

Pulmonary fungal infection with hyalohyphomycosis associated with zygomycosis and Actinomyces spp. in a patient with ankylosing spondylitis

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ABSTRACT

Ankylosing spondylitis (AS) can be associated with extra-articular manifestations, among which we find pulmonary disorders. Fibrosis of the pulmonary apices is seen in up to 30% of the cases, and cyst formation is less common, being seen in advanced cases. Colonization of those cavities is a rare complication. A patient with a diagnosis of AS since 1998 with axial involvement and history of pulmonary tuberculosis treated in 2002 and 2007, developed bilateral aspergillosis of the pulmonary apices associated with zygomycosis and *Actinomyces* spp. The patient had been hospitalized to investigate complaints of weight loss, nocturnal diaphoresis, productive cough, and lesion in both lung apices. He was submitted to right upper pulmonary lobectomy after identification of a fungus ball on chest X-ray and CT scan, which was confirmed by a fibrobronchoscopy and biopsy for anatomopathological exam. The patient evolved without expansion of the right lung and underwent another fibrobronchoscopy that suggested occlusion of the middle lobar bronchus. Repeat thoracotomy did not confirm the findings of the last fibrobronchoscopy, but the right lung failed to expand. The patient developed septic shock refractory to treatment and died.

Keywords: ankylosing spondylitis, hyalohyphomycosis, zygomycosis, actinomycosis.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic autoimmune inflammatory disease affecting mainly the axial skeleton, but it can also affect peripheral joints. It can be associated with different extra-articular manifestations, such as uveitis, enthesitis, and gastrointestinal and pulmonary manifestations, among others. Fibrotic infiltrative changes simulating tuberculosis might be seen in the apices of the lungs. The development of cysts may be followed by fungal colonization, such as *Aspergillus*, especially in advanced disease. We report the case of a patient with AS with pulmonary manifestation who died due to severe pulmonary fungal infection with hyalohyphomycosis associated with zygomycosis and *Actinomyces* spp.

CASE REPORT

A 49-year old male with a history of AS since 1998 was referred to the Rheumatology outpatient clinic of the Hospital das Clínicas of UFPR in May 2006.

He complained of lumbar pain and morning stiffness. He had a history of pulmonary tuberculosis treated with rifampin (RIF), isoniazid (INH), and pyrazinamide (PZA) for six months. The chest X-ray showed fibrosis of the pulmonary apices, pulmonary function tests showed restrictive changes, and inflammatory activity tests were abnormal, with an increase in C-reactive protein and Erythrocyte Sedimentation Rate (ESR); the sputum was negative for acid-alcohol fast bacilli (AAFB); electrocardiogram and echocardiogram did not show any abnormalities.

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In April 2007, the patient still had the same complaints, but he denied paroxysmal nocturnal dyspnea, orthopnea, fever, and weight loss. The chest X-ray showed bilateral reticular opacities in the apices. A CT scan showed bilateral apical fibro retractile lesion with multiple cystic, aerated cavities, and an infiltrate in the left posterior apical segment. Sputum was once more negative for AAFB, and the Mantoux test was positive (10 mm). Serology for HIV was negative. Treatment for tuberculosis, with rifampin, isoniazid, and pyrazinamide, was instituted.

In July 2007, patient also complained of dry cough. All drugs were maintained. In October 2007, he still complained of dyspnea, the cough became productive and worse at night, and he presented a 3-kg weight loss in one month.

In July 2008, persistent dyspnea and cough productive of yellowish secretion, associated with nocturnal diaphoresis, but no weight loss. He was admitted to the Pneumology Service to be investigated. A CT scan of the chest showed cavitations in both lung apices with a material inside suggestive of a fungus ball. Fibrobronchoscopy confirmed the radiologic findings. Once more, AAFB were not present in four different sputum samples. Direct exam of the lung biopsy showed the presence of septate hyaline hyphae with 45° ramification. Culture of the lung biopsy was positive for *A. fumigates*. Anatomopathological exam of the lung biopsy was suggestive of a fungus ball by hyalohyphomycosis. It was decided to refer the patient to be evaluated by the Thoracic and Cardiovascular Surgery Department to plan the therapeutic strategy.

In August 2008 his symptoms worsened. He was waiting to be admitted by the Thoracic and Cardiovascular Surgery Service. In October 2008 the condition of the patient deteriorated and he was admitted to the Cardiac Surgery ICU. Preoperative posteroanterior chest X-ray (Figure 1A) showed chronic lesions in both lung apices. Preoperative axial chest CT scan (Figure 1B) showed the presence of a cavitary lesion in the right lung apex with an ovoid mass, and a crescent of air between the mass and the wall of the cavity. Two other masses were identified in the left apex (aspergilloma).

It was decided to perform bilateral lobectomy at different surgical times. Firstly, the patient underwent a right upper lobectomy without interurrences. Macroscopic anatomopathological study identified reddish purple lung tissue with foci of anthracosis and a 9.0 x 3.0 x 2.5 cm cavity with a pasty, dark, fetid material. Microscopic analysis identified an extensive fibrous pneumopathy with chronic and acute inflammation and fungal infection with hyalohyphomycosis associated with zygomycosis and *Actinomyces* spp. (Figure 2).

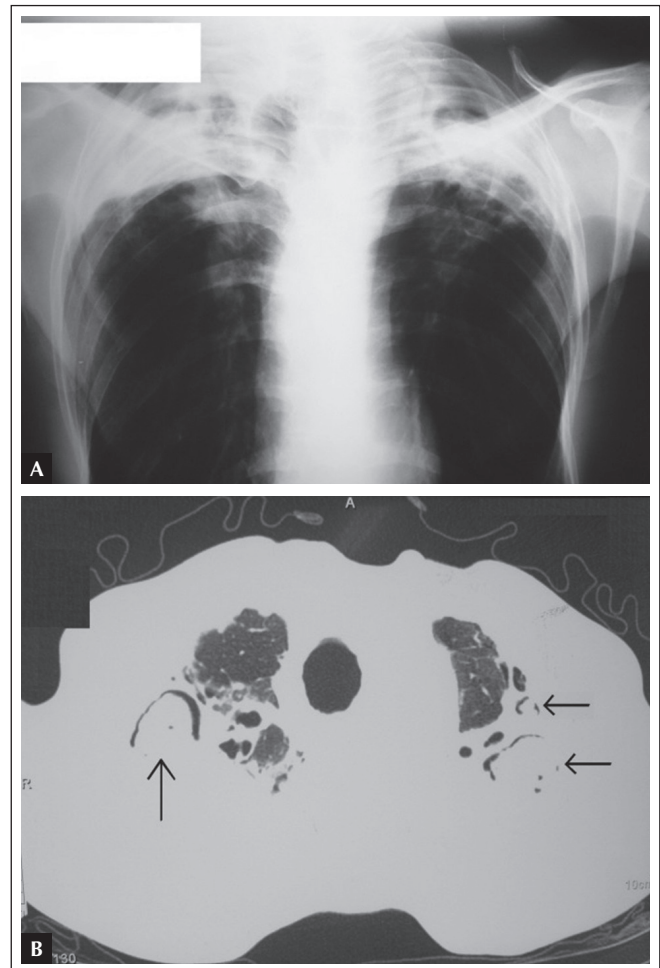


Figure 1. A) Preoperative posteroanterior chest X-ray showing chronic lesions in both apices. **B)** Preoperative axial chest CT scan showing a mass in the right lung apex and two in the left apex.

On the third postoperative day, the patient developed right lung atelectasis. An emergency fibrobronchoscopy was suggestive of occlusion of the middle lobar bronchus; however, a new thoracotomy did not confirm this finding. On subsequent days, the right lung failed to expand and the patient developed septic shock refractory to treatment, and the patient eventually died.

DISCUSSION

We presented a rare case of AS with a severe mixed fungal lung disease. The prevalence of lung disease in patients with AS ranges from 0 to 30%¹. Apical lung fibrosis, such

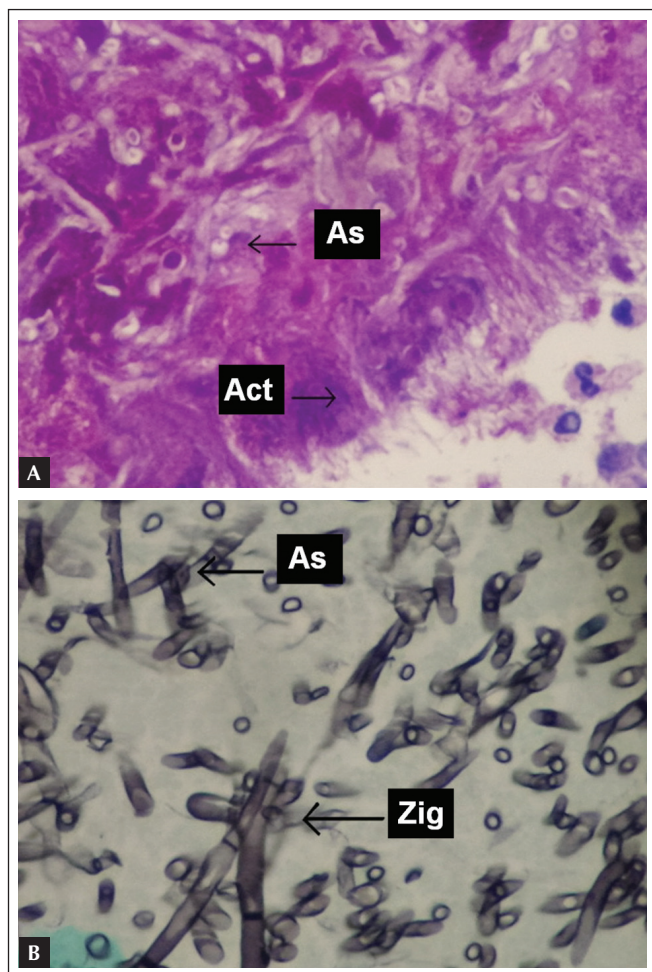


Figure 2. **A)** Histological slide of the fungus ball from the lung biopsy of October 2008 showing hyphae and asexual spores, suggestive of *Aspergillus* spp. (As) associated with *Actinomyces* spp. (Act). (PAS staining; 400x). **B)** Histological slide of the fungus ball from the lung biopsy of October 2008 showing *Aspergillus* sp. hyphae. (As – note the 45° septa) and *Zygomycetes* (Zig – note thicker hyphae with 90° septa). (Grocott staining; 400x).

as the one presented by this patient, is the main pulmonary manifestation. Cavitory lesions are not as common². Lung disease has been attributed to mechanical factors (the rigidity of the thoracic spine is responsible for a restrictive disorder) and interstitial lung inflammation³. For those reasons, patients with AS on immunosuppressors have a higher risk of developing lung infections. Tuberculosis is the lung infection more common in patients with AS with pulmonary fibrosis⁴. *Aspergillus* spp. infection (aspergilloma) develops inside a

preexisting pulmonary cavity, such as that resulting from prior tuberculosis. Our patient was treated for tuberculosis in another service and had apical fibrosis and cavitations. Although, to our understanding, the presence of tuberculosis was never confirmed, a new treatment with three drugs was reinstated because the possibility of pulmonary mycosis had not been considered. The association of AS and aspergillosis is rare. Rosenow *et al.*⁵ described aspergilloma in just five (0.2%) out of 2,080 patients with AS.

In hyalohyphomycosis, the causative agents present as hyaline, septate hyphae with closed angle ramifications, while in zygomycosis ramifications show a 90° angle⁵.

On radiological evaluation, aspergillomas appear as an oval to roundish mass with soft tissue opacity inside a pulmonary cavity. Typically, they are separated from the cavity wall by an aerated space known as the crescent air sign. Aspergillomas move according to the position of the body of the patient. Although patients with aspergilloma can be asymptomatic, most of them have symptoms such as cough, dyspnea, and hemoptysis⁵.

Besides aspergilloma, aspergillosis can also present as chronic necrotizing pulmonary aspergillosis (CNPA) and invasive aspergillosis (IA). Treatment with amphotericin B, alone or associated with flucytosine, can show excellent results in cases of IA, but aspergillomas do not show a good response to this treatment. Newer broad spectrum agents, such as itraconazole and fluconazole, have shown encouraging results with less toxicity⁷. When pharmacotherapy is ineffective, surgical resection is indicated⁵.

Franquet *et al.*⁶ described the case of a patient with AS for 15 years with hemoptysis, progressive dyspnea, weight loss, and fever. The patient denied history of tuberculosis. Imaging exams showed extensive bilateral apical fibrosis, and a cavitory lesion with an ovoid mass inside with crescent air sign. Microbiology showed septate fungal hyphae at a 45° angle, compatible with *Aspergillus* spp. Clinical evolution, imaging exams, and microbiological findings of their patient was similar to ours.

Elliott *et al.*⁷ reported the case of a patient with AS for 35 years who developed CNPA and aspergilloma, which was treated successfully with systemic antifungal therapy. The patient had been admitted with consumptive syndrome, productive cough, dyspnea, and fever. He was treated with itraconazole for six months. In our patient, unlike the patient of Elliott *et al.*⁷, surgery was indicated.

At the beginning of the decade of 1970, Kennedy *et al.*⁸ reported the case of two male patients with AS, apical lung fibrosis, and cavity, who developed fungal infection with a

combination of different agents. In this report, a combination of fungal strains suggestive of *Aspergillus* spp., *Zygomycetes*, and *Actinomyces* spp. was identified.

We conclude that vigilance and follow-up of lung disease in patients with long-standing AS, especially in those patients with pulmonary symptoms, are required. The possibility of pulmonary mycosis should be raised in case of poor response to drug therapy or when the evolution is not compatible with the pulmonary involvement of AS and/or tuberculosis. We suggested individualized evaluation of each case with imaging exams (chest X-ray and CT scan), respiratory endoscopy, microbiological tests, and multidisciplinary follow-up to minimize the morbidity and mortality of those patients.

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