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
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.

**References**

1. Israel AK, Velez MJ, Staicu SA, Ambrosini R, McGraw M, Agrawal T. A unique case of secondary pulmonary alveolar proteinosis after e-cigarette, or vaping, product use–associated lung injury. *Am J Respir Crit Care Med* 2020;202:890–893.

2. Costello JF, Moriarty DC, Branthwaite MA, Turner-Warwick M, Corrin B. Bronchoalveolar lavage cytology in pulmonary alveolar proteinosis. *Am J Clin Pathol* 1996;106:504–510.

3. Burkhalter A, Silverman JF, Hopkins MB III, Geisinger KR. Diagnosis and management of alveolar proteinosis: the rôle of electron microscopy. *Thorax* 1975;30:121–132.

4. Mikami T, Yamamoto Y, Yokoyama M, Okayasu I. Pulmonary alveolar proteinosis. Diagnosis using routinely processed smears of bronchoalveolar lavage fluid. *J Clin Pathol* 1997;50:981–984.

5. Trapnell BC, Nakata K, Bonella F, Campo I, Griesse M, Hamilton J, et al. Pulmonary alveolar proteinosis. *Nat Rev Dis Primers* 2019;5:16.

6. Mukhopadhyay S, Mehrad M, Dammert P, Arrossi AV, Sarda R, Brenner DS, et al. Lung biopsy findings in severe pulmonary illness associated with e-cigarette use (vaping). *Am J Clin Pathol* 2020;153:30–39.

7. Kim ES, Kim E-C, Lee S-M, Yang S-C, Yoo C-G, Kim YW, et al. Bacterial yield from quantitative cultures of bronchoalveolar lavage fluid in patients with pneumonia on antimicrobial therapy. *Korean J Intern Med (Korean Assoc Intern Med)* 2012;27:156–162.

8. Ishii H, Tazawa R, Kaneko C, Saraya T, Inoue Y, Hamano E, et al. Clinical features of secondary pulmonary alveolar proteinosis: pre-mortem cases in Japan. *Eur Respir J* 2011;37:465–468.

9. Muthumalage T, Friedman MR, McGraw MD, Ginsberg G, Friedman AE, Rahman I. Chemical constituents involved in e-cigarette, or vaping product use–associated lung injury (EVALI). *Toxics* 2020;8:E25.

Copyright © 2020 by the American Thoracic Society