Lung Findings in a Patient with a History of Nicotine Vaping and Cannabis Smoking

WINSTON McCORMICK, BS; YIGIT BAYKARA, MD; AYESHA SIDDIQUE, MD; LANCE VAN TRUONG, DO; MEL CORBETT, MB, BCh, BAO; SEAN M. HACKING, MB, BCh, BAO

ABSTRACT

We report a collection of lung findings in a patient with a remote history of cigarette smoking, but now engaged in heavy nicotine vaping with daily edible and combustible cannabis use. Computed tomography (CT) imaging demonstrated numerous, small, and bilateral nodules with ground-glass appearance. The largest nodule is demonstrated in the right upper lung lobe. Clinically the differential diagnosis at this time included hypersensitivity pneumonitis and sarcoidosis. Atypical infection, particularly of a fungal etiology, and metastatic malignancy were also considered. Initial pathology of the right lung needle biopsy revealed alveolar septal thickening with associated atypical pneumocyte proliferation, suggestive of atypical adenomatous hyperplasia (AAH). Subsequently the patient underwent wedge resection of the right upper, middle and lower lobes. Pathology examination revealed pulmonary Langerhans cell histiocytosis (PLCH) in the upper and lower lobes, with CD1a staining highlighting the aggregates of Langerhans cells. Vascular changes were also present including intimal thickening of muscular pulmonary arteries, consistent with pulmonary hypertensive changes. Background lung parenchyma demonstrated respiratory bronchiolitis, smoking-related interstitial fibrosis, an organizing thrombus in muscular artery and associated pneumocyte hyperplasia.

KEYWORDS: lung findings, Langerhans cell histiocytosis, nicotine vaping, cannabis smoking

INTRODUCTION

Smoking has long been understood to be associated with findings of lung injury, chronic obstructive pulmonary disease (COPD) as well as malignancy. Today the proportion of female COPD patients with a history of smoking is 72.8%, while in males it has been found to be 92.7%.[1] It is estimated that cigarette smoking can explain around 90% of lung cancers in men, and 70 to 80% in women.[2]

In recent years, smoking cigarettes has fallen out of public favor in exchange for smoking cannabis, as well as vaping both nicotine and cannabis. The health effects of vaping are largely unknown, but vaping can cause vaping-related lung injury.[3] The data pertaining to the physical health effects of long-term cannabis use is also limited.[4]

Regrading vaping, a six-case cluster has been reported from the University of Utah,[5] and image changes have been demonstrated in a range of cases[6] by the University of California. The Centers for Disease Control and Prevention (CDC) now refers to this syndrome as e-cigarette, or vaping, product use–associated lung injury (EVALI).[3] However, despite the accumulation of data demonstrating both the clinical and imaging features of vaping-associated lung injury, the pathology can be relatively non-specific and is still poorly understood. Butt et al.[7] have postulated that histologic changes in vaping-associated lung injury represent airway-centered chemical pneumonitis, secondary to one or more inhaled toxic substances, instead of an exogenous lipoid pneumonia.

Cannabis or marijuana refers to the dried flowers and leaves of the plant *Cannabis sativa L* which contains δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).[8] Today, marijuana is categorized as a hallucinogen and considered to be controlled Schedule 1 substance with no currently accepted medical usage. Clinically, the effects of cannabis could vary depending on different formulations, as well as in both the method and intensity of use, such as combustion vs vaping.

Cases of pulmonary Langerhans cell histiocytosis (PLCH) have long been understood to occur in the setting of cigarette smoking, and they predominantly affect young adult smokers.[9] Any potential relationships to vaporized nicotine and cannabis oil, as well as combustible cannabis are not as well understood. One case report[10] documents PLCH in a 36-year-old male with minimal cigarette smoking and daily marijuana use while another[11] documented PLCH in a 19-year-old man who smoked half a pack of cigarettes and seven marijuana joints per day. A UK-wide cohort of 106 patients with PLCH demonstrated that 25% of patients were current smokers, 71.7% ex-smokers, and 6% reported smoking cannabis.[12]

Herein, we present lung findings from a patient with chronic nicotine vaping and cannabis smoking who had a remote history of cigarette smoking. Current trends include a shift away from smoking tobacco, and with the growing legalization of marijuana, vaporization of both marijuana and nicotine is on the rise. Examining lung findings from patients with a history of both cannabis and electronic vaping could be important for defining the risk of potential lung injury for the world population at large.

CASE REPORT

A 44-year-old female presented to the Rhode Island Hospital Emergency Department (ED) for left chest wall pain that radiated to her back and was rated as a 10/10 in pain intensity. Her past medical history was significant for hyperlipidemia and fibromyalgia. She had had a cholecystectomy and a tubal ligation after two spontaneous vaginal deliveries. The patient had a remote history of cigarette smoking, but now engaged in heavy, everyday nicotine vaping, with both daily edible and combustible marijuana use. Complete metabolic panel and complete blood count in the ED were unremarkable. Troponin, hepatic function tests, and lipase levels were within normal limits. The patient left against medical advice before a complete work-up could be pursued.

Her out-patient primary care physician ordered a chest computed tomography (CT) scan which revealed exostosis on the sixth rib of the left hemithorax and an incidental, small, right-sided ground-glass nodule in the right upper lobe. Pulmonary function tests (PFT) were obtained and were unremarkable. The decision was made to re-assess the lung nodule in three months due to lack of pulmonary symptoms at that time.

Repeat chest CT demonstrated a marked enlargement of the primary lung nodule compared with the previous CT scan, measuring up to 2.2 cm with a 4 mm central solid component (**Figure 1**). Numerous bilateral smaller ground-glass nodules that are more prominent in the upper lobes were also apparent (**Figure 2**). There was no evidence of cysts. The decision was made to pursue CT-guided biopsy of the primary nodule one month after this result. Additional chest CTs were obtained immediately after the biopsy and one month after the biopsy. The chest CT obtained immediately after the lung biopsy revealed interval increase in size of the upper lobe lesions. Differential diagnosis at this time included hypersensitivity pneumonitis and sarcoidosis. Atypical infection, particularly of a fungal etiology, and metastatic malignancy were also considered. CT one month after the biopsy revealed increased solid components within the numerous lesions, raising concern for Wegner's vasculitis. Findings were inconsistent with vaping-related lung injury.

Initial pathology of the right lung needle biopsy revealed alveolar septal thickening with associated atypical pneumocyte proliferation **(Figure 3**), suggestive of atypical adenomatous hyperplasia (AAH). Clinical and radiological correlation was recommended by the consultant anatomical pathologist at the time of biopsy diagnosis.

QuantiFERON gold TB test was negative, and antineutrophil cytoplasmic antibody (ANCA) and angiotensin converting enzyme (ACE) levels were within normal limits. Rheumatoid factor (RF) was undetectable, and the erythrocyte sedimentation rate (ESR) was not elevated. The decision was made to pursue wedge resection of the right upper, middle and lower lobes.

Figure 1. CT findings demonstrating the largest nodule (white arrow) with ground-glass appearance is seen in the right upper lobe on non-contrast CT is indicated in the coronal plane.

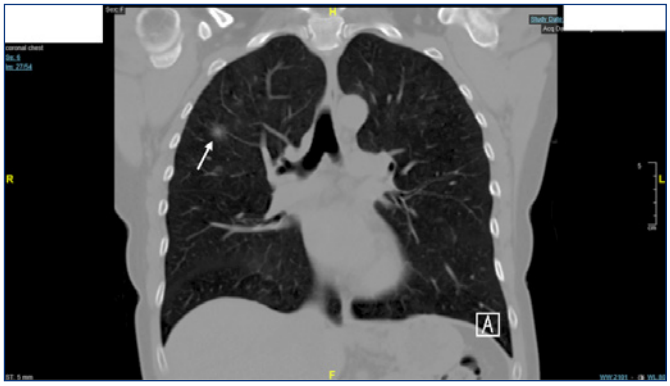


Figure 2. CT findings demonstrating the numerous, small, and bilateral nodules (white arrows) with ground-glass appearance on non-contrast CT is indicated in the coronal plane.

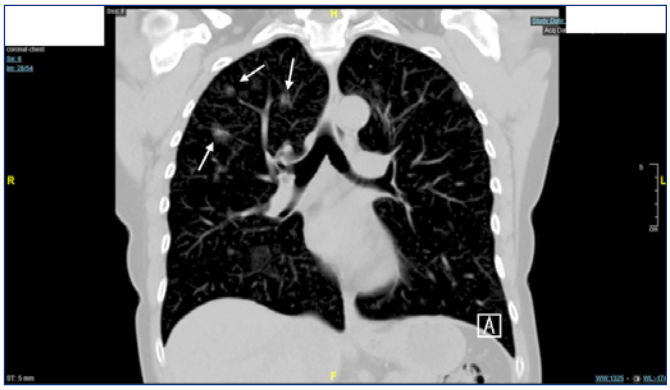
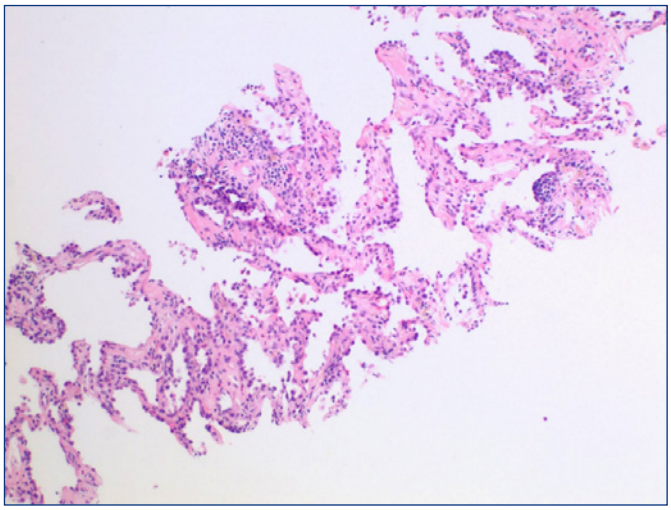


Figure 3. Initial pathology of the right lung needle biopsy revealed alveolar septal thickening with associated atypical pneumocyte proliferation, suggestive of atypical adenomatous hyperplasia (10x).



Pathology examination of the right upper lobe revealed a tan-white spongy nodule measuring 0.5 x 0.4 x 0.3 cm which lies 1 mm from the inked resection margin. Histologic evaluation revealed stellate-shaped areas found mostly in the periphery of the lungs containing sparse cellular proliferations (**Figure 4**). Higher power microscopic evaluation demonstrated proliferation of small, spindled Langerhans cells admixed with abundant eosinophils (**Figure 5**). CD1a stain highlights the aggregates of Langerhans cells (**Figure 6**). Vascular changes were also present including intimal thickening of muscular pulmonary arteries, consistent with pulmonary hypertensive changes. Background lung parenchyma demonstrated respiratory bronchiolitis, smoking-related interstitial fibrosis and an organizing thrombus in muscular artery found in the right middle lobe wedge resection. Associated pneumocyte hyperplasia was also noted. Repeat chest CT seven months after surgery revealed no residual disease.

Figure 4. Pulmonary Langerhans cell histiocytosis (LCH) in the upper and lower lobes (10x).

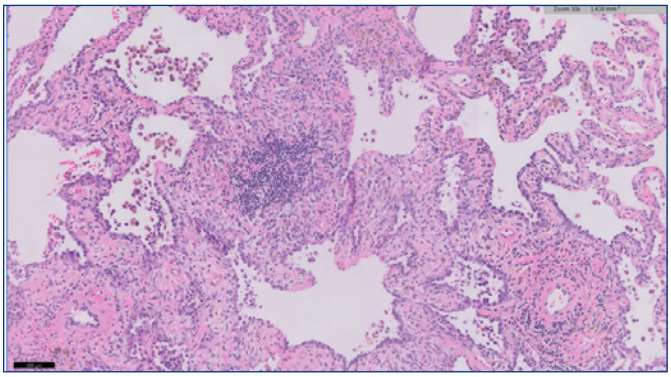


Figure 5. Prominent eosinophilic inflammation (20x).

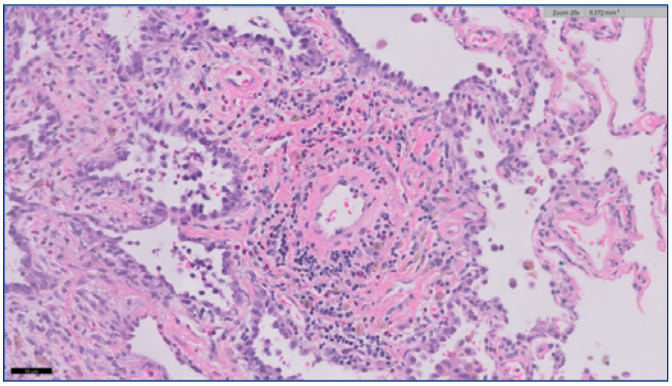
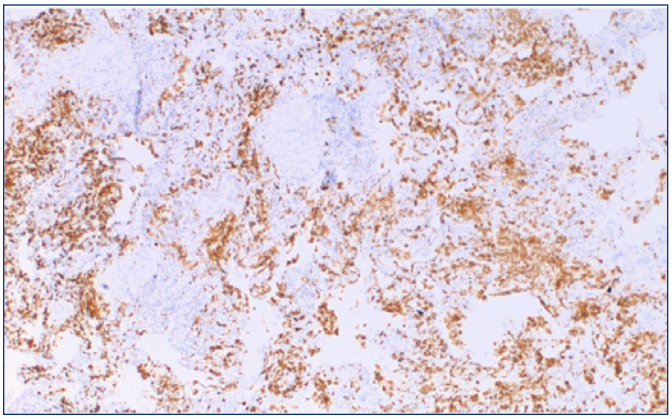


Figure 6. CD1a stain highlighting the aggregates of Langerhans cells (4x).



DISCUSSION

Langerhans cell histiocytosis (LCH) represents a clonal proliferation of Langerhans cells, tissue-resident macrophages found primarily in the epidermis and papillary dermis that also function as antigen-presenting cells.[13] In LCH, tumor cells are often found prominently disseminated, particularly to lymph nodes and the skin. Langerhans cells are characterized by Birbeck granules which stain positive for CD1a, S100, and Langerin.[13,14] Contrary to what was previously believed, LCH is now understood to be a clonal process with mutations including BRAF c.1799T>A (p.Val600Glu).[13]

LCH is a class of neoplasm that contains a wide spectrum of clinical presentations.[13,14] It is predominantly a disease of the pediatric population and may be self-limiting.[13-15] The self-limiting forms are associated with particularly good prognoses.[14] Typical disease features include eosinophilic granulomas secondary to lytic bone lesions, most commonly in the skull and long bones, exophthalmos, polyuria, and the Letterer-Siwe disease: a fulminant clinical syndrome which includes hepatosplenomegaly, lymphadenopathy, skin rash, and pancytopenia.[13, 15] Furthermore, LCH can present in nearly any organ except the kidney, and it may present as single- or multi-organ disease.[9,13,16]

One manifestation of LCH is PLCH, which occurs typically in cigarette smokers aged between 20–40 years.[9,17] The correlation between cigarette smoking and PLCH is so strong that the disease has been called a smoking-related illness.[17,18] Indeed, PLCH is the most common LCH in adults,[19] and the most common presenting symptoms include cough and dyspnea on exertion, yet one-third of patients may be asymptomatic.[16,17,19] Pulmonary function testing often reveals a decreased diffusion capacity of carbon monoxide, reduced vital capacity, normal or increased residual volume, and preserved total lung capacity, however it is often normal in early disease.[9, 18,19]

PLCH remains a rare and poorly understood disease of active young-adult cigarette smokers whose exact etiology is unknown. Our patient's presentation was typical, in that she was asymptomatic and was incidentally identified as having a single ground-glass nodule that rapidly advanced to involve the bilateral lungs. Indeed, the chest imaging is often abnormal and can be the first clue toward pathology.[16] Nonetheless, she was outside the typical age-range for PLCH, and her smoking history was remote. So strong is the

link between active cigarette smoking and PLCH that cessation of smoking can lead to remission of PLCH.[17,19] Given this patient's remote cigarette smoking history and the fact that PLCH is often rapidly progressing, as her case was, it is unlikely that cigarette smoking played a role in her disease.[9]

By contrast, this patient presented with active nicotine vaping and marijuana smoking. Her presentation suggests that inflammation due to heated smoke, nicotine itself, or some compound in smoked marijuana may be the underlying culprit in the pathogenesis of PLCH. The current molecular understanding suggests a *BRAF or MAPK* mutation is responsible for PLCH and that it is therefore monoclonal.[9,13,15,18] Inflammation could be a driving factor involved in PLCH pathogenesis. Most recently, mice models have shown that BRAF-V600E mutations increase dendritic cell responsiveness to stimuli, including chemokines, while mutant cells accumulate in the lungs of cigarette smoking-exposed mice is due to both increased cellular viability and enhanced recruitment.[20]

This patient underwent multilobe right lung wedge resections which revealed PLCH. Current treatments rely on cigarette smoking cessation followed by observation.[15,18] If PLCH does not resolve, corticosteroids, systemic chemotherapy such as cladribine, with some consideration given to *BRAF* or *MEK* inhibitors, is used.[15,16,19] Our patient did not receive systemic chemotherapy and continued to vape nicotine and smoke marijuana. Lung transplant is pursued in some patients with refractory disease or in those with limited life expectancy.[9,16]

Many of the findings in the lungs were non-specific. These included vascular changes including intimal thickening of muscular pulmonary arteries, consistent with pulmonary hypertensive changes, with background lung parenchyma demonstrating respiratory bronchiolitis, smoking related interstitial fibrosis, an organizing thrombus in muscular artery and associated pneumocyte hyperplasia.

The vascular changes consistent with pulmonary hypertensive could possibly be a consequence of smoking cannabis and tobacco, as well as vaping nicotine. Tobacco smoking has been found to be significantly more common in patients with pulmonary arterial hypertension compared to control subjects.[21] However, the correlation of nicotine vaping and cannabis smoking to pulmonary hypertension is still obscure. Additionally, pulmonary hypertension can occur in the setting of PLCH due to vascular dysfunction.[22] Further suggesting the findings of pulmonary hypertension in this patient could be multifactorial in etiology.

Respiratory bronchiolitis is commonly found in smokers, but has also been reported in patients using electronic nicotine delivery systems.[23] The findings of an organizing thrombus could be secondary to vaping, as studies have demonstrated even short-term exposure to the JUUL e-cigarettes increases the risk of thrombotic events by modulating platelet function, such as aggregation and secretion.[24] Pneumonocyte hyperplasia is extremely non-specific and can represent any response or injury to respiratory epithelium.

Despite the history of electronic nicotine vaping, findings consistent with a diagnosis of vaping-related lung injury including acute fibrinous pneumonitis, diffuse alveolar damage, or organizing pneumonia accompanied by bronchiolitis were not seen.[7] It is worth mentioning that even though no histologic findings are necessarily specific for EVALI, foamy macrophages and pneumocyte vacuolization can be useful diagnostic clues in an appropriate clinical context.[7]

Much remains to be understood about both vaping lung injuries and the long-term effects of cannabis smoking.[4] One case report details the presence of vanishing lung syndrome in a patient who vaped nicotine and smoked cannabis, but other deleterious physical effects of simultaneously using both substances, particularly PLCH, have not been documented.[25] This patient's presentation suggests that PLCH should be considered in any patient who vapes nicotine, smokes cannabis, or both, and who presents with rapidly progressing lung nodules. It also suggests wedge resection could be considered for any patient who fails initial conservative therapy.

Although cigarette smoking has rapidly declined in popularity, nicotine vaping and cannabis smoking, long seen as safe options, are exploding in popularity. Much remains to be understood about the long-term effects of both electronic vaping and cannabis smoking on the lungs.

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Authors

Winston McCormick, BS, Warren Alpert Medical School of Brown University.

Yigit Baykara, MD, Department of Pathology and Laboratory Medicine, Rhode Island Hospital and Lifespan Medical Center, Warren Alpert Medical School of Brown University.

Ayesha Siddique, MD, Department of Pathology and Laboratory Medicine, Rhode Island Hospital and Lifespan Medical Center, Warren Alpert Medical School of Brown University.

Lance Van Truong, DO, Department of Pathology and Laboratory Medicine, Rhode Island Hospital and Lifespan Medical Center, Warren Alpert Medical School of Brown University.

Mel Corbett, MB, BCh, BAO, Department of Otolaryngology/ Head and Neck Surgery, University Hospital Galway, National University of Ireland.

Sean M. Hacking, MB, BCh, BAO, Department of Pathology and Laboratory Medicine, Rhode Island Hospital and Lifespan Medical Center, Warren Alpert Medical School of Brown University.

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Correspondence

Sean M. Hacking, MB, BCh, BAO
Department of Pathology and Laboratory Medicine,
Rhode Island Hospital and Lifespan Medical Center,
593 Eddy St, APC 12, Providence, RI, 02903
sean_hacking@brown.edu