A case of pulmonary semi-invasive aspergillosis developing fatal acute exacerbation

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A 80-year-old male was referred for detailed examination of left apical fibrotic changes in the chest radiograph. Six years later, several cavitary lesions with thickening of the pleura developed. Anti tuberculosis therapy had no effects. Despite intravenous administration of antibiotics, the cavities became larger and the infiltrates progressed to the left lower lobe. The air crescent was observed in one of the cavities. Repeated sputum examinations revealed *Aspergillus niger* only. With administration of anti fungal drug, infiltrates were faded. Four months after the cessation of antifungal drug high fever associated with new infiltrates developed. Sputum culture showed *Aspergillus flavus*. Infiltrates over the entire left lung field and in the right upper lobe were observed. On CT film necrotic lung tissue was strongly suggested in the cavity. The patients died of respiratory failure. Although initial course of the presented case was compatible with semi-invasive pulmonary aspergillosis (SIPA), fluminant and fatal exacerbations which may be very unusual in SIPA, developed in later. The mycetoma-like ball may be occasionally made of necrotic lung parenchyma instead of fungal mycelia in SIPA.

Key words: pulmonary aspergillosis, invasive, lung ball, mycetoma, exacerbation

INTRODUCTION

Pulmonary aspergillosis has been classified into four types. They include invasive pulmonary aspergillosis (IPA), semi-invasive pulmonary aspergillosis (SIPA), pulmonary aspergilloma and allergic bronchopulmonary aspergillosis [1]. The individual type is not specie-dependent but depends on immunologic condition of the host. SIPA is a chronic, indolent, and localized form of Asperillus infection which develops in not severely immunocompromized patients. Typically, SIPA resembles tuberculosis and the fungus is actively involved in producing the inflammatory process that leads to tissue necrosis and cavity formation. Sometimes the mycetoma is present in the cavity as a secondary phenomenon [3]. The prognosis of SIPA is usually good and majority of the deaths is due to other causes [1].

In this report we describe a case of SIPA which developed fluminant and fatal exacerbations. We also discussed mechanisms of the air crescent which developed during acute exacerbations because computed tomography (CT) strongly suggested that the mycetoma-like ball was made not of fungal mycelia but necrotic lung parenchyma.

CASE PRESENTATION

A 80-year-old male was referred from a general physician for detailed examination of an abnormal infiltrate on a chest radiograph. He had been underwent gastrectomy at 43 year-old and coronary bypass at 60-year-old. As shown in Fig. 1 there were mild fibrotic changes at left apical region. Purified protein derivative (PPD) reaction was negative. Sputum examination revealed no mycobacterium. It was decided to follow up at outpatient clinic.

Six years later, several cavitary lesions along with thickening of the pleura developed on the left apical region of chest radiograph (Fig. 2). The wall of the cavity was not smooth on CT film. Mycobacterium was not found by sputum examination. The patient was suffering from renal failure (creat. 2.3 mg/dl). Pulmonary infection with non-tuberculus mycobacterium was suspected. Daily administration of rifampicin 300 mg, isniazid 100 mg, clarythromycin 400 mg was begun.

Five months later, the patient complained of persistence of low grade fever (~37˚C) with increases of dark sputum expectorations. Oral ciprofroxacin produced no improvement. The chest radiograph obtained 7 days later showed progression of the infiltrates (Fig. 3). On the chest CT film, wall of the cavities were indurated and the pleura became thicker.

On admission the axillary temperature was 38.4˚C. The major laboratory findings were WBC 9.100 /μl (eosino. 4%), creat. 2.1 mg/dl, CRP 24.6 mg/dl and KL-6 1563 U/ml (normal limit, <500 U/ml). The sputum culture revealed a few colonies of Candida spp and Stenotrophomas maltophilia but no mycobacterium. No malignant cells were detected in the sputum. No improvements of serum abnormalities and radiological findings were attained by administration

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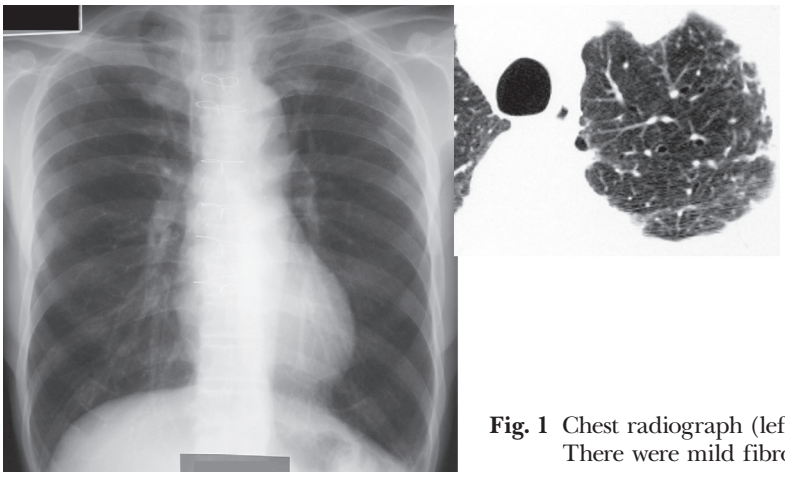

Fig. 1 Chest radiograph (left) and CT (right) obtained at first visit. There were mild fibrotic changes at left apical region.

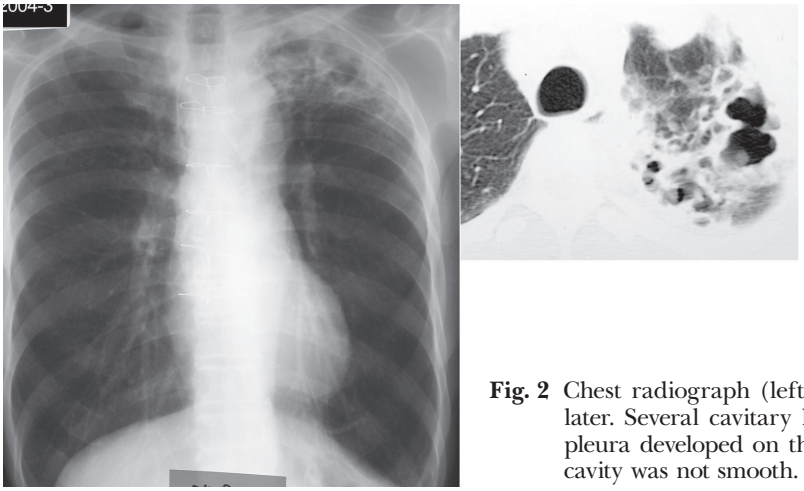

Fig. 2 Chest radiograph (left) and CT (right) obtained six years later. Several cavitary lesions along with thickening of the pleura developed on the left apical region. The wall of the cavity was not smooth.

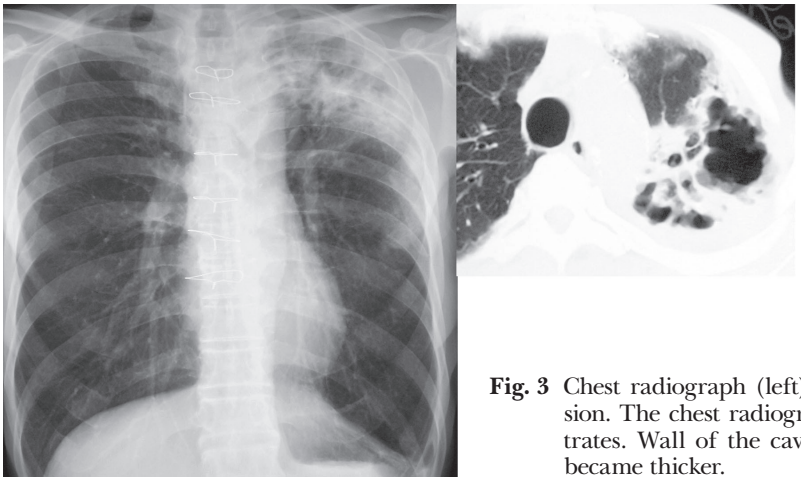

Fig. 3 Chest radiograph (left) and CT (right) obtained on admission. The chest radiograph showed progression of the infiltrates. Wall of the cavities were indurated and the pleura became thicker.

of anitibiotics including cefoperazone/sulbactum and meropenem. Repeated sputum examinations revealed *Aspergillus niger* only. Chest radiograph showed the cavity became larger and further progression of the infiltrates to the left lower lobe with thickening of lower lobe bronchi (Fig. 4). The air crescent was seen in axial image of multi-slice CT. On frontal and lateral images multiple thin-walled cavities and an infiltrate with airbronchograms were observed in the left upper lobe (S^{1+2} and S^{3}). On the seventh hospital day, WBC raised to 14.000/μl (granulocytes 77.3%) and intravenous administration of itraconazol and pazufloxacin begun. On the 20th hospital day, CRP decreased to 8.7 mg/dl. β-D-glucan on this day was yet high as 58.4 pg/ml (normal limit, $<$10 pg/ml), and thus antifungal drug was changed to micafungin. On the 30th hospital day, infiltrates in the lower lobes were faded. One week later, CRP fell to 4.0 mg/dl and he discharged from the hospital with changing antifungal drug from micafungin to oral itraconazol.

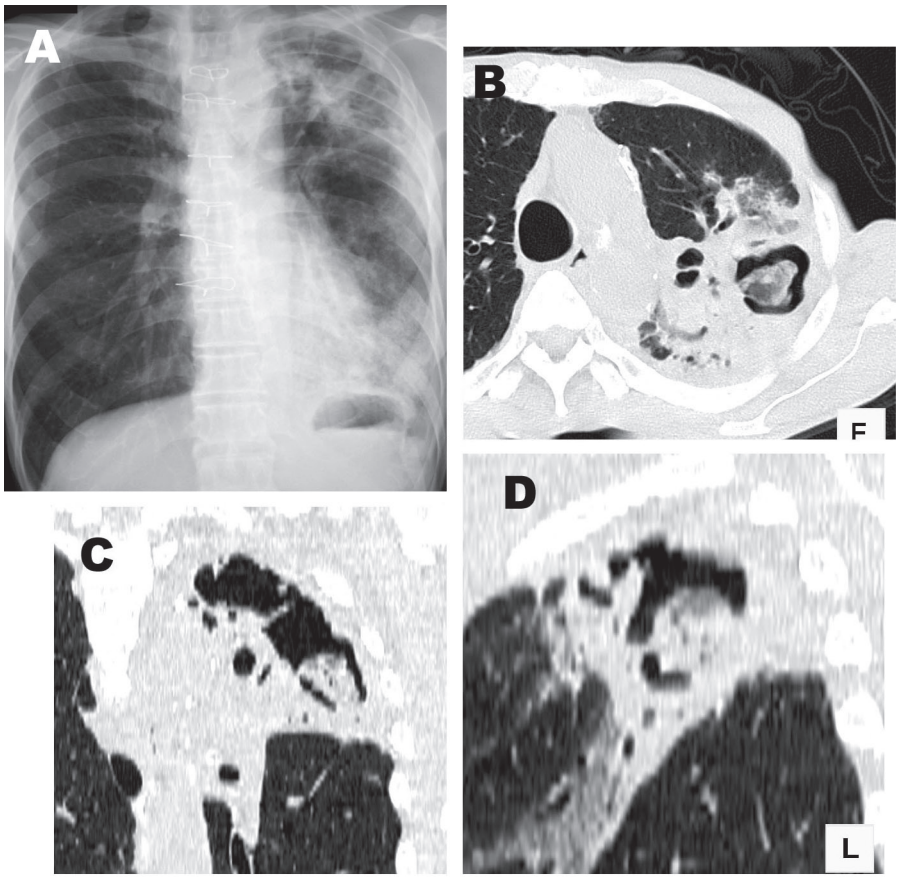

Fig. 4 Chest radiograph (A) and axial (B), frontal (C) and lateral (D) images of multislice CT obtained on 7th hospital day. The cavity became larger and further progression of the infiltrates to the left lower lobe. The air crescent was observed in axial image. In frontal and lateral images infiltrates with airbronchograms were observed in the left upper lobe (S^{1+2} and S^{3}).

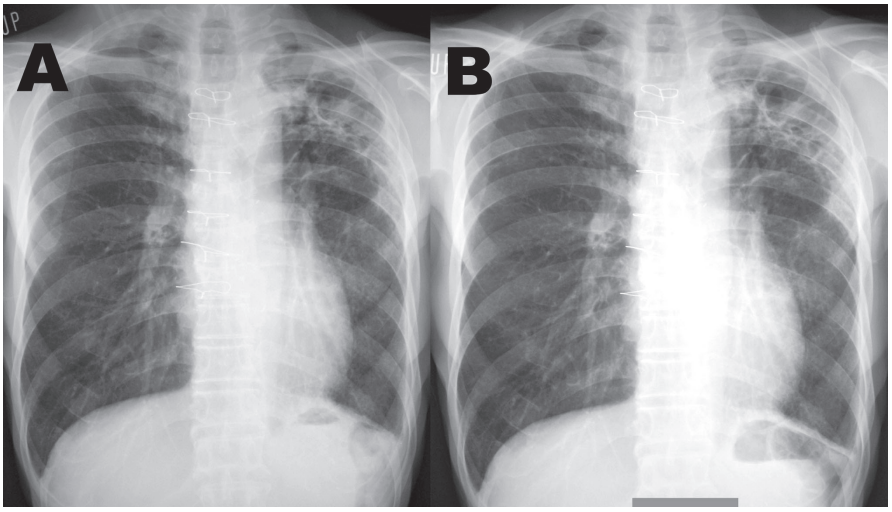

Fig. 5 Chest radiographs obtained at discontinuation (A) and 1 month after discontinuation of oral itraconazol (B).

The sputum examination repeated at outpatient clinic for six months. The results were *Serratia marcescens*, then *Aspergillus niger*, *Serratia marcescens* and *Aspergillus flavus*, and finally *Serratia marcescens*. No apparent signs or symptoms of worsening of aspergillosis were noted in this term. This was confirmed by chest radiograph as well (Fig. 5A). CRP obtained after six months' treatment oral itraconazol was still low as 0.19 mg/dl. By these reasons oral itraconazol was discontinued. There was no progression of infiltrates on the chest radiograph obtained one month later (Fig. 5B).

Four months after the cessation of antifungal drug fever above 38˚C associated with new infiltrates on chest radiograph developed. On readmission WBC 20.900/μl (granulocytes 90.0%), CRP was 29.8 mg/dl,

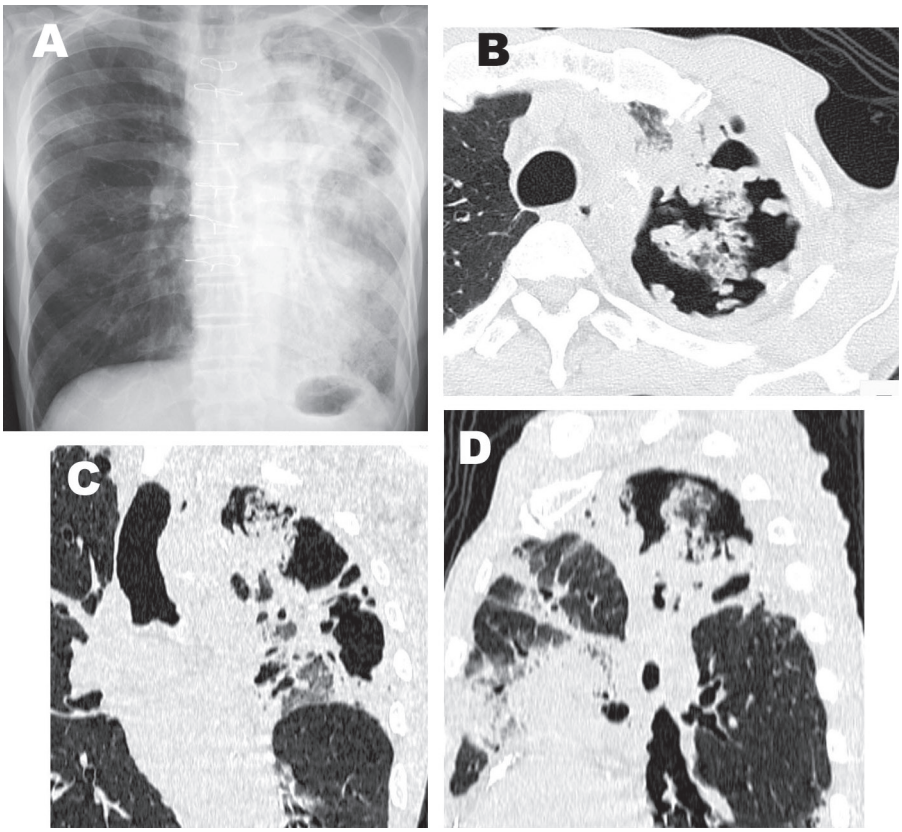

Fig. 6 Chest radiograph (A) and axial (B), frontal (C) and lateral (D) images of multi-slice CT obtained on the second admission. Infiltrates on entire left lung field and in the right upper lobe were seen. In frontal and lateral images a few bronchi penetrate through the intracavitary masses.

and sputum culture showed only *Aspergillus flavus*. Chest radiograph demonstrated infiltrates on entire left lung field and another infiltrate was seen in the right upper lobe. Some of them were pleural-based suggestive of pulmonary infarctions. On CT film the size of the cavity increased. The air crescent was seen on axial image. However, on lateral and frontal images some bronchi penetrating in the intracavitary masses were seen. This finding strongly suggested that the intracavitary mass was made of necrotic lung parenchyma instead of fungal mycelia (Fig. 6). Intravenous micafungin and flomoxef were begun. On the next day of admission, flomoxef was changed to meropenem. The sputum culture was positive for Aspergillus flavus only. Blood culture was negative. On the fourth hospital day, the fever resoluted but infiltrates on the lower lobes tended to increase. On the 9th hospital day, CRP remained high at 21.1 mg/dl and right-sided pneumothorax developed. Insertion of the chest tube and mechanical ventilation were instituted. He died of respiratory failure on the 14th hospital day. Autopsy was not permitted.

DISCUSSION

SIPA is an indolent, destructive process of the lung due to invasion by Aspergillus species. SIPA is usually seen in middle aged and elderly patients with documented or suspected underlying lung disease like COPD, inactive tuberculosis, radiation therapy, and pneumonconiosis. It also has been described in the patients with mild immunosuppression including those with diabetes mellitus, those undergoing low-dose corticosteroid therapy, and those with connective tissue disease [1]. The patient usually presents with fever, cough, sputum production, and weight loss of 1 to 6 months' duration. The chest radiograph usually shows an infiltrative process in the upper lobes or the superior segment of the lower lobes (S^6). A cavity with fungal ball may be seen in nearly one half of the cases. Adjacent pleural thickening is a characteristic finding [1]. Clinical features of the presented patient fulfill the criteria of SIPA [1]: Clinical and radiologic features consistent with the diagnosis; Isolation of Aspergillus species by culture from sputum or from bronchoscopic or percutaneous samples; and Exclusion of other conditions with similar presentations, such as active tuberculosis, atypical mycobacterial infection, chronic cavitary histoplasmosis, or coccidioidomycosis.

When the air crescent appears on chest radiograph of the patient with pulmonary aspergillosis two distinct pathological states should be considered; the one is fungal ball formation and the other is necrotic lung ball. The fungal ball, which is characteristic of either pulmonary aspergilloma or SIPA, occurs within preexisting cavity and the ball consists of masses of fungal mycelia, inflammatory cells, fibrin, mucus, and tissue debris [3]. In contrast, the necrotic lung ball is specific to invasive aspergillosis and the ball consists of necrotic pulmonary tissue infiltrated with fungus [3, 4]. The necrotic lung ball in IPA follows to multiple pulmo-

nary nodules with halo-sign. These nodules represent hemorrhagic infarction and some of them later possess air-crescent by secondary to necrosis [1, 5]. In the present case, the air crescents were seen on axial images of CT taken in both the first and the second admissions. However, on lateral and frontal images of the second admission some bronchi penetrated in the intracavitary masses. This finding strongly suggested that the ball was made not of fungal mycelia but necrotic lung parenchyma.

Clinical course of the presented patient before the first admission was typical for SIPA. When acutely exacerbated, the air crescent developed. The CT finding strongly suggested that the air crescent was made of necrotic lung tissue. Although the necrotic lung ball is one of the characteristic features of IPA, the air crescent in this patient was neither preceded by multiple nodules nor halo sign. Therefore, it is not possible to call this lesion as necrotic lung ball. Whether the air crescent is made of fungal mycelia of necrotic tissue cannot be discriminated by conventional CT. As shown in the present case, existence of bronchi in the ball is clearly demonstrated by multi slice CT. We suggest that air crescent found in SIPA does not necessarily represent mycetoma. In a few SIPA cases Aspergillus may be much invasive and develop fluminant process like PIA.

Why acute exacerbation developed two times in this patient with mild renal failure is not known. Antifungal drugs were effective in the first episode but not in the second episode. As shown in CT films destruction of lung parenchyma may have deteriorated clinical course of the second exacerbation. In this sense, earlier detection of exacerbation may be important. Since SIPA is a chronic and indolent form of Asperillus infection resembling tuberculosis, if the physician does not have notion of acute exacerbation early diagnosis is very hard. We propose that cavitary lesion with mild fibrosis in the lung apex should be carefully followed-up with plane chest radiograph and occasional CT examination. Moderate fever and sputum expectoration may be one of signs of exacerbation.

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