Archives of Disease in Childhood

Life-threatening hypersensitivity pneumonitis secondary to e-cigarettes

Journal:	<i>Archives of Disease in Childhood</i>
Manuscript ID	archdischild-2019-317889.R1
Article Type:	Short report
Date Submitted by the Author:	18-Sep-2019
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Keywords:	General Paediatrics, Respiratory, Adolescent Health

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Title: Life-threatening hypersensitivity pneumonitis secondary to e-cigarettes

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Keywords:

Hypersensitivity pneumonitis, e-cigarettes, respiratory failure, vaping, enzyme-linked immunosorbent assay (ELISA), tobacco

Word count (excluding title page, abstract, references, figures and tables): 1416

Confidential: For Review Only

Abstract:

We report a case of hypersensitivity pneumonitis in a young person secondary to vaping. He presented with a putative diagnosis of asthma and required Extracorporeal Membrane Oxygenation (ECMO) because of intractable respiratory failure. He developed a critical illness and steroid myopathy and required prolonged rehabilitation. Our patient fulfils diagnostic criteria for hypersensitivity pneumonitis (HP) secondary to e-cigarettes with a positive exposure history, deterioration after skin prick testing, specific serum IgM antibodies against the implicated liquid raising the possibility that the relevant antigen was present in that liquid and radiological and histopathological features compatible with acute HP. There are two learning points. The first is always to consider a reaction to e-cigarettes in someone presenting with an atypical respiratory illness. The second is that we consider e-cigarettes as 'much safer than tobacco' at our peril.

Introduction:

Hypersensitivity Pneumonitis (HP) is an immune mediated reaction that follows the inhalation of antigens or chemicals and mainly affects the alveoli, interstitium and bronchioles. There are two main categories of HP: Acute/inflammatory and Chronic/fibrotic (1). Putative antigen triggers are diverse and the list is ever increasing. Pathogenesis is attributed to a combination of type III (immune complex-mediated) and type IV (delayed) hypersensitivity reactions. Though any environment with sufficient amount of antigen can cause HP, there is evidence that a second hit such as viral infection or endotoxin exposure may be needed to induce the disease.

Flavoured e-cigarettes liquids contain airway irritants and toxicants such as propylene glycol (PG), vegetable glycerine (VG), and many different flavouring chemicals that have been implicated in the pathogenesis and worsening of lung diseases, and which likely induce respiratory effects not seen in tobacco smokers. Additionally thermal decomposition of PG and VG, the base constituents of e-liquids, produces reactive carbonyls, including acrolein, formaldehyde, and acetaldehyde, which have known respiratory toxicities (2). It is possible that the pulmonary manifestations associated with vaping represent a range of disease processes. What is important however that clinicians should consider the possibility of pulmonary disease associated with vaping when patients report recent use, especially when other causes are not identified as the recent epidemic highlights (3).

Case:

A previously healthy 16 year old boy presented to the emergency department with a 7 day history of fever, cough and increasing difficulty breathing despite oral antibiotics and inhaled salbutamol. There was no previous confirmed diagnosis of asthma and he was not on any regular controller treatment with inhaled corticosteroids. He deteriorated rapidly and required non-invasive, conventional and, then high frequency oscillation ventilation and finally transfer for ECMO because of intractable respiratory failure. He had 3 days of

venovenous ECMO, and treatment with broad spectrum intravenous antibiotics, intravenous hydrocortisone, a macrolide and antifungals. He was stepped down to the paediatric respiratory ward 10 days after his admission on 4 litres/minute nasal cannula oxygen, and inhaled bronchodilators and oral corticosteroids for a putative diagnosis of asthma. He developed a critical illness and steroid myopathy and required prolonged rehabilitation.

Further questioning revealed that he had recently started to use e-cigarettes fairly frequently, using two different liquids, purchased over the counter. During his convalescence he mentioned that at some point he had used both the liquids in question though was unable to recollect the exact sequence of use and in particular which one he had used immediately prior to becoming unwell. The listed ingredients of both the liquids were identical except for the un-named flavourings (see below). He had smoked cannabis a year previously but not recently. He had no recent bird or farm animal exposure or any recent travel.

The results of the investigations during his acute illness were:

- A CT chest 6 days after admission (Figure 1) showed bilateral ground glass changes in the upper and mid-zones with perihilar bronchial wall thickening and retained secretions in the dependant airways.
- Bronchoalveolar lavage (BAL) in PICU and a later expectorated sputum sample both showed moderate numbers of macrophages, neutrophils and eosinophils (20%) – consistent with active inflammation.
- First spirometry 22 days after admission showed Forced Expiratory Volume in 1 s (FEV₁) was 3.52 L, z score -1.91 and Forced Vital Capacity (FVC) 3.68 L, z score -2.73. Total Lung Capacity (Helium dilution) was 5.91 L, z score -0.82 and transfer factor, TLC_{Oc} SB [mmol/min/kPa) was 9.02, z score -0.92.
- The only evidence of infection was a nasopharyngeal aspirate positive for Rhinovirus.
- He had a raised C-reactive protein, but negative tests for autoimmune disease, vasculitis and avian precipitins.
- He had a negative skin prick test (SPT) to e-cigarettes Liquid 1 and Liquid 2 (with identical ingredients but different flavourings: 0.3 % nicotine, VG, mono-PG,

flavourings; neither had a comprehensive list of ingredients) the positive control was 5 mm; so the clinical picture was not that of IgE mediated reaction. However, this does not exclude an adverse reaction to e-cigarettes. Indeed, eight hours after SPT he deteriorated with chest tightness, difficulty breathing and widespread wheeze requiring oxygen, intravenous and nebulised salbutamol and an increased dose of oral steroids. We postulated that this exacerbation of symptoms occurred due to antigen re-exposure in the setting of his pre-existing acute HP (4) with the eliciting antigen in either or both of the E-cigarette liquids.

He was discharged home 35 days after admission with a plan to slowly taper oral steroids. This led to worsening respiratory status and he returned to the emergency department on one occasion and was admitted on other requiring intensive treatment for respiratory distress and wheeze. He was categorical that he had not used any more e-cigarettes and there were no other obvious triggers in the environment; however we did not specifically test him for any respiratory viruses and the clinical worsening was attributed to a too rapid taper of steroids. He had a repeat CT chest 44 days after presentation (Figure 1) which showed patchy areas of ground glass opacification throughout both lungs which had improved considerably since the previous scan but there were ground glass appearances in new areas including the right lower lobe.

A surgical lung biopsy was obtained 50 days after his first presentation as he continued to be symptomatic and further treatment with pulsed methylprednisolone was contemplated. The biopsy showed (Figure 1): alveolar spaces containing macrophages and evidence of haemorrhage. A few alveolar spaces lined by fibrin suggesting early hyaline membrane formation. No granulomas were identified. Of note, the lung biopsy and the CT appearances are likely to have been modified by the very significant ventilation and high doses of steroids.

The presence of an eliciting antigen in either or both of the E-cigarette liquids was further investigated by developing an in-house enzyme-linked immunosorbent assay (ELISA) to detect antibodies specific to the E-cigarette liquid constituents. Serum samples were obtained from the patient on day 50 (no serum was available for analysis of the immunological assay in the academic department prior to Day 50) and 112 days from 1st

presentation, the latter following treatment with high dose pulsed methylprednisolone and abstinence from E-cigarettes. Sera were also obtained from five healthy donors (median age 21 years old, range 20-23; 3 male and 2 female) who had never smoked tobacco or used E-cigarettes.

IgG antibodies binding to both E-cigarette liquids were detected at similar levels in all serum samples (from both the patient and the controls), suggesting the presence of cross-reactive antibodies in all individuals. As shown in Figure 1, fewer samples were positive for specific IgM antibodies and the patient had IgM specific for Liquid 1, but not Liquid 2, raising the possibility that the eliciting antigen was present in Liquid 1. Healthy control 1 also had IgM antibodies specific for Liquid 1, again suggesting the occurrence of cross-reactive antibodies in some non-exposed individuals.

Fourteen months after the initial presentation, he was asymptomatic with normal spirometry (FEV₁ 4.35 L, z score -0.65 and FVC 5.12 L, z score -0.16).

Discussion:

This previously well young person presented with a catastrophic respiratory illness. For such to be the very first presentation of asthma would be virtually unheard of.

Our patient fulfils diagnostic criteria for HP secondary to e-cigarettes. There was a positive exposure history, and importantly, deterioration after SPT. We detected serum IgM antibodies against the implicated liquid raising the possibility that the eliciting antigen was present in the vaping liquid, however we acknowledge these are not specific, being present in a control ; a previous patient had no supportive immunological evidence (5). Antibodies associated with HP are usually of IgG class, IgM class antibodies can also be involved (6).

The CT pattern was typical for acute HP with ground glass opacities predominantly in upper and middle lobes and mosaic attenuation; other features such as centrilobular diffuse micronodular pattern were not seen, likely because of previous corticosteroid therapy. The histopathology was compatible, but the pathological features of acute HP are poorly characterized because patients are rarely (if ever) biopsied. Findings include intra-alveolar fibrin, neutrophil accumulation with or without findings of acute lung injury, and possible

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2
3 small vessel vasculitis; poorly formed, non-necrotising, granulomas may be seen (4,7). Our
4 patient had evidence of inflammation (BAL and biopsy) and hyaline membrane formation
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7 Conclusions:
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10 There are two important lessons here. The first is always to consider a reaction to e-
11 cigarettes in someone presenting with an atypical respiratory illness. The second is that we
12 consider e-cigarettes as 'much safer than tobacco' at our peril.
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Figure 1: Radiology - immunology--histopathology correlation in a case of hypersensitivity pneumonitis:

Concentration of Liquid 1 specific IgM.

Concentration of Liquid 2 specific IgM.

First CT scan, day 6 from first presentation.

Second CT scan, day 44 from first presentation.

Lung biopsy showing inflammation and hyaline membrane formation

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