

## CASES

## Chronic necrotizing pulmonary aspergillosis in a patient with diabetes and marijuana use

Tamara Leah Remington MD MSc, Jeffrey Fuller PhD, Isabelle Chiu MD

A 29-year-old man with type 1 diabetes presented to the emergency department with shortness of breath and chest pain that had lasted for one week. The patient initially reported no systemic symptoms. However, upon further questioning, he stated that he had felt generally unwell for the past year, with fevers, night sweats and weight loss. He had not been coughing and had not felt chest pain or shortness of breath before this presentation. He had no recent travel history or sick contacts. The patient was taking insulin and pantoprazole. In addition, he reported that he had been inhaling marijuana daily through a vapourizer for the past 18 months to relieve neuropathic pain secondary to his diabetes. The marijuana was street purchased and always from the same supplier. He did not use any other illicit substances, and he was not taking any narcotics at the time of admission, but he had used oxycodone periodically during the previous year to relieve neuropathic pain. The patient worked as a professional in an urban area.

His diabetes had been diagnosed one year earlier and was heralded by a six-month history of neuropathy. He was also found to have diabetic retinopathy. Two months after the diagnosis, the patient had received treatment for community-acquired pneumonia with evidence of infiltrate in the left lower lobe on chest radiograph. A follow-up radiograph was not performed. Computed tomography of the patient's abdomen several months later, performed for unrelated reasons, had shown evidence of ongoing left basilar and pleural consolidation.

On physical examination, the patient's temperature was 36.6°C, his heart rate was 80 beats/min, his respiratory rate was 18 breaths/min and his blood pressure was 125/85 mm Hg. He had an oxygen saturation of 100% on room air. A respiratory examination showed decreased air entry to his left lung base. The rest of the examination was unremarkable.

A radiograph of the patient's chest showed a left pneumothorax with air space disease in the

left lower lobe (Figure 1). Computed tomography of the chest showed a left pneumothorax and left lower lobe consolidation with cavitation, likely communicating with the pleura (Figure 2). Despite treatment with a chest tube, the pneumothorax persisted. Video-assisted thoracoscopic surgery was done for diagnostic and therapeutic purposes. Diffuse pleural adhesions were found, which required decortication and a wedge resection of the superior segment of the left lower lobe.

Tissue samples from the wedge resection grew *Aspergillus rugolosa*, confirmed by DNA sequencing, a *Penicillium* species and a non-sporulating fungus. Samples of the patient's pleural fluid grew *Aspergillus fumigatus*. Histopathologic examination of biopsy specimens confirmed parenchymal and pleural invasion by hyphal elements (Figure 3). The result of a serum galactomannan test was negative, as was an immunoglobulin E assay for *A. fumigatus*.

The patient's immunoglobulins were normal, with the exception of a mildly low level of immunoglobulin G4. HIV serology was negative, lymphocyte subsets were within normal limits and complement proteins C3 and C4 were normal. The patient's complete blood count differential was within normal limits. Fungal cultures of several samples of the patient's marijuana grew *Penicillium* species, *Aspergillus versicolor* and *Aspergillus ochraceus*. Samples from the patient's vapourizer did not grow any fungal species.

**Competing interests:**

Isabelle Chiu has received fees from Pfizer Canada.

This article has been peer reviewed.

The authors have obtained patient consent.

**Correspondence to:**

Tamara Leah Remington, remingto@ualberta.ca

CMAJ 2015. DOI:10.1503/cmaj.141412

### KEY POINTS

- Chronic necrotizing pulmonary aspergillosis is an uncommon but serious form of pulmonary *Aspergillus* infection.
- Patients with diabetes or any other immunocompromising condition should be cautioned about inhaling marijuana because it is known to contain fungi.
- Physicians should consider fungal infections in their differential diagnosis for pulmonary disease in patients with diabetes, particularly those who use marijuana.
- Safety of marijuana use, including vapour inhalation, needs to be established.

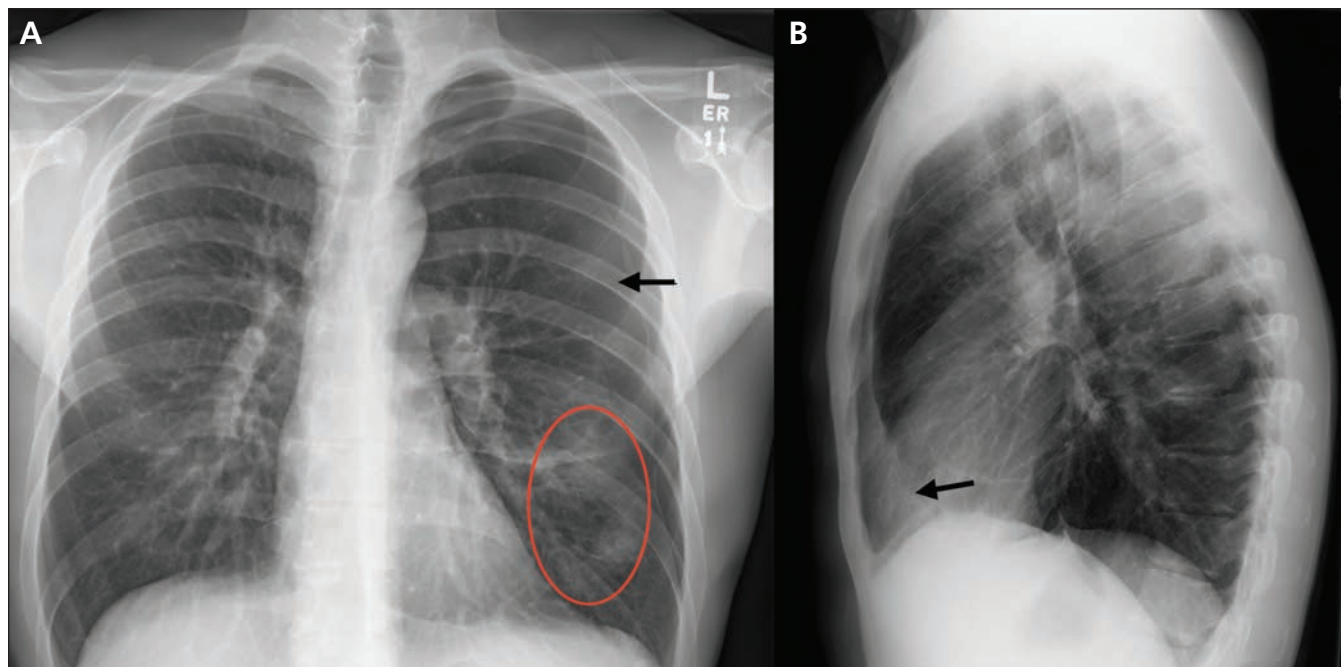


Figure 1: Radiograph of the chest on admission of a 29-year-old man with type 1 diabetes who presented to the emergency department with shortness of breath and chest pain. (A) Posterior–anterior view showing left pneumothorax (arrow) and air space disease in the left lower lobe (circle). (B) Lateral view showing left pneumothorax (arrow). The left lower lobe consolidation seen on the posterior–anterior view is poorly identified on the lateral view.

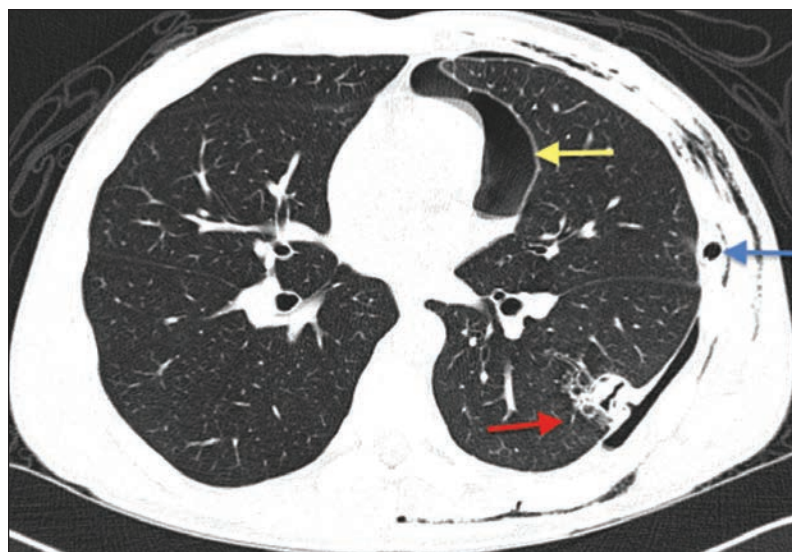


Figure 2: Computed tomography of the chest showing consolidation and cavitation in the left lower lobe, annexing the pleura (red arrow). Pneumothorax (yellow arrow), a chest tube (blue arrow) and subcutaneous emphysema are also shown.

The patient's pneumothorax resolved after surgery. He was given a six-month course of voriconazole, with radiologic and symptomatic resolution.

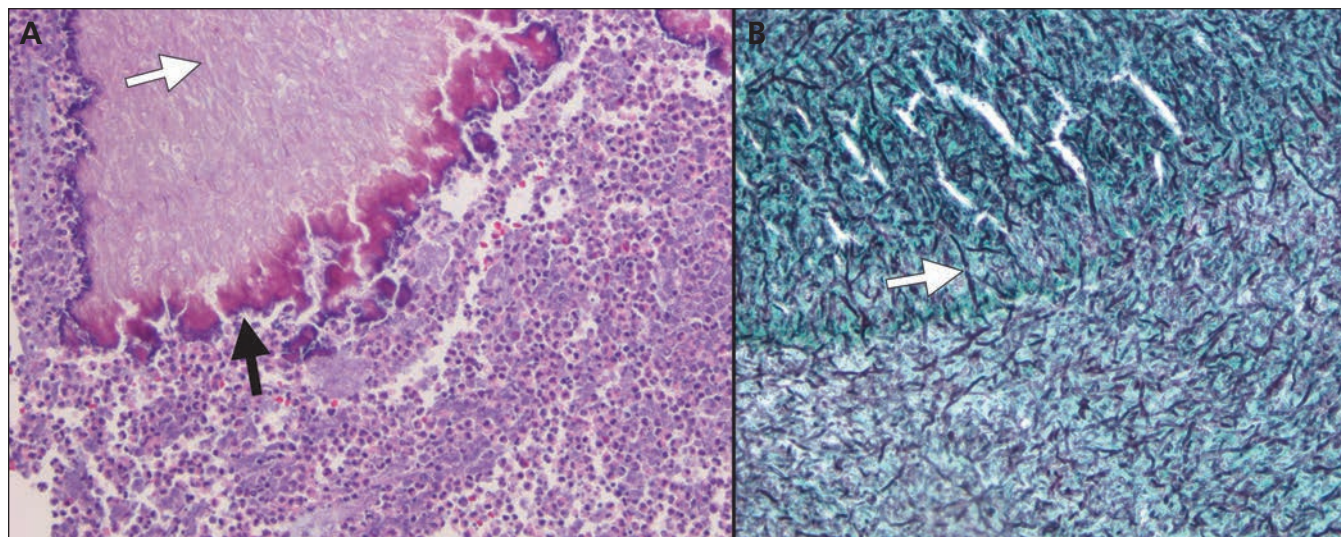
## Discussion

Our patient had chronic necrotizing pulmonary aspergillosis and a fungal empyema. We postulate that the fungal infection started one year ear-

lier, when the patient's diabetes was newly diagnosed. The presence of retinopathy and neuropathy at that time suggests that the patient had a prolonged period of hyperglycemia, which put him at risk for chronic necrotizing pulmonary aspergillosis. Our patient's chest radiograph one year before the current presentation showed infiltration of the lower left lobe, which was treated as community-acquired pneumonia. Computed tomography of the abdomen six months later showed consolidation of the lower left lobe without cavitation, likely representing progression of the original infiltrate. The cavity probably developed within the consolidative area in the ensuing months, eventually rupturing and causing a pneumothorax.

Chronic necrotizing pulmonary aspergillosis is a semi-invasive *Aspergillus* infection seen in patients with mild forms of immunosuppression, such as diabetes, and in patients with chronic lung disease caused by mycobacterial infection or chronic obstructive pulmonary disease.<sup>1</sup> Infection starts after the germination of conidia inhaled from the environment. Patients typically present with fever, weight loss and cough;<sup>2</sup> the median duration of symptoms before diagnosis is six months (range 2–18 mo).<sup>1</sup> Typical findings on imaging include a pulmonary cavity alone or within an area of consolidation.<sup>1</sup> A biopsy is usually needed to establish the diagnosis by showing parenchymal invasion. Patients require treatment with antifungal agents for several months.





**Figure 3:** Histopathologic examination of biopsy specimens from the wedge resection of the left lower lobe of the lung. (A) Hematoxylin and eosin stain showing fungal elements (white arrow) within a bronchiole (black arrow) surrounded by inflammatory cells. (B) Gomori methenamine silver stain showing diffuse fungal elements (white arrow) within a bronchiole (original magnification  $\times 40$ ).

A case series involving 43 patients showed that the condition predominantly affected men, that the median age of patients was 60 years and that patients who received itraconazole therapy had a median survival of 62 months.<sup>1</sup> Chronic necrotizing pulmonary aspergillosis is uncommon, and a patient's prognosis depends on several variables including comorbidities, age and the antifungal agent used to treat the infection. Further studies using more potent agents, such as voriconazole or posaconazole, are needed.

Our patient's infection was cured with surgical resection and six months of voriconazole therapy. This duration of therapy is consistent with the length of treatment reported effective in the literature for both chronic necrotizing pulmonary aspergillosis and *Aspergillus* empyema. Preferred treatment of an invasive *Penicillium* (non-*P. marneffeii*) lung infection is unclear, but three months of voriconazole therapy was effective in patients with HIV and *P. marneffeii* infection.<sup>3</sup>

#### Association with marijuana use

We believe the patient's marijuana was the source of his infection. Kurup and colleagues showed a heavy burden of fungi in street-purchased marijuana, including *Aspergillus*, *Mucor* and *Penicillium* species.<sup>4</sup> Fungi were isolated from both the marijuana itself and its smoke, whereas smoke from commercial cigarettes did not yield any fungal growth.<sup>4</sup> Cultures of our patient's marijuana grew several fungi; however, the samples used for culture were from marijuana purchased in 2013, and our patient likely acquired his infection in 2012.

Showing a causal link between the marijuana and the infection is not possible, but the nonster-

ile nature of the marijuana provides support for it being the source of infection. In addition, the isolation of multiple fungi from the patient's lung suggests infection from an environmental source with a heavy burden of several different fungi. Invasive infection with *A. rugolosa* is uncommon — we found only one other case report of human disease in the literature.<sup>5</sup> Our patient's lung biopsy also grew a *Penicillium* species. A case series and review of invasive *Penicillium* (non-*P. marneffeii*) infections identified only six cases of pneumonia, with three of the patients having no underlying lung disease or immunosuppression.<sup>6</sup>

We found several case reports of patients with invasive *Aspergillus* infections and marijuana use, with most of the patients being highly immunocompromised. Vaschetto and colleagues reported a case of invasive pulmonary aspergillosis in a man with diabetes who used marijuana.<sup>7</sup> Similar to our patient, that patient did not have structural lung disease and was not otherwise immunosuppressed. Gargani and colleagues reported that one patient, similar to ours, presented with pneumothorax and was found to have a pleural-based abscess containing *Aspergillus*,<sup>8</sup> and Bal and colleagues described chronic necrotizing pulmonary aspergillosis in a patient with marijuana dependence.<sup>9</sup>

Vapourizing the marijuana, rather than smoking, may have increased our patient's exposure to viable fungi in the plant. Vapourization releases active cannabinoids at a lower temperature than that needed for combustion, thus reducing potential exposure to toxins.<sup>10</sup> However, that lower temperature could allow for a heavier burden of thermotolerant fungi, such as *Aspergillus*, to survive.

Other sources could be responsible for our patient's pulmonary fungal infection. We were not able to culture any fungi from several samples of various parts of the vapourizer. We did not culture the water source used for the vapourizer, which could have been a potential infection source. Handling of the marijuana itself, aside from smoking or vapourizing, may have been sufficient to provide exposure to fungal conidia. Other factors such as the duration for which the marijuana was stored before use and its storage conditions may have contributed to fungal growth. Furthermore, *Aspergillus* and *Penicillium* are ubiquitous moulds, and the environment at the patient's house or work could have been a source. In addition, the patient's diabetes may have predisposed him to pulmonary fungal infection. Finally, our patient could have had a subtle immunodeficiency that we were not able to detect that contributed to his having a multifungal pulmonary infection.

With recent changes regarding medical marijuana prescribing in Canada, this case highlights a potential risk of marijuana use. We were unable to find any large studies examining the absolute risk of pulmonary fungal infections in patients who use marijuana. Confounding factors including the rarity of such infections, patient immunosuppression and the ubiquitous nature of environmental moulds would make such a study difficult. However, we believe enough evidence exists to suggest that patients, particularly those who are immunocompromised, should be cautioned about marijuana use and the risk of pulmonary fungal infection. More studies are needed to establish the safety of marijuana and vapourization, as well as the claim by medical marijuana suppliers that their products are free of contaminants such as fungi.

## References

1. Nam HS, Jeon K, Um SW, et al. Clinical characteristics and treatment outcomes of chronic necrotizing pulmonary aspergillosis: a review of 43 cases. *Int J Infect Dis* 2010;14:e479-82.

2. Saraceno JL, Phelps DT, Ferro TJ, et al. Chronic necrotizing pulmonary aspergillosis: approach to management. *Chest* 1997;112:541-8.
3. Supparatpinyo K, Schlamm HT. Voriconazole as therapy for systemic *Penicillium marneffeii* infections in AIDS patients. *Am J Trop Med Hyg* 2007;77:350-3.
4. Kurup VP, Resnick A, Kagen SL, et al. Allergenic fungi and actinomycetes in smoking materials and their health implications. *Mycopathologia* 1983;82:61-4.
5. Hubka V, Kubatova A, Mallatova N, et al. Rare and new etiological agents revealed among 178 clinical *Aspergillus* strains obtained from Czech patients and characterized by molecular sequencing. *Med Mycol* 2012;50:601-10.
6. Lyratzopoulos G, Ellis M, Nerringer R, et al. Invasive infection due to *Penicillium* species other than *P. marneffeii*. *J Infect* 2002;45:184-95.
7. Vaschetto R, Kroumova V, Olivieri C, et al. Early diagnosis of invasive pulmonary aspergillosis in a young immunocompetent patient. *New Microbiol* 2012;35:77-82.
8. Gargani Y, Bishop P, Denning DW. Too many mouldy joints — marijuana and chronic pulmonary aspergillosis. *Medierr J Hematol Infect Dis* 2011;3:e2011005.
9. Bal A, Agarwal AN, Das A, et al. Chronic necrotizing pulmonary aspergillosis in a marijuana addict: a new cause of amyloidosis. *Pathology* 2010;42:197-200.
10. Abrams DI, Vizoso HP, Shade SB, et al. Vaporization as a smokeless cannabis delivery system: a pilot study. *Clin Pharmacol Ther* 2007;82:572-8.

**Affiliations:** Division of Infectious Diseases (Remington, Chiu), Faculty of Medicine and Dentistry, University of Alberta; Provincial Laboratory (Fuller), Alberta Health Services; Department of Laboratory Medicine and Pathology (Fuller), University of Alberta, Edmonton, Alta.

**Contributors:** All of the authors contributed to the conception and design of the article, including drafting the manuscript and making necessary revisions. All of the authors approved of final version to be published and have agreed to act as guarantors of the work.

**Acknowledgements:** The authors thank Dr. Juan Moreno for his expertise with pathology specimens, including taking and interpreting photographs, and Wanda Mauricio for assistance with fungal identification.

The section Cases presents brief case reports that convey clear, practical lessons. Preference is given to common presentations of important rare conditions, and important unusual presentations of common problems. Articles start with a case presentation (500 words maximum), and a discussion of the underlying condition follows (1000 words maximum). Visual elements (e.g., tables of the differential diagnosis, clinical features or diagnostic approach) are encouraged. Consent from patients for publication of their story is a necessity. See information for authors at [www.cmaj.ca](http://www.cmaj.ca).