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## Fatal Aspergillosis Associated with Smoking Contaminated Marijuana, in A Marrow Transplant Recipient\*

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A 34-year-old man presented with pulmonary aspergillosis on the 75th day after marrow transplant for chronic myelogenous leukemia. The patient had smoked marijuana heavily for several weeks prior to admission. Cultures of the marijuana revealed *Aspergillus fumigatus* with morphology and growth characteristics identical to the organism grown from open lung biopsy specimen. Despite aggressive antifungal therapy, the patient died with disseminated disease. Physicians should be aware of this potentially lethal complication of marijuana use in compromised hosts.

Invasive aspergillosis has become a significant cause of death in immunosuppressed patients. Patients with acute leukemia and lymphoma are particularly susceptible.<sup>1</sup> Postulated risk factors include granulocytopenia, and treatment with corticosteroids, antibiotics and cytotoxic chemotherapy.<sup>2</sup> Qualitative disorders of granulocyte function described in acute leukemia may also increase the risk of *Aspergillus* infection.<sup>3</sup> Because *Aspergillus* species are found in soil, air, and vegetable matter (including tobacco), inadvertent exposure is likely. We report a case of disseminated *Aspergillus fumigatus* infection in a bone marrow transplant recipient associated with the use of contaminated marijuana.

### CASE REPORT

A 34-year-old man with Philadelphia chromosome-positive chronic myelogenous leukemia was admitted to the hospital for an allogeneic bone marrow transplant (BMT) following chemotherapy and splenectomy. He was pretreated with cyclophosphamide, total body irradiation and intrathecal methotrexate and maintained on cyclosporin and corticosteroid prophylactic therapy. His course was complicated by acute graft-vs-host disease (GVHD) that resolved on high-dose steroid therapy. He was discharged in good condition on the 39th day after BMT. His drug regimen included cyclosporin, prednisone (30 mg twice daily), ketoconazole (200 mg daily), and gamma globulin (32 g intravenously every two weeks).

The patient remained transfusion-independent and clinically well

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until day 75 post-BMT when he had two generalized tonic-clonic seizures. Lumbar puncture yielded normal CSF. Brain CT scan was unremarkable. Magnetic resonance imaging of the brain showed two parietal nodules. Chest roentgenogram revealed multiple nodules, several of which were cavitory. Bronchoalveolar lavage was not diagnostic by Gram-stain, KOH wet mount or bacterial culture. The patient was empirically started on intravenous amphotericin-B therapy. Open lung biopsy was performed, which revealed septate hyphae in the direct KOH wet mount of the tissue.

Fungal cultures of the lung tissue and bronchial lavage fluid subsequently grew *Aspergillus fumigatus*; viral cultures yielded cytomegalovirus. Further history revealed that the patient had been smoking marijuana daily for several weeks prior to admission. Culture of his marijuana yielded *Aspergillus fumigatus*. Pathologic examination of the submitted lung tissue revealed both fungal and cytomegaloviral pneumonitis.

Despite aggressive therapy with amphotericin B and the experimental drug DHPG (9-[1,3 dihydroxy-2 propoxymethyl] guanine), the patient developed a progressive interstitial pneumonia that required intubation and ventilatory support. He continued to deteriorate with worsening of his pulmonary status, development of cholestatic jaundice and renal insufficiency. The addition of high-dose steroid treatment did not improve his condition. He expired 110 days after bone marrow transplantation. Autopsy revealed disseminated aspergillosis involving the lung, endocardium and brain, together with cytomegaloviral pneumonitis.

### DISCUSSION

*Aspergillus* spores are ubiquitous and are the most frequently found fungus in the environment. Increased concentrations of spores have been noted in winter months. Pathogenicity of the *Aspergillus* species has to do with properties of the spores; namely their light weight, thick walls and small size which allow for their growth in terminal bronchioles. Host predisposing factors are most often related to the presence of underlying pulmonary disease such as asthma, possibly cystic fibrosis, old tuberculous cavitory disease, and/or to alterations in immune function such as in chronic granulomatous disease<sup>4</sup> or neoplasia.<sup>1</sup>

In acute leukemia, invasive pulmonary aspergillosis classically occurs in the setting of prolonged granulocytopenia and often presents with unremitting fever and development of pulmonary infiltrates in the face of antibiotic therapy.<sup>1,5</sup>

Diagnosis of aspergillosis is often difficult to establish without lung biopsy.<sup>1</sup> Blood culture and *Aspergillus* precipitins are not helpful. Sputum culture is positive in about 30 percent of patients, but may be useful in the diagnosis of invasive disease in selected patient subgroups.<sup>6</sup> Nasal cultures have been reported to help identify patients at risk for aspergillosis.<sup>7</sup> Recently, detection of *Aspergillus* antigen has been described and seems to offer some advantage over the methods mentioned above.<sup>8</sup> Our patient's presentation was atypical in that he developed invasive aspergillosis two months after BMT and weeks after recovery of his neutrophil count.

We evaluated the possible role that marijuana had served as a source of exposure to *Aspergillus* organisms. A sample of the patient's marijuana grew two morphotypes of *Aspergillus fumigatus*, one blue-green and one white colony type. Final identification was based on microscopic characteristics of vegetative growth. Both produced thin-walled, smooth conidiophores with flask-shaped vesicles. Conidia were columnar and phialides were uniseriated. Each colonial

morphotype was isolated and each could be converted on subculture to both the white and blue-green colony types. Both morphotypes grew at 45°C. The same identification procedures were used to speciate the *Aspergillus* from the patient's lung biopsy specimen. The presence of both white and blue-green colony types of *Aspergillus fumigatus* in both the patient's and marijuana specimens suggests that the same strain of *Aspergillus fumigatus* was present in the marijuana and in the lung biopsy from the patient.

Exposure to marijuana has been implicated in other diseases. In 1981, marijuana was identified as the cause of a multistate outbreak of salmonellosis.<sup>9</sup> Some observers noted the association of respiratory tract fungal infection with the use of contaminated marijuana.<sup>10,11</sup> Kagen<sup>12</sup> demonstrated the presence of *Aspergillus* in 11 of 12 marijuana samples and showed that the spores passed easily through contaminated cigarettes and most marijuana smokers had precipitins against *Aspergillus*.

The present case shows that smoking marijuana may subject immunosuppressed patients to the potential of serious opportunistic fungal infection. Physicians caring for such patients should be aware of this potentially lethal complication, especially since patients may smoke marijuana to relieve nausea from chemotherapy.

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## Recurrent Paroxysmal Complete Heart Block Induced by Vomiting\*

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**A woman had a 40-year history of vomiting associated with syncope. Spontaneous and induced vomiting was predictably associated with sinus bradycardia, paroxysmal atrioventricular block, and ventricular asystole. The clinical and laboratory studies carried out to illustrate the mechanism of this unusual complication of vomiting demonstrated it to be due to a vagovagal reflex initiated by distension of upper esophagus.**

Vomiting is a protective reflex stimulated mainly by afferents from the gastrointestinal tract.<sup>1</sup> The efferent control of vomiting is via the vagi and sympathetic system. It is normally accompanied by slight tachycardia or bradycardia.<sup>1</sup> Unlike swallowing,<sup>2,3</sup> symptomatic disturbances of cardiac rhythm have not been well documented with vomiting.<sup>4</sup>

#### CASE REPORT

A 52-year-old woman, who was otherwise in good health, was admitted following a fainting episode during vomiting which occurred after moderate alcohol intake. While being monitored in the casualty department, she again vomited and felt faint, and it was noticed that she developed transient complete AV block. She admitted to episodes of loss of consciousness, all associated with vomiting, since the age of 10 to 12 years. On admission, detailed clinical examination, including physical examination of the cardiovascular and nervous systems, chest x-ray film, and 12-lead electrocardiogram, did not disclose any abnormality.

An electrophysiology study showed normal atrioventricular conduction. The AH and HV intervals were 70 and 50 ms, respectively. Incremental atrial pacing provoked AV nodal Wenckebach periodicity at a pacing rate of 160 bpm.

Vagal and other provocative maneuvers were performed after insertion of a temporary transvenous pacing system. Carotid sinus massage, eyeball pressure, and oropharyngeal stimulation did not provoke any conduction abnormalities. The heart rate and blood pressure response to the Valsalva maneuver were normal. Swallowing of a large bolus of food was not associated with any change in cardiac rhythm. Ipecacuanahna, an emetic, was given to reproduce and further document the problem. Three bouts of ipecac-induced vomiting were associated with sinus bradycardia, complete AV block, and ventricular asystole each time lasting up to 20 s (Fig 1A). Ipecac provocation was repeated on the following day after pretreatment with intravenous atropine (1.2 mg). This resulted in sinus tachycardia and prevented heart block during all subsequent bouts of vomiting (Fig 1B). Barium swallow and upper gastrointestinal endoscopy did not reveal any functional or structural abnormality of the esophagus. The patient was treated by implantation of a permanent demand ventricular pacemaker which was programmed to a rate of 40 bpm.

To further investigate the mechanism of paroxysmal complete AV heart block, inflation of balloons at different levels of the esophagus with electrocardiographic monitoring was undertaken. Simultaneous inflation of two, 22-mm diameter balloons at the same level in

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