



Commentary

Lipid-Laden alveolar macrophages and vaping: Lessons from EVALI

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Widespread electronic cigarettes use, more commonly called vaping, has garnered increasing attention from clinicians, researchers, and public health officials alike. Originally intended as a smoking cessation tool, vape pens have instead become popular among young, never smokers [1]. The last decade has seen a steady rise in vape pen use among teenagers, and vaping now supersedes conventional cigarettes as the most common modality of nicotine consumption among the youth [2,3]. Realizing that a new generation of nicotine addiction is on the rise, public health officials have called for tightened regulations on vape pen sales including raising the minimum age for nicotine purchase and discontinuing flavoured vape products [4].

The public health implications of widespread vaping took on new meaning in the summer of 2019 when the first cases were reported of E-cigarette or Vape product use associated Acute Lung Injury (EVALI). Primarily described in young men, EVALI resulted in a known 2807 cases and 68 deaths in the United States [5]. Patients predominantly presented with idiopathic respiratory failure and were found to have diffuse, bilateral infiltrates on lung imaging, and negative infectious work up. A Centers for Disease Control and Prevention (CDC) investigation identified vape pen use as a unifying feature across cases, with use of tetrahydrocannabinol (THC) containing vape pens being particularly common among affected individuals. Prior to the EVALI outbreak, case reports had detailed a range of respiratory illnesses related to vape pen use including eosinophilic lung disease, diffuse alveolar hemorrhage, and non-specific acute lung injury [6]. A common feature across these multiple clinical manifestations has been the finding of lipid-laden macrophages (LLM) in the alveolar spaces of affected individuals, raising questions about the possible role of these macrophages on lung injury development and progression.

The potential role of LLM in vaping-related acute lung injury has been the subject of intense research interest since the EVALI outbreak last year. LLM, also called pulmonary foam cells, describe a class of phagocytic white blood cell that contain fatty deposits as seen on Oil

Red O staining. LLM have been described in a variety of respiratory conditions, including interstitial, medication-induced, and infectious processes [7]. Their presence in vaping-related lung injury was first noted in a case of acute lung injury in 2012, and during the 2019 EVALI outbreak over 80% of lavage samples that underwent Oil Red O staining identified LLM [6]. Whether LLM serve as a non-specific marker of lung injury, a marker of vaping or THC use, or as a pathophysiologic inflammatory agent remains to be seen.

In this issue of *EBioMedicine*, Shields et al. [8] report on the first studies evaluating the presence and potential inflammatory effects of LLM in healthy vape pen users. The authors describe a cross-sectional study of bronchoalveolar lavage samples collected from daily vape pen users, as compared to populations of never smokers and conventional cigarette users. They found that LLM were not specific to EVALI, and instead were identified in nearly all conventional cigarette users, about half of vape pen users, and rarely in the never smoker population. LLM presence in vape pen users was further associated with elevated levels of the inflammatory cytokines IL-4 and IL-10 in bronchoalveolar lavage fluid. Though the study was not designed to determine temporality or causality of the inflammatory cytokines noted in vape pen users, their work exhibits a number of strengths that should be highlighted. Firstly, this work represents the largest known bronchoscopy study ($n = 64$) evaluating the presence of LLM in healthy populations. Further, this study builds on a growing body of scientific knowledge demonstrating an association between vape aerosol exposure and inflammation at the alveolar level. Lastly, through careful history taking and confirmatory urinary testing, this study was able to identify populations of patients without concurrent THC exposure for subgroup analysis, thereby excluding THC exposure as a potential confounder, and highlighting vape pen use itself as a likely contributor to lung inflammation.

The work by Shields, et al. builds on our understanding of vape pen aerosols as a pro-inflammatory agent on respiratory epithelium. The elevated inflammatory cytokines seen in vape pen users is in keeping with prior work demonstrating elevated neutrophil elastase and metalloproteases in the airway epithelium [9], and altered transcriptomes of alveolar macrophages of healthy individuals exposed to vape aerosols [10]. The study by Shields, et al. additionally highlights LLM as a nonspecific marker of vape pen and cigarette smoke exposure, and not necessarily a pathognomonic feature as had originally been suspected, suggesting that alveolar inflammation arises through a parallel process to LLM development.

Despite assurances that vaping presents a safer alternative to conventional cigarettes for nicotine consumption, increasing evidence

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points to the potential harms of vape pen use on respiratory health. The public health balance favouring vaping as a risk reduction tool for smokers has now been counterbalanced by uptake of vaping among young, never smokers, and mounting evidence of the inflammatory impact of vape aerosols on the respiratory tract. Additional research is warranted to better characterize the impact of vape aerosols on respiratory health so that responsible, and timely, public health action can be taken.

Author contributions

The author confirms sole responsibility for conception, literature review, and manuscript preparation.

Declaration of Competing Interest

Dr. Jonas reports personal fees from Dawnlight, Inc, outside the submitted work.

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