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Marijuana Smoking in Patients With Leukemia

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Summary: *Worldwide, marijuana (cannabis) is a widely used drug. The incidence of marijuana smoking is increasing and is second only to tobacco as the most widely smoked substance in the general population. It is also the second most commonly used recreational drug after alcohol. Some adverse effects of marijuana smoking have been documented; however, the number of studies on the pulmonary effects of marijuana in individuals with leukemia is limited. In our case series, we report on 2 men with acute myeloid leukemia with miliary nodular lung patterns on computed tomography of the chest due to heavy marijuana use. We also report on 2 patients with acute lymphocytic leukemia who had a history of smoking marijuana and then developed lung opacities consistent with mold infection.*

Introduction

Use of marijuana (cannabis) is common by many people worldwide.[1] The incidence of marijuana smoking is increasing, second only to tobacco as the most widely smoked substance in the general population.[2] It is also the second most commonly used recreational drug after alcohol.[3] As of publication, 23 states plus the District of Columbia allow marijuana to be used as a medicinal drug and 4 states have passed measures to make its recreational use legal.[4,5] However, the US Drug Enforcement Administration still considers marijuana to be a schedule 1 substance.[6] Marijuana is a greenish-gray mixture of the dried, shredded leaves, stems, seeds, and flowers of *Cannabis sativa*. Preparations of *C sativa* have been used for their euphoric effects.[7] The most psychoactive constituent compound in marijuana is tetrahydrocannabinol (THC), which is rapidly absorbed from the lungs and binds to endogenous cannabinoid receptors in the central nervous system.

The potency of THC in marijuana has risen from approximately 4% in the early 1980s to as much as 30% in the 2000s.[8] The most common method of marijuana use is smoking, either as a rolled cigarette (joint), through a water-filled pipe (bong), or the hookah, with coal used to vaporize water and then mixed with tobacco. The bong is considered the most harmful method.[9] Marijuana can be inhaled up to the peak inspiration, holding the hot fumes for as long as possible prior to slow exhalation. Such smoking technique results in a greater deposition of toxic substances, such as tar and carbon monoxide, as well as damage to the lung parenchyma typically seen in those who smoke tobacco cigarettes.[10-12]

The gaseous and particulate composition of marijuana is similar to tobacco cigarettes, except that the active component in tobacco is nicotine (compared with THC in marijuana).[13] An accurate study of adverse effects of marijuana is difficult to perform due to its illegal status in many states, various smoking techniques, and its shorter duration of use compared with tobacco.[14] In addition, tobacco smoking is frequently a confounding factor in marijuana studies, although some pulmonary adverse effects of marijuana smoking have been documented and include cough, dyspnea, bronchitis, pneumomediastinum, spontaneous pneumothorax, and apical lung bullae.[15-18]

Marijuana mold contamination has also been reported.[19] The association between nodular pneumonia and bronchiolitis, with its associated miliary micronodular pattern, and smoking marijuana has been described in the literature.[20] However, the effect of marijuana smoking in immunocompromised populations has not been studied, except for a few case reports.[20]

Case Series

We describe 4 cases of nodular lung lesions seen on computed tomography (CT) of the chest in patients

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with leukemia who smoked marijuana. Two patients had acute lymphocytic leukemia (ALL) and 2 had acute myelogenous leukemia (AML). The patients with ALL responded well to treatment and their nodular lung lesions resolved with antifungal therapy. Both patients with AML died due to disseminated fungal infection.

The Table summarizes the clinical presentation, treatment, and outcomes of each of the 4 case patients.

Acute Lymphocytic Leukemia

Case 1: A 27-year-old man with a history of ALL and marijuana and cigarette smoking developed neutropenia while on chemotherapy and was started on antibiotic prophylaxis (levofloxacin) and fluconazole. He was discharged home with neutropenia. He continued to smoke cigarettes and marijuana.

On a second visit, he was admitted to the hospital with neutropenic fever. CT of the chest was performed and demonstrated a new 1.08-cm cavitary nodule (Fig 1). Findings on bronchoscopy, Gram stain, fungal stain, acid-fast bacilli smear, viral polymerase chain reaction, and the respective cultures were all negative. He was treated with voriconazole 300 mg twice a day for 3 months and micafungin 150 mg every day for 6 weeks.

CT findings obtained 2 months later showed the nodule dramatically decreased in size from 1.08 to 0.1 cm.

Case 2: A 20-year-old man presented with B-cell ALL. One week after receiving chemotherapy, he presented with bilateral eye pain, photophobia, sore throat, nonproductive cough, rhinorrhea, and low-grade fever for 5 days. He had been in contact with his niece who had upper respiratory tract infection with cough. He missed his dose of prophylactic levofloxacin the previous night. Except for bilateral erythema of his eyes, nasal congestion, fever (100.1 °F), and sore throat, findings on the remainder of his physical examination were normal.

Laboratory studies revealed a white blood cell (WBC) count of 80 cells/mm^3; all other values were normal. A respiratory viral panel from nasopharyngeal sampling was positive for human metapneumovirus. Chest x-ray revealed no evidence of pneumonia. HIV testing was negative.

His last use of marijuana was 1 day prior to his hospital admission.

Findings on CT of the chest showed a nodular consolidation pattern consistent with fungal infection (Fig 2). He was treated with oral voriconazole 200 mg twice a day for 3 months. Following treatment completion, the nodular lesion resolved, as evidenced on follow-up CT.

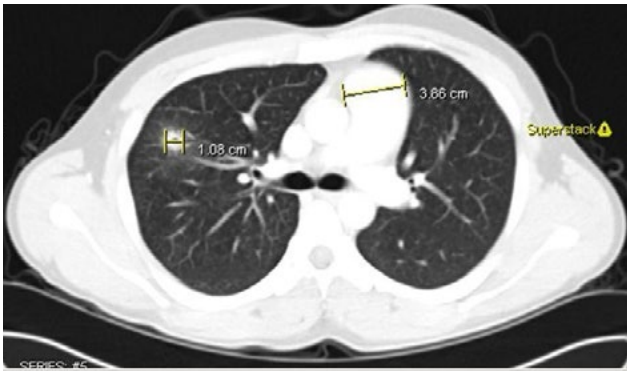

Fig 1. — Computed tomography of the chest reveals a 1.08-cm cavitary nodule that responded to voriconazole treatment.

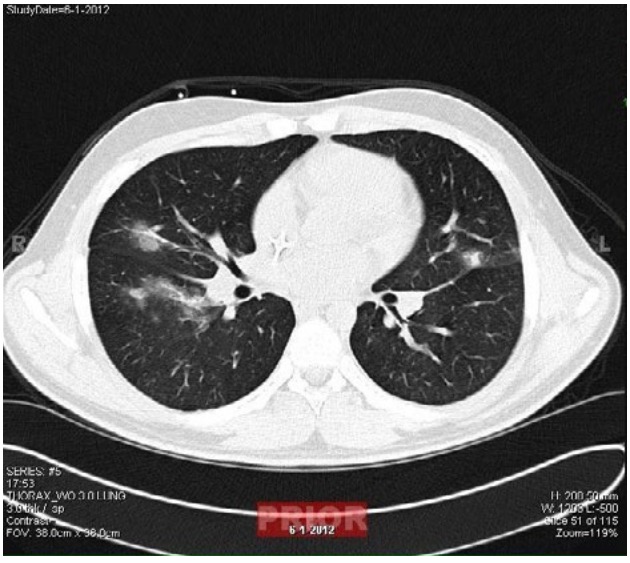

Fig 2. — Computed tomography of the chest showed a nodular pneumonia infiltrate consistent with mold infection.

Table. — Summary of the Case Series

Case No.	Malignancy	Clinical Signs	Antifungal Prophylaxis	Antifungal Treatment	Outcome
1	ALL	Neutropenic fever	Fluconazole /levofloxacin	Voriconazole/micafungin	Favorable
2	ALL	None	Fluconazole /levofloxacin	Voriconazole	Favorable
3	AML	None	Posaconazole	Liposomal amphotericin B Voriconazole	Death
4	AML	Neutropenic fever	Posaconazole	Liposomal amphotericin B Micafungin Voriconazole	Death

ALL = acute lymphocytic leukemia, AML = acute myelogenous leukemia.

Acute Myelogenous Leukemia

Case 3: A 36-year-old man with a history of AML presented with declining neutrophil levels. He was in remission after several cycles of chemotherapy, and he had received a matched unrelated donor allogeneic stem cell transplant. The prior chemotherapy course was complicated by *Streptococcus mitis* bacteremia with acute respiratory distress syndrome and septic shock.

His history was significant for smoking 1 pack of cigarettes per day for 22 years and smoking marijuana up until his hospital admission. He also had a history of alcohol abuse (quit 11 years ago) and a history of heroin, cocaine, and methamphetamine abuse (stopped 12 years ago).

CT of the chest demonstrated ground-glass pneumonia that resolved within a few weeks with corticosteroid therapy. Findings on CT at a previous follow-up visit were normal. Results from respiratory viral and atypical pneumonia panels of a nasopharyngeal specimen were negative, as was a sputum culture. A miliary nodular pattern was noted on repeat CT and was most likely due to his heavy marijuana use (Fig 3).

A review of systems was unremarkable and findings on physical examination were normal. His white blood cell count was 5280 cells/mm^3 and a lymphocyte count was 560 cells/mm^3. Results on serum galactomannan testing were positive, but repeat testing was negative. Findings on pulmonary function testing were normal. Cardiac testing revealed an ejection fraction of 57%.

Despite taking posaconazole as prophylaxis, he died 2 months later from disseminated fungal infection. The infection was demonstrated on a histopathology examination from a skin lesion but was not able to grow on culture.

Case 4: A 53-year-old man with relapsed AML was admitted to the hospital for reinduction chemotherapy. A review of systems was unremarkable, and findings on physical examination were normal. This patient had a history of smoking 1 pack of cigarettes a day for 22 years and smoking marijuana twice a week for the same duration. Laboratory studies were ordered and revealed a white blood cell count of 3340 cells/mm^3 and a platelet count of 73,000 cells/mm^3.

Findings on CT of the chest revealed ground-glass pneumonia and a miliary pattern due to bronchiolitis (negative on serum galactomannan testing; Fig 4). He received chemotherapy and posaconazole prophylaxis, but he later developed neutropenic fever. He also developed altered sensorium initially thought to be caused by use of pain medication or due to disseminated *Fusarium* infection from an injury to his right great toe and his right second toe, revealing eschar-like lesions. His medication was switched to amphotericin B and later to voriconazole and high-dose micafungin. However, several weeks later the patient succumbed to disseminated *Fusarium* infection.

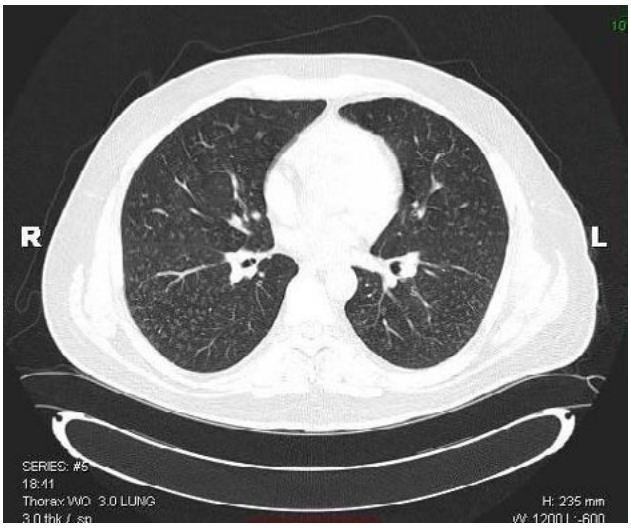

Fig 3. — Computed tomography of the chest demonstrates a miliary reticulonodular pattern presumed to be due to bronchiolitis related to smoking marijuana.

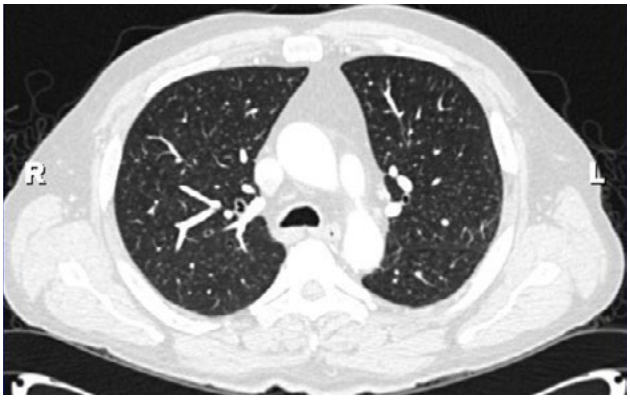

Fig 4. — Computed tomography of the chest showed ground-glass pneumonia and a miliary pattern due to bronchiolitis related to smoking marijuana.

Discussion

Marijuana, hash, and hash oil are the 3 main forms of cannabis. Cannabis contains more than 500 chemicals.[21] Both natural and synthetic cannabinoids are thought to possess neuroprotective properties. The impact of marijuana smoking on respiratory health has some similarities to that of tobacco smoking[14]; however, studies conducted on marijuana smoking are subject to confounding use of tobacco as well as other social factors.[3,14,22,23]

Marijuana is commonly used by adolescents and young adults.[21] The incidence of marijuana smoking has increased in the western world, possibly because of the euphoric effects of cannabis and the loosening legal restrictions.[4,21] Rarely, marijuana use can trigger acute myocardial infarction by inducing coronary artery vasospasm[24]; marijuana use may also be associated with atrial fibrillation.[25] Marijuana smoking has been implicated as a causative factor in traditionally

tobacco-related tumors of head, neck,[26] and lung,[27] as well as in cases of transitional cell carcinoma.[28]

Tobacco smoking is also a recognized behavioral risk factor for periodontal disease, and marijuana smoking likely contributes to this risk in a similar fashion.[29] Daily use of marijuana is associated with moderate to severe liver fibrosis, and its misuse may be a risk factor for cerebrovascular disease — this is particularly true among young people.[30,31] Marijuana use may adversely affect the mucous membranes and the skin, as well as cause Raynaud phenomenon and arteritis.[32] Long-term, heavy cannabis use has also been associated with cognitive dysfunction, leading to attention and memory impairment.[33,34]

Marijuana smoke contains up to twice as many polyaromatic hydrocarbons as tobacco smoke.[27] These hydrocarbons, along with other carcinogenic compounds found in marijuana smoke and the technique of marijuana smoking, suggest that an associated risk of malignancy may be present. Numerous case reports, cohort, and case-control studies have examined the effect of marijuana smoking on the risk of malignancies but with variable results.[35-38]

One cohort study looked at such a link for 40 years.[39] The authors examined approximately 50,000 Swedish military recruits during the years 1969 and 1970 who were between 18 and 20 years of age and who also used marijuana.[39] The cohort was followed until 2009. After taking into account the baseline use of marijuana and alcohol, as well as various respiratory and socioeconomic conditions, the study authors concluded that the study participants who were heavy smokers had more than a twofold risk of developing lung cancer.[39]

Use of marijuana as a medicinal agent is also gaining in popularity among individuals with cancer to treat neuropathic pain and to stimulate appetite due to the potent, antiemetic properties of cannabis.[40,41] One historic report from 1997 concluded that nearly one-third of clinical oncologists surveyed supported the use of marijuana as an antiemetic agent.[42] Another survey from Colorado, where recreational marijuana use has become legal and more prevalent, concluded that approximately one-fifth of physicians support use of medical marijuana, and more than 60% believe that it poses serious mental and physical health problems.[43]

Regarding the pulmonary effects of marijuana, the relationship between marijuana smoking and respiratory complications is poorly understood. Short-term exposure has been associated with bronchodilation, and adverse effects of long-term marijuana smoking include cough, dyspnea, chronic bronchitis, spontaneous pneumothorax, and apical lung bullae.[10-12]

A miliary nodular pattern, similar to what is seen in cases of miliary tuberculosis and disseminated fungal infection, has also been seen in individuals who use marijuana[44]; this was true for 2 of our cases. The pattern is comparable with respiratory bronchiolitis commonly seen among those who smoke cigarettes. Respiratory bronchiolitis is characterized by accumulation of tan- or yellow-pigmented, "smoker" macrophages in the bronchiolar lumens, with associated chronic inflammation and fibrosis extending from respiratory bronchioles to the alveolar wall.[44,45] This distinct finding of miliary micronodular imaging should alert physicians to include synthetic marijuana abuse in the differential diagnosis.[46]

Regular smoking of marijuana may cause alveolar macrophage damage, and the immune systems of individuals who smoke marijuana on a regular basis may be unable to fight against inhaled pathogens such as bacteria, fungi, or cease the growth of tumor cells.[47] Marijuana use is also known to increase the accumulation of alveolar macrophages, which trigger an inflammatory response.[45] Cannabis may also cause squamous metaplasia in the bronchial tree, thus increasing an individual's susceptibility to infection and cancer. In addition, cannabis may inhibit the production or function of cytokines, possibly leading to the inability of the immune system to fight infections.[43] Because THC is a general "immunosuppressant" affecting macrophages, natural killer cells, and T cells, its use as a medicinal agent in patients with preexisting immune deficits might have serious consequences.[48] Several infectious complications from marijuana smoking have been reported.[49] In 1 case, a 46-year-old man who was immunocompetent presented with a 1-week history of fever, headache, cough, dyspnea, and with evidence of a healed ulcer on his left upper lip.[50] Findings on transbronchial biopsy supported a diagnosis of herpes simplex virus–related bronchiolitis and pneumonitis due to long-term marijuana use.[50] This study illustrated marijuana-induced squamous metaplasia that promoted replication of the herpes simplex virus in the lower respiratory tract.

Results of an Australian study suggest that tuberculosis could be spread after sharing a bong with an individual with pulmonary tuberculosis.[51] Of the 45 people who shared the same bong, 29 tested positive for latent tuberculosis; several cases of active tuberculosis also occurred.[51] On typing of *Mycobacterium tuberculosis*, all of the isolates were identical.[51]

Marijuana can also become contaminated with various molds such as *Aspergillus*, Mucorales, and *Fusarium*.[52] In a single study, marijuana was cultured and its mold load was compared with that of tobacco.[53] The result was significant: 100,000 colony-forming units of mold on marijuana vs 200 colony-forming units on tobacco.[53]

Marijuana smoking has been linked to the development of invasive pulmonary aspergillosis in immunocompromised individuals, including those with cancer and neutropenia. One of the earliest reports found of pulmonary aspergillosis due to inhaling marijuana

was in a patient with chronic granulomatous disease; it was published in 1975.[54] Following this report, the development of bronchopulmonary aspergillosis due to smoking marijuana was highlighted again in 1978.[55] Subsequently, case reports of pulmonary aspergillosis in individuals with cancer or those needing transplantation have been reported and include small-cell lung cancer,[56] colorectal cancer,[57] leukemia,[58] and bone marrow[59] and renal transplants.[60]

Other fungal infections directly or indirectly linked to smoking include cryptococcosis, coccidioidomycosis, paracoccidioidomycosis, and penicilliosis. These infections have been primarily related to smoking tobacco, but marijuana may also play a role. Although no reports have been published, ingestion of fungally contaminated marijuana is a cause for concern among persons who are immunocompromised. However, other relevant examples have been published: Following a bone marrow transplant, 1 patient developed hepatic *Mucor* infection after ingesting naturopathic medications, and another individual with neutropenia developed disseminated fusariosis after eating cereal contaminated with the pathogen.[49]

Confirming the diagnosis of invasive fungal infection in severely immunocompromised patients remains a challenge for infectious diseases specialists. Coagulation abnormalities and coexisting thrombocytopenia may preclude invasive procedures for tissue harvesting, and sputum cultures are neither sensitive nor specific. In a setting where cultures may be difficult to obtain, a non–culture-based diagnostic modality, such as CT, can be used as an alternative approach based on revised definitions and guidelines.[61,62] Imaging data support using CT of the chest for the early detection of invasive pulmonary aspergillosis in severely immunocompromised patients.[61,62] Most patients (94%) presented with at least 1 macronodule (nodule diameter ≥ 1 cm) on CT of the chest.[63] In a study conducted by Marchiori et al,[64] findings on CT helped to differentiate between invasive fungal infection and organizing pneumonia.

Prophylaxis, empirical therapy, and treatment for probable or proven fungal infection are 3 strategies for the prevention and treatment of individuals at high risk for fungal infection.[65] Invasive fungal infection produced by yeasts and molds is the main infectious cause of death in patients with hematological malignancies; therefore, antifungal prophylaxis is recommended.[66,67] Clinical practice guidelines from the Infectious Diseases Society of America[62] recommend intravenous or oral voriconazole as first-line therapy for invasive pulmonary aspergillosis.

Conclusions

Marijuana smoking can be dangerous and life threatening in the setting of neutropenia and T-cell immunodeficiency, although other risk factors and lifestyle practices may contribute to this pulmonary pathology. Marijuana smoking is associated with fungal pneumonia due to the possible inhalation of mold spores on the leaves of the marijuana plant. This is because marijuana cigarettes typically do not have a filter to prevent spore inhalation, which is generally in contrast to cigarettes. Marijuana can also damage the lungs and impair local lung immune responses, thus possibly predisposing those who smoke marijuana to invasive pulmonary fungal infection. Bronchiolitis may also occur in those who smoke marijuana because the small airways of the lungs may become irritated when hot smoke is inhaled — this can also occur with smoking tobacco, breathing air pollution and other types of smoke, and being exposed to chemical irritants.

The findings from this case series highlight the need to consider antifungal prophylaxis and cessation of marijuana use among patients with prolonged neutropenia and concomitant marijuana use. In addition to miliary tuberculosis and endemic mycosis, invasive fungal infections possibly related to cannabis use should also be included in the differential diagnosis of those who demonstrate a nodular pattern and represent a susceptible host.

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