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Case Report

E-Cigarettes Induced Lung Disease in Adult and Adolescent Population

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Abstract

Background: Use of E-cigarettes as an alternative to smoking tobacco became available to adults and children in the mid 2000s and the percentage of children and adolescents who are using vaping devices has increased significantly from 11.7 % in 2017 to 20.8 % in 2018. Recently, there has been an increase in reported cases of development of acute respiratory symptoms and hypoxemia associated with vaping marijuana. The clinical presentations are variable but lung biopsiesshowed respiratory bronchiolitis associated with interstitial lung disease, organizing pneumonia and lipoid pneumonia. The mechanism of injury is unclear but it is believed that heating of vape liquids leads to production of aldehydes and tocopherol acetate or Vitamin E. In September 2019 the CDC reported over 450 cases of lung disease associated with e-cigarettes, some of which were fatal.

Objective: Discuss association between vaping cannabis and lung disease. Cannabis, an old and known substance, used for centuries, is now leading to new lung disease and fatalities when its oils are inhaled in vaping form. Increase awareness of vaping cannabis associated medical sequelae.

Methods: 3 cases of adolescents who presented to the emergency department with acute respiratory symptoms, hypoxemia and respiratory failure requiring ET intubation following the use of vaping cannabis.

Results: There is significant association between use of vaping cannabis and lung disease.

Conclusion: There growing concern about increased use of electronic devices to inhale cannabis oils. We report three cases of acute lung disease in adolescents who presented with acute respiratory symptoms after vaping cannabis.

Keywords: E cigarettes, Cannabis use, Vaping, Adolescents, Adults, Lung disease, ARDS.

Introduction

Cigarette smoking continues to be prevalent among the pediatric population. When the electronic cigarettes or "vaping" became available, it quickly became a widely used alternative to tobacco[1]. The National Youth Tobacco Survey revealed threefold increase in e-cigarette use between 2011and 2013 in adolescents who had no history of smoking cigarettes[1].

As of December 2019, the number of electronic –cigarette or vaping product use –associated lung injury (EVALI) patients who were hospitalized is more than 2400 across the US(2). 52 deaths have been reported[2]. The majority of the patients (78%) were younger than 35 years old[2]. The patients affected by EVALI reported respiratory symptoms (95%), constitutional symptoms (85%), and gastrointestinal symptoms (77%), developing from two days to several weeks. About 47% of patients developed respiratory failure requiring mechanical ventilation and Intensive Care Unit care. Most patients exhibited consolidation and ground glass opacitiesin the lower lung fields on chest radiograph. Histologically, the lesions appeared as diffuse alveolar damage, acute fibrinous pneumonitis and organizing pneumonia[2].

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In the recent months, we treated 3 patients presenting with pneumonitis following use of e- cigarettes.

Case 1

The patient gave verbal consent for the case report and imaging but was unable to physically sign due to infection control measures.

A 16-year-old male with history of asthma, irritable bowel syndrome, esophagitis, gastritis, anxiety disorder and cannabis use disorder presented with 1-day history of intractable nausea and vomiting. In the Emergency Department he was afebrile with a temperature of 98.3F, pulse- 110 beats per minute, respiratory rate of 18 breaths per minute, blood pressure of 137/74 and oxygen saturation of 96%.

The patient reported worsening gastrointestinal symptoms with abdominal pain and vomiting in the last year leading to 30 lb weight loss in the last two months. The patient's laboratory workup showed white blood count 26.9 per microliter, hemoglobin 15.5 g/dL, hematocrit 44.5 %, and platelets 449,000 per microliter. Comprehensive chemistry panel showed, glucose elevated at 168 mg/dL, blood urea nitrogen was 9 mg/dL, creatinine 0.68mg/dL and his anion gapwas elevated at 14, the rest of the results were normal. The patient's kidney and liver function tests were within normal limits. C-reactive protein was elevated at 30.24 mg/dL. The patient's home medications included pantoprazole 20 mg daily, lorazepam 1 mg every 6 hours as needed, ondansetron 4 mg every 4 hours as needed, and cannabidiol (CBD) oil as needed for back pain. Patient urine drug screen was positive for cannabinoids. The patient was admitted for gastrointestinal workup, and received a dose of metronidazole 500mg and ceftriaxone 1g /50 ml premix. The patient's abdominal CT scan showed diffuse colitis and mild hepatomegaly with fatty infiltration.

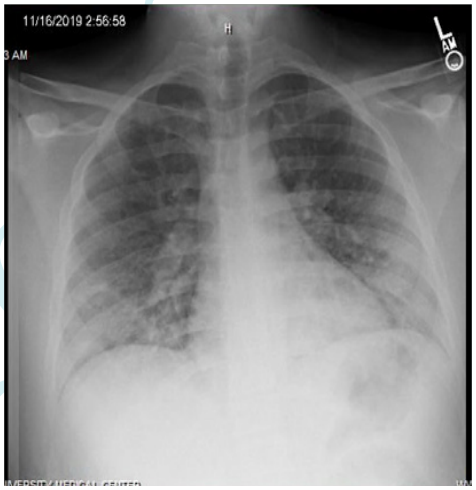
On admission day 2, the patient's gastrointestinal symptoms improved, however he developed sudden shortness of breath and his oxygen saturation decreased into the low 80's. At the time his vital signs showed temperature of 101.5F, respiratory rate of 30 breaths per minute, pulse of 62 beats per minute and blood pressure 103/52. A portable chest x ray showed "increased opacification in the lower lungs bilaterally concerning for acute respiratory distress syndrome (ARDS), pulmonary edema or pneumonia. There was no evidence for pleural effusion or pneumothorax. The patient was transferred to the Pediatric Intensive Care Unit on 5 L facemask and increased to opti-flow 6 L at 60 %. He was started on Ceftriaxone and azithromycin while in the PICU and his lab workup showed a WBC of 17.4 10*3/µL, hemoglobin of 13.9 g/dL, hematocrit of 41.3 % and platelet count of 376,000/µL. His complete chemistry work-up was within normal limits with the exception of elevated CRP 32.76 and prolactin at 0.52. Patient had an extensive immunology work up which was also negative for Influenza A/B, Parainfluenza and RSV. The patient began to improve and was able to be titrated down to room air by day 4 of admission. The follow up chest x ray showed improved aeration.

Psychiatry was consulted on admission day 4 to assist in managing the patient's anxiety. He endorsed long history of anxiety beginning at age 14, which frequently manifested with inability to fall asleep and vomiting. The patient used increasing amounts of cannabis to treat his insomnia. He admitted to difficulty concentrating, difficulty with memory and with behavior at home.

Patient has had 3 suicide attempts in the past, none requiring hospitalization. Patient denies smoking cigarettes or any other tobacco. He drinks alcohol 2-4 times a month and "avoids intoxication." He tried marijuana in 7th grade and did not use again until freshmen year of high school and has since been increasing its use. He smokes 1 gram of cannabis weekly; he uses vape pens, concentrate products and flower at random. He states that he cannot control his anxiety and it is present for most of the day, every day. He reports being tiered often with episodes of irritability.

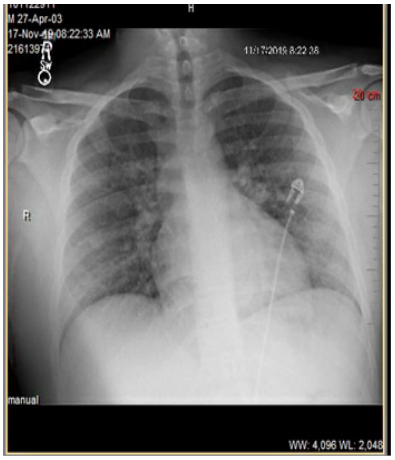
The patient was diagnosed with anxiety disorder and cannabis use disorder based on the criteria of Diagnosis and Statistical Manual of Mental Disorders 5 edition (DSM-5), based on the patient's excessive anxiety and worry, difficulty controlling his worry, physical manifestations, increased irritability and increased fatigue.

This is the first chest X-ray:



After 2 days on 8L of oxygen, the patient was weaned down to 6L and then slowly to room air and was he was able to breath spontaneously and comfortably. The follow up chest x ray showed improvement.

The follow up chest x ray showing improvement.



The patient's condition continued to improve and his vomiting subsided. Once the patient was stable, he was discharged with close follow up and multiple resources for his ongoing substance use.

Case 2

The patient gave verbal consent for the case report and imaging but was unable to physically sign due to infection control measures.

The patient is a 17 year old female with a past medical history of depression disorder, anxiety disorder, who presented after an intentional overdose on 20-40 tabs of bupropion XL 150 mg and an unknown quantity of venlafaxine 37.5 mg after an argument with her mother. In the Emergency Department, the patient's vital signs showed temperature of 98F, pulse 118 beats per minute, respiratory rate 21 breaths per minute and oxygen saturation of 96%. Her physical exam was significant for altered mental status with confusion and disorientation, dilated pupils and tachycardia. GCS eye score was 4, GCS verbal was 5 and-GCS motor sub score was 6 (out of 15).

The patient lab workup showed white count 9.9 10*3/µl, hemoglobin 13 g/dL, platelets count 28010* 3/µL. Comprehensive chemistry was normal except for aspartate aminotransferase 56U/L and alanine aminotransferase 63 U/L. Kidney function was normal., magnesium was 1.7 mg/dL Urine Drug Screen was positive for cannabinoids and blood alcohol level was 0.071. Electrocardiogram was significant for sinus tachycardia. QTC was 426 ms.

The patient was admitted to the pediatric intensive care unit. She continued to appear confused and disoriented and exhibited visual hallucinations as well as respiratory distress secondary to right lung pneumonitis, likely due to aspiration. Her vital signs showed temperature of 99.9 F, pulse of 120 beats per minute, respiratory rate of 40 beats per minute. Pulse oxygen saturation was at 89% and her lab workup showed sodium of 131 mmol/L and potassium 3.4 mmol/L. Chest X-ray showed hazy densities in both lungs, greater on the right than on the left. No pneumothorax was visible.

The patient received intravenous fluids, and ampicillin-sulbactam.

Psychiatry was consulted on admission day 1 to assist with management of agitation, hallucinations, inattention and nystagmus. due to acute toxic encephalopathy (delirium) due to intentional ingestion of extended release bupropion and extended release venlafaxine.

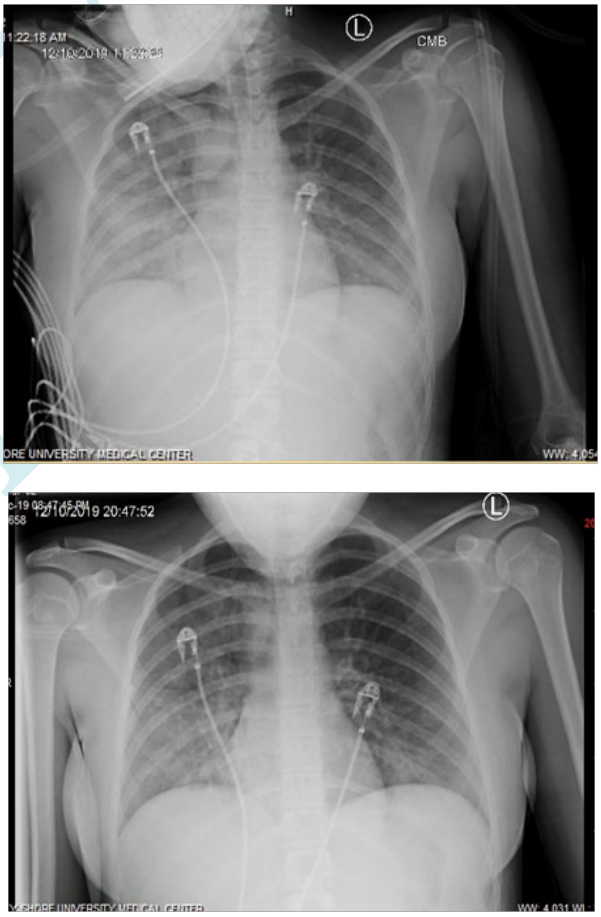
The acute hypoxic respiratory distress with bilateral lung infiltrates she manifested was believed to be a result of vaping cannabis and nicotine prior to admission and/or aspiration. The patient received 15L of optiflow, methylprednisolone 50 mg every 12 hours for vaping induced lung injury, Unasyn 3 g every 6 hours and quetiapine 25 mg for delirium and cyproheptadine for its effect on bupropion overdose. Due to the effects of the bupropion and venlafaxine the patient was started on Q 4 EKG with concern for conduction delay. Initial EKG was tachycardic but QRS was within normal limits. Subsequent EKGs were stable throughout the stay.

During psychiatric evaluation the patient reported a turbulent home life and admitted that the overdose followed an argument with her mother. The patient reported persistent depression, hopelessness and vague suicidal ideations. She admitted to anxiety and has been vaping cannabis and nicotine daily and persistently and her last dose was prior to the intentional overdose. She also admitted to drinking alcohol sporadically.

The diagnosis of delirium was made according to the Diagnosis and Statistical Manual of Mental Disorders 5 edition (DSM-5) based on acute onset of disturbance of attention and awareness, impaired cognition, agitation and sleep disturbance in the context of acute ingestion. The Confusion Assessment Method confirmed this for Pediatric ICU (CAM-PICU). The patient was also diagnosed with depression disorder and cannabis use disorder

The patient was transferred to a psychiatric inpatient unit for mental health stabilization when she was medically cleared.

The chest x ray was obtained and showed "The patient is rotated towards the right. Hazy densities are noted in both lungs, greater on the right than the left."



Case 3

The patient gave verbal consent for the case report and imaging but was unable to physically sign due to infection control measures.

This is a 20 y/o female with a past medical history of asthma, depression disorder, anxiety disorder, ADHD and cannabis use disorderwho presented with 3 days of cough, fever, and shortness of breath. The patient admitted to ongoing can-

nabis and nicotine use. The patient contacted her primary care physician and was prescribed clarithromycin. However, since she did not improve, she was referred for COVID testing and her viral PCR for SARS-CoV-2 returned negative. In the Emergency Department the patient was tachypneic and tachycardic. She was febrile to 101.2 F, pulse 113 beats per minute, respiratory rate 22 breath per minute.Her oxygen saturation was 88%. White count was 14.5* 3 /µL, hemoglobin 12.7g/dl, hematocrit 37.1%, platelet count 334 10* 3/µL, neutrophil percent 92.8 %. The comprehensive chemistry panel showed sodium 131 mmol/L, potassium 3.7mmol/L, chloride 98 mmol/L, glucose 118, urea nitrogen 9mg/dL and creatinine 0.80mg/dL, aspartate aminotransferase was 46U/L, C-reactive protein 27.55 mg/dl. D-dimmer 777, lactate dehydrogenase 479U/L, sedimentation rate 85 mm/h. Chest radiograph revealed bilateral lower lobe infiltrates with multifocal airspace opacities. Pneumothorax was not seen. She received Zithromax and ceftriaxone IV and was admitted for hypoxemia and was placed on 5L oxygen by nasal cannula. Electrocardiogram showed normal sinus rhythm.

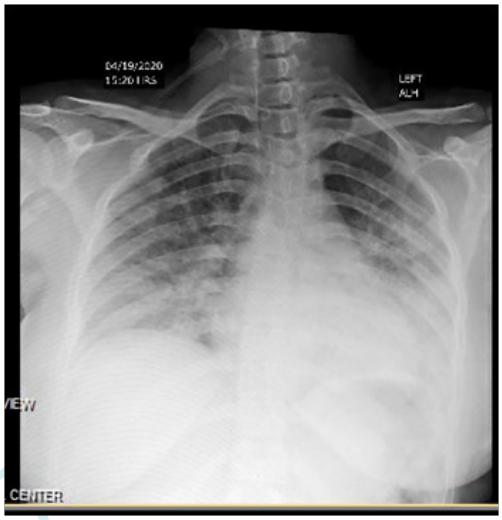
Since infection was in the differential diagnosis, the patient was tested for mycoplasma pneumonia IGG and legionella antigen that were negative. Viral panel for influenza, parainfluenza, RSV, pertussis, coronaviruses and chlamydia pneumonia were negative. Nasal MRSA was negative. Urine drug screen was positive for cannabinoids and negative for other drugs. Pulmonary embolism was ruled out as well.

The patient was diagnosed with EVALI and was treated with steroids, empiric antibiotic and oxygen supplementation. She competed 4 additional days of azithromycin and received incentive spirometer.

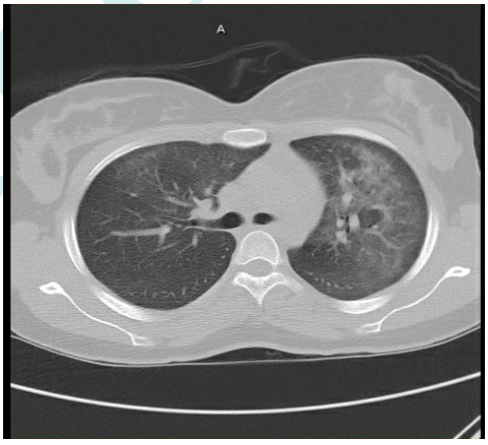
Psychiatry was consulted on 2nd day of hospitalization for worsening anxiety after the patient became upset and anxious about being isolated from her family and made suicidal statements. She reported a substantial history of physical and emotional abuse by her father. Patient denied depression, anhedonia, hopelessness, helplessness, crying spells, suicidal or homicidal behavior. She denied changes in sleep or appetite, and difficulty concentrating. She denied symptoms consistent with posttraumatic stress disorder such as nightmares, flashbacks, and hypervigilance and avoidance behaviors. She endorsed however, persistent anxiety with occasional panic attacks. She has been treated with desvenlafaxine 100 mg daily and quetiapine 25 mg. The patient disclosed that she has been smoking marijuana since the 9th grade and cigarettes since 10th grade. She has been smoking vape nicotine and marijuana for the past several years and she smokes multiple times a day. She stated that she smoked prior to her presentation.

The diagnosis of anxiety disorder and cannabis use disorder was made according to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) based on the patient' report of anxiety and panic attacks and the presence of cannabis in the urine. Under the psychiatric recommendation the patient continued with her home medications and hydroxyzine 25 mg twice daily was added. The patient's symptoms improved and she was discharged with referral for drug consulting and psychiatric care.

The patient's chest X-ray, which is significant, showed"multifocal, bilateral airspace opacities concerning for an infectious process" as shown below:



The patient's CT scan shown below revealed bilateral ground glass opacities, left worse than right,right lower lobe sub segmental atelectasis and/or scarring and left lower lobe linear densities, whichwas felt to reflect scarring. A 4 mm left upper lobe ground glass nodule was noted. The patient also had ground glass nodule that was < 6 mm and the patient would require 6-12 month follow up followed by 2 year follow ups until 5 years of no change. The patient was subsequently discharge home after completing clarithromycin treatment.



The 3 cases presented above are consistent with other patients' clinical presentation reported in the literature. The patient in case 1 presented with gastrointestinal symptoms consisting of vomiting and respiratory symptoms such as shortness of breath and oxygen desaturation. The other 2 patients in cases 2 and 3 presented with respiratory symptoms only. In all the 3 cases, the diagnosis of EVALI was made by exclusion. The psychiatric intervention should include smoking and vaping cession as well as treatment of the underlying anxiety or other mental health diagnosis.

Literature Review

During 2007, electronic nicotine -delivery system or electronic cigarettes were introduced in the USA, intended to be a safer alternative to smoking tobacco[3]. These are devices that are

structured to aerosolize a liquid that can be inhaled. The e-cigarettesconsist of a cartridge (or tank) which contain a solution, a heating element and electric power source. The solution may contain nicotine, propylene glycol and vegetable glycerin or a combination of the two[4]. The first version of the e-cigarette was disposable and its appearance was similar to a conventional cigarette. As time evolved the device incorporated refillable cartridges and rechargeable lithium batteries[3], and this structure progressed to a device which includes heating elements, temperature control and reduced resistance[3].

The E- cigarette solution usually consists of propylene glycol, vegetable glycerin, or both. It became apparent that the higher the percentage of propylene glycol in the solution, the stronger the flavor and sensation. The solution may contain different concentrations of nicotine from none to 5.4%[4] and it may contain flavors such as fruit, menthol orcandy. The flavors were attractive to the youth, which promoted its use[4]. When the liquid in the e- cigarette is heated, an aerosol is produced which contains a solvent, which could contain one or more flavorings with or without nicotine[3,5]. A rapid cooling which follows the evaporated liquidforms the aerosol which is inhaled or "vaped"[3]. When the e-cigarettes were introduced to the market, it was believed that they would be less harmful when compared to non-electronic cigarettes.

The use of e-cigarettes has increased from 1.5 % to 11.3% among high school students from 2011 to 2016[4]. Less than 50% of youth who reported tobacco use also used e-cigarettesand other tobacco products. These adolescents frequently reported the use of other substances such as marijuana and alcohol use[4]. Many adolescents admitted that curiosity, peer influence, low cost, availability and the experience of the inhaled flavors attracted them to use and repetitive use[4].

According to[6] companies of e-cigarettes target adolescents in their advertising operations, taking advantage of social media and their product design and flavors. The FDA established a Deeming Rule in 2016 to broaden tobacco regulations to other products including e-cigarettes, cigars, hookahs, and pipes. However, flavorings, except menthol, are forbidden from traditional cigarettes, but this does not apply to e-cigarettes. The American Academy of Pediatrics has taken a stand against sale of e-cigarettes to children under 18 years, and opposes the sale of sweet flavored e-cigarettes. The American Thoracic Society is a major proponent of upholding the same restrictions and regulations for e-cigarettes as combustible cigarettes. E-cigarettes aerosols can also contain formaldehyde and acetaldehyde, although in less abundance than the amounts found in old-fashioned cigarettes. Diacetyl is a flavoring additive in some e-cigarettes, which has been associated with severe bronchiolitis obliterans. 25.3% of high school students recounted present use of tobacco merchandise in 2015, and 13.0% described using more than one type of item. In this population, e-cigarettes were reportedly most widely used at 16.0%, then cigarettes at 9.3%, then cigars, hookahs, smokeless tobacco, and pipes in that order. 7.4% of middle school students claimed to have trialed a tobacco method, with e-cigarettes also most employed in this population at 5.3%, then cigarettes at 2.3%, then hookahs, smokeless tobacco, cigars, and pipes, in descending trend. Although the prevalence of cigarette smoking in minors has decreased over the years, alternative products have been on the rise. The term "vaping" encompasses more than just e-cigarette use; for example, a hookah pen may be referred to as a vape, but an entity separate from an electronic cigarette. Cigarette smoking has been correlated to mild obstruction of airways and reduced pulmonary function progression in teenagers, in addition to heightened likelihood of acquiring idiopathic pulmonary fibrosis, and increased susceptibility to future addiction to other substances. As cannabis is the most frequently used illegal drug in the nation, adolescents are also vulnerable to use, especially in those who have used nicotine products. Cannabis has been shown to damage cognitive and executive functions, and MRI data in young adults delineated the effects of cannabis use in altering the appearance of the left nucleus accumbens, a reward and motivation processing area, and right amygdala, a center of fear and emotional response. Animal studies have shown changes in dendritic branching and synaptic connections on repeated exposure to cannabis. Inhalation of volatile substances is also a significant problem among adolescents, with glue and shoe polish and gasoline most commonly inspired. Other products include spray paints, correction fluids, nitrous oxide, and other aerosols. In the early 2000s, about nine percent of surveyed 12 to 17-year-old children in the nation had manipulated inhalants, with 80% professing initial use before age 15 years, and more than one fifth of this using nitrous oxide. Inhalant use has been connected with brain, heart, liver, and kidney injury, as well as death. Educating the public, especially minors, of these dangers can help forestall further addictive crises to new products and devices[6].

An increase in use of e-cigarettes showed, over time, that theycould cause adverse health effects including cardiovascularеffects such as myocardial infarction, lung lesions, pneumothorax, thermal injuries due to explosions leading to burns and facial injuries. E-cigarettes were also determined to cause respiratory tract irritation, cough, increased blood pressure, tachycardia, and promote nicotine addiction. Studies have shown that e-cigarettes can be addictive leading to psychological effects[3,6,7].

E-cigarettes induce lung disease as defined by the following criteria:

1. Use of e-cigarettes and related products 90 days prior to the onset of symptoms.
2. Pulmonary infiltrates on imaging
3. Absence of other etiologies causing the lesions (infection, neoplasm).

The pathogenesis leading to pulmonary pathology is unknown at present due to the large variety of products available in the market. Since youth tend to inhale combusted cannabinoids concentratesin a process called "dabbing" for a fast hallucinogenic effect, the pathogenesis was linked to the vaping products[3].

Studies have shown that 80 % of vaping products associated with lung injuries contained THC and 48 out of 51 specimens obtained during bronchoalveolar lavage contained Vitamin E acetate that is used as diluent[3]. It became apparent that when Vitamin E acetate is heated and aerosolized, it can produce ketones that, when inhaled, can irritate the airways leading to an inflammatory cascade[3].

Sujith V. Cherian et al. identified most cases of e-cig-

arette lung injury in young males ages 19-27 years. 16% of patients were under 18 years. Those patients presented clinically with respiratory and gastrointestinal symptoms. The cardinal gastrointestinal presentation was nausea and abdominal pain. The prominent respiratory symptoms were shortness of breath, cough, and pleuritic chest pain. Some patients exhibited constitutional signs such as fevers and chills. The majority of the patients were tachypneic and tachycardic and some progressed to respiratory failure with hypoxia with oxygen saturation below 88% requiring mechanical ventilation. Chest radiographsoften showed bilateral hazy or consolidative opacities and computerized tomography images were significant for ground glass and consolidative opacities located in the lower-lobes. Some cases that present with acute respiratory distress syndrome show dense consolidation in the lung bases, other cases present with diffuse patchy and confluent consolidative opacities as seen in cryptogenic organized pneumonia or with upper lobe ground glass opacities and air trapping patterns commonly seen in hypersensitivity pneumonitis.

Thakrar et. al. reported that both nicotine and cannabis electronic cigarettes were related to acute respiratory sickness. Bronchoalveolar lavage was completed in nine of twelve teenage patients with e-cigarette or vaping product use-associated lung injury (EVALI), which uncovered lipid-laden macrophages (pulmonary foam cells, or phagocytes with fat deposits) and preeminent neutrophils (acute inflammatory cells). 100% had ground glass opacities (lung tissue thickening and filling of air spaces, worse in lower lobes), 92% had ground glass nodules, or focal densities, in the center of the secondary pulmonary lobule, and 75% had nonaffected areas between the pleura, or lung membrane, and the body wall. 75% also had lymphadenopathy, 50% had thickened bronchial walls, and another 50% had small pleural effusions, or excess fluid between pleural layers. This appears similar to lung damage from toxic inspiration. Five patients testified to use of cannabis and nicotine, five described nicotine use only, and two reported cannabis use only. The patients in the study reported both systemic and respiratory complaints, such as nausea or vomiting, cough, shortness of breath, chest pain, and abdominal pain. Fever, malaise, and muscle aches have also been noted. An increased white blood cell count was found in nine of the patients (blood count was not drawn in one patient), lactate dehydrogenase (a marker of tissue damage) was high in ten of the patients (not done in two patients), and C-reactive protein (inflammatory marker) was elevated in all of the patients.

As the public has been utilizing electronic cigarettes for more than fifteen years, EVALI presents a serious problem as it resembles findings in chronic smokers with weakened gas exchange. The findings are also analogous to diffuse alveolar damage, seen in early phases of acute respiratory distress syndrome, a type of respiratory failure, and acute interstitial pneumonitis[2].

In a study by Bisconti et. al. 29 male patients diagnosed with primary spontaneous pneumothorax were enrolled. Two lung samples were taken from each individual, though four patients had bilateral operations, totaling 33 procedures(wedge resections of blebs and lung apicectomy and pleurodesis). Of the 29 patients, 21 patients (72.4%) had a history of tobacco and cannabis smoking, two patients (7%) smoked cannabis only, three patients (10.3%) smoked tobacco only and three patients (10.3%) did not smoke tobacco or cannabis[7]. The patients admitted to smoking hours prior to the onset of the pneumothorax. The goal was to detect cannabinoids in the lungs of those who smoke marijuanathat present with histological findings consistent with endoalveolar accumulation of pigmented macrophages (desquamative interstitial pneumonia like reaction). Those with primary spontaneous pneumothorax who either did not smoke or reported smoking only tobacco were control subjects. As a result of the study, "spontaneous pneumothorax secondary to marijuana" was recommended to become a new diagnostic classification. 100% of specimens, including the control group, had bullous and/or vesicular emphysema (expanded alveoli), 84.8% had pleural interstitial fibrosis (lung tissue scarring), and 63.6% had chronic, generalized inflammation[7]. However, a desquamative interstitial pneumonia-like reaction, which is rare and due to macrophage deposits, was typical of eight patients who admitted to smoking cannabis, and one patient who admitted to smoking only tobacco. Morris et. al. similarly established pigmented macrophages in the lungs of those with a history of marijuana smoking at autopsy, considered to be dose-dependent as well[8] Out of the 33 procedures in the study, 22 specimens tested positive for tetrahydrocannabinol (THC), cannabinol (CBN), and cannabidiol (CBD), and only 19 of those associated with these specimens recounted smoking marijuana[7]. A previous study discovered that smoking both cannabis and tobacco profoundly escalated the chance of developing primary spontaneous pneumothorax, in contrast to those who never smoked and those who smoked only tobacco products[9]. Marijuana forms bullae, or air pockets, in the lungs, and multiple mechanisms have been proposed, including high pressure/ barotrauma from protracted inhalation, toxic substances working directly on the lung, and a reduction in lung elasticity due to inflammatory mediators. Wu et al. claimed that marijuana causes accumulation of three times more tar in the lungs than tobacco[10]. Interestingly, in two of the subjects who had undergone bilateral lung biopsies, quitting smoking after the first operation affected a modest decline in the desquamative interstitial pneumonia-like reaction and reversion to a collection of histiocytes, or macrophage precursors, rather than the full phagocytic macrophage form, suggesting improvement[7].

Hancox and Sears, in their study, mentioned that in an observational study of 8932 subjects with cannabis use disorders, cannabis use was correlated with a higher possibility of pneumonia, asthma, and COPD when compared to non-cannabis users, regardless of tobacco using status[11]. They also cited a propensity to greater airway resistance and total lung capacity in marijuana smokers[12]. In a different paper, the deterioration of lung function that parallels the dose of tobacco smoking did not apply to marijuana, with 5-20 joint years showing FEV1 (amount of air exhaled in one second) course equal or surpassed to that of non-smokers, yet more than 20 joint years of marijuana smoking caused significant damage. Also, smokers using cannabis have a greater chance of obtaining COPD diagnosis due to elevated FVC (forced vital capacity, volume of exhaled air) values, meaning smaller FEV1/FVC ratio, a ratio which is decreased in obstructive lung disease due to air trapping in the lungs[13]. A Scottish study remarked on a 0.3% growth in the occurrence of COPD for each joint year of marijuana smoking[14]. However, because most people who smoke marijuana also smoke tobacco, noted over 80% in one study, the collective outcome is difficult

to control[12].

The diagnosis of these cases is of exclusion. An evaluation should include various respiratory pathogens including COVID-19 virus. Respiratory viral panel, urine antigen testing for streptococci and legionella, sputum and blood cultures, and serology for fungi are imperative. Bronchoscopy may be required and a thorough history of vaping taken.

Blount et. al. observed that in a sample of 51 confirmed and probable EVALI patients, vitamin E acetate was distinguished in bronchoalveolar-lavage (BAL) fluid in 48 of 51 patients with lung injury (94%). One patient also had coconut oil in the BAL fluid and another patient a diluent terpene without vitamin E acetate or THC detected. The two EVALI patients whose BAL samples were negative for toxic substances were classified as probable, rather than confirmed, EVALI cases. These samples were compared to those of 99 healthy participants consisting of nonsmokers, those who smoked tobacco cigarettes, and those who used nicotine-containing e-cigarettes. Interestingly, in the well group, 5.1% were found to have THC in BAL fluid whereas 25.6% had positive urine THC testing[15]. In the non-EVALI subjects, none of the BAL samples were positive for the priority toxicants tested, including vitamin E acetate, plant oils, medium chain triglyceride oil, coconut oil, petroleum distillates, and diluent terpenes. Of the EVALI patients, 77% purportedly used THC products, 67% claimed to use nicotine products, and 51% reportedly used both products. Out of 47 EVALI patients tested for THC, 40, or 85%, had measurable THC or related metabolites. 9 of 11 subjects who denied using THC were discovered to have THC or THC metabolites in their BAL fluid[15]. Meanwhile, of those who admitted to using THC, 47 of 50 had THC or its metabolites exposed in BAL fluid. The amount of use and duration of time between last use of vaping or e-cigarette products and onset of symptoms were not established. Of note, pure THC oil has a thickness likened to vitamin E acetate. Vitamin E-acetate has been revealed in THC vaping substances, however, to the date of the study, none was found in nicotine products by the FDA (nicotine products usually have a thinner liquid consistency). Vitamin E acetate is a congealing substance placed in illegal marijuana vapes and electronic cigarettes. It can enter lung surfactant to arrange itself among phospholipids. This can cause the surfactant to convert from a gel to a liquid crystalline, which would instigate respiratory failure due to inability to preserve surface tension. Heating vitamin E acetate can also create ketene, a pulmonary irritant. EVALI cases were initially reported in August 2019, and vitamin E acetate was reported to emerge in vaping and e-cigarette liquids in late 2018 or early 2019. This study was published in February 2020[15].

Most of the research conducted on e-cigarettes and its impact on the users' health was done in the general population. The prevalence of smoking among individuals who have mental illness is about 70% higher than for those without[15]. As we observed in the cases presented, the patients also had mental illness such as anxiety and depression. The Cummings et al. study compared e- cigarette use in individuals with mental illness to those without mental illness.

A national, large scale survey demonstrated that people diagnosed with mental health conditions, including anxiety, depression, and other categories, were more likely to have tried e-cigarettes (14.8%) than those without such diagnoses (6.6%), and they were also more likely to have used medications intended for quitting smoking (52.2% versus 31.1%), in addition to a higher probably of utilizing multiple cessation aids[16]. Those with mental health conditions presently smoking were also more vulnerable to prospective e-cigarette use than those currently smoking without such diagnoses (over 60% versus 45%. 40% of those in the survey with psychiatric afflictions smoking cigarettes at the time claimed to have tried e-cigarettes, compared to 28.7% of those smoking without mental health burden. Quitting smoking was the second highest reason by percentage for consuming e-cigarettes, at 55.2%, superseded only by the reason of "just because" at 68.9%[16]. Therefore, this may reflect misperception of e-cigarettes as a means to stop smoking tobacco cigarettes, and may also mirror the proclivity to use smoking cessation devices in those with mental infirmity. The number of smokers is estimated to be about 70% more for those with psychiatric disorders than for those without. Other substance use disorders tend to be highly comorbid with smoking, at 64%, with 45% of those with mood disorders smoking, and 38% of those with anxiety disorders smoking. Psychiatric patients use about one third to one half of all cigarettes retailed nationally. As Williams et. al. called this population a tobacco-disparity group in 2013, this highlights the need for more studies targeting this specific group and a need for more focused treatment here[17]. As e-cigarettes are often marketed for smoking termination, yet they tend to be more of a smoking substitution, those with mental health conditions are affected more so by these claims than those without. In the 2012 survey, 3111 participants reported currently smoking, 3676 were previously smoking, and 3254 never smoked more than 100 lifetime cigarettes. 27.8% of subjects classified as presently smoking and 26% of those who last smoked within the past year identified themselves as having a mental condition, whereas only 13.4% of those who never smoked and 16.4% who last smoked more than one year ago identified themselves as having psychiatric illness[16].

Conclusion

Initially introduced as the safer alternative to cigarettes, the advent of the E-cigarette or vape product has drastically changed the landscape of tobacco and THC consumption. This particular delivery system allows vendors to manipulate flavors, THC/nicotine content and additives without much standardization across products. The variable options and the "safe" marketing have made these products particularly popular with adolescent population and have exposed this very vulnerable population to new pathology related to these products. Researchers are currently focusing on establishing diagnostic criteria and prognostic factors to help the medical community better understand the effects of these products, initially focusing on the possible additives found in these products such as Vitamin E acetate and the systemic damage it can cause in users. Unfortunately, as the sample size of the user's increases, it is becoming more important to study how these products affect physiologic function as a whole. There appears to be some difference between patients who use exclusively THC, THC and nicotine, or exclusively nicotine products. There is a need for additional research with an increased sample size in order to further elucidate these differences in the general population. Some of the findings that have been

suggested can range from vague changes such as generalized inflammation of the lung tissue to interstitial fibrosis typically seen in chronic long-term smokers. There is also a believed combined effect noted in users who combine THC and nicotine, which can lead to an increased incidence of spontaneous pleural effusions. There is potential to correlate the severity of these symptoms by monitoring the changes in the FVC, and the FEV1/FEC ratios that can have a prognostic effect, but these findings have not been confirmed on a large scale. Another potential complication with further research is the difficulty in quantifying the actual amount of use per each patient, as the contents of the vaping mixtures are not standardized across the board. It is an imperative recommendation for more extensive and larger sample research moving forward to further elaborate on the differences and nuances among these findings to help physicians intervene and educate their patients prior to severe, irreversible damage.

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