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Isolated pleural aspergillosis: Case description and challenges in management

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**ABSTRACT**

Aspergillus species are ubiquitous fungi in the environment. They are responsible for a wide variety of clinical syndromes including allergic manifestations, saprophytic colonization, and invasive disease, which can disseminate. Aspergillus fumigatus is the most common Aspergillus species to cause human infection, and the respiratory system is the primary portal of entry. Although pulmonary aspergillosis is well-characterized, pleural aspergillosis in the absence of pulmonary infection is rare and difficult to treat. The ubiquity of Aspergillus species in the environment underscores the importance of host factors in colonization and infection. We outline the case of a 73-year-old man who presented with dyspnea and constitutional symptoms. Following a thorough workup including systematic exclusion of more common entities, he was diagnosed with isolated pleural aspergillosis. In the absence of considerable supporting literature we discuss the diagnosis, clinical course and management challenges of this rare entity.

**KEYWORDS**

Aspergillus; empyema; thoracic surgery; antifungals; pleural effusion

**Objectives**

- Recognize the clinical presentation and epidemiologic characteristics of pulmonary and pleural aspergillosis.
- Review the challenges in the diagnosis and management of isolated pleural aspergillosis.

**Pre-test**

1. List the principal host factors that increase risk of pulmonary and pleural aspergillosis.
2. Describe the management dilemmas associated with isolated pleural aspergillosis.

**Case**

A 73-year-old man presented with progressive shortness of breath on exertion and fatigue over several months. His past medical history was significant for diabetes mellitus (well-controlled; HbA1C = 0.058), hypertension, hyperlipidemia, and stage T3N0 rectal adenocarcinoma (without recurrence over 7 years following neo-adjuvant chemotherapy, radiation and local excision). He had no other evidence of immunocompromise. He emigrated from Korea in 1998. He had a 25-pack per year smoking history. He denied all pertinent respiratory exposures including occupational or infectious exposures. His family history was non-contributory.

His symptoms evolved, from fatigue initially to shortness of breath on exertion, decreased appetite, and unintentional weight loss. He was thin and pale, but initial examination was otherwise unremarkable. Restaging CT thorax/abdomen/pelvis performed two months prior to his annual surveillance Oncology visit did not reveal evidence of malignant recurrence. Long-standing right pleural thickening and calcification (thought to represent previous pleural tuberculosis) as well as mild apical parapneumonic emphysematous changes were seen. Serial complete blood counts were drawn. Hemoglobin was down-trending (101 to 75 g/L); WBC only mildly increased (10 to 12 E9/L). Inflammatory markers were elevated (CRP = 175 mg/L). Colonoscopy and gastroscopy were unremarkable.
He was admitted to hospital for workup of anemia and possible occult malignancy.

In-patient CT thorax, performed 4 months following his initial resting CT scan, revealed a new right-sided pleural effusion (Figure 1) with new irregular pleural thickening, enhancement, and stranding concerning for malignancy, but no new parenchymal disease. On interventional radiology-guided pleural biopsy, mycobacterial and bacterial cultures were negative, but no other cultures were performed. Pathology revealed benign fibrofatty tissue with acute inflammatory infiltrate (no malignancy). Mycobacterial and fungal stains of pathology samples were negative. Serum sputum samples were negative for mycobacteria. He was discharged home.

In follow-up 12 days later he endorsed worsening of symptoms including persisting dyspnea. He was cachectic, and reduced air entry was noted to the right base. Imaging demonstrated right pleural effusion accumulation, prompting diagnostic and therapeutic thoracentesis. 400 cc of sero-sanguinous fluid was removed (cell count unprocessable; LDH > 4200U/L, Protein = 51 g/L, Glucose = 0.4 mmol/L; cytology negative for malignancy). Pleural fluid bacterial and mycobacterial cultures were negative. Fungal culture was positive for Aspergillus fumigatus complex.

He was re-admitted to hospital three weeks later on return of this unexpected result. An intra-pleural catheter was inserted. Drainage was purulent. Pleural fluid fungal cultures again grew A. fumigatus. Cytology, bacterial culture, and mycobacterial culture were again negative. Serum galactomannan was 4.54 (Platelia™ Aspergillus Ag: non-reactive < 0.5). He was initiated on voriconazole with two oral loading doses of 400 mg (6 mg/kg) followed by 250 mg (4 mg/kg) PO BID for presumed isolated pleural aspergillosis. Serial drug level measurements were not performed. Given the patient’s presentation and epidemiological risk factors, there was ongoing concern for pleural tuberculosis as the primary cause of his illness, with A. fumigatus representing secondary infection introduced during the first pleural biopsy procedure. Therefore, he underwent repeat pleural biopsy 8 days later. Pathology showed fungal hyphae consistent with Aspergillus (negative for malignancy). Mycobacterial culture and Mycobacterium tuberculosis complex PCR from pleural tissue were negative. Mycobacterial sputum and bronchoalveolar lavage (BAL) cultures were negative.

Symptoms persisted after four weeks of voriconazole, and Thoracic Surgery was consulted for surgical source control. Bronchoscopy, thoracoscopy and thoracotomy were performed. Significant pleural calcification and dense fibrosis were noted. The patient underwent partial 7th rib resection (for optimal access), major decortication, and multiple chest tube insertions (Figure 2). Intra-operative pleural fluid cultures were positive for A. fumigatus (mycobacterial and bacterial cultures negative; cytology negative) while pleural tissue bacterial, mycobacterial, and fungal culture were negative (although fungal filaments were seen). Following surgery, re-expansion of the right lung was limited by chronic fibrothorax. Post-operative course was otherwise uneventful. Voriconazole was continued throughout hospitalization and after discharge. He improved, with resolution of shortness of breath and constitutional symptoms reported in clinic 6 weeks postoperatively. CRP was 39 mg/L, and decreased to 12 mg/L six months following surgery. CT thorax at that time showed a very small residual pleural effusion. Thoracentesis was repeated (cell count unprocessable; LDH = 1800U/L; Protein < 20 g/L; Glucose < 0.2 mmol/L). Pleural fluid was negative for malignancy, bacteria and mycobacteria. Fungal filaments were seen on microscopy and pathology, but did not grow on fungal culture.

He was maintained on antifungal therapy for a cumulative treatment of 13 months. Voriconazole was discontinued after the onset of worsening bilateral neuropathic leg symptoms, which after investigation were felt to represent an adverse drug effect. These symptoms resolved off therapy, with no recurrence of disease under approximately seven months of follow-up since discontinuation.

**Discussion**

There is a paucity of literature regarding isolated pleural aspergillosis. Presenting symptoms include cough with variable expectoration, hemoptyis, shortness of breath and constitutional symptoms. Patients are more often male (72–83%) and aged above fifty.

Host risk factors can be divided into immunosuppressive and structural factors. Invasive aspergillosis occurs more in those with prolonged neutropenia, haematological malignancies, advanced HIV, solid organ transplant, and severe liver disease, following immunosuppressive therapies and from subtle immune defects. Furthermore, higher mortality was observed in patients with fungal empyema who are immunocompromised. Regarding pre-existing pulmonary disease, tuberculosis and COPD are most commonly described. Pre-existing cavitary or bullous lesions, pneumothorax or fistulae can provide routes of entry into the pleural space. In the immunocompetent patient, pleural aspergillosis is most often an iatrogenic complication of surgery or other invasive procedure.

The origin of our patient’s pleural Aspergillus infection is unclear. The respiratory system is the most common portal

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**Figure 1.** CT scan showing complex right sided pleural effusion.
of entry in invasive aspergillosis and thus spread from the lungs to the pleura is most likely. Subtle pulmonary defects, including the mild apical emphysematous changes seen on his CT thorax, may have served as a portal of entry. Iatrogenic spread to the pleura, for example at the time of the first pleural biopsy, is less likely given his symptoms preceded all procedures and there was no alternate cause of his pleural disease found, despite extensive work-up to rule out tuberculosis and malignancy.

Our patient was immunocompetent, making pleural fungal infection unusual. Importantly, his longstanding pleural damage, possibly representing remote pleural tuberculosis, may have been a predisposing factor. Aspergillus empyema following tuberculosis has previously been reported.1,8

Pleural fungal infections are diagnosed on the basis of isolation of a fungal species from pleural samples.4,7 Isolation on more than one occasion is preferred.1,7 Growth of fungus in culture allows for identification of the specific organism involved, however risks representing contamination. The observation of tissue-invasive septate hyphae on pathology allows for confirmation of invasive fungal infection. Other complementary tests (galactomannan, 1,3-β-D-glucan, and genomic detection methods) are increasingly emphasized in aiding diagnosis.10 Radiographic findings in pleural fungal infections include pleural thickening, pleural effusion and an air-fluid level,1,6,7,11 whereas pulmonary cavities, progressive fibrosis, and classic descriptions (the “halo sign” and “air-crescent sign”) can be seen in pulmonary aspergillosis.5

Pharmacological,6 surgical,1,3 and combination treatment have been described. The comparative success of these modalities in isolation or combination has not been evaluated. Guidelines support surgical resection of Aspergillus-infected tissue when lesions erode into the pleural space.4,9 Post-surgical complications including air leak and respiratory failure underscore the importance of appropriate patient selection.3 An individualized approach to surgical candidacy is emphasized, based on patient-specific factors (immune status, comorbidities, and disease burden).9 At minimum, less invasive source control measures such as chest tube insertion, to decrease the burden of disease, are highly recommended.4,9

From a pharmacological perspective, systemic, intra-pleural and inhaled antifungal therapy for Aspergillus empyema have been described.1,6 Oral voriconazole was found to have excellent penetration into the pleural cavity;6,11 however, therapeutic drug levels have been shown to be compromised by a draining chest tube.6 This highlights the art of balancing source control with maintaining optimal intra-pleural antifungal concentrations.

Landmark trials5 and guidelines4,9 favour voriconazole as the preferred antifungal for invasive aspergillosis. The optimal duration of antifungal treatment continues to be a management dilemma, and commonly ranges from several months to years. Recurrent antifungal drug courses often need to be administered.2 With an estimated 15–18% mortality from Aspergillus empyema,1 the consequences of under-management (pleural fibrosis, restrictive pulmonary defects and disability)3 must be weighed against the morbidity and mortality from invasive procedures, and adverse drug effects from prolonged antifungal courses.

Our patient was managed with a combination of surgery and prolonged oral voriconazole therapy. Considering burden of disease, he was considered to have a favourable response.

**Post-test**

1. Immunosuppression and pre-existing pulmonary disease are the two major risk factor categories for pulmonary aspergillosis. Immunocompromise can be iatrogenic or due to underlying disease. Pulmonary disease (including COPD and tuberculosis) and existing structural damage (bullae, fistulae, pneumothorax) also predispose to infection and pleural spread.

2. The available literature suggests that the optimal management of pleural aspergillosis combines pharmacological (prolonged antifungal therapy) and surgical (source control) modalities. Careful patient selection for invasive surgery is important given complication risks. The optimal duration of antifungal treatment is unknown.

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