Life-threatening hypersensitivity pneumonitis secondary to e-cigarettes

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ABSTRACT

We report a case of hypersensitivity pneumonitis (HP) in a young person secondary to vaping. He presented with a putative diagnosis of asthma and required extracorporeal membrane oxygenation because of intractable respiratory failure. He developed a critical illness and steroid myopathy and required prolonged rehabilitation. Our patient fulfils diagnostic criteria for 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 that 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 is 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 transferred 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 L/min 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 figure 1).

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 paediatric intensive care unit (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 1s (FEV1) was 3.52 L, z score −1.91 and forced vital capacity
Figure 1  Radiology—immunology—histopathology correlation in a case of hypersensitivity pneumonitis: concentration of liquid 1 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.

(FVC) 3.68 L, z score −2.73. Total lung capacity (helium dilution) was 5.91 L, z score −0.82 and transfer factor (TLCOc 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, 8 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 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 that 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 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 first 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; three men and two women) 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. Antibodies associated with HP are usually of IgG class; IgM class antibodies can also be involved.*

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 characterised because patients are rarely (if ever) biopsied. Findings include intra-alveolar fibrin, neutrophil accumulation with or without findings of acute lung injury and possible small vessel vasculitis; poorly formed, non-necrotising, granulomas may be seen. Our patient had evidence of inflammation (BAL and biopsy) and hyaline membrane formation.

CONCLUSIONS
There are two important lessons here. 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.

Contributors NN: reviewed case notes and wrote parts of case (as indicated). MH, SG and PD: contributed to clinical management. LF and IT; consultant immunologists supervised ILC to develop the immunologic assay and wrote part of the case (as indicated). AB: professor of paediatric respirology reviewed drafts and suggested major improvements and agreed on the final draft. JMB: consultant respiratory paediatrician in charge of the patient’s respiratory care, suggested writing case report for this patient, collated contributions from the other authors, obtained images, obtained informed consent from the patient, wrote substantial parts of case (as indicated), reviewed drafts and suggested improvements and agreed on the final draft and is the corresponding author.

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