CASE REPORT

# Oxalosis Around a Pulmonary Fungus Ball (Aspergilloma)

*H. Uğur Pabuççuoğlu, MD[1]; Esra Özkara, MD[1]; Emel Ceylan, MD[2]; Atilla Akkoçlu, MD[2]; Baran Uğurlu, MD[3]*

[1] *Dokuz Eylül University, Medical School, Department of Pathology, İzmir, Turkey*
[2] *Dokuz Eylül University, Medical School, Department of Chest Diseases, İzmir, Turkey*
[3] *Dokuz Eylül University, Medical School, Department of Thoracic and Cardiovascular Surgery, İzmir, Turkey*

## Abstract

A 41-year-old man with a previous history of tuberculosis presented with hemoptysis and a pulmonary cavitation in the left upper lobe. Persistent hemoptysis ultimately led to left upper lobectomy. Histopathological examination of the surgical specimen revealed a fungus ball with numerous birefringent calcium oxalate crystals either within the mycelium and in the adjacent lung parenchyma. The final diagnosis was pulmonary aspergilloma with oxalosis. The finding of calcium oxalate crystals in the absence of other oxalosis-related conditions can be regarded as a diagnostic clue for *Aspergillus* infection.

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**Key words:** *aspergillosis, fungus ball, calcium oxalate, oxalosis*

## Introduction

Aspergillosis is a group of diseases caused by a species of the genus *Aspergillus*. A. *fumigatus* is the most frequently encountered member of the genus in human infections, followed by A. *niger*, A. *flavus* and A. *terreus* (1). Pulmonary aspergillosis is broadly categorized as allergic aspergillosis, colonizing aspergillosis (aspergilloma) and invasive aspergillosis. Allergic aspergillosis develops as a consequence of hypersensitivity to the aspergillus antigens while in invasive aspergillosis the mycelia are present in the lung tissue causing considerable tissue damage. Colonizing aspergillosis is characterized by development of a fungus ball which simply is an intracavitary accumulation of fungal cells, representing a fungal colony formed by concentric layers of mycelium. This frequently results from fungal colonization of preformed cavities caused by other diseases such as tuberculosis, histoplasmosis and sarcoidosis (2,3). The principal clinical feature of aspergilloma is recurrent hemoptysis which may necessitate surgical removal (2).

In 1973, Nime and Hutchins (4) reported the associaton of calcium oxalate deposition (oxalosis) with aspergillosis. Since this first report, several solitary case reports of oxalosis associated with aspergillosis appeared in the literature (5-11) and this association is mentioned in textbooks on fungal pathology (1,12). We report an additional case of oxalosis associated with pulmonary aspergilloma.

***Correspondence:*** *Dr. H. Uğur Pabuççuoğlu*
*Patoloji Bölümü,*
*Dokuz Eylül Üniversitesi, Tıp Fakültesi*
*İnciraltı, İzmir, Türkiye*
*e-mail: ugur.pabuccuoglu@den.edu.tr*

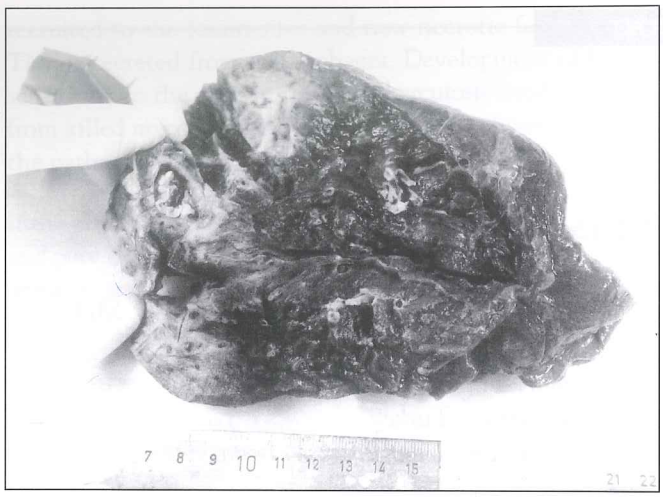

**Figure 1.** *Cross section of apical cavity in the left upper lobe containing friable material.*

## Case Report

A 41-years-old male patient was admitted with hemoptysis, malaise, sweating and weight loss. He had smoked a pack of cigarettes per day for 25 years and had Type II diabetes mellitus for 2 years. Last year he had been treated for lung tuberculosis. At his first presentation a year ago, acid fast bacilli (AFB) were seen in abundance (4+) in his sputum. A cavitary lesion and surrounding satellite lesions were present in the left lung apex. Prior to treatment, it was established that the bacilli were sensitive to Ethambutol, Isoniazide, Rifampicin and Streptomycine. AFB disappeared from the sputum within the first month of treatment. Treatment was continued with Isoniazide+Rifampicin+Morphozinamide+ Ethambutol for 3 months and then with Isoniazide+ Rifampicin for 9 months.

Soon after completion of treatment, complaints such as malaise, sweating, weight loss and expectoration of clear and bloody sputum reappeared. Physical examination was unremarkable and tuberculous activation was not present. A chest X-ray revealed a 5x5 cm lesion with cavitary appearance in the left pulmonary apex. Computed tomography displayed a nodular solid mass in the basal part of the cavity, compatible with a fungus ball. No source of hemoptysis was detected during bronchoscopy.

Laboratory findings revealed an increased erithrocyte sedimentation rate (123 mm/hr) and leukocytosis (13 700/ $mm^3$). Blood chemistry was within normal limits except for a high glucose level (149 g/dL). No AFB was found in the direct examination of the sputum and of the bronchial lavage fluid. Bronchial lavage cytology was non-specific. In the follow-up period, persistent hemoptysis necessitated surgical removal and a left upper lobectomy was performed.

The lobectomy specimen submitted for pathological examination was formalin-fixed and showed an apical nodular

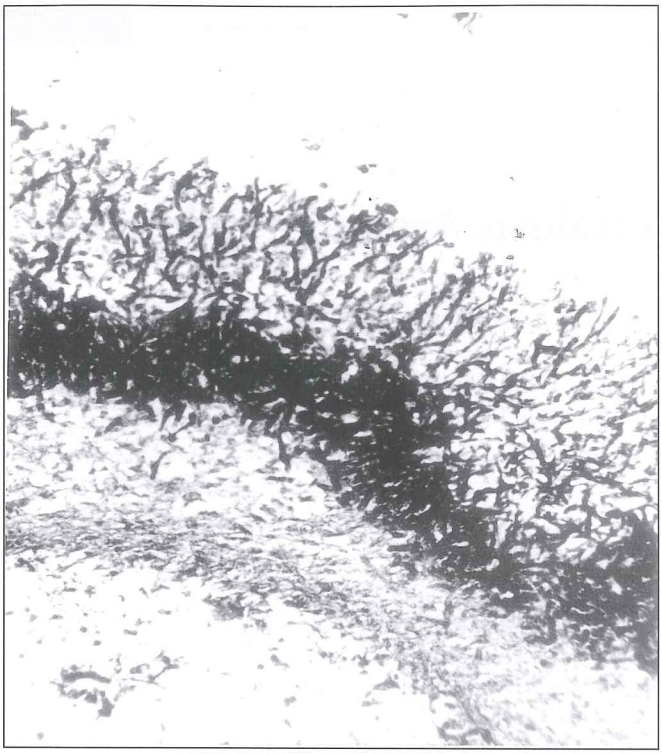

**Figure 2.** *Fungal mycelium showing zonation of hyphal growth with hyphae displaying dichotomous branching (GMS, x100).*

lesion measuring 4x3.5 cm with a central cavity 2 cm in diameter and containing a grayish-white friable material (Fig. 1). Microscopically this material consisted of fungal mycella which were partly necrotic. The hyphae displayed regular septation and dichotomous branching with branches arising at acute angles (Fig.2). Conidia or conidial heads (conidiophores) were not observed. The cavity wall was lined with chronic inflammatory granulation tissue with numerous crystals and foreign body giant cells. Some of the giant cells had engulfed the crystalline material which was mostly arranged as radiating clusters (Fig.3). By polarized light, the intra and extracellular crystals were strongly birefringent (Fig. 4). In the adjacent parenchyma, rare granulomas with central caseous necrosis, interstitial fibrosis and cuboidal metaplasia of alveolar epithelium were observed. No acid-fast bacilli were encountered in these granulomas with Ziehl-Neelsen stain and no crystals were found in uninfected lung parenchyma. In view of the fungal morphology and the associated oxalosis, the final diagnosis was "aspergilloma with oxalosis" resulting from colonization of a cavity caused by tuberculosis. Culture for fungal species identification was not possible because the specimen was fixed in formalin.

A year later, the patient was readmitted with coughing, fever, malaise and weight loss complaints. Chest radiography and computerized tomography showed multiple cavitary lesions in the lower lobe of the left lung along with micronodular densities scattered in the surrounding parenchyma.

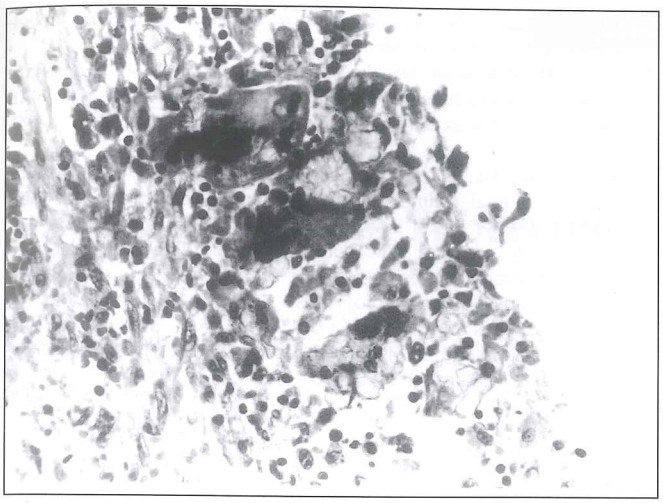

**Figure 3.** *Clusters of crystals inside the giant cells in the lung parenchyma adjacent to the fungus ball (H&E, x200).*

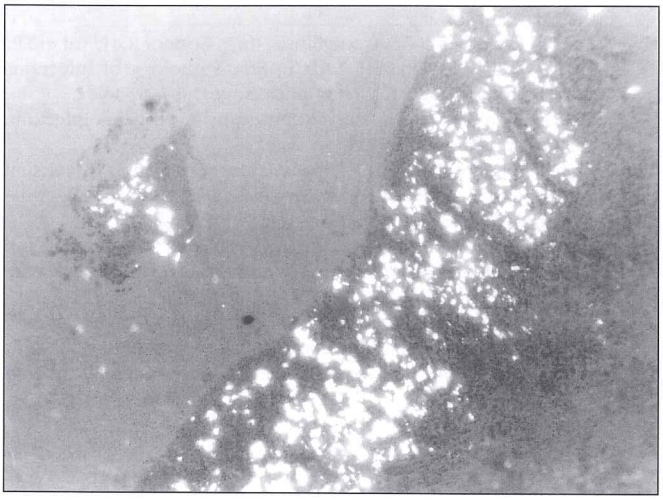

**Figure 4.** *Birefringence of crystals which are located within the mycelium and in the adjacent lung tissue (H&E, x40).*

Cavities were suggestive of aspergilloma but the sputum cytology and culture was found to be negative for *Aspergillus*. Direct smear of the sputum for acid fast bacillii examined on 3 different days were negative. In line with the clinical diagnosis of chronic necrotizing aspergillosis, the treatment was planned as Liposomal Amphotericine B 100 mg/day for 30 days. Sputum culture was reported to be positive for AFB twenty days after initiation antifungal therapy. Isoniazide + Rifampicin + Morphozinamide + Ethambutol were started and the treatment was continued for 12 months. After the completion of Amphotericine therapy, Itraconazole 30mg/day was administered for 8 months. Twelve months later, except for a single persistent cavity, complete resolution of all the other cavities were observed by computerized tomography. At present the patient is in good health and free of active disease.

## Discussion

In the original report by Nime and Hutchins (4), 11 cases of oxalosis associated with aspergillosis had been described. The calcium oxalate deposits were found in infected tissues of the lung or in the paranasal sinuses. In three cases the offending agent was identified as *A. niger* and in one case as *A. fumigatus*. In the remaining seven cases the type of *Aspergillus* could not be identified.

Oxalic acid is a mycotoxin known to be released by some *Aspergillus* species including *A. niger*, *A. fumigatus* and *A. flavus* (9). This reacts with tissue and blood calcium to precipitate calcium oxalate (5,8,9). The calcium oxalate crystals exhibit diverse shapes such as rosettes, sheaflike groupings, dumbbell, needle, ellipsoid or biconcave and they are strongly birefringent (6,8). Most reported cases of oxalosis are associated with *A. niger* (4-11).

The calcium oxalate crystals are found either in the fungus ball or tissues adjacent to fungal mycelium (4). In tissues, crystals are observed within the inflammatory granulation tissue and inside the histiocytic giant cells (7). These may also be encountered in pulmonary cytological specimens such as bronchoalveolar lavage (11), sputum and pleural fluid (6,8). It has been suggested that the presence of birefringent calcium oxalate crystals associated with an acute inflammatory background in cytological specimens, excluding urine, should be regarded as a clue to *Aspergillus* infection (6,8).

Nime & Hutchins (4) again were the first to draw attention to the role of oxalic acid production by the fungus being an important factor in causing local tissue injury. They also described the effects of widespread oxalosis involving the kidney. Kurrein *et al.*(5) reported a patient who died of massive hemorrhage and suggested the role of oxalic acid in blood vessel damage. Ghio *et al.* (9) showed that calcium oxalate crystals associated with *A. niger* infection complexed significant iron onto their surface. They postulated that the injury after oxalate deposition is due to this complexing with iron which may result in increased oxidant generation and alveolar macrophage activation.

In aspergillomas conidiophores and conidia are frequently observed which may lead to the species identification (2). Although we could not observe these typical structures necessary for the diagnosis of aspergillosis, the presence of oxalosis along with a fungal morphology compatible with *Aspergillus* led to the diagnosis of aspergilloma. In the absence of other oxalosis-related conditions, detection of these cystals can be a diagnostic clue for *Aspergillus* infection (2).

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*İstanbul and spring. Photography by Orhan Arseven*