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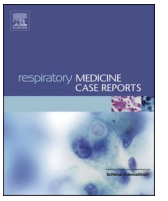

Case Report

A case of pulmonary co-infection with *Aspergillus fumigatus* and Mucorales in a patient with sarcoidosis

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ABSTRACT

A 54-year-old woman with fever and cough presented with left upper lobe consolidation and para-aortic and hilar lymphadenopathies and was diagnosed with sarcoidosis, and her condition improved spontaneously. Over the next 15 years, the patient experienced seven similar episodes and was treated with glucocorticoids for the first time in the eighth episode, but subsequently died of respiratory failure. The autopsy revealed diffuse alveolar damage and co-infection with *Aspergillus fumigatus* and Mucorales in the lungs and mediastinum. The clinical course and autopsy results suggest that glucocorticoids caused the growth of fungi already infected in the patient, and co-infection with the other.

1. Introduction

Sarcoidosis is a disease that often remits spontaneously, whereas immunosuppressive therapies such as glucocorticoids are used when the disease progresses and causes life- or organ-threatening disease [1]. However, since there are many sarcoidosis mimics, including infection [2], and sarcoidosis itself and glucocorticoids increase the risk of infection [3], careful consideration is required when initiating the treatment.

We present a case with a diagnosis of sarcoidosis via a multidisciplinary study (MDD), died of diffuse alveolar damage (DAD) due to co-infection with *Aspergillus fumigatus* and Mucorales after administration of glucocorticoids for a life-threatening disease following multiple episodes of fever, pulmonary consolidation, and lymphadenopathies over 15 years.

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2. Case presentation

A 54-year-old woman was admitted to our institution with a cough and fever. A chest computed tomography (CT) scan revealed consolidation of the left upper lobe with para-aortic and hilar lymphadenopathies (Fig. 1A). Although the laboratory tests revealed an increased inflammatory response, the results were insufficient for a definitive diagnosis (Table 1). She was a dressmaker and had no history of cigarette smoking, allergies, or overseas travel. Moreover, she did not have any known predisposing conditions, such as diabetes mellitus or immunocompromised status. Assays of the bronchoalveolar lavage (BAL) fluid showed a cell count of 2.1×10^5/μL, with a differential cell count of 63 % macrophages and 30 % lymphocytes and a CD4/8 ratio of 6.70. No pathogens were detected in the BAL fluid.

To confirm the diagnosis, an open lung biopsy of the left S3 segment was performed, which revealed a non-caseating epithelioid cell granuloma with surrounding fibrosis filling the alveolar space (Fig. 1B). Granulomatous vascular involvement was also observed. Although granulomas were found to contain multinucleated giant cells at times, accompanied by occasional coagulation necrosis, Grocott staining revealed no fungal elements, and cultures for bacteria, fungi, and acid-fast bacilli were negative. There was also no evidence of malignancy or lymphoma. Based on a MDD, she was diagnosed with nodular sarcoidosis, and treatment was planned. However, thereafter the patient's symptoms spontaneously improved, and chest CT findings improved two months later (Fig. 1C). No other organ involvement in sarcoidosis, including lesions of the eye, heart, or skin, was observed.

Over the next 15 years, the patient experienced seven similar episodes of fever, pulmonary consolidation, and lymphadenopathies, with her condition improving spontaneously each time. Blood and sputum cultures were repeated several times. However, no pathogens, including acid-fast bacilli, were detected. Fifteen years after the initial episode, a posterior mediastinal mass was detected for the first time (Fig. 2A). Although transesophageal endoscopic ultrasonography-guided fine-needle aspiration was performed, no malignant cells or pathogens were detected. This was followed by a spontaneous reduction in the mass over three months (Fig. 2B).

One month later, the patient presented with a fever, and a new, large posterior mediastinal mass with bronchial stenosis and

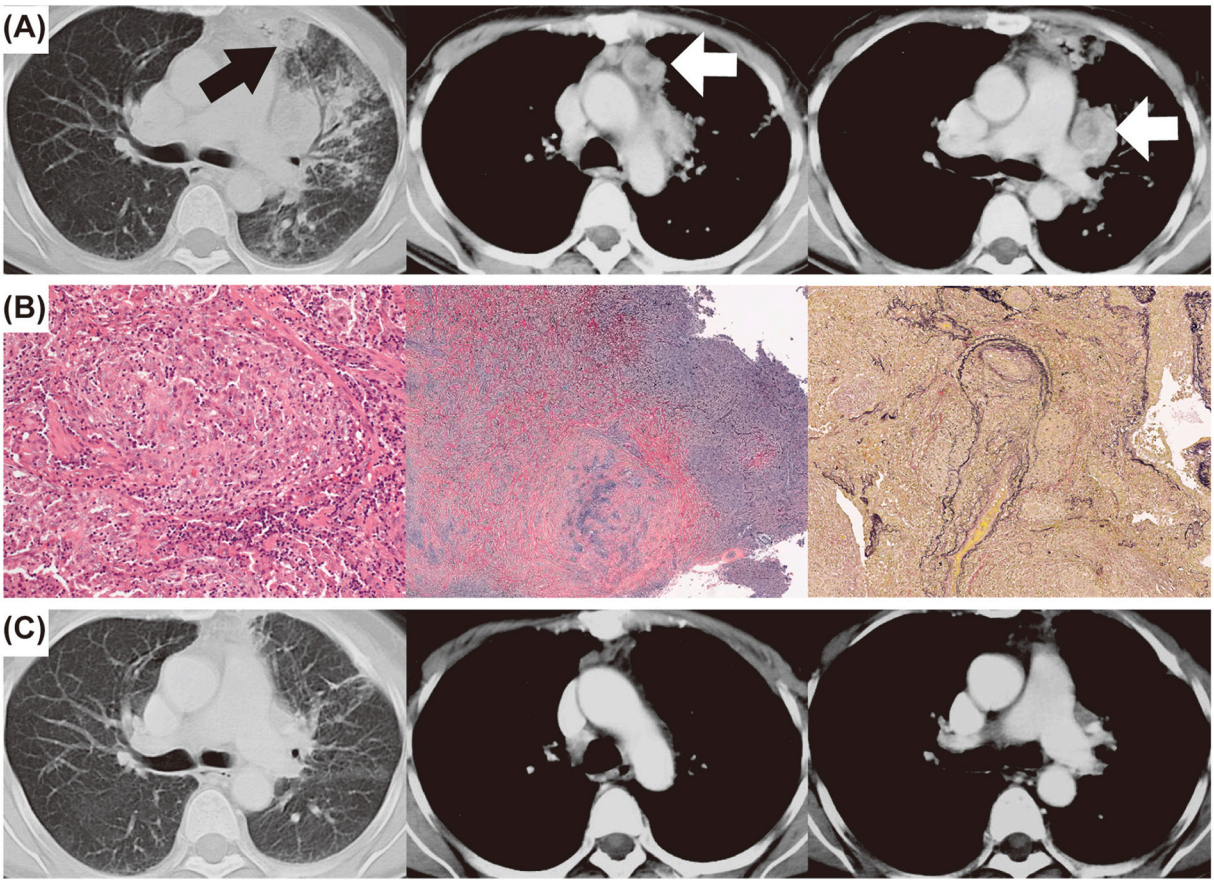

Fig. 1. Chest CT and histopathological findings on initial admission
(A) Consolidation of the left upper lobe (black arrow) and para-aortic and hilar lymphadenopathies (white arrows) were observed. (B) Histopathological images of biopsy specimens from the left lung show a non-caseating epithelioid cell granuloma containing multinucleated giant cells (left: H&E staining, × 200), coagulation necrosis at the center of the granuloma and fibrosis surrounding it (middle: Masson-trichrome staining, × 50), and granulomatous involvement of a pulmonary artery (right: EVG staining, × 100). (C) The lesions demonstrated in Fig. 1A had improved two months later. Abbreviations: CT, computed tomography; EVG, Elastica van Gieson; H&E, hematoxylin and eosin.

Table 1
Laboratory findings on admission to our institution.

Hematology		**Biochemistry**	
WBC	15400/μL	TP	7.6 g/dL
Neu	87.70 %	Alb	3.5 g/dL
Lym	5.20 %	AST	56 IU/L
Eos	0.60 %	ALT	48 IU/L
RBC	394 × 10^4/μL	ALP	389 IU/L
Hb	11.8 g/dL	LDH	454 IU/L
Hct	36.50 %	Cr	0.52 mg/dL
Plt	26.3 × 10^4/μL	BUN	6 mg/dL
Serology		**Infectious investigations**	
CRP	234 mg/L	Beta-D glucan	(−)
KL-6	172 U/mL	Aspergillus galactomannan antigen	(−)
sIL-2R	1330 U/mL	Quantiferon-TB	(−)
CEA	3.8 ng/mL		
CYFRA 21-1	<1.0 ng/mL		
NSE	7.1 ng/mL		
ACE	10.2 (8.3–21.4) IU/L		
Lysozyme	18 μg/mL		
RF	(−)		
ANA	< x40		
PR3-ANCA	(−)		
MPO-ANCA	(−)		

The values in parenthesis indicates the normal reference range for ACE.
Abbreviations: ACE, angiotensin converting enzyme; ALT, alanine-aminotransferase; ANA, antinuclear body; AST, aspartate-aminotransferase; BUN, blood urea nitrogen; CEA, carcinoembryonic antigen; Cr, creatinine; CRP, C-reactive protein; CYFRA 21-1; cytokeratin 19 fragment; Hb, hemoglobin; Hct, hematocrit; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; Ly, lymphocytes; Mo, monocytes; MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic antibody; Neu, neutrophils; NSE, neuron-specific enolase; Plt, platelets; PR3-ANCA, proteinase-3-*anti*-neutrophil cytoplasmic antibody; RBC, red blood cells; RF, rheumatoid factor; sIL2R, soluble interleukin-2 receptor; TP, total protein; WBC, white blood cells.

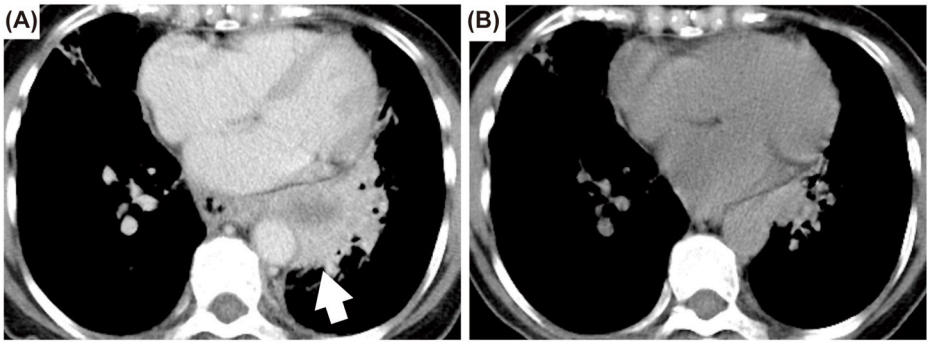

Fig. 2. Chest CT findings at the seventh episode.
(A) A posterior mediastinal mass (white arrow) was observed. (B) The lesion demonstrated in Fig. 2A had improved three months later. Abbreviations: CT, computed tomography.

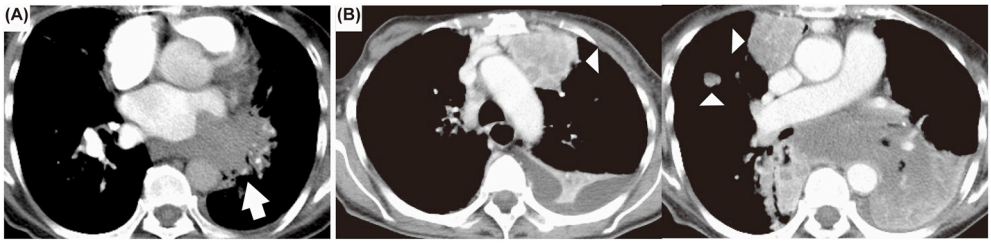

Fig. 3. Chest CT findings at the eighth episode.
(A) A newly appearing posterior mediastinal mass (white arrow) was observed. (B) Newly appearing multiple pulmonary nodules (arrow heads) were observed 27 days after the administration of PSL. Abbreviations: CT, computed tomography; PSL, prednisolone.

compression of the pulmonary artery and vein was observed (Fig. 3A). An ultrasound cardiogram revealed that the left atrium was compressed by a posterior low-echoic mass and a tricuspid regurgitation pressure gradient (TRPG) of 47 mmHg, indicating pulmonary artery hypertension. Blood tests showed an elevated inflammatory response, and due to abnormal liver function, a hepatic biopsy was performed; however, no malignant cells or pathogens were detected. The Aspergillus galactomannan antigen test was negative. Because the high fever persisted despite the administration of antibiotics and was accompanied by atrial fibrillation, the patient was treated with oral prednisolone (PSL) (30 mg/day) for sarcoidosis starting on day 8. Although the TRPG decreased to 29 mmHg, high fever persisted. Bronchial lavages were performed to exclude the possibility of infection; however, no pathogens were detected. BAL could not be performed because of the narrowing of the left lower lobe bronchus. Subsequently, on day 20, the PSL dose was increased to 60 mg/day. However, multiple bilateral pulmonary nodules appeared on day 35 (Fig. 3B), and the patient's respiratory status gradually deteriorated. Following a CT-guided lung biopsy of the nodule in the upper lobe of the left lung, high-dose methyl-PSL (1000 mg/day) was administered on day 36 and continued for three days. On day 38, upon detection of filamentous fungi in a CT-guided lung biopsy specimen, we suspected pulmonary aspergillosis and administered liposomal amphotericin B. However, the patient died of acute respiratory failure on the following day. Thereafter, the patient's samples were found to be positive for Aspergillus galactomannan antigen.

An autopsy revealed that the lungs were diffusely dark red and enlarged, with multiple bilateral pulmonary nodules and a large mass in the posterior mediastinum (Fig. 4A). Macroscopic observations revealed no other lesions, except in the thoracic region. Histopathological examination revealed DAD throughout the lobes in the exudative to organizing phase (Fig. 4B). Although no clear evidence of sarcoidosis was detected in any sample, multinucleated giant cells and fibrosis were observed around the interlobular veins, suggesting residual sarcoidosis lesions (Fig. 4C).

Abscesses were formed within the lung nodules in the right upper lobe (Fig. 4D), with filamentous fungi with 45° branching (Fig. 4E, F). Through the sequence analysis of Internal Transcribed Spacer, Domains 1 and 2 (D1/D2), and β-tubulin, *Aspergillus fumigatus* was identified (examined at Osaka Metropolitan University Graduate School of Medicine).

Extensive alveolar hemorrhage, necrosis, and neutrophilic infiltration were observed in the left lower lobe, with vascular invasive fungi (Fig. 4G, H). In addition, filamentous fungi with 90° branching were observed inside the necrotic inflammatory area, with numerous giant cells within the posterior mediastinal mass (Fig. 4I). These fungi were distributed to spread from the posterior mediastinum to the pulmonary hilum. The sequence associated with the order Mucorales was detected in paraffin sections from the posterior mediastinal mass through the sequence analysis of 18S rDNA (examined at the National Institute of Infectious Diseases). This species could not be identified because of DNA fragmentation caused by formalin fixation.

3. Discussion

In this case, the patient was diagnosed with sarcoidosis via a MDD upon initial admission. In addition, multinucleated giant cells and fibrosis around the interlobular vein observed on autopsy were suggestive of residual lesions of sarcoidosis. Posterior mediastinal masses appeared at the last two episodes were lesions occasionally observed in sarcoidosis as well [4]. Therefore, we considered that the posterior mediastinal mass due to sarcoidosis caused severe symptoms, and finally administered glucocorticoids in the last episode; however, the patient eventually developed fatal DAD due to fungal co-infection.

While the positive seroconversion of Aspergillus galactomannan antigen during the last episode may indicate that the patient was infected with *Aspergillus fumigatus* in the terminal phase, it is well known that patients with sarcoidosis can develop Aspergillus-related lung disease, leading to severe morbidity and mortality [5]. Consequently, it is also possible that the patient was already infected with *Aspergillus fumigatus* before the administration of glucocorticoid. As for the Mucorales, the similarity of the imaging findings between the mediastinal mass where Mucorales was detected at autopsy and the mass observed in the second to last episode suggests that the patient was possibly infected with Mucorales four months before death. However, patients without apparent immunodeficiency rarely become infected with Mucorales [6]. Although it is unclear which fungal infection preceded in this case, the clinical course and autopsy results suggest that glucocorticoids caused the growth of fungi already infected in the patient and co-infection with other fungi.

Co-infection with *Aspergillus fumigatus* and Mucorales can occur in patients with some background that affects their immune competence [7]; however, this is not a common event, and it is even rarer when it occurs in patients with sarcoidosis [8]. However, it is important to note that the administration of glucocorticoids, one of the standard treatments for sarcoidosis, led to a serious situation in this case. When a new lesion appears in a patient with sarcoidosis, histopathological examination is important because it is difficult to determine whether the lesion is truly due to sarcoidosis based on the clinical course and imaging findings alone. In addition, it should be noted that histopathological examination is also important for diagnosing Mucorales, as there are no useful blood test markers and the yield of cultures from respiratory samples is extremely low [9].

4. Conclusion

If a patient with sarcoidosis presents with a different lesion than previously seen, operative tissue biopsy tests should be performed for a definitive diagnosis, as long as the patient can tolerate the tests, as immunosuppressive treatment for "sarcoidosis mimics" can lead to severe outcomes. We hope that the findings from atypical cases of sarcoidosis, such as those reported herein, will provide insights that are helpful to clinicians and patients alike.

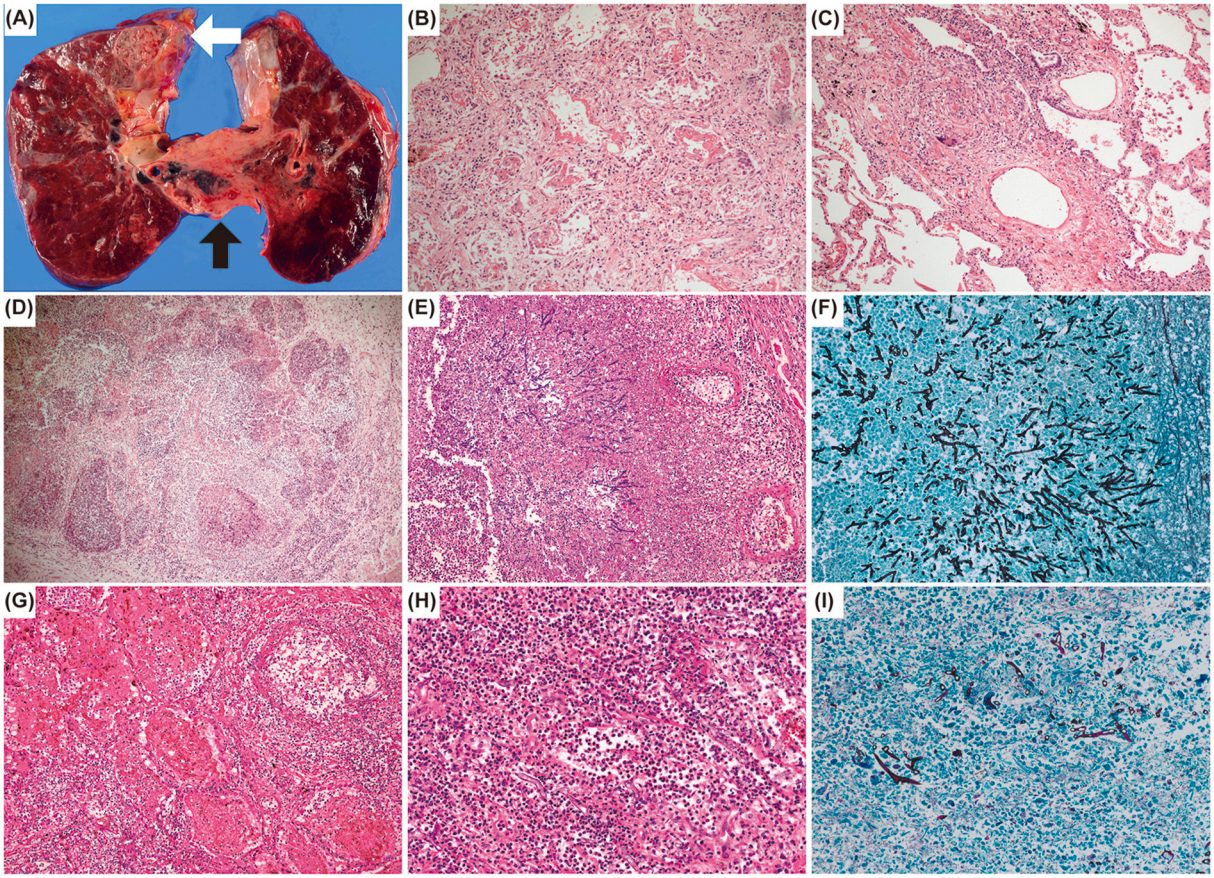

Fig. 4. Pathological findings in the autopsy.
(A) The lungs were diffusely red, enlarged and partly hemorrhagic, with a nodule (white arrow) and a posterior mediastinal mass (black arrow). (B) The majority of the right upper lobe revealed diffuse alveolar damage with hyaline membrane formation, shedding and hyperplasia of alveolar epithelia, and mural and intra-alveolar fibrosis (H&E staining, × 100). (C) Occasionally, multinucleated giant cells were observed in the fibrous venous wall in the left upper lobe (H&E staining, × 100). (D) Abscesses were observed in many areas of the lung. The figure shows those inside a nodule in the left upper lobe (H&E staining, × 50). (E) In those abscesses, filamentous fungi were observed (left upper lobe: H&E staining, × 100). (F) Filamentous fungi, branching at 45°, were observed (left upper lobe: Grocott staining, × 200). (G) Extensive alveolar hemorrhage, necrosis and neutrophilic infiltration were observed (left lower lobe: H&E staining, × 100). (H) Filamentous fungi were found inside the abscess and in the vessels (left lower lobe: H&E staining, × 200). (I) Filamentous fungi with irregular non-septate hyphae, branching at 90°, were observed (posterior mediastinal mass: Grocott staining, × 200). Abbreviations: CT, computed tomography; H&E, hematoxylin and eosin; PSL, prednisolone.

CRediT authorship contribution statement

Tomoya Sagawa: Writing – original draft. **Seiko Ohno:** Writing – review & editing. **Yoji Urata:** Writing – review & editing, Data curation. **Tamiko Takemura:** Writing – review & editing, Data curation. **Mamiko Niki:** Writing – review & editing, Data curation. **Yukihiro Kaneko:** Writing – review & editing, Data curation. **Shigeki Nakamura:** Writing – review & editing, Data curation. **Takashi Umeyama:** Writing – review & editing, Data curation. **Yoshitsugu Miyazaki:** Writing – review & editing, Data curation. **Tatsuya Yuba:** Writing – review & editing. **Chieko Takumi:** Writing – review & editing. **Noriya Hiraoka:** Writing – review & editing.

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Declaration of competing interest

With regard to the Potential Conflict of Interest, S.N. received speaking fees from MSD Co., Ltd. and Pfizer Japan Inc., and Y.K. received a manuscript fee from Maruishi Pharmaceutical. Co., Ltd.

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