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Vaping-associated illness: a reassessment

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Abstract

Background In 2019, there was widespread presentation of respiratory distress as well as other organ system involvement in patients with a history of vaping. There continue to be reports of vaping-associated illness (VAI). This has come to be known as e-cigarette and vaping product associated lung injury (EVALI). The mechanism of injury remains unclear.

Objectives This study reexamines the clinical characteristics of patients affected by vaping and suggests that lung injury may not be the primary organ dysfunction but be part of a larger systemic illness.

Methods This is a retrospective chart review of all patients presenting to one hospital identified as having vaping-associated illness

Results Fourteen patients were identified ranging in age from 15 to 33 years. Patients had a broad range of clinical severity. Respiratory symptoms occurred in 64%, gastrointestinal symptoms in 57%, fever in 78%, neurological symptoms in 15% and other constitutional symptoms in 50%. 35% presented with no respiratory symptoms.

Conclusion While the lungs are certainly involved in vaping-associated illness, recognizing the extent of involvement of other organ systems may provide insight into the pathophysiology of the disease. Providers should be aware that vaping-associated illness presents with a multitude of symptoms outside of lung injury, such as abdominal pain, headache or even fever.

Keywords Vaping, E-cigarette, Abdominal pain, Lung injury

Background

In mid to late 2019, physicians noted a cluster of patients who presented with lung injury associated with use of electronic cigarettes, or vaping. This was reported by the CDC [1] and very quickly investigators in numerous states echoed the finding [2]. Initial reports describing the outbreak were published shortly thereafter [3–5]. Subsequently, additional case reports and series confirmed this cluster and focused on lung injury as the feature of the illness associated with vaping [6–10]. For example, while Blagev et al. noted that constitutional symptoms were present in their patients with lung injury, their conclusion, "Lung injury associated with e-cigarettes or vaping remains a clinical diagnosis with symptoms that overlap infectious and other lung diseases," focused on the pulmonary symptoms [7]. This is logical given the plausible mechanism of injury of irritants or contaminants inhaled into the lungs. Blount et al. detected vitamin E acetate in bronchoalveolar lavage fluid in patient with EVALI [11]. They hypothesized that the interaction of phosphatidylcholine with tocopherol could interfere with surfactant function or alternatively heating vitamin E acetate could create the reactive compound ketene which is a potential irritant [11]. However, investigators also noted that while lung injury was the most easily observed feature of the cluster of illness associated with vaping, it was not the exclusive feature. Numerous patients presented with abdominal pain as a primary complaint with lung injury noted incidentally during the course of work up for abdominal pain. This

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vaping-associated illness epidemic was then eclipsed by the Covid-19 pandemic. The purpose of this case series is to reexamine the clinical features of the patients who presented with vaping associated illness at our institution.

Methods

Patients who were seen in the emergency department with symptoms consistent with vaping associated illness covering a period from May 1, 2019 until September 9, 2019 were identified from provider recollection. Additionally, the medical records were searched for ICD 10 codes J68.0, J68.9, J69.1, J80, and U07.0. These codes correspond with bronchitis and pneumonitis due to chemicals, gases, fumes and vapours; unspecified respiratory condition due to chemicals, gases, fumes and vapours; pneumonitis due to inhalation of oils and essences; acute respiratory distress syndrome; and vaping-related disorder, respectively. A total of 15 patients were identified based on the above search criteria and 14 patients were included for analysis who met criteria for confirmed or probable EVALI [4]. Data was collated from the electronic medical record and abstracted using a data collection table. The Institutional Review Board for this hospital approved this study without patient consent for retrospective chart review since no personally identifiable information was recorded.

Results

Primary data are listed in Tables 1, 2, and 3. Of the 14 patients identified, ages ranged from 15 to 33 years (mean of 21.1 years), and nine (64%) were male. All patients admitted to a history of vaping among whom 10 (71%) admitted to using tetrahydrocannabinol (THC) or had a urine drug screen during the visit positive for THC. Admissions to the hospital occurred in 11 patients (78%) with a length of stay ranging from 2 to 11 days with a mean of 5.2 days. Respiratory support was provided for eight patients (57%) ranging from simple nasal cannula (six patients, 43%), high flow cannula (one patient, 7%), and endotracheal intubation (one patient, 7%).

Presenting symptoms included respiratory symptoms (cough, shortness of breath, chest pain) (nine patients, 64%); gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhea) (eight patients, 57%); fever (11 patients, 78%); neurological symptoms (headache; two patients, 15%) and other constitutional symptoms (malaise, fatigue, weight loss, musculoskeletal pain; seven patients, 50%). Five patients had respiratory symptoms but not gastrointestinal (36%). Four patients had gastrointestinal symptoms but not respiratory (28%). One patient (7%) had an initial complaint of fever but neither respiratory nor gastrointestinal symptoms. All patients had some form of imaging (chest xray and/or chest CT) that showed pulmonary infiltrates (mostly basilar). Five patients (36%) had abdomino-pelvic imaging (abdominal xray or ultrasound or CT) but no patient who had abdominal imaging showed any obvious pathology in the abdomen or pelvis. All patients who had measurement of inflammatory markers showed some elevation: Total WBC mean 16.0 X 1000 (range 8.6—27) (normal 4.5—10.5), ESR mean 89 mm/hr (range 54—136) (normal 0—20), CRP mean 242 mg/L (range 105—338) (normal less than 10), procalcitonin mean 0.35 ng/mL (range 0.07—0.72) (normal less than 0.50). Elevation of transaminases was also observed in 11 patients (78%). Albumin level was decreased in 12 patients (86%).

Infectious work up was generally negative including blood cultures, sputum cultures, respiratory pathogen panel (RPP) (included multiplex PCR testing for adenovirus, B pertussis, coronavirus (but not SARS-CoV2), influenza, parainfluenza, metapneumovirus, respiratory syncytial virus, enterovirus / rhinovirus, Mycoplasma pneumonia, chlamydia pneumonia), urine Legionella antigen. However, two patients were positive for Mycoplasma IgM and IgG; one patient was positive for Legionella antibody and Mycoplasma IgM and IgG; one patient was positive for Legionella antibody and Mycoplasma IgG.

Antibiotics were at least initially started on 13 patients (93%). Antibiotics included ceftriaxone, azithromycin, vancomycin, levofloxacin, clarithromycin, amoxicillin with clavulanic acid, doxycycline, cefixime. Nine patients (64%) were treated with steroids. There was no mortality in this case series.

Discussion

Although vaping products have been available for years and are also used world-wide, there was a sudden appearance of vaping associated illness in the United States in the fall of 2019. This has come to be known as EVALI, e-cigarette and vaping product associated lung injury, but the etiology and pathophysiology is still to be determined. While lung injury is part of the case definition, lung injury is often accompanied by and may be eclipsed in severity by other symptoms such as abdominal pain and vomiting. In fact, in this series lung injury was occasionally discovered as an incidental finding in the course of exploring other symptoms. Additionally, this case series demonstrates that there is a wide range of severity of lung injury from incidental findings in patients presenting with other complaints and not requiring inpatient admission to respiratory failure requiring endotracheal intubation and mechanical ventilation. While systemic symptoms have been noted previously [4, 12–14], identifying vaping associated illness as specifically vaping

Table 1 Patient demographics and presenting symptoms

Patient	Age (years)	Sex	Diagnosis	Vaping	Fever	Presenting symptoms	Duration of symptoms	Number of ER visits	History of asthma or other respiratory disease	THC use	Drug screen result
A	15	F	bibasilar pneumonia	yes	yes	fever, abdominal pain, nausea, vomiting	3 days	1	none	yes	n/a
B	16	M	fever	yes	yes	fever	10 days	3			n/a
C	17	M	bibasilar pneumonia	yes	no	cough, fever, chest pain	7 days	2			n/a
E	17	F	bilateral pneumonia	yes	yes	fever, joint pain, abdominal pain, nausea, difficulty breathing, tachypnea	3 days	1	RAD		n/a
F	17	M	bilateral pneumonia	yes	no	cough, fever, diarrhea, difficulty breathing, nausea, vomiting	5 days	1			n/a
G	18	M	bibasilar pneumonia	yes	yes	nausea, vomiting, diarrhea, back pain, abd pain	9 days	3		yes	THC
H	20	M	bilateral pneumonia	yes	yes	abd pain, vomiting	5 days	2		yes	THC
O	20	F	pneumonia, pharyngitis	yes	no	fever, cough, chest pain, body aches, sore throat		1		yes	
I	20	F	gastroenteritis, pneumonia	yes	yes	vomiting, diarrhea, cough	5 days	1		yes	THC
J	21	M	bilateral pneumonia	yes	yes	fever, malaise, cough, headache, shortness of breath	4 days	1			THC
K	24	M	pneumonia	yes	yes	fever, malaise, shortness of breath	5 days	1 (+1 urgent care)		yes	THC
L	25	M	bilateral pneumonia	yes	yes	weakness, fever, weight loss, cough, abdominal pain	14 days	1		yes	
M	32	F	bilateral pneumonia, hypoxemia	yes	yes	cough, fever, shortness of breath, headache	4 days	1 (+1 urgent care)	asthma, chronic sinusitis	yes	
N	33	M	IBD, SIRS, pneumonia, hypoxemia	yes	yes	malaise, weight loss, nausea, fever	3 months	1			THC

Table 2 Imaging and laboratory results

Patient	Age (years)	Sex	Imaging modality	Imaging findings	Negative infectious findings	Positive infectious findings	WBC count	CRP	ESR	Procalcitonin	Lactate	Blood culture	Sputum culture	Other findings	Other results	AST	ALT	Albumin
A	15	F	abd CT, CXR, chest CT	bibasilar infiltrates	RPP, urine Legionella, Mycoplasma pneumonia IgM (IFA)	Legionella antibody, Mycoplasma pneumonia IgM, IgG	14.7	219	113		n/a	no growth	n/a		RF neg	55	76	2.4
B	16	M	CXR, chest CT	bilateral pulmonary infiltrates	urine Legionella, mycoplasma IgM, HIV, RPP, Lyme, West Nile	Legionella antibody, Mycoplasma pneumonia IgG	20.6	334	106		n/a	no growth	n/a	IgE 1935	RF neg	80	NE	2.1
C	17	M	CXR, chest CT	bibasilar infiltrates	RPP, strep		10.9	272	n/a		n/a	n/a	n/a			133	123	2.4
E	17	F	CXR, abd u/s	bilateral interstitial infiltrates R > L	RPP, urine legionella, Mycoplasma pneumonia IgM (IFA), monospot, ANA, RF	Mycoplasma pneumonia IgM and IgG	11.4	263	136		n/a	no growth	n/a			40	NE	2.1
F	17	M	CXR, chest CT	diffuse bilateral groundglass opacities with peripheral sparing	RPP		12.3	183	77		n/a	n/a	n/a			NE	NE	3.1
G	18	M	abd CT, CXR, chest CT, abd u/s	groundglass opacities with centrilobular nodules	RPP, urine Legionella, hepatitis panel		17.2	252	98		n/a	no growth	n/a			166	129	2.1
H	20	M	CXR, abd CT, chest CT	bilateral basilar groundglass opacities	RPP, urine Legionella, Lyme, Ehrlichia, Mycoplasma pneumonia IFA, HIV	Mycoplasma pneumonia IgM and IgG	24	290	81		513	coag neg staph; repeat no growth	NG			39	NE	2.3
O	20	F	CXR	patchy infiltrate R lung base	RPP, strep, monospot, EBV IgM	EBV IgG	10.1	105				no growth	n/a			10	17	3.7

Table 2 (continued)

Patient	Age (years)	Sex	Imaging modality	Imaging findings	Negative infectious findings	Positive infectious findings	WBC count	CRP	ESR	Procalcitonin	Lactate	Blood culture	Sputum culture	Other findings	Other results	AST	ALT	Albumin
I	20	F	CXR, chest CT	bilateral reticular infiltrates	RPP, urine Legionella		20.7	165	80		n/a	no growth				NE	NE	2.6
J	21	M	CXR, chest CT	bilateral lower lobe consolidations	RPP, HIV		8.6	338	67	0.16	1.3	no growth	n/a			NE	62	3.1
K	24	M	CXR, chest CT, abd u/s	extensive bilateral ground glass infiltrates, mediastinal lymphadenopathy	RPP		17	261	66	0.72	2	no growth	n/a			214	333	2.8
L	25	M	CXR, chest CT	extensive bilateral consolidation with lower lobe predilection	RPP, urine Legionella, hepatitis panel		14.9	229	90	0.07	1.3	no growth	n/a			NE	66	3.3
M	32	F	CXR, chest CT	extensive bilateral airspace consolidation	RPP, urine Legionella		27	292	103	0.16	0.9	no growth	BAL neg CX, AFB, fungal	ANA, RF neg		45	NE	2.2
N	33	M	CXR, chest CT	bilateral groundglass opacities most pronounced lung bases	RPP		14.9	181	54	0.65	1.9	no growth	n/a			38	NE	3

Table 3 Clinical course and treatment

Patient	Age (years)	Sex	Was patient admitted?	Hospital length of stay	Respiratory support required	Antibiotics	Steroids?	Comments
A	15	F	yes	9 days	nasal cannula 3 LPM	ceftriaxone, azithromycin, vancomycin; doxycycline, cefixime	no	infiltrate was incidental
B	16	M	yes	7 days	nasal cannula 1.5 LPM	Augmentin, azithromycin, ceftriaxone	no	
C	17	M	no			clarithromycin	no	works around pools, chlorine
E	17	F	yes	4 days	nasal cannula	ceftriaxone, azithromycin	no	history of irritable bowel syndrome
F	17	M	no			clarithromycin	yes	
G	18	M	yes	3 days		azithromycin	yes	admitted for abd pain, had endoscopy
H	20	M	yes	7 days	high flow	azithromycin, vancomycin	yes	
O	20	F	no			azithromycin	no	
I	20	F	yes	7 days	nasal cannula	azithromycin	yes	
J	21	M	yes	2 days	n/a	ceftriaxone, azithromycin	yes	
K	24	M	yes	3 days	nasal cannula 3 L	levofloxacin, ceftriaxone, azithromycin	yes	
L	25	M	yes	2 days			yes	
M	32	F	yes	11 days	intubated	azithromycin, ceftriaxone, doxycycline	yes	
N	33	M	yes	2 days	nasal cannula	azithromycin, ceftriaxone	yes	

associated lung injury downplays the contribution of other systems in the manifestation of this illness. While direct injury to the lungs from something that is inhaled would make sense from a mechanistic point of view, the extrapulmonary symptoms challenge this model.

There are multiple etiologies that could explain the association of both pulmonary and extrapulmonary symptoms. Abdominal symptoms in vaping associated illness could be secondary to a primary lung injury as may be seen with abdominal pain that is associated with pneumonia. Not only can pneumonia be accompanied by abdominal pain in children but acute abdominal pain may be the presenting symptom in children with pneumonia [15]. Mesenteric lymphadenopathy has been observed to correlate with abdominal pain in some pediatric patients with pneumonia [16]. Alternatively, lung injury could be secondary to a more systemic etiology such as absorption of a toxin. Vitamin E acetate may contribute to the pathogenesis of EVALI by converting to ketene gas [17]. A different study found an association with the age of the coil used for vaping with lung injury in a mouse model [18]. Nicotine intoxication causes cholinergic symptoms which may result in nausea, vomiting, diarrhea and respiratory difficulty [19]. Systemic symptoms could be secondary to activation of the inflammatory cascade. This can be seen in cytokine storm which has been associated with non-infectious as well as infectious etiologies such as Covid-19 [20]. Cytokine storm can manifest with low albumin level that would be consistent with capillary leak [20–22]. Hypoalbuminemia was seen in 12 of 14 patients in this series. COVID-19 can result in nausea, vomiting, diarrhea and abdominal pain in addition to respiratory symptoms [23]. EVALI was also found to associated with hemophagocytic lymphohistiocytosis [24]. While symptoms of EVALI overlap with symptoms of COVID-19 [25, 26], the pathogenesis of multiple system involvement may be very different for the two diseases. COVID-19 is mediated by the spike protein of the virus binding to ACE2 receptors which are expressed in multiple tissues including lung and intestine [23]. Multiple organ dysfunction syndrome has also been described in reaction to multiple etiologies, infectious and non-infectious [27]. Systemic symptoms could reflect a generalized hypersensitivity reaction. Allergic reactions commonly present with rash and difficulty breathing but more severe reactions may also involve gastrointestinal, cardiovascular and neurologic components [28]. Hypersensitivity reaction has been previously reported in association with vaping [9, 29]. In this series, one patient displayed markedly elevated IgE level that could be consistent with hypersensitivity reaction. The high percentage of THC use seen in patients with vaping associated

illness could explain gastrointestinal symptoms similar to cannabis hyperemesis syndrome [30].

Further, part of the case definition of EVALI is that there is no other infectious cause identified. However, there could be a primary lung injury from vaping with accompanying secondary superinfection [31]. The infectious work up detected four patients in our cohort who had positive serology for Mycoplasma IgM and / or IgG. All of these patients were negative for Mycoplasma IgM IFA. Additionally, two patients also tested positive for Legionella serology. A diagnosis of Legionnaires' disease was not confirmed because these patients tested negative for Legionella urinary antigen. The urinary antigen test is considered to have higher sensitivity and specificity than serological testing [32, 33]. No nucleic acid based testing for Legionella was done in this series of patients. Although there was not any infectious etiology consistently identified in all or most cases, this does not rule out the possibility of a novel virus or other pathogen that has not yet been described in this cohort.

The large percentage of patients identified in this review who presented without respiratory symptoms suggests that lung injury is not the primary mechanism of injury in vaping-associated illness but rather one of several potential organ systems that may be affected.

Limitations

During the time interval examined there was no specific ICD 10 code for vaping associated illness so it is possible that some patients may have been excluded from this series. Although the symptoms associated with vaping resemble the spectrum of symptoms that may be seen with cytokine storm, no specific cytokines were measured in this patient population. While multiplex PCR was performed to attempt to identify possible infectious etiology to explain the symptoms, it is possible that next generation sequencing might have revealed a common infectious etiology. It does not seem that other investigators performed a systematic search to rule out viral etiology such as examination of tissues samples by electron microscopy or attempts to isolate virions through physicochemical means. Thus, the possibility of a secondary infectious contributor to the symptoms associated with vaping cannot be completely ruled out.

Conclusions

Cases of illness associated with vaping peaked during the summer of 2019 but continue to occur sporadically. The name EVALI focuses attention on injury to the lung only and implies a direct causal relationship. The term EVALI may be remain useful when the area of interest is specifically lung disease. However, illness associated with vaping often involves multiple extrapulmonary systems and the mechanism of injury may reflect an indirect cause such as systemic cytokine storm. For these reasons, this author favors a more encompassing term such as vaping associated illness (VAI). This shift in focus would encourage practitioners to include VAI in the differential when evaluating patients with a broad array of symptoms from respiratory distress to abdominal pain and vomiting to headache to fever to malaise. This should also keep VAI in the differential even though fewer cases are being reported since triggering of this reaction might be higher with certain ingredients of vaping fluid but could still potentially occur even when the fluid is reformulated. Lastly, although VAI could explain a broad range of symptoms associated with vaping, it remains a diagnosis of exclusion and infectious etiology, including Covid-19, should still be ruled out.

Article summary

Why is this topic important? Despite fears regarding the safety of vaping, people continue to vape and cases of vaping-associated illness continue to be reported. Understanding the presentation of mechanism of vaping-associated illness is important to be able to provide quality patient care.

What does this study attempt to show? This study reexamines the variety of clinical presentation of vaping-associated illness and attempts to gain insight into the underlying pathophysiology of the illness.

What are the key findings? 64% of patient with vaping-associated illness presented with respiratory symptoms but an almost equal number, 57%, presented with gastrointestinal symptoms and one patient had a complaint of fever with neither respiratory nor gastrointestinal symptoms.

How is patient care impacted? Providers should not identify vaping-associated illness with respiratory symptoms exclusively but keep in mind that vaping can present with a wide range of complaints and affect multiple organ systems.

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Author's contributions

J.S. conceived of the study, acquired and interpreted the data, drafted the manuscript, approved the submitted version and is personally accountable for the accuracy and integrity of the work.

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Availability of data and materials
All data can be found in the included tables.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The Institutional Review Board for this hospital, Western Institutional Review Board, approved this study without patient consent for retrospective chart review since no personally identifiable information was recorded. The author certifies that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.
Written informed consent was not obtained from subjects or parent or legal guardian due to the retrospective nature of the data collection and informed consent was not required by the institutional review board.

Consent for publication
Not applicable as per above.

Competing interests
The authors declare no competing interests.

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