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Lipid-Laden Macrophages Are Not Diagnostic of Pulmonary Alveolar Proteinosis Syndrome and Can Indicate Lung Injury

To the Editor:

We read with interest the recent case report by Israel and colleagues that describes a young woman that presented with acute hypoxemia, bilateral pulmonary infiltrates, and a history of e-cigarette use (1). The authors concluded that this was a case of pulmonary alveolar proteinosis (PAP) secondary to vaping-associated lung injury on the basis of the radiological and cytological findings presented. The case presented is undoubtedly interesting, and the report raises several important topical issues, including the spectrum of e-cigarette– or vaping-associated lung injury (EVALI) and the utility of lipid-laden macrophages in BAL fluid. However, we have some remarks regarding this case and the suggested association between EVALI and PAP.

PAP is a rare syndrome characterized by progressive alveolar surfactant accumulation and hypoxemic respiratory failure and is categorized as primary, secondary, or congenital. Primary PAP accounts for the vast majority of cases and is caused by the disruption of GM-CSF (granulocyte–macrophage colony–stimulating factor) signaling, by GM-CSF autoantibodies (autoimmune PAP, accounting for 90% of cases), or by genetic mutations involving the GM-CSF receptor. Secondary PAP occurs in various conditions that cause altered function or a reduced number of alveolar macrophages resulting in abnormal surfactant clearance in the lung (2).

The case presented by Israel and colleagues is not entirely convincing for secondary PAP, and we believe it is more likely that either infection or EVALI was the principal issue for this patient. First, "crazy-paving" is not pathognomonic of PAP, and there are many other causes, including acute lung injury and lipoid pneumonia, both of which could be present as a result of EVALI in this case (3). Second, the presence of lipid-laden macrophages in BAL fluid is nonspecific, and although Oil-Red-O–positive cells are certainly a feature of PAP, they are present in many types of lung disease (4). Furthermore, the presence of periodic acid–Schiff–positive material again is not indicative of PAP alone and can be seen in a spectrum of pulmonary pathology (5). In this case, no biopsy was performed, and a label of secondary PAP was made on the basis of BAL and computed tomography findings. This is not the current best practice; indeed, all patients should have GM-CSF autoantibodies checked when PAP is suspected, and if there is no known secondary cause of PAP and GM-CSF signaling is intact, then a lung biopsy is needed to truly determine the presence of PAP syndrome (2). Finally, the rapid response to antibiotics and steroids, neither of which are effective therapies for primary or secondary PAP, go against this being a case of secondary PAP. Moreover, it would take several months for the alveolar macrophage pool to replenish/repair and export accumulated lipids, which is evidenced by the delayed response to inhaled GM-CSF seen in cases of autoimmune PAP (6). We conclude that this case more likely represents either infectious or inflammatory acute lung injury possibly related to EVALI, but the paucity of evidence cannot confirm secondary PAP.

Although we disagree that this is a case of secondary PAP, it highlights the importance of carefully interpreting the presence of lipid-laden macrophages in the lung. It has been demonstrated that in a mouse model of EVALI, there was altered surfactant phospholipid homeostasis and foamy macrophages but no evidence histologically of PAP lung disease (7). There have been numerous reports of Oil-Red-O macrophages in EVALI (8), but this likely represents lung injury resulting in abnormal surfactant production from type II pneumocytes or from altered macrophage function resulting in lipid accumulation. Hence, the interpretation of lipid-laden macrophages must be treated cautiously. With the increased recognition of EVALI as a novel pulmonary condition, there has been renewed focus on lipid-laden macrophages, but we conclude that foamy macrophages in EVALI likely indicate lung injury, and caution should be given to using this finding as a diagnostic marker (9). ■

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

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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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