

E-cigarette or vaping product use associated lung injury in the time of COVID-19: A clinical dilemma

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Abstract

AIM: To report on the clinical, laboratory and radiological findings of adolescents who presented during the SARS-CoV-2 surge with symptoms of COVID-19, did not test positive for the infection and were diagnosed with e-cigarette and vaping product use associated lung injury (EVALI). Methods: A retrospective review of 12 cases of EVALI admitted to the Bristol Meyers Squibb Children's Hospital between February 2020 and June 2020 was conducted. Results: The ages of the patients ranged from 14 to 19 years. There were 6 males and 6 females. Three patients had a past history of anxiety, depression or other psychiatric/mental health disorder, nine had prolonged coagulation profile (PT,PTT and/or INR) and eleven had elevated inflammatory markers. Eleven needed respiratory support. All 12 were negative for SARS-CoV-2 PCR. Four were tested for IgG Antibodies and were negative. As these cases were admitted to rule out COVID infection, initial treatment included hydroxychloroquine. Steroids were started only after SARS-CoV-2 PCR was shown to be negative. Urine THC was positive in all cases. CXR and CT findings showed ground glass opacities. CONCLUSIONS: Clinical and radiological features are similar in both EVALI and SARS-CoV-2 infection. Inflammatory markers are elevated in both conditions. A detailed social and substance use history in patients presenting with 'typical' COVID pneumonia like illness is important. EVALI should be ruled in early to start the appropriate treatment. Given the ongoing pandemic, pediatricians and other health care providers need to be aware of other conditions that can masquerade as SARS-CoV-2.

E-cigarette or Vaping product use Associated Lung Injury (EVALI) in the time of COVID-19: A clinical dilemma

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Introduction

“Vaping” is the process in which liquid substances such as nicotine or Tetrahydrocannabinol (THC) are heated in a device and the aerosolized particles are inhaled. Several devices are available on the market with

the most common being e-cigarettes and vaping pens¹. The substances used in vaping pods can contain additives to aid in aerosolization and flavoring to increase marketability to adolescents². One of the most common additives is Vitamin E acetate which in combination with THC has been shown to cause increased inflammation and alveolar damage leading to E-cigarette or Vaping product use Associated Lung Injury (EVALI)³. EVALI was first described in 2019 and as of January 14, 2020 according to the CDC data, there have been 2668 hospitalized patients and 68 deaths caused by EVALI. Of these hospitalized patients, 66% were male. 82% of patients reported using THC containing products and 33% reported sole use of THC products.⁴

Although no specific tests or markers are available for the diagnosis of EVALI, there are certain characteristic presenting features. Patients present with an acute respiratory illness (cough, shortness of breath and/or chest pain), constitutional symptoms (fever, chills) and/or gastrointestinal symptoms (abdominal pain, nausea, vomiting, and diarrhea) in addition to a positive history of e-cigarette or vaping use.^{3,5} These symptoms are non-specific and can be due by other respiratory viruses causing pneumonia thus making EVALI a diagnosis of exclusion.

Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, was first discovered at the end of 2019 in Wuhan, China. The first reported cases in the United States were in January 2020 and its rapid spread was labeled a pandemic by the World Health Organization in February⁶. The symptoms of COVID-19 in children are very similar to EVALI and include fever, cough, shortness of breath and gastrointestinal symptoms like abdominal pain, vomiting, diarrhea and nausea.^{7,8},

At the Bristol Meyers Squibb Children's Hospital located in Central New Jersey, coincident with the surge of the COVID-19 pandemic in New Jersey, we noted a 6-fold increase in the number of EVALI cases from March 2020 to June 2020, compared to the 1 year period prior to the start of the COVID surge. We present a series of twelve patients initially suspected to have COVID-19 pneumonia but were subsequently diagnosed with EVALI. We describe the diagnostic dilemma that we were initially presented with.

Table 1 describes the demographics, clinical findings, laboratory findings, and respiratory support for each patient.

Two cases (Cases #2 and #4) were chosen from the series of 12 to highlight the overlapping features between EVALI and COVID. This study was approved by the Rutgers-Robert Wood Johnson Medical School Institutional Research Board.

DEMOGRAPHICS ,PAST MEDICAL HISTORY AND LABORATORY FINDINGS

A retrospective review of 12 cases of EVALI admitted to the Bristol Meyers Squibb Children's Hospital between March 2020 and June 2020 was conducted. The ages of the patients ranged from 14 to 19 years. There were 6 males and 6 females. Three patients had a past history of anxiety, depression or other psychiatric/mental health disorder, nine had prolonged coagulation profile (PT, PTT and/or INR) and eleven had elevated inflammatory markers. Only three patients needed an ICU admission for respiratory support, while eight patients received respiratory support on the floor.

Case 2

A 17 year old male with history of Attention Deficit Hyperactivity Disorder presented with fever (to a maximum of 102.7F) and shortness of breath for 5 along with 3 weeks of cough, congestion and rhinorrhea. He was previously treated with 2 days of amoxicillin by his primary care doctor. Vital signs upon presentation to the ED were temperature of 100.4, Pulse rate of 142 beats per min. Respiratory rate of 22 breaths per minute a blood pressure of 126/70 and pulse oximetry showed a room air saturation of 91% . Chest x-ray showed bibasilar infiltrates and CT scan showed multifocal opacities throughout the lung. There were no known COVID-19 exposures. He admitted to vaping every other day for a year with occasional using Tetrahydrocannabinol (THC) vaping pen. Infectious workup was significant for a negative nasopharyngeal swab for SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) , a negative Respiratory viral panel (RT PCR) test, a positive mycoplasma IgM but the confirmatory Immunofluorescent assay later

reported negative. Laboratory workup was revealing for elevated Prothrombin time (PT) 21.3 sec, Partial Thromboplastin Time (PTT) 40 sec and international normalized ratio (INR) 1.86 sec, Procalcitonin 0.37 mg/mL, D-Dimer 1115 ng/mL and Ferritin 529 ng/m(normal values in Table 1 footnotes). Hydroxychloroquine was initially started for presumed COVID-19 infection and the patient received 2 doses, before COVID-19 test results were available. Once COVID was ruled out on hospital day 2, Methylprednisolone was started to treat the EVALI. Five days of Azithromycin and 1 day of Levofloxacin were used as well to treat a possible mycoplasma infection. Vitamin K was used to treat the coagulopathy. During his 6 day hospital stay a maximum of 4L nasal cannula at 30 percent FiO2 was required and he was weaned to room air on hospital day 5.

Case 4

A 17 year-old male with depression, and history of illicit drug use was transferred to our hospital from an outside institution due to worsening respiratory distress. He initially presented with 10 days of fever and harsh, dry cough. Patient has a history of vaping nicotine and THC multiple times a day for past 5 years. He was prescribed azithromycin for community acquired pneumonia by Urgent Care prior to presentation to our hospital. Symptoms continued to worsen, and the patient presented to emergency room with increased respiratory rate and hypoxemia, with pulse oximetry reading of 84% on room air. Chest x-ray showed bilateral interstitial opacities, elevated fibrinogen >1000 mg/dL, D-dimer 2457 ng/mL C-reactive protein (CRP) 35.6 mg/dL and erythrocyte sedimentation rate (ESR) 83 mm/hr . Hydroxychloroquine was given for 2 days for presumed COVID-19 pneumonia. This was discontinued when multiple nasopharyngeal SARS-CoV-2 RT-PCR tests returned negative. At the outside hospital, his respiratory support escalated to a maximum requirement of nasal cannula 55L, and FiO2 of 50% and upon transfer, he was intubated for respiratory failure. Repeat Nasopharyngeal SARS CoV-2 RT-PCR testing, which was again negative. Methylprednisolone was started to treat the EVALI. He was extubated on hospital day 12 and was discharged with no supplemental oxygen on hospital day 19.

Discussion

This case series describes twelve pediatric patients with EVALI who presented during the COVID-19 pandemic surge in New Jersey. All patients presented with clinical, laboratory and/or radiological findings that raised suspicion of COVID-19 but subsequently tested negative for COVID-19 by RT-PCR nasopharyngeal swab, in some cases multiple times(Cases# 9,10). According to the CDC, confirmed cases of EVALI have history of e-cigarette use 90 days prior to presentation, pulmonary infiltrates on CXR or CT scan, absence of pulmonary infection at initial presentation either by culture or respiratory viral panel, no alternate plausible diagnosis⁹.Our patients reported vaping anywhere from 3 months to 5 years prior to admission. All but one of our patients(Case #8) fit the CDC definition of EVALI.

It is possible that some of the patients had COVID-19 but their tests were false negatives, either due to the sensitivities in the RT-PCR test or errors in collecting the sample.^{17,18} However, many of the patients were tested multiple times and remained negative making the diagnosis of COVID pneumonia much less likely. Additionally, cases 10,11 and 12 had SARS-COV-2 IgG antibody testing done, which was also negative, however the antibody was done within a week of presentation. Antibody testing was not available when the cases 1-9 presented. However SARS-COV-2 IgG antibody was negative in case#8 six weeks after onset of symptoms.

Studies describing the clinical features of EVALI and COVID-19 in pediatric patients are relatively recent. Both EVALI and COVID-19 pediatric patients can present with fever, cough, shortness of breath and chest pain¹⁰⁻¹². Both can also present with nonspecific gastrointestinal symptoms such as abdominal pain, nausea vomiting and diarrhea ⁵. We are not aware of any studies that have compared the clinical presentation of these two entities in children.

Radiological findings in EVALI pediatric patients can show diffuse bilateral symmetric ground-glass lung opacities, consolidation and a lower lobe predominance on CT.¹³. While the data on pediatric COVID-19 CT imaging is scarce, a large study in the adult population by Bernheim et.al. described that the

typical COVID-19 CT scan would show “bilateral and peripheral ground-glass and consolidative pulmonary opacities” however many patients had CT scans that lacked all or some of those features^{14,15}. Radiological features are not specific to these conditions and there are no specific features to distinguish EVALI from COVID-19 on chest imaging. Figure 2 shows CT images of a 19 year old patient who was admitted with EVALI and a 21 year old male who was admitted at the same time with COVID pneumonia.

Laboratory findings in both COVID-19 and EVALI can show elevated liver function tests, inflammatory markers such as ferritin, d-dimer, C-reactive protein, and procalcitonin and coagulopathy¹⁶⁻¹⁸. Coagulation abnormalities and inflammatory dysregulation have been described in both EVALI and COVID-19. Khanijo and colleagues described elevated inflammatory markers such as CPR, ESR and procalcitonin in their series of 24 patients with EVALI. Hematological, biochemical, inflammatory and immune marker abnormalities have been described in COVID-19 and they are used for risk stratification in the disease¹⁹. All patients in our series demonstrated abnormalities in coagulation profile.

Lymphopenia has been described as a feature of COVID-19.²⁰ This has not been described in EVALI and could be a helpful distinguishing feature between the two conditions. None of our patients had lymphopenia. However, in pediatric COVID-19 cases only a small proportion of patients exhibit Lymphopenia.²¹

In our series, patients who presented early in the COVID surge were started on Hydroxychloroquine, which was the recommendation at that time⁷. Many of these patients were tested multiple times (up to 3 times) and were treated with therapies aimed at treating COVID-19 such as Hydroxychloroquine. Early in the surge steroids were contraindicated in patients with COVID-19 and were therefore withheld till results became available. Only after a thorough history uncovered vaping use and other causes of pneumonia ruled out was treatment with steroids begun, generally on hospital day 2 or 3, depending on when the results of COVID testing were available. The currently recommended treatment of EVALI includes use of dexamethasone²² with several studies showing short term benefit including decreasing mortality rates. Steroids were contraindicated for the treatment of COVID early in the pandemic however recent emerging data are supporting the use of steroids.

There are several factors that have been implicated in the higher susceptibility of smokers and vapers to COVID-19. Vaping causes increased mucosal permeability and impaired muco-ciliary clearance, which is the first line of defense²³. Additionally, smokers are shown to have a higher surface expression of ACE2 receptors, which is the binding site for SARS-CoV2²⁴.

It is possible that due to the shelter in place order in our area with schools and workplaces closed during the pandemic surge, adolescents are finding more opportunities to vape beyond the reach of principals and teachers⁹. This is likely exacerbated by the fact that those who vape are more likely to have underlying anxiety and depression and isolation has been shown to cause increased stress and depression^{25,26} Four of the 12 patients in this series had an underlying mental health diagnosis.

Given the commonalities in presentations, but differences in treatments between the two relatively new diseases, COVID-19 and EVALI, it remains crucial to elicit a detailed social and substance use history in patients presenting with ‘typical’ COVID pneumonia like illness. Given the ongoing pandemic, Pediatricians and other health care providers need to be aware of other conditions that can masquerade as SARS-CoV-2.

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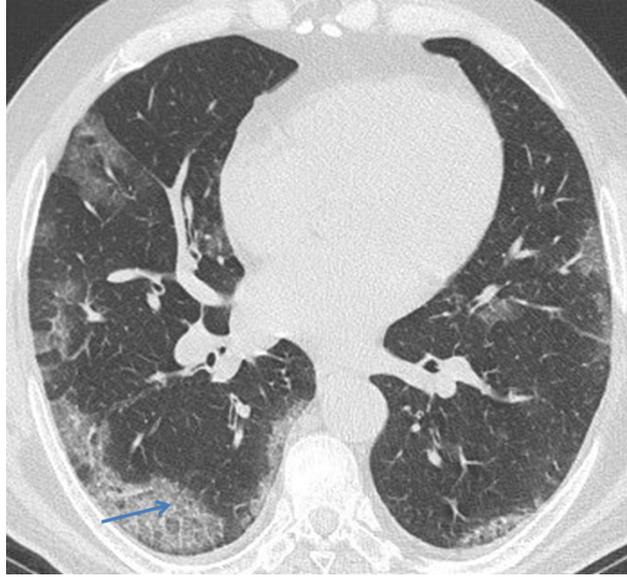
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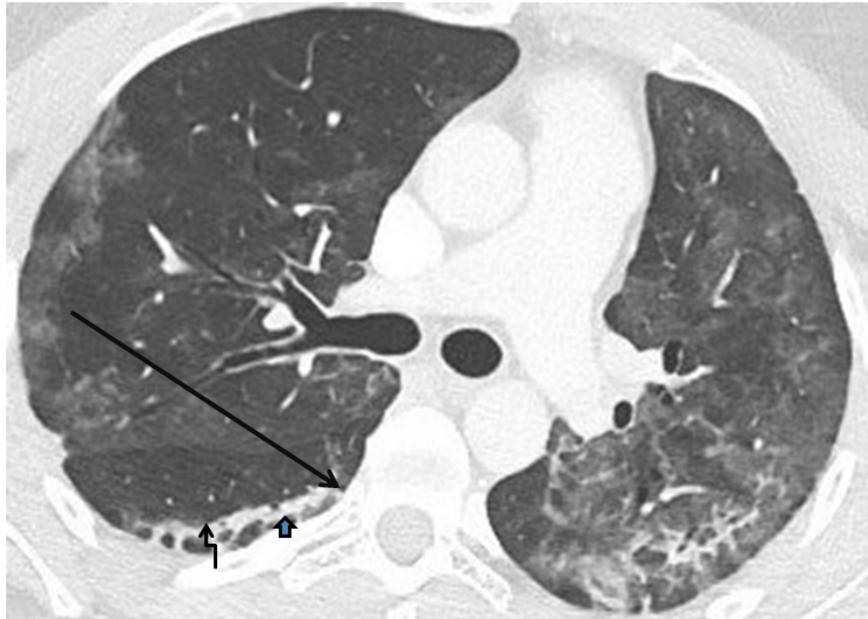
DH-Evali Cases Table 6.23.20 (Daniel Helfgott).docx available at <https://authorea.com/users/347898/articles/473401-e-cigarette-or-vaping-product-use-associated-lung-injury-in-the-time-of-covid-19-a-clinical-dilemma>

19 year old with EVALI



Axial 1mm thick image shows peripheral, bilateral, symmetrical mid lung zone ground glass opacities. Right lower lobe subpleural crazy paving pattern (arrow)

21 year old with COVID pneumonia



1 mm thin axial image through the level of the carina shows multifocal ground glass opacities in the upper lungs. In the lower lobes there are parallel linear band (arrow) with subpleural sparing (arrow head) and peribular bands (curved arrow).