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# Video-assisted thoracic surgery for a case of chronic progressive pulmonary aspergillosis undergoing haemodialysis complicated by anorexia nervosa: a case report

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**Keywords**
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## Abstract

We describe the case of a 37-year-old female with chronic progressive pulmonary aspergillosis (CPPA) with anorexia nervosa (AN) while undergoing haemodialysis for renal failure, who had video-assisted thoracic surgery (VATS) due to recurrent haemoptysis. She was referred to the Department of Respiratory Medicine for evaluation of an abnormal chest shadow. She was diagnosed with CPPA by serological examinations, radiological features, and bacterial culture. She was initially treated with oral antifungal therapy and transcatheter embolization. VATS lobectomy was eventually performed despite the AN and haemodialysis because of poorly controlled haemoptysis. The postoperative course was uneventful, and the final histopathological examination confirmed CPPA.

## Introduction

Pulmonary aspergillosis is a collective term used for a number of conditions caused by *Aspergillus* infection. Chronic progressive pulmonary aspergillosis (CPPA) is recognized as an opportunistic infection that mainly develops in patients with immunocompromised or malnutritional status. However, the number of immunocompetent patients with CPPA has been increasing recently due to factors such as ageing, chronic pulmonary diseases, use of anti-cancer drugs or immunosuppressive drugs, and invasive operations [1–2].

Anorexia nervosa (AN) is a chronic disease with progressive cachexia caused by malnutrition, which may result in various complications and is thought to be a risk factor for *Aspergillus* infection. However, few studies exist regarding pulmonary aspergillosis in AN patients. In this report, we present a rare case of a Japanese woman with AN who developed pulmonary aspergillosis, and describe the clinical and pathophysiological characteristics of pulmonary aspergillosis in the patient. We also made comparisons with previous reports.

## Case Report

A 37-year-old woman, suffering from AN since she was 15 years old (at 15 years of age, body weight = 50 kg, body mass index = 21.9), had been attending the Department of Psychosomatic Medicine at Saitama Medical University Hospital. In March 2005 (at the age of 24), her symptoms of overeating and persistent self-induced vomiting worsened, and her body weight dropped to 26 kg. In May 2005, she was referred to the Department of Nephrology at Saitama Medical University Hospital due to serum hypokalaemia (K = 2.8 mEq/L) and acute renal failure (Cr = 2.46 mg/dL). She was hospitalized immediately and treated accordingly to improve her condition. Afterwards, the same symptoms recurred, and she finally started

haemodialysis due to chronic renal failure in 2013. She has been receiving haemodialysis three times a week. A central venous port catheter was implanted into her left subclavian vein for parenteral nutritional management. Two years later (June 2015), she started having bloody sputum. Chest radiograph and computed tomography (CT) showed an abnormal chest shadow on the right upper lung field (Fig. 1A). She was then referred to the Department of Respiratory Medicine at Saitama Medical University Hospital for further investigation. Blood tests revealed an anti-aspergillus precipitating antibody, while aspergillus antigen and β-D glucan were negative. *Aspergillus* was not detected in the sputum culture or even in the bronchoscopy performed on 5 October 2015. Her serological and radiological features implied pulmonary aspergillosis, and she was first treated with haemostatic agents. However, haemoptysis worsened in April 2017. Chest radiological examinations showed an exacerbation of the infiltrative shadow and appearance of a new intracavitary ball in the preexisting cavity with thicker walls (Fig. 1B). Therefore, she was admitted for further treatment on 13 May 2017.

Upon admission, her status was as follows: conscious; coherent; height, 150.9 cm; body weight, 25.2 kg; body mass index, 11.1; body temperature, 37.4°C; blood pressure, 81/49 mmHg; pulse, 88/min and regular; $SpO_2$ 95% (room air). There were no palpable lymph nodes. Cardiac and respiratory sounds were almost clear, with no hepatosplenomegaly and no pitting oedema on either of the lower limbs. She was cachectic and pale, but generally, her condition seemed to be satisfactory. She had a history of AN, gastro-oesophageal reflux disease, aspiration pneumonia and secondary amenorrhea for years due to her eating disorder. Her medications were 1 mg Flunitrazepam, 20 mg Mianserin, 25 mg Hydroxyzine, 2700 mg potassium gluconate, and 15 mg Lansoprazole. Blood tests revealed anaemia (Hgb = 8.6 g/dL), elevated white cell count of $13.4 \times 10^3/\mu L$ (78% neutrophils and 11.8% lymphocytes), increased C-reactive protein (CRP = 15.71 mg/dL), renal failure (Cr = 1.71 mg/dL), and decreased total protein (TP = 5.9 g/dL) and albumin levels (ALB = 2.9 g/dL). The serological examinations for *Aspergillus* were the same in 2015. Tumour markers related to lung cancer, such as CEA and

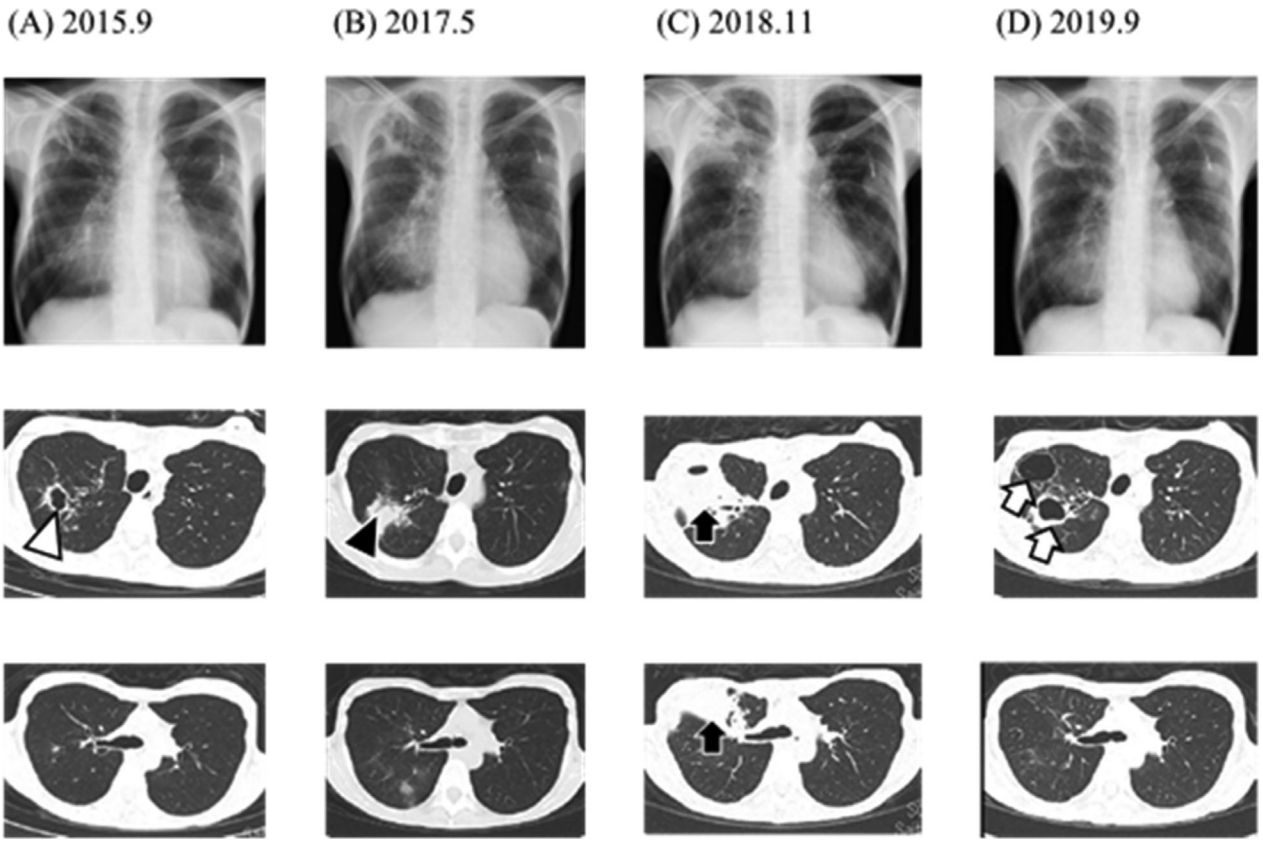


**Figure 1.** Clinical course and changes in radiographic findings. (A) Chest imaging on the first visit showed cavitary lesions in the right upper lobe (white arrowhead). (B) A cavitary lesion with a fungus ball (black arrowhead) was observed in the right lower lobe. (C) CT scan showing enlargement of fungus balls and inflammation inside the large cavity in the right upper lobe (black arrow) and infiltration in the right middle lobe (black arrow). (D) Improvement was observed in chest imaging after dose adjustment of voriconazole; multiple cavities in the right upper lobe still existed (white arrow).

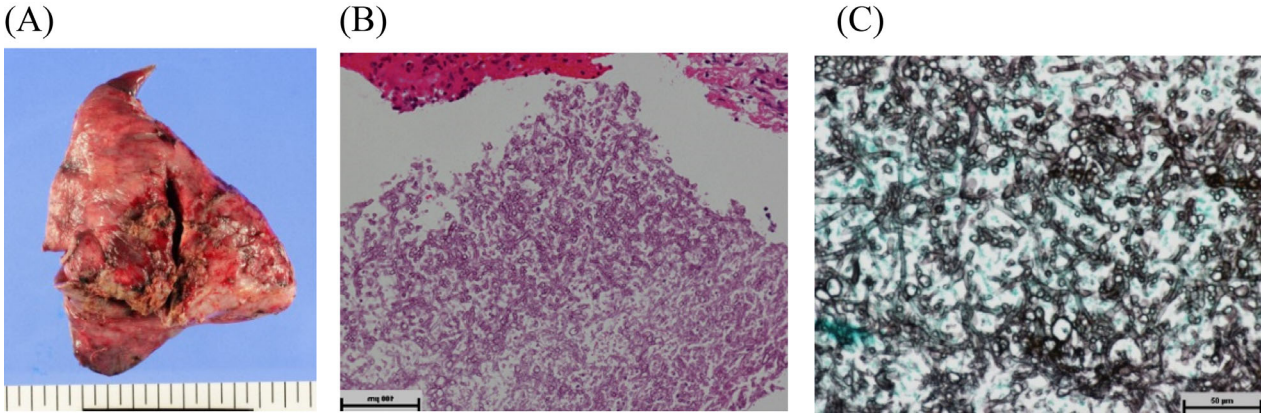


**Figure 2.** (A) Gross view of the right upper lung with necrotic and cavity lesions. (B,C) photomicrograph: Microscopic findings of intracavity materials showing multiple fungal hyphae with dichotomous branching, characteristic of *Aspergillus* species; (B) haematoxylin–eosin stain (×200), (C) Grocott's silver stain (×400).

CYFRA, were negative. Sputum culture was positive for *Aspergillus fumigatus*, resulting in a diagnosis of CPPA. Due to the continuous bleeding, bronchial artery embolization (BAE) was performed using gel-foam strips. She was also treated with Voriconazole (VRCZ) 250 mg/day. These treatments reduced her symptoms to some extent for a year and a half, but frequent haemoptysis recurred from October 2018. Radiological findings showed enlargement of the cavitary formation with consolidation and increased spherical nodules in the preexisting cavity in addition to the new appearance of infiltrates in the middle lobe (Fig. 1C). Although we considered repeating transcatheter embolization therapy, we first increased the dose of VRCZ from 250 mg/day to 300 mg/day because the serum level of VRCZ had been low at 2.0 μg/mL. This resulted in gradual improvement of CT images (at 4.2 μg/mL of serum levels of VRCZ) (Fig. 1D). However, since haemoptysis was refractory, the patient was referred to the Department of General Thoracic Surgery at Saitama Medical Center, Jichi Medical University Hospital, Saitama, Japan, for surgery in November 2019. We explained the risk of the operation due to her cachectic status and written informed consent was obtained from the patient and her parents and a video-assisted thoracic surgery (VATS), right upper lobectomy and right S6 segmentectomy, was performed on 23 January 2020. The cavity with fragile materials macroscopically existed in the right upper lobe and right S6, and intracavitary materials microscopically contained hyphae that were positively stained with Grocott's silver stains. These hyphae were uniform and regularly septated with dichotomous branching, which was consistent with *Aspergillus* infection (Fig. 2). The postoperative course was unremarkable and her haemoptysis has resolved.

## Discussion

We considered this operative case of CPPA to be difficult because of cachexia in a patient with AN undergoing haemodialysis.

Chronic kidney disease is a major complication in patients with AN [3]. Several studies demonstrated that around 70% of AN patients have impaired renal function throughout their lives, which is more than 5 times that of the general population [4,5]. The prevalence of end-stage renal dysfunction may be as high as 5.2% [6]. Considering the increasing number of AN patients and the resultant increasing population of ageing AN patients, it is highly expected that the demand for dialysis among these patients will increase in the future. The mechanism of the deterioration of renal function in AN may be caused by dehydration and hypokalaemia secondary to persistent self-induced vomiting and/or lack of fluid/food intake. The decrease in effective circulating volume results in tubular disorders and an increase in aldosterone and prolonged hypokalaemia may cause tubular atrophy, interstitial fibrosis, and cyst formation most prominently in the renal medulla [7,8]. Thus, the correction of dehydration and appropriate potassium supplementation for hypokalaemia is considered essential in preventing the progression of renal damage. VRCZ should be administered orally rather than intravenously to patients with renal dysfunction [9]. No special dosage adjustment is required with oral administration. In the present case, serum VRCZ concentration was relatively low. When the CT-images worsened, it was found that she frequently refused to take VRCZ due to her mental disorder, resulting in lower blood levels and hence disease progression. Therefore, it is important to check whether AN patients are compliant with their medications.

**Table 1. Summary of previously published case reports of pulmonary aspergillosis and our case.**

| Case | Age | Sex | BMI | Renal function | AN (years) | Subtype | Antifungal treatment | Serological examination | | | Operation |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | β-D glucan | Aspergillus Ag | Aspergillus Ab | |
| Our case | 37 | F | 11.1 | Impaired | 22 | CPPA | VRCZ | Normal | Negative | Positive | VATS |
| 1 [17] | 27 | F | 15.0 | Normal | 9 | SPA | None | Normal | Negative | (N/A) | VATS |
| 2 [19] | 19 | F | (N/A) | Normal | 4 | SPA | ITCZ | (N/A) | (N/A) | (N/A) | Thoracotomy |
| 3 [20] | 31 | F | 12.5 | Normal | 5 | SPA | None | (N/A) | Negative | Positive | Thoracotomy |

**AN, anorexia nervosa; BMI, body mass index; CPPA, chronic pulmonary progressive aspergillosis; F, female; ITCZ, itraconazole, N/A, not available; SPA, simple pulmonary aspergillosis; VATS, video-associated thoracic surgery, VRCZ, voriconazole.**

According to the Japanese domestic guideline for the management of deep-seated mycosis 2014, chronic pulmonary aspergillosis (CPA) occurs in two subtypes; simple pulmonary aspergillosis (SPA) and CPPA [10]. CPPA generally progresses slowly and is characterized by repeated cycles of exacerbations and remissions. In this case, malnutrition and haemodialysis treatment were considered to be the causes of immunodeficiency. Previous studies have shown decrease in white blood cell counts, dysfunction of granulocyte bactericidal ability, decrease in IgG concentration, and qualitative impairment of T-cell function in patients with AN [11–13]. Patients undergoing haemodialysis had impairment of cell-mediated immunity, phagocytosis, and antibody production [14–16]. These findings suggest that this present case may be susceptible to *Aspergillus* infection. As far as the retrieval is concerned, there were only four reports regarding pulmonary aspergillosis in AN patients, and three of these were operative cases [17–20]. The main differences between the other three cases and our case are as follows; (1) all other cases had SPA while our patient had CPPA, (2) in contrast to our case, the other cases did not have any renal dysfunction, and (3) there were disparities in the length of duration of AN (4–9 years vs. 22 years) and body mass index (BMI) (12.5–15 vs. 11.1). These results indicated that our patient had a more severe condition (Table 1). The operation was successfully performed, and her quality of life drastically improved.

In summary, we described a rare case of CPPA with AN while undergoing haemodialysis. The progressive cachexia caused by malnutrition and haemodialysis may have led to her chronic immunocompromised condition, resulting in *Aspergillus* infection and disease progression. Although continuous careful observations will be necessary because of her lasting malnutrition and immunosuppressive status, we demonstrated that VATS lobectomy can be a treatment of choice for CPPA with haemoptysis even in cases that exhibit a cachectic condition due to AN.

## Disclosure Statements

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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