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Reply to McCarthy *et al.*

From the Authors:

Despite a decline in reported e-cigarette– or vaping-associated lung injury (EVALI) cases within the United States, the underlying cause for EVALI's severe and debilitating respiratory failure affecting more than 2,600 individuals remains poorly understood. Our case report uniquely highlights an adolescent female patient presenting with bilateral crazy-paving on chest imaging (1). In the cell block preparation of the BAL, we observed extracellular granular to globular proteinaceous material that was periodic acid–Schiff positive and diastase resistant. We further validated these findings with electron microscopy (EM) and demonstrated lamellar bodies, which represent surfactant (2–5). These findings are most consistent with secondary pulmonary alveolar proteinosis (PAP) after EVALI. Our case highlights the heterogeneity of presentations as well as one of the many different subgroups of susceptible cohorts.

We appreciate McCarthy and colleagues' reading of the case as well as their comments demonstrating the global impact of EVALI despite most reported cases being in the United States. We agree with McCarthy's assessment that Oil-Red-O–stained macrophages are not specific and not diagnostic for secondary PAP, as it can be seen in multiple forms of lung injury (6). The topic of Oil-Red-O staining has been the centerfold of much EVALI debate and remains a nonspecific finding adding to the complexity of its diagnosis. We also agree with McCarthy and colleagues that future autoantibody testing for GM-CSF (granulocyte–macrophage colony–stimulating factor) is warranted in this patient because autoimmune PAP cannot be excluded without this testing. However, we disagree with most of the additional comments highlighted below.

Specifically, it is highly unlikely for infection or lung injury alone to be the primary cause for the radiologic, cytologic, and, in particular, EM findings (2). BAL fluid and blood cultures were performed early in the patient's presentation. BAL can sterilize quickly (7); however, the patient was unlikely to have bacterial pneumonia because she did not respond to antibiotics and had no growth on BAL or blood cultures. Furthermore, chest imaging demonstrated bilateral and diffuse interstitial opacities, which are more consistent with viral, mycoplasma, or pneumocystic pneumonitis, but mycoplasma, *Pneumocystis*, and viral PCR on BAL were all negative, making infection highly unlikely. BAL cell block preparations in acute and resolving pneumonia usually show more abundant neutrophils and macrophages. The pink amorphous material associated with these conditions is composed predominantly of fibrin and would not show lamellar bodies on EM (3). In addition, acute lung injury likely did play a role in this patient's presentation, but our case contrasts starkly from prior radiologic and cytologic findings of EVALI case reports, as highlighted in our initial report (1, 6).

Most importantly, we take significant concern to the authors' statement that making a diagnosis of secondary PAP by BAL and computed tomography is "not the current best practice." In a review of prior literature, the diagnosis of PAP can safely and precisely be done without lung biopsy (4, 8). In our case, lung biopsy was considered, but the risk of worsening the patient's already tenuous respiratory status outweighed the benefit of a tissue specimen when a diagnosis could be made with cytologic samples (3, 5).

Lastly, the response to steroids highlights the importance of treating the underlying etiology contributing to secondary PAP. In addition to cartridge cessation, steroids have assisted in recovery in those hospitalized with suspected or confirmed EVALI (6). We postulate that this case may be different from other EVALI presentations either because of an underlying genetic predisposition or heavy metal toxicity, such as silica, present in the e-cigarette cartridge or delivery system (9). Silica is not common to all e-cigarette cartridges but is a known cause of secondary PAP. Relevant to future U.S. Food and Drug Administration regulations on e-cigarette products, consideration should be taken in screening for heavy metals in e-liquids or subsequent aerosolized byproducts.

In conclusion, the letter from McCarthy and colleagues highlights the lack of specificity of Oil-Red-O staining in EVALI cases. The culmination of bilateral and diffuse crazy-paving on chest computed tomography as well as extensive cytologic evaluation with lamellar bodies on EM and periodic

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acid–Schiff–diastase staining strongly supports the original diagnosis of secondary PAP due to e-cigarette aerosol exposure and not acute lung injury or infection alone. Future grouped analyses of rare case reports of EVALI and testing of previous biospecimens from affected patients with EVALI may provide a greater insight into the underlying pathophysiology of EVALI in subsets of susceptible individuals. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Expression of Concern: Disruption of Platelet-derived Chemokine Heteromers Prevents Neutrophil Extravasation in Acute Lung Injury

The editors of the *American Journal of Respiratory and Critical Care Medicine* and the *European Respiratory Journal* have been alerted to the duplication of scanning electron microscopy images in three articles published in three separate journals. Figure 1C, top right panel, in the *AJRCCM* article "Disruption of Platelet-derived Chemokine Heteromers Prevents Neutrophil Extravasation in Acute Lung Injury" (1), also appears as Figure 2b in the *ERJ* article "Pioglitazone attenuates endotoxin-induced acute lung injury by reducing neutrophil recruitment" (2), and as Figure 2A, top right panel, in the *PLoS One* article "Simvastatin Reduces Endotoxin-Induced Acute Lung Injury by Decreasing Neutrophil Recruitment and Radical Formation" (3). In addition, Figure 2d in the *ERJ* article (2) was also published as Figure 2A, right column, middle row, in the *PLoS One* article (3).

The lead authors, Dr. Grommes and Dr. Soehnlein, have assured the *AJRCCM* and *ERJ* editors that this was an inadvertent (although inappropriate) use of identical images in the same control conditions and that there was no fraudulent intention; the authors wish to apologize for their mistake. The editors have jointly discussed this matter and have agreed that, as the duplicate images represent negative and positive control conditions, the results and conclusions of the studies were not affected by this issue. The editors would like to thank the authors for their prompt cooperation in this matter; they would also like to thank the reader who brought the duplicated panels to the attention of the journals. ■

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