

Aspergillosis Presenting as Multiple Pulmonary Nodules in an Immunocompetent Cannabis User

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Abstract

Aspergillus has been identified as a contaminant of cannabis and other smoked plant matter. We report a case of pulmonary aspergillosis in an immunocompetent marijuana user with a history of chronic cough. The incidental diagnosis of multiple pulmonary nodules was made during imaging for an unrelated complaint. The diagnosis of aspergillosis was made via pathology, and the patient was treated with voriconazole. *Aspergillus* contamination of plant matter, including marijuana, has been described. Physicians should be aware that pulmonary aspergillosis is an uncommon (but potentially life-threatening) complication of cannabis use.

Keywords: Cannabis; Marijuana; Aspergillosis; Multiple pulmonary nodules

Case Report

A 46-year-old man with a history of hypertension and chronic cough presented to the emergency department with neurologic symptoms, including ataxia and left-sided weakness. He denied fevers, chills, weight loss, anorexia, chest pain, or any acute respiratory symptoms. He was afebrile, with a blood pressure of 126/80 mmHg, heart rate of 99 beats per minute, respiratory rate of 16 breaths per minute, and pulse oximetry of 100% on room air. His physical exam was unremarkable, with the exception of sustained nystagmus and left-sided hemiparesis. The patient underwent computed tomography to rule out acute cerebrovascular occlusion or arterial dissection. During this CT angiogram of his head and neck, multiple pulmonary nodules (including a spiculated mass measuring 4 cm × 1 cm × 1.2 cm in size in the left upper lobe) were incidentally discovered. His neurologic imaging was otherwise unremarkable. He was discharged from the hospital after resolution of his symptoms, which were attributed to a transient ischemic attack. Over the next several months, he underwent further evaluation of his lung nodules. A dedicated chest CT demonstrated an irregular, spiculated opacity in the left upper lobe, other smaller nodules, centrilobular and paraseptal emphysema (Figure 1). The pathology from a CT-guided biopsy was equivocal, showing rare groups of atypical epithelioid cells, in a background of acute inflammatory cells and hemosiderin-laden macrophages. A Positron Emission Tomography (PET) scan demonstrated increased uptake in the left upper lung in the area of the known mass, suggestive of malignancy. He was then referred to cardiothoracic surgery for video-assisted thoracoscopic surgery (VATS) and wedge biopsy.

The patient and his family were prepared for a diagnosis of lung cancer. However, the pathology report from his biopsy indicated

a large fungus ball with abundant compact and laminated mycelium, consistent with *Aspergillus* species. There was no evidence of parenchymal invasion, infarcts, or vascular thrombi by pathology. No cultures were obtained at the time of biopsy due to the high suspicion for malignancy based on the prior testing. Based on the pathology, the Infectious Diseases (ID) service was consulted for recommendations.

On further questioning, the patient denied prior lung disease. At the time, he did not carry a diagnosis of COPD, had never previously taken inhaled or systemic glucocorticoids, and had no history of tuberculosis. He denied exposures to construction or recent renovations that may have predisposed him to infection. He was not receiving any immunosuppressant therapy. He had undergone recent HIV testing, which was negative. He had no history or findings to support prolonged neutropenia or underlying immune deficiency. The patient was a longstanding smoker, with over a 30 pack/year history. He also reported heavy, daily alcohol use, but had no diagnosis or findings consistent with cirrhosis. He admitted to smoking one pipe of marijuana daily for over 30 years, but denied other recreational drug use.

The patient's pathology result was consistent with a non-invasive aspergilloma. However, closer review of his initial chest CT also demonstrated peripheral patchy infiltrates, raising concern for invasive disease. On the basis of these characteristic radiologic findings, he was diagnosed with possible invasive aspergillosis. The patient was given a loading dose of voriconazole (400 mg orally for two doses), then 200 mg orally twice daily for one month, with a plan for ID follow-up to assess his need for further medication and liver function monitoring. The patient was counselled extensively on the need for abstinence from alcohol given the risk of voriconazole-induced hepatotoxicity. Unfortunately, he was lost to follow-up in clinic. We were able to contact him by telephone recently, and he reported resolution of his symptoms.

Discussion

A variety of disease processes manifest as multiple pulmonary nodules (Table 1). In this patient, tissue biopsy provided the ultimate diagnosis of aspergillosis. Despite the ubiquity of *Aspergillus* spores in the environment, invasive infections with this mold remain uncommon. Invasive aspergillosis, saprophytic (includes chronic infection and aspergilloma), and allergic bronchopulmonary aspergillosis (ABPA) are the three typical classifications of pulmonary disease states. The treatment recommendations for *Aspergillus* infection are based on the category of disease and symptomatology.



Figure 1: Computed tomography of the chest demonstrating multiple pulmonary nodules and a spiculated lung mass in the left upper lobe. Characteristic radiologic findings that have been reported with *Aspergillus* infection include ground glass attenuation surrounding a nodule (halo sign), the later crescent sign (air from a cavity surrounding a mass), or cavity lesions [9].

Table 1: Differential diagnosis of multiple pulmonary nodules.

Malignancy	Metastatic lesions	
	Non Hodgkins Lymphoma	
	Kaposi's Sarcoma	
Infectious	Bacterial	
		Septic Emboli
	Fungal	
		Aspergillosis (and other mold infections)
		Blastomycosis
		Coccidiomycosis
		Cryptococcosis
	Histoplasmosis	
Non-infectious inflammatory conditions		
	Polyangiitis (formerly known as Wegener's granulomatosis)	
Pulmonary AVM's		
Pneumoconiosis		
	Coal Worker's Pneumoconiosis	
	Silicosis	

Pulmonary *Aspergillus* infection causes a spectrum of disease, ranging from fulminant and disseminated infection in the immunocompromised to a chronic, indolent presentation among the immunocompetent. Pulmonary aspergillosis can present with a multitude of manifestations, ranging from asymptomatic to symptoms of cough, shortness of breath, hemoptysis, pleurisy, and fever. In an attempt to standardize the definition of invasive aspergillosis, three diagnostic criteria were developed. These include host immunodeficiency, clinical symptoms of characteristic imaging (Figure 1), and microbiologic confirmation of *Aspergillus*.

A Consensus Committee of members of the European Organization for Research in Treatment of Cancer-Invasive Fungal Infection Cooperative Group and the National Institute of Allergy and Infectious Disease Mycoses Study Group has attempted to standardize the diagnosis of invasive aspergillosis for clinical and epidemiologic research. The certainty of invasive aspergillosis is defined as proven, probable, or possible [1]. Proven invasive aspergillosis requires histopathological documentation of infection, as well as a positive culture result in a specimen from a normally sterile site [2]. In invasive pulmonary aspergillosis, the most common causative organism is *Aspergillus fumigatus*, followed by *Aspergillus flavus*.

The definition of probable invasive aspergillosis requires fulfillment of criteria within 3 categories: host factors, clinical manifestations (symptoms, signs, and radiological features), and microbiological evidence [2]. This patient failed to meet the criteria for possible invasive *Aspergillus* infection due to the host factor criteria; he did not have an identified immunocompromised state. He did, however, meet criteria for invasive aspergillosis through clinical manifestations of chronic cough and radiologic evidence of invasive aspergillosis. Although supporting culture data was not available, he had direct pathologic evidence of fungal disease. This patient most likely had an aspergilloma given evidence of a fungal ball on pathology; however, the radiologic finding of infiltrates raised suspicion for invasive aspergillosis. The decision was made to treat the patient conservatively for invasive infection.

One potential source of *Aspergillus* infection is cannabis use. The term cannabis refers to the *Cannabis* plant (typically *C. sativa*), while marijuana is used more specifically to describe the crushed

flowers and tops of the plants. Cannabis smoking has been associated with a variety of intrathoracic disease states, including pneumothorax, pneumomediastinum, and upper lung zone bullae [3]. Chronic cannabis use is also linked to chronic cough and increased sputum production. Proposed mechanisms for the lung injury associated with cannabis use include widespread bronchial inflammation, dysregulated growth of respiratory epithelium, and dysfunction of alveolar macrophages [4].

The contamination of marijuana with *Aspergillus* has been previously described, and the presence of decaying vegetation with appropriate humidity is thought to provide the matrix for the growth of *Aspergillus*. In one study of fungal contamination of tobacco and marijuana, three of seven of the studied marijuana samples contained *Aspergillus* spores. While contaminated tobacco contained 200-300 colony-forming units per gram (CFU/g) of mold, the contaminated marijuana had 10⁴-10⁷ CFU/g. Other opportunistic molds were also identified in the marijuana samples, including *Penicillium*, *Fusarium*, *Acremonium*, *Rhizopus*, and *Scedosporium* species [3]. One fascinating reference from the International Association for Property and Evidence describes recommendations for preventing the growth of *Aspergillus* in seized marijuana samples [5]. Quality controls exist to identify contamination in prescription cannabinoids, like dronabinol; however, any individual who smokes marijuana is potentially at risk for aspergillosis [6].

Immunocompromised patients, particularly those who are neutropenic or on chronic corticosteroids, are at highest risk of developing pulmonary aspergillosis (Table 2). The incidence of aspergillosis among patients with leukemia was reported as 5% in one multicenter study [7]. Patients who smoke cannabis to relieve chemotherapy-induced nausea may be at particularly high risk. At least one death has been attributed to disseminated aspergillosis after bone marrow transplant in a marijuana user; cultures of the marijuana confirmed the same morphotype of *Aspergillus fumigatus* found in the patient's lung biopsy [8]. Unfortunately, in our case, samples of the patient's marijuana were not available for mycological comparison.

The severity of invasive *Aspergillus* infection is increased in immunocompromised patients; without therapy, invasive pulmonary aspergillosis almost always results in a severe or fatal pneumonia. The recommended treatment for invasive aspergillosis is voriconazole for a minimum of six to twelve weeks [2,9]. In immunosuppressed patients, treatment is typically extended until radiographic resolution of infection with consideration for the duration of immunosuppressive therapy. When invasive *Aspergillus* infection is suspected, treatment should be initiated immediately.

Invasive aspergillosis is a well-known opportunistic infection in post-transplant patients, and those receiving chemotherapy. However, invasive aspergillosis in immunocompetent hosts has been described rarely in the literature, usually manifested as sinusitis or pulmonary disease. In one reported case, a 35-year-old immunocompetent man had an extensive *Aspergillus* infection, including mediastinal lymph node, esophageal, and pulmonary involvement [10]. The patient was evaluated for immunodeficiency as he denied a history of cannabis or other drug use, previous respiratory illness, or underlying pulmonary

Table 2: Risk factors for invasive aspergillosis.

Neutropenia	
Drug-induced immunosuppression	
Prolonged corticosteroid therapy	
Chronic obstructive pulmonary disease	
Chronic granulomatous disease	
Critical Illness	
Diabetes mellitus	
Marijuana use	
Cavitation	
	Tuberculosis

disease; his immunodeficiency evaluation was negative. The authors suggested that alveolar invasion by *Aspergillus* may have occurred due to a partial defect in the alveolar macrophages and neutrophils which typically protect the lung from infection [10]. The role of this proposed mechanism in our patient is unclear.

Clinicians should be aware of the possibility of invasive aspergillosis among cannabis users, and consider this infectious process in the evaluation of patients with multiple pulmonary nodules. Additionally, immunocompromised patients should be educated on the risk of developing a pulmonary *Aspergillus* infection with continued cannabis use.

Consent

The patient was consented for this case report via witnessed telephone consent by the authors.

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