# E-cigarette or Vaping-Associated Acute Lung Injury and Hemophagocytic Lymphohistiocytosis

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abstract

In this report, we describe the case of a 17-year-old boy with progressive respiratory failure requiring extracorporeal support who met clinical criteria for a presumptive diagnosis of electronic cigarette or vaping-associated acute lung injury (EVALI), with clinical, pathologic, and laboratory evidence of hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS). The patient in our report had a history of tetrahydrocannabinol and nicotine electronic cigarette use for months leading up to his presentation of fever, headache, emesis, and weight loss with respiratory distress. Multiple potential diagnoses were explored, and the patient's respiratory status improved, and he was initially discharged from the hospital. Roughly one week later, the patient was readmitted for worsening respiratory distress. The patient then met sufficient criteria for a potential diagnosis of HLH and MAS (elevated ferritin level, inflammatory markers, and cytopenia) to warrant a bone marrow aspirate, which revealed rare hemophagocytic cells. Given the severity of his symptoms and laboratory evidence of HLH and MAS, the patient was started on a course of steroids and anakinra. Although laboratory markers improved after treatment, the patient's respiratory failure worsened, ultimately progressing to a need for mechanical ventilation and extracorporeal support and leading to worsening multiorgan system failure and, ultimately, death. To the best of our knowledge, this is the first report of a patient with a presumptive diagnosis of EVALI with evidence of HLH and MAS, raising the possibility that macrophage activation may play a role in the pathogenesis of EVALI.

Electronic cigarette (e-cigarette) use, or vaping, has been associated with inhalational and/or chemical acute lung injury. An estimated 1479 lung injury cases associated with the use of e-cigarette products have been reported to the Center for Disease Control and Prevention in the United States, and 33 deaths have been confirmed in 24 states.[1] Since the first reported association between the use of e-cigarettes and pulmonary illness in a 20-year-old male sailor in 2014,[2] multiple case reports and case series have appeared (see Table 1). Established criteria for the diagnosis of acute lung injury associated with e-cigarette use are awaited, although a surveillance definition for probable and confirmed cases was reported by the Center for Disease Control and Prevention in August 2019.[3–6] Acute respiratory distress syndrome (ARDS) has been reported, and associated pathologic findings seen in patients with vaping-induced lung injury include acute eosinophilic pneumonia, lipoid pneumonia, diffuse alveolar

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damage, diffuse alveolar hemorrhage, hypersensitivity pneumonitis, and rare giant cell interstitial pneumonitis. The majority of patients who vaped and became ill used nicotine products combined with tetrahydrocannabinol- or cannabidiol-containing products. An association of vaping with injury or involvement of other organ systems has not been reported. We report here a case of electronic cigarette or vaping-associated acute lung injury (EVALI) that had a number of characteristics consistent with hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which, to our knowledge, has not been described previously.

**TABLE 1** Summary of Studies on Vaping-Induced Lung Injury

| Study Name | Male Sex, % | Median Age | No. Patients | Mortality, *n* (%) | $Pao_2/Fio_2$ Ratio | Mechanical Ventilation, % | Hospital Length of Stay |
|---|---|---|---|---|---|---|---|
| Layden et al[3] | 83 | 19 y | 53 | 1 (1.8) | 189 (9 patients) | 32 | 6 d |
| Maddock et al[5] | 83 | 24 y | 6 | 0 (0) | N/A | 16 | N/A |
| Triantafyllou et al[6] | 100 | N/A | 6 | 0 (0) | N/A | 33 | 8 d |

N/A, not applicable.

## CASE DESCRIPTION

A 17-year-old white male patient was admitted to the hospital with persistent emesis, an inability to tolerate oral intake, weight loss, headache, and intermittent fevers (maximum temperature: 39.5°C). The patient endorsed a history of marijuana and nicotine vaping, including daily marijuana and e-cigarette use.

A complete blood count and the results of a basic metabolic panel were within normal limits. A cerebrospinal fluid (CSF) examination, sent for persistent headache, revealed 1 white blood cell per μL, a protein level of 19 mg/dL, and a glucose level of 74 mg/dL. Results of bacterial CSF cultures and a CSF viral encephalitis panel were negative, including for enterovirus. He had mild splenomegaly on an abdominal ultrasound.

On hospital days 3 and 4, he was noted to be tachypneic and hypoxemic, with crackles heard on auscultation. A chest radiograph revealed diffuse bilateral interstitial opacities. Azithromycin was started for presumed pneumonia. Respiratory distress and hypoxemia worsened, and he was transferred to the PICU with acute hypoxemic respiratory failure requiring high-flow nasal cannula (HFNC) at 20 L/minute and 100% oxygen. Ceftriaxone and trimethoprim-sulfamethoxazole (TMP-SMX) to treat *Pneumocystis jiroveci* pneumonia (PJP) were added. A chest computed tomography (CT) scan done on hospital day 6 revealed diffuse ground-glass opacities, mediastinal and hilar adenopathy, and splenomegaly. The lactate dehydrogenase level was elevated at 591 U/L, the CD4 count was low at 250 cells per μL (HIV test results nonreactive), the C4 level was low at 15 mg/dL, the ferritin level was elevated at 753 ng/mL, the fibrinogen level was elevated at 752 mg/dL, the C-reactive protein level was elevated at 9.5 mg/dL, and the erythrocyte sedimentation rate was elevated at 64 mm/hour. An infectious etiology was not found. The differential diagnosis at that time included other systemic illnesses, such as iatrogenic and/or systemic autoimmune disorders, or hematologic process. Given symptom improvement with TMP-SMX treatment, however, PJP was at the top of the differential diagnosis, although vaping-related acute lung injury could not be excluded. He was discharged from the hospital on hospital day 11 with a plan to complete a TMP-SMX course for presumed PJP and did not receive steroids.

Nine days later, he returned with a presyncopal event in the presence of persistent fever (maximum temperature 39.8°C) and headache. He was readmitted to the PICU. He denied interval drug use, including e-cigarette use. On readmission, he was tachycardic to 110 beats per minute and was stable on room air with an oxygen saturation of 100%. His respiratory status deteriorated rapidly, and support was quickly escalated to HFNC on hospital day 1 for hypoxemic respiratory failure.

An extensive investigation to identify infectious, autoimmune, and oncologic causes of the patient's respiratory failure and persistent fever was undertaken. An echocardiogram did not reveal an intracardiac shunt. A chest CT scan was performed (see Fig 1), which revealed decreased intensity but increased area of ground-glass opacities of the bilateral upper lobes, residual mild reticular opacities in the anterior portions of the upper lobes, unchanged ground-glass opacity in the lingula, diffuse ground-glass opacity, and interstitial thickening in both lower lobes (overall improved but more diffuse than before) extending to the periphery. Mediastinal lymph nodes, the largest measuring at 9 to 10 mm in short axis, were unchanged, as was bilateral mild hilar lymphadenopathy.

A bronchoscopy with bronchoalveolar lavage (BAL) and an open-lung biopsy was performed on hospital day 8. A pathology assessment of the lung biopsy specimen revealed acute and organizing diffuse alveolar damage with squamous metaplasia. BAL fluid demonstrated reactive bronchial cells, alveolar macrophages, inflammation, and red blood cells. Oil Red O staining on BAL fluid revealed cytoplasmic lipid accumulation in a few scattered

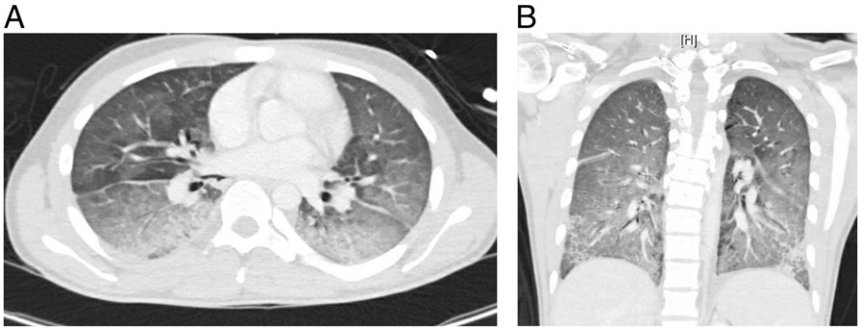


**FIGURE 1**
A and B, Axial and coronal images of chest CT scan revealing diffuse ground-glass opacities.

macrophages, consistent with previous reports of EVALI. Stains were negative for bacterial and fungal organisms. Immunohistochemical stains were negative for Epstein-Barr virus, cytomegalovirus, herpes simplex virus, and acid-fast bacilli. CD68 PG-M1 immunostaining was also performed, with no evidence of hemophagocytosis. The results of a respiratory viral pathogen panel were negative. The patient received empiric ceftriaxone on admission, pending blood culture results, and coverage was broadened to vancomycin and cefepime given a worsening clinical status. He completed a 14-day course of TMP-SMX for PJP, although there was no evidence found of PJP on the biopsy specimen, on polymerase chain reaction, or on β-D glucan testing. Cefepime was continued for a 10-day course for clinical sepsis.

The patient was noted to have pancytopenia on hospital day 4, with a white blood cell count of 1900 cells per μL, a hemoglobin level of 10.5 g/dL, and a platelet count of 107 000 cells per μL. The peripheral smear revealed no evidence of malignancy. The patient's CD3, CD4, and CD8 counts were all below normal limits (CD3 count: 330 cells per μL [normal range: 801–2684]; CD4 count: 215 cells per μL [normal range: 447–1682]; CD8 count: 199 cells per μL [normal range: 259–973]). B-cell counts were normal. The immunoglobulin G level was also decreased to 492 (normal range: 700–1600) mg/dL. On hospital day 5, laboratory test results were consistent with hyperferritinemic syndrome, with the ferritin level increasing to a peak of 4529 ng/mL from 846 ng/mL on admission. The triglyceride level was, however, within the normal limit.

As a result, the patient was started on a pulse steroid course on hospital day 6, with intravenous methylprednisolone at 1 g daily for 5 days followed by high-dose steroids; improvement in symptoms, cytopenia, inflammatory markers, and the ferritin level was seen. A bone marrow aspirate was performed on hospital day 8, with evidence of rare hemophagocytic cells on aspirate smears (see Fig 2). Further testing for HLH and MAS was performed. The soluble interleukin-2 receptor level was at the upper limit of normal (827 μ/mL; normal range: 137–838) but was drawn after 3 days of treatment with high-dose steroids. Natural killer cell cytotoxicity expressed as lytic units was low (2.2 U; normal range: >2.6) but was also measured after initiating steroids. CD107a expression was below normal range (mean channel fluorescence: 181; normal range: 257–678). However, perforin testing could not be performed simultaneously. Results of the patient's 21-gene familial HLH genetic panel were negative (Invitae Corporation, San Francisco, CA). Given the laboratory test results and bone marrow aspirate findings, the patient was started on intravenous anakinra at 1 mg/kg per dose intravenously every 6 hours for presumed HLH and MAS on hospital day 11; further improvement in inflammatory markers and the ferritin level was seen, but his respiratory status continued to worsen. Anakinra was subsequently discontinued on hospital day 17 because of a lack of further clinical response and concern for the possibility of anakinra-related lung injury.

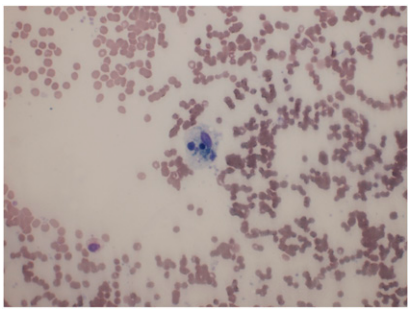

**FIGURE 2**
Bone marrow biopsy specimen revealing histiocyte engulfing a few erythrocytes and hemosiderin pigment, a finding that can be seen in hemophagocytosis.

The patient continued to be persistently hypoxemic despite escalation of HFNC respiratory support (see Figs 3 for chest radiograph) (Fig 4). Notably, he demonstrated striking positional changes in oxygen saturation. On hospital day 15, he was intubated and placed on mechanical ventilation. Initial ventilator settings were tidal volume 340 mL (~6 mL/kg), positive end-expiratory pressure 15 cm $H_2O$, respiratory rate 22 breaths per minute, and 100% fraction of inspired oxygen ($F_{IO_2}$) with inhaled nitric oxide at 20 ppm. The oxygenation index (OI) after intubation was 35.9 (mean airway pressure, 23 cm $H_2O$; $F_{IO_2}$, 100%; $Pa_{O_2}$, 64 mm Hg; $Pa_{O_2}/F_{IO_2}$ ratio of 64), supporting a diagnosis of severe ARDS. His oxygenation improved initially to an OI of 10.2, and his peak pressures decreased to 25 cm $H_2O$. He remained profoundly hypoxemic. A

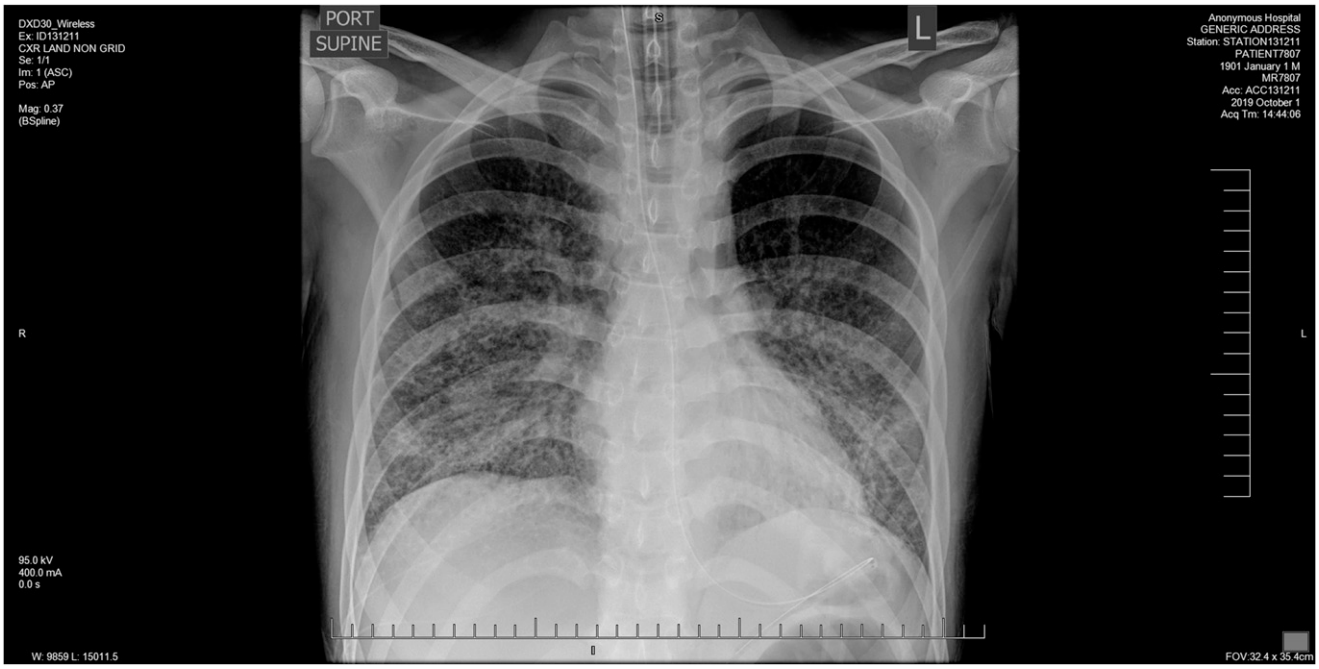


**FIGURE 3**
Preintubation chest radiograph.

bronchoscopy was repeated on hospital day 16, and no endobronchial lesions, significant secretions, bleeding, or mucous plugs were found.

On hospital day 17, the oxygen saturations were 85% on 100% $F_{IO_2}$, with an OI of 37.7 and a $Pa_{O_2}/F_{IO_2}$ ratio of 53 on maximal tolerated ventilator settings. He was cannulated to venovenous extracorporeal membrane oxygenation (ECMO) to permit lung rest, minimize barotrauma, and maximize chances for lung recovery.

While the patient remained on ECMO support, sedation was weaned, and the patient was extubated to HFNC on hospital day 18. He became agitated within 3 hours after extubation and had cardiac arrest necessitating cardiopulmonary resuscitation for 2 minutes before the return of spontaneous circulation. The patient was reintubated and placed on mechanical ventilation at ECMO rest settings. An echocardiogram at that time revealed decreased left ventricular systolic function, and milrinone infusion was initiated. The patient suffered a second bradycardic cardiopulmonary arrest 8 hours later. Transition to venoarterial ECMO was not successful, and return of spontaneous circulation could not be obtained. The patient died on hospital day 18. The case was accepted and the autopsy was performed by the Office of the Chief Medical Examiner of New York.

## DISCUSSION

E-cigarettes are battery-powered devices that allow users to inhale aerosolized substances. E-cigarette aerosol generally contains fewer toxic chemicals than conventional cigarette smoke. However, e-cigarette aerosol has substances known to have adverse health effects, including ultrafine particles, heavy metals, volatile organic compounds, and other harmful ingredients. Products containing tetrahydrocannabinol are commonly delivered by e-cigarettes. Of persons who vaped and became ill, 80% reported having used both nicotine and tetrahydrocannabinol or cannabidiol products. E-cigarette–related pulmonary illness has been described in multiple studies.[3–6]

This is the first report, to our knowledge, relating a case of EVALI to a syndrome consistent with HLH and MAS. Reports of vaping-associated pulmonary illness have demonstrated a spectrum of presentations ranging from mild self-resolving illness to severe ARDS and death.[3] Our patient had progressive acute hypoxemic respiratory failure with severe ARDS that continued to worsen despite ECMO support. In their report, Layden et al[3] describe 53 patients with pulmonary illness related to e-cigarette use: 32% required intubation and mechanical ventilation, 9% developed ARDS, and 2 required ECMO support. There was 1 death. The patient who died in their report had a prolonged illness that also initially improved to the point of being discharged from the hospital, only to be readmitted shortly thereafter with progressive respiratory failure and ARDS requiring intubation and mechanical ventilation a week after hospitalization, similar to our patient's clinical course. This suggests a biphasic clinical course of the e-cigarette–associated pulmonary illness, with the second phase being more severe. Early use of high-dose

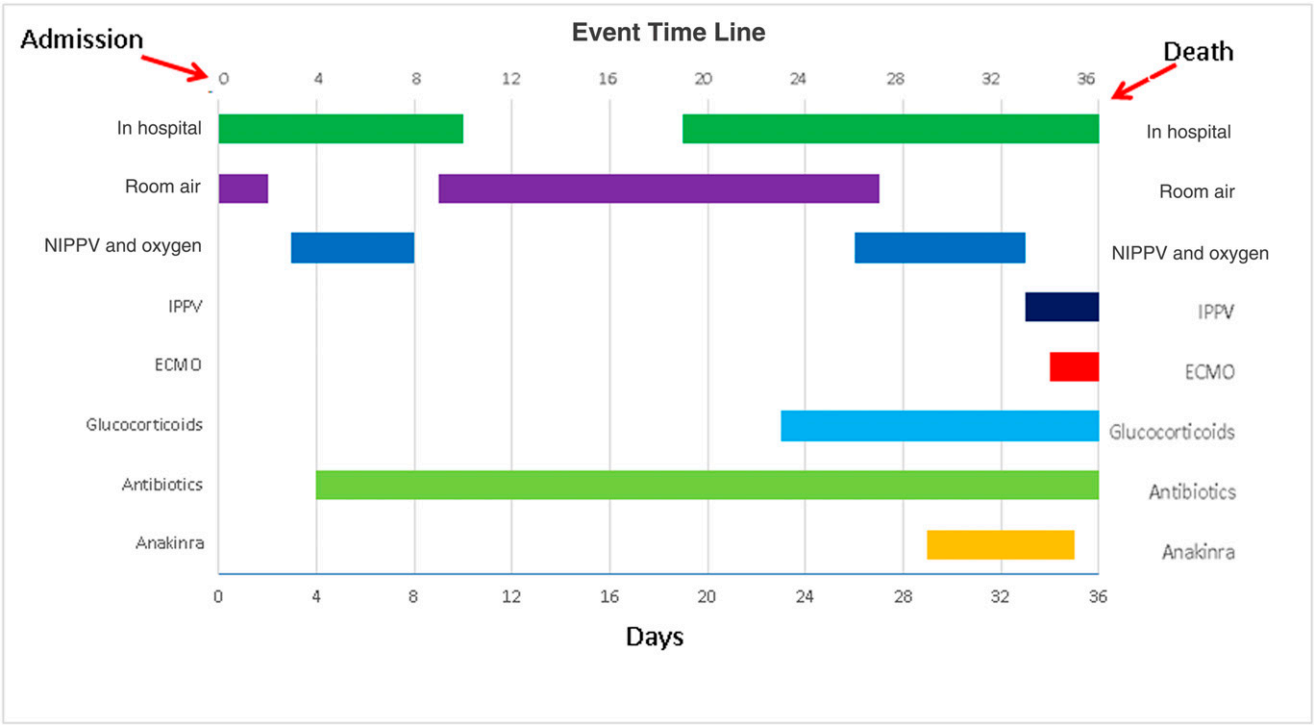


**FIGURE 4**
Summary of patient's course of illness. IPPV, invasive positive pressure ventilation; NIPPV, noninvasive positive pressure ventilation.

steroids has been reported and is presumably associated with positive outcomes.[3,7] Ultimately, our patient succumbed to progressive multisystem organ failure, as evidenced by myocardial dysfunction with depressed left ventricular function and HLH and MAS.

Reported findings of vaping-induced lung injury include organizing pneumonia and/or diffuse alveolar damage, fibroblast plugs, hyaline membranes, fibrinous exudates, type 2 pneumocyte hyperplasia, and interstitial organization.[8]

HLH is a syndrome of immune system activation that is either inherited (primary HLH) or acquired secondary HLH and MAS.[9,10] Familial HLH typically presents in early childhood, whereas secondary HLH and MAS is often triggered by another disease process. Both the diagnostic criteria and treatment options are evolving as more is learned about the pathophysiology of HLH and MAS.[10,11] Additionally, anakinra has emerged as a potential first-line therapy for severe HLH and MAS.[10,11] This patient met 6 of the 8 diagnostic criteria from the HLH 2004 trial, consistent with the diagnosis.[9] He had fever, organomegaly, cytopenia, hemophagocytosis in the bone marrow, low natural killer cell activity, and a high ferritin level. He did not have a high triglyceride level or a significantly elevated soluble interleukin 2 level. Although therapy directed at the HLH and MAS did improve these symptoms, it did not improve his pulmonary disease.

In summary, we report a rare association between a presumptive diagnosis of EVALI and evidence of HLH and MAS.

## ABBREVIATIONS

ARDS: acute respiratory distress syndrome
BAL: bronchoalveolar lavage
CSF: cerebrospinal fluid
CT: computed tomography
e-cigarette: electronic cigarette
ECMO: extracorporeal membrane oxygenation
EVALI: electronic cigarette or vaping-associated acute lung injury
$F_{IO_2}$: fraction of inspired oxygen
HFNC: high-flow nasal cannula
HLH: hemophagocytic lymphohistiocytosis
MAS: macrophage activation syndrome
OI: oxygenation index
PJP: *Pneumocystis jiroveci* pneumonia
TMP-SMX: trimethoprim-sulfamethoxazole

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