Cannabis use in the Immunocompromised increasing rates of Pulmonary Aspergillus

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Cannabis use in the Immunocompromised increasing rates of Pulmonary Aspergillus

Abstract
Cannabis use is an emerging remedy among immunocompromised patients. The lack of regulation surrounding marijuana treatment creates a culture of concern for patients. The act of inhalation further inhibits these patients’ immune response to pathogens. Additionally, marijuana cultures are heavily contaminated with Aspergillus fungus. This review assesses the evidence for a correlation between cannabis use in the immunocompromised and cases of pulmonary aspergillus.

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Cannabis use in the Immunocompromised increasing rates of Pulmonary Aspergillus

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A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 9, 2019
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Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[redacted]
Abstract

Background
Cannabis use is an emerging remedy among immunocompromised patients. The lack of regulation surrounding marijuana treatment creates a culture of concern for patients. The act of inhalation further inhibits these patients’ immune response to pathogens. Additionally, marijuana cultures are heavily contaminated with Aspergillus fungus. This review assesses the evidence for a correlation between cannabis use in the immunocompromised and cases of pulmonary aspergillus.

Methods
Exhaustive search of available medical literature using CINAHL, MEDLINE-PubMed, and Web of Science databases. Keywords searched included cannabis, immunocompromised, Aspergillosis, and pulmonary Aspergillus. Studies were assessed for quality using the GRADE criteria.

Results
There were no formal studies found, but published case reports of patients that smoked marijuana during an immunocompromised state were included. Five case reports met eligibility criteria and were included in this review. These reports documented a link between immunocompromised hosts and pulmonary aspergillus after using cannabis. Three of the reports had documented positive aspergillus growth in the cannabis cultures. Two of the reports resulted in death of the patient from aspergillus. The case reports have very low quality of evidence.

Conclusion
The use of marijuana during an immunocompromised state may be associated with increased risk of pulmonary aspergillus. Patients with minor immunosuppression may also be at an increased risk of fungal infection. Cannabis has also been associated with increased risk of pneumothorax and cardiac asystole. Providers should consider counseling their patients on these risks. Additional research is needed to further evaluate the link between cannabis use and Aspergillus infections.

Keywords
Cannabis, marijuana, immunocompromised, pulmonary Aspergillus
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Table 1: Characteristics of reviewed case reports

List of Abbreviations

IPA  Invasive Pulmonary Aspergillus
AM  Alveolar Macrophages
BMT  Bone Marrow Transplant
CT  Computed Tomography
Cannabis use in the Immunocompromised increasing rates of Pulmonary Aspergillus

BACKGROUND

Cannabis use has been an emerging treatment for patients with immunosuppression due its ameliorative properties for pain, nausea and abdominal discomfort. Ironically, these patients are at an increased risk for opportunistic infection due to their state of health. In a survey of oncologists, 44% would recommend marijuana to their patients undergoing chemotherapy. Although marijuana is a powerful and beneficial drug, there’s no regulation to the marijuana industry creating an unsafe product for immunocompromised patients. In particular, Aspergillus spores have been cultured in marijuana. Inhalation of these spores may cause pulmonary disease depending on the immune response of the user.

Alveolar macrophages (AM) are critical immune effector cells that dominate the distal lung spaces. Their role in lung immune function is to destroy pathogens and initiate an inflammatory response. AM are the first line defense against inhaled Aspergillus fungus. Tashkin et al found that regular marijuana smoking impairs the function of AM, decreasing the users immune response. For immunocompromised
patients, the damaged AM places them at higher risk for Aspergillus infection.\textsuperscript{6}

Aspergillus is an opportunistic fungus whose spores are found globally in soil, water and plants.\textsuperscript{6} Inhalation of the spores introduces the foreign pathogen into the lungs. A healthy immune system will typically ward off this opportunistic invader, but a weakened immune system welcomes infection. The rates of documented Aspergillus are increasing, and a critical risk factor for development is neutropenia. Symptoms are nonspecific and diagnosis can be troublesome, particularly when caring for the immunocompromised.\textsuperscript{5}

Marijuana use throughout the world is increasing. Over 13.5 million adults in the United States admit to marijuana use.\textsuperscript{7} In conversation with H. Burns, FNP-C, ACHPN (July 2018) since the rise of the opioid endemic in the United States, healthcare providers have shifted to recommend marijuana for patients in order to avoid opioids. This has become notable in the palliative care setting, where immune deficient patients are opting for marijuana to treat their pain and chronic disease. Inhaling marijuana provides fast relief to the brain and is the most efficient method for THC delivery,\textsuperscript{8} placing patients at a higher risk of Aspergillus exposure. Kagen et al\textsuperscript{3} found 13 of 14 marijuana samples were positive for Aspergillus. Verweij et al\textsuperscript{2} found 100,000 colony-forming units of fungus on marijuana samples.
Ruchlemer et al found a large amount of mold on medical cannabis, with the most common being Aspergillus.

Does marijuana use in immunocompromised patients increase pulmonary Aspergillus?

**METHODS**

An exhaustive search of available medical literature using CINAHL, MEDLINE-PubMed, and Web of Science was conducted. The following search terms were used: cannabis, marijuana, immunocompromised, and aspergillosis. The search results were narrowed to include articles written in the English language. References from relevant articles were searched for additional sources. No formal studies were found, only published case reports. Included were the case reports of immunocompromised patients who used marijuana during treatment and developed pulmonary aspergillus. Studies and case reports were excluded if the patient was not immunocompromised or using marijuana. The quality of the relevant articles was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group guidelines.⁹
RESULTS

The initial literature search produced 13 articles for review. After screening abstracts and titles for eligibility, 4 articles\textsuperscript{10-13} were selected that met the inclusion criteria. All four articles were published case studies (see Table I). An additional case\textsuperscript{6} was found, but the marijuana was cultured prior to marijuana use and the patient did not develop Aspergillus.

Hamadeh et al

This case\textsuperscript{10} described a 34-year-old male with a history of chronic myeloid leukemia. He presented with two tonic-clonic seizures on the 75\textsuperscript{th} day after a bone marrow transplant (BMT). Diagnosis of pulmonary Aspergillus was accomplished through lung biopsy and bronchial lavage fluid cultures. He died 35 days after diagnosis from disseminated aspergillosis despite aggressive treatment. He admitted to smoking marijuana daily for several weeks prior. His marijuana culture was positive for the same Aspergillus species found in biopsy.\textsuperscript{10}

Sutton et al

This case\textsuperscript{11} described a 60-year-old white male with a history of small cell lung cancer. Eight days into a hospital stay the patient presented with fever and pulmonary infiltrates on chest x-ray. He died 10 days later from pneumonia. Aspergillus was identified as the
organism postmortem. He had been smoking 3-4 marijuana joints per day after his sixth chemotherapy cycle. His marijuana was never cultured.\textsuperscript{11}

\textbf{Kravitz et al}

This case\textsuperscript{12} described a 46-year-old male with undiagnosed acute myeloid leukemia. Patient presented with fevers, exertional dyspnea, tachypnea, and hypoxemia. His white blood cell count was 62 000 with 81\% blasts. His condition did not improve with chemotherapy induction and antibiotics. His chest computed tomography (CT) showed bilateral multiple focal nodular infiltrates. A lung biopsy could not be performed due to his delicate condition. With his long history of smoking a marijuana and tobacco mixture, he was then given empirical high dose amphotericin B for 25 days. His condition then improved. His marijuana mixture was cultured and grossly positive for Aspergillus. It is thought this patient was colonized with Aspergillus from his marijuana and then became neutropenic from the leukemia, causing the development of pulmonary Aspergillus.\textsuperscript{12}

\textbf{Cescon et al}

This case\textsuperscript{13} described a 65-year-old male with a history of colorectal cancer who presented at a routine oncology follow-up appointment with cough, fever, and dyspnea. Bacterial pneumonia was assumed and patient was given a seven-day course of antibiotics.
After finishing the antibiotics he presented to the emergency department with progressive dyspnea, hemoptysis, and fever. The CT scan showed a 4.3 cm cavitation in his lung field. A fine needle aspiration diagnosed Aspergillus and the presence of plant matter in his lung. He was prescribed Voriconazole for three months with improvement. This patient had smoked marijuana daily for six weeks prior to his presentation and denied tobacco use.13

**Ruchlemer et al**

This case6 described a 19-year-old male with Burkitt’s lymphoma. He was undergoing chemotherapy treatment and encountering recurrent nausea and vomiting refractory to prescription medications. He wanted to try marijuana as an alternative method. Prior to marijuana use the plant was cultured and generated a massive growth of Aspergillus. This patient avoided exposure and risk of pulmonary consequences because the appropriate steps were taken.6

**DISCUSSION**

Marijuana use in an immunocompromised state has a risk of increasing pulmonary Aspergillus. The published case studies demonstrate a correlation between marijuana inhalation and development of Aspergillus infection.10-13 These immunocompromised patients actively used marijuana during their treatments and had
confirmatory biopsy or marijuana culture. Kagen et al\textsuperscript{3} identified that there is not a correlation between quantity of marijuana and exposure risk to fungal spores. With 48\% of oncologists admitting that they would prescribe marijuana if it was federally legal, there is a recognizable risk for more Aspergillus cases to emerge.\textsuperscript{1} With Cannabis becoming legalized in many states throughout the USA, it is easy to overlook the plant as a potential vehicle of infection. As healthcare providers we need to educate our patients about the possible risks associated with marijuana use, and we need to entertain a high index of suspicion when a neutropenic patient is utilizing medical marijuana.

In addition to pulmonary Aspergillus, there have been increased rates of pneumothorax and cardiac asystole associated with marijuana.\textsuperscript{14-17} Marijuana users demonstrate structural change within their lung.\textsuperscript{4} Airspace dilation with bullae are commonly found on histology, predisposing patients to pneumothorax.\textsuperscript{14} Additionally, marijuana inhalation affects the autonomic nervous system in dose dependent manner,\textsuperscript{15} stimulating sympathetic activity at low doses\textsuperscript{16} and parasympathetic activity at higher doses.\textsuperscript{17} This increased vagal tone has been associated with asystole in 2 case reports.\textsuperscript{17,15} There has also been a report of a patient with structural heart disease consuming marijuana followed by sequential ventricular fibrillation.\textsuperscript{18} These case reports highlight additional risks associated with marijuana
use. Until safety criteria can be established, we must understand there are a multitude of risks, even in those who are not immune deficient.

All of the case reports\textsuperscript{10-13} assessed in this review provided very low quality of evidence based on the GRADE guidelines. There have been other case reports published that highlight marijuana use in the immunocompromised linked to pulmonary disease, but these cases do not include a definitive diagnosis of Aspergillus.\textsuperscript{19} Diagnosing pulmonary Aspergillus is onerous when dealing with patients who are immunocompromised.\textsuperscript{5} These patients cannot always tolerate a lung biopsy, the gold standard for diagnosis.\textsuperscript{5} There are other tests available that would confirm pulmonary Aspergillus, but the diagnostic criteria will not be discussed here.

Khwaja et al\textsuperscript{19} described a case series of four patients with leukemia who smoked marijuana during their treatments. Two of the patients developed fungal infections diagnosed by CT and the third patient had a positive serum galactomannan test,\textsuperscript{19} an assay used in patients with hematologic malignancy to diagnose Aspergillus.\textsuperscript{5} Although these patients developed fungal infections while using marijuana during their immunocompromised state, a definitive culture of Aspergillus was not obtained.\textsuperscript{19} The lack of Aspergillus culture is the restricting factor in the case report series.
Additional case reports\textsuperscript{20-21} published revealed Aspergillus infection in patients with chronic disease who also smoked marijuana. Gargani et al\textsuperscript{20} described the case of a male suffering from rheumatoid arthritis who was on daily 5 mg prednisone. The patient supplemented his treatment with daily marijuana use for the analgesic properties. During his self-medication treatment he developed a pneumothorax that was refractory to chest tube management. Excision of the bullae lead to the diagnosis of an aspergilloma from Aspergillus. An additional case reported a patient with COPD and a 34-year history of smoking 20 marijuana joints a day. He suddenly developed worsening lung function leading to a diagnosis of an aspergilloma, confirmed by sputum culture.\textsuperscript{20} Remington et al\textsuperscript{21} described a 29-year-old male with a history of type 1 diabetes who smoked marijuana daily for 18 months for neuropathic pain relief. This patient presented with a lobar consolidation that failed improvement with antibiotics. Tissue samples were obtained and the culture grew Aspergillus. His marijuana was also cultured and positive for the offending fungus.\textsuperscript{21} These additional case reports\textsuperscript{20,21} highlight the importance of considering fungal infections when a patient presents with pulmonary complaints and a history positive for marijuana use. Polen et al\textsuperscript{22} reported only 3% of marijuana users had their marijuana history in their medical record. This lack of disclosure is a combination of patient fear and poor history
In order to provide exceptional healthcare, providers must guarantee patient privacy and elicit a detailed social history at every visit. Providers should properly educate their patients on the potential risks associated with marijuana, regardless if the patient has an immunocompromised status.

The number of studies on the pulmonary effects of marijuana are finite, especially within those of an immune deficient state. Additional research is required to magnify the risks of marijuana use across all populations throughout the world. Investigation and reviews are necessary to quantify the risks and create guidelines for both healthcare providers and patients.

**CONCLUSION**

The association between marijuana use in the immunocompromised and pulmonary Aspergillus has not been proven. The case reports demonstrate that the cannabis-induced structural and immunologic changes within the lung in combination with contaminated marijuana may increase the risk of developing pulmonary Aspergillus. Marijuana use in immune deficient patients should be documented at every visit and providers must counsel patients on the potential risks associated with cannabis exposure.
There are minimal published case reports on marijuana use associated with pulmonary Aspergillus in the immunocompromised. Immunosuppression is a baseline risk factor for infection, and providers need to be aware of the additional risks if their patients choose to utilize marijuana for symptom management. As more patients medicate with cannabis and with more healthcare providers recording this data, there may be a rise in published case reports further documenting this link. From the current review, practitioners should inquire about marijuana use in their patients and have a high suspicion for pulmonary fungal infections.
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