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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]



A 56-Year-Old Woman With COPD and Multiple Pulmonary Nodules*

Ammar Sakkour, MD; Tisha Wang, MD; and Donald Tashkin, MD

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A 56-year-old woman with COPD was referred to the pulmonary clinic for the evaluation of multiple pulmonary nodules. One month prior, a routine chest radiograph (Fig 1) revealed a left upper lobe nodule. She denied cough, fevers, shortness of breath, weight loss, night sweats, or chest pain. She had a long history of dyspnea on exertion that was unchanged from her baseline values. Three years prior, COPD had been diagnosed based on the results of pulmonary function tests and a CT scan of the chest showing moderate-to-severe emphysema. No nodules were seen at that time. She had no other significant medical history, and was receiving only fluticasone, nasal budesonide (Rhinocort; AstraZeneca; Wilmington, DE), and hormone replacement therapy. The patient was a 30-pack-year tobacco smoker and had quit 8 years prior. She reported a 10-year history of heavy marijuana use and continued to smoke marijuana cigarettes daily. The findings of a recent Papanicolaou smear as well as a mammogram had been negative. She denied any occupational exposures, recent travel, or HIV risk factors. The findings of a review of her physiologic systems were negative for symptoms suggestive of collagen vascular disease.

Secondary to the abnormal chest radiograph, a CT scan of the chest was obtained (Fig 2). The patient was referred by her internist for a CT scan-guided transthoracic needle biopsy of the left upper lobe

*From the Division of Pulmonary and Critical Care Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA. The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article. Manuscript received June 27, 2007; revision accepted July 16, 2007. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (www.chestjournal.org/misc/reprints.shtml).

Correspondence to: Tisha Wang MD, UCLA Pulmonary and Critical Care, Box 951690, 37-131 CHS, Los Angeles, CA 90095-1690; e-mail: tiwang@mednet.ucla.edu

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FIGURE 1. Chest radiograph reveals upper lobe nodule.

nodule. Pathology findings from the biopsy returned as necrotic tissue without evidence of neoplasm or infection. A repeat CT scan-guided biopsy 1 week later was again nondiagnostic and revealed predom-

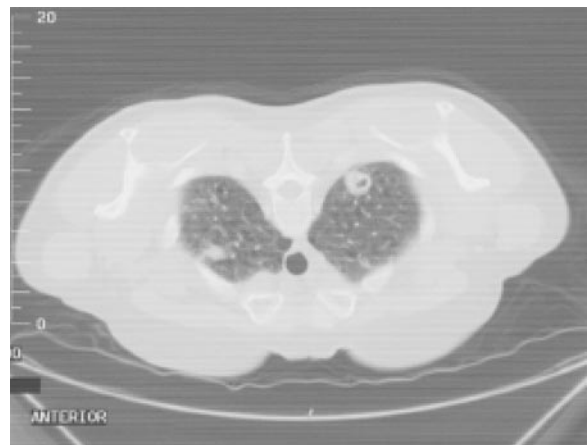


FIGURE 2. Chest CT scan showing bilateral upper lobe pulmonary nodules, with the largest measuring 1.8 cm in the apical posterior segment of the left upper lobe with cavitation.

inantly fibrous tissue. She was subsequently seen in the pulmonary clinic, and a bronchoscopy with BAL was performed.

Laboratory Findings

Hemogram findings were within normal limits with a WBC count of 7.1×10^3 cells/ μ L. Findings of serology tests for coccidiomycosis and cryptococcal as well as a test for urine Histoplasma antigen were negative. The result of an HIV test was also negative. BAL fluid cultures returned negative for infectious etiologies with the exception of one colony

of *Candida albicans*, which was felt to be clinically insignificant.

Clinical Course

Given repeated nondiagnostic studies, the patient was admitted to the hospital to undergo video-assisted thorascopic surgery with biopsy of the nodules. The nodule in the left upper lobe was grossly cavitory, and a thorascopic subsegmental resection of the apical posterior segment was performed.

What is the diagnosis?

What predisposed the patient to this condition?

Diagnosis: Invasive pulmonary aspergillosis

Answer: Heavy marijuana use

DISCUSSION

Marijuana remains the most commonly used illegal drug in the United States. Nearly 45% of teenagers try marijuana before finishing high school. Marijuana use has been shown to increase the prevalence of a variety of pulmonary symptoms, including chronic cough, sputum production, wheezing, and recurrent bronchitis. These symptoms lead to increased health-care utilization among habitual marijuana smokers, who have more outpatient visits for respiratory and nonrespiratory illness compared to nonsmokers. Cases of pneumothorax, pneumomediastinum, and upper lung zone bullae have been reported in association with marijuana smoking, and its use has also been linked to the development of opportunistic infections in patients with HIV and other immunocompromised states. The mechanism of effect in marijuana smoking for predisposing the patient to pulmonary infections has not been clearly elucidated but is felt to be related to its impairment of mucociliary activity and alveolar macrophage function. Impairment in the function of T-helper lymphocytes and the skewing of their differentiation away from T-helper type 1 cells, which are important for cellular immunity, by Δ^9 -tetrahydrocannabinol, the major active ingredient in marijuana, could also contribute to the increased risk for pulmonary infection.

Another reason why smoking marijuana may be a risk factor for invasive pulmonary aspergillosis, in particular, is that the growth of this fungal organism in samples of marijuana has been observed. In a study from the Netherlands, Verweij et al reported the contamination of seven of seven marijuana samples with mold. Three of the seven samples were contaminated with *Aspergillus* species. Of 10 samples of confiscated marijuana at the Drug Enforcement Agency of the Department of Justice in Washington DC, Chusid and colleagues found that 2 grew *Aspergillus fumigatus* and all showed heavy growth of various saprophytic fungi. Kagen et al were able to show serum precipitins to at least one *Aspergillus* antigen in 13 of 23 marijuana-smoking subjects compared to 1 of 10 non-marijuana smoking individuals. Fungal inhalation studies in these marijuana smokers demonstrated the unimpeded passage of *A fumigatus* through the marijuana cigarettes in both lit and unlit conditions.

Several case reports have documented the association of invasive aspergillosis and marijuana smoking in the settings of chronic granulomatous disease, acute leukemia, bone marrow transplantation, renal transplantation, and chemotherapy for small cell

lung cancer, and in a patient with a defective polymononuclear oxidase enzyme system. A case of allergic bronchopulmonary aspergillosis has also been reported in association with the smoking of moldy marijuana. In the majority of these cases, the fungus that was recovered from the patient was the same as that identified in the patient's marijuana.

In the setting of HIV disease, marijuana use is a significant independent risk factor for the development of opportunistic pulmonary infections. Invasive pulmonary aspergillosis has been identified as a late complication of AIDS. In a series of 13 patients with HIV and aspergillosis, 4 of 6 patients surveyed smoked marijuana regularly, while data were not available for the remaining 7 of the 13 patients.

To our knowledge, this is the first documented case of invasive pulmonary aspergillosis associated with marijuana smoking in a patient without clinical evidence of an immune deficiency. One case has been reported of an otherwise healthy 23-year-old marijuana and tobacco smoker in whom necrotizing granulomas developed with evidence of a fungal element on pathology. A specific fungus was never identified, but the authors hypothesized that the necrotizing granulomas were the result of either fungal infection or hypersensitivity to inhaled fungi. In our patient, invasive pulmonary aspergillosis was diagnosed based on the results of a biopsy performed with video-assisted thorascopic surgery showing caseating granulomas and granulomatous pleuritis, with evidence of *Aspergillus* species and thrombosed vessels in the center of one of the nodules.

In the current medical era of immunosuppressant medications and more aggressive therapies for cancer, invasive pulmonary aspergillosis will continue to be a significant problem. The association of marijuana and invasive pulmonary aspergillosis is an important one given the common recreational use of marijuana. In addition, the patients most likely to use medical marijuana are also the ones who are most susceptible to potentially fatal fungal infections. It appears that marijuana itself can also impair the lung's defenses sufficiently to cause a serious infection by an organism that may be delivered in the inhaled smoke, as evidenced by this case of invasive pulmonary aspergillosis in a patient without clinical evidence of an immune deficiency. Although the source of the *Aspergillus* in this case could well have come from the marijuana the patient smoked, her personal supply of marijuana was not assayed for fungal contamination.

Our patient was initially treated with amphotericin B in the hospital but was unable to tolerate it due to nausea and renal failure. Because voriconazole was not yet available at that time, she was placed on a

3-month course of itraconazole. A follow-up chest radiograph 3 months later revealed fading of the previously seen nodular opacities. The patient has continued to do well without further sequelae or residual pulmonary symptoms. Unfortunately, however, she continues to smoke marijuana.

CLINICAL PEARLS

1. *Regular marijuana smoking leads to cough, sputum production, wheezing, recurrent bronchitis, and increased outpatient visits for respiratory and nonrespiratory illness.*

2. *Marijuana is often contaminated with *Aspergillus* and other species of mold.*

3. *Invasive pulmonary aspergillosis has been associated with marijuana smoking in a variety of immunocompromised states.*

4. *It is important to ask about marijuana use during the taking of a medical history, both in immunocompromised patients presenting with severe pulmonary infection and in the rare patient with invasive pulmonary aspergillosis occurring without a known immune deficiency.*

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