy is key to obtaining a correct diagnosis. Patients with HP and chronic pulmonary aspergillosis often have decreased physical strength, and attending physicians are often reluctant to perform bronchoscopy. Repeated *Aspergillus* antigen testing to confirm positive conversion is an alternative if bronchoscopy is unavailable. Antibiotics and antifungal drugs are frequently administered at an early stage to severely immunocompromised patients with fungal infections, and it is often difficult to determine the cause of fever. Even if a fungus cannot be identified on culture, as in this case, a definitive diagnosis can be made based on a bronchoscopy biopsy.

In this case, even after beginning the intravenous infusion of micafungin, the aspergilloma opacity worsened, and the patient's condition only improved after switching to voriconazole. Micafungin or voriconazole should only be used in severely ill patients who do not respond to other azole therapy, such as itraconazole[10)11)]. However, intravenous antifungal drugs are required in patients with severe disease. Micafungin infusion has fewer side effects than voriconazole infusion, and

the response rates are similar[9]. In this case, intravenous micafungin and oral voriconazole did not cause any significant side effects, and after switching to oral voriconazole, the patient's fever and cavitary nodule were reduced. Oral administration of voriconazole may be effective as an initial treatment in patients with severe *Aspergillus* infections who can take oral medications, as in this case.

In summary, we have described the clinical course of severe nonfibrotic HP complicated by CPPA. When diagnosing CPPA in a patient with HP, a re-examination of *Aspergillus* antigens can help, and a bronchoscopy that looks for tissue diagnosis may improve the prognosis.

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