# Going Deeper into the Pathology of Vaping-Associated Lung Injury

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**Julie McDowell:**

By the end of 2019, the CDC had reported over 2,000 hospitalizations and numerous confirmed deaths due to vaping-associated lung injury. While research into the pathology of vaping-associated lung injury is in its early phases, Dr. Brandon Larsen and his pathology colleagues at the Mayo Clinic, published research in the New England Journal of Medicine in early October 2019, finding that lung injuries from vaping most likely are caused by direct toxicity or tissue damage from noxious chemical fumes.

In addition, Dr. Larsen and his colleagues published subsequent correspondence in the same publication, cautioning clinicians against performing lipid stains on bronchial fluid or lung tissue from adult patients. In this CAPcast interview, Dr. Larsen discusses what CAP members need to know about the pathology of vaping associated lung injury.

Dr. Larsen, let's begin with your finding published in early October. Could you summarize your findings and explain the significance that your team found that no evidence of tissue injury caused by lipid accumulation, which appears to be an initial potential culprit?

**Dr. Brandon Larsen:**

Sure, happy to discuss this. So, we got involved in this story, initially, because we started seeing early reports come out in the clinical literature that described an observation in some patients where lipid-laden macrophages were identified in their bronchoalveolar lavage fluid. And it was assumed, based on that finding, that vaping-associated lung injury must represent some form of lipoid pneumonia, and people were suggesting that the problem was associated with oil accumulation or oil clogging the lungs, and that was how it was described in the media and some of these reports.

And we began seeing lung biopsies from these patients in our nationwide consultation practice here at Mayo Clinic in Arizona, and it became obvious to us, very early on, that there was no histologic evidence of lipid or oil accumulation in the lungs of these patients. Instead, what we saw in virtually every case, was an acute lung injury process that bore a striking resemblance to the type of injury you see with a toxic chemical fume exposure. Airway-centered acute lung injury in various stages of evolution.

And so, we undertook this study. We took 17 cases that we had reviewed, and looked at the histopathology and all of the lung biopsies, and that's exactly what we saw in the end. All cases showed an airway-centered acute lung injury process with either diffuse alveolar damage, or acute fibrinous pneumonitis, or organizing pneumonia with bronchiolitis and foamy macrophage accumulation. And the reason why we believe that was significant is, it changed the dialogue about what is actually occurring in the lung with vaping. And up until that point, as I already mentioned, it was assumed that the problem was simply a problem of lipid accumulation, but the type of injury we were seeing suggested a much different type of problem, some sort of toxic inhalational injury. And then, that has now spurred on additional efforts to identify exactly what kind of compound may be behaving in that manner.

**Julie McDowell:**

Can you share any updates on your research findings since the publication of this initial study?

**Dr. Brandon Larsen:**

Sure. So, we have continued to see the same types of findings in subsequent cases that we've seen, we continue to review these. In terms of research findings that have been published, I would note that there has been one additional pathology series that's been published shortly after ours was, headed by Sanjay Mukhopadhyay at the Cleveland Clinic and his collaborators, and they saw exactly the same thing that we saw. They saw no evidence of exogenous lipoid pneumonia in any of these cases, but instead saw an acute lung injury process suggesting some type of toxic chemical fume exposure.

And subsequent to that, there have been additional studies that have been released by the CDC and others. The CDC has now identified vitamin E acetate as a contaminating material in almost all cases of patients with vaping-associated lung injury, which is really interesting. And in their most recent report from December in the New England Journal, the CDC actually references another study that is coming out of Ireland, looking at what happens when vitamin E acetate is heated, and in fact, vitamin E acetate is transformed or pyrolyzed into a toxic Ketene gas it seems, which provides a perfect explanation for how vitamin E contamination in vape fluid produces a toxic inhalational injury in the lungs. The story has actually come around quite a bit since we first published our findings.

**Julie McDowell:**

Now, there's been some disagreement over the best tests to use to distinguish vaping-associated lung injury from other causes of acute lung injury. And you and your colleagues recently indicated, in correspondence to the New England Journal, that you didn't recommend lipid stains. Can you explain the risks associated with using this diagnostic approach?

**Dr. Brandon Larsen:**

Sure. So, it was understandable that clinicians were interested in having a diagnostic marker to aid in the diagnosis of patients with vaping-associated lung injury, and those early observations that indicated that lipid-laden macrophages could be identified in BAL fluid from these patients, led people to get excited about whether oil Red O stains or lipid stains could be used to diagnose this condition. The problem with that is, as has been known among the cytopathology community for a long time, those studies have problems, probably the most important of which is their lack of specificity. And Oil Red O or lipid positive macrophages in BAL fluid can be identified in almost any cause of acute lung injury, be it from infection, autoimmune disorders, other types of drug reactions, and not just vaping-associated lung injury.

Again, we've known this for a long time, and in fact, these lipid stains have largely been discarded from contemporary clinical practice, precisely because of that non-specificity. And of course, in addition, they have a number of technical problems associated with them, as anybody who has performed these stains or actually interpreted them in the laboratory knows full well. So, our recommendation early on, was that these studies should not be relied upon to make a diagnosis of vaping-associated lung injury, or to distinguish vaping-associated lung injury from some other cause of acute lung injury.

**Julie McDowell:**

So, what tests or diagnostic approaches should pathologists take in these cases?

**Dr. Brandon Larsen:**

So, I think it's important for pathologists to recognize that a diagnosis of vaping-associated lung injury is not a diagnosis that's made by the pathologist alone. This is a diagnosis of exclusion, it requires clinical input. It's essentially a clinical pathologic diagnosis that requires exclusion of other causes of acute lung injury. And those elements include an infectious disease workup, workup for autoimmune disease with appropriate laboratory testing, all those things that clinical colleagues do for us when they work up a patient with acute lung injury of any cause. And for the pathologist who is involved in a case where vaping-associated lung injury is suspected, I think it's important to think about two things when it comes to testing and specimen handling.

Number one, and most importantly, pathologists must remember to perform a workup for infection when they see a biopsy from these patients, or BAL fluid from these patients. You need to be performing your special stains for microorganisms, your GMS or silver stains for fungi and other studies, because identification of infection, or ruling out infection, is really key in determining the appropriate therapy for these patients.

Number two, resist the urge to freeze tissue to perform Oil Red O or lipid stains.

Clinicians may request this testing and it's perfectly reasonable to perform that on BAL fluid, as long as the clinicians understand the severe limitations of that testing. But I personally would not recommend, nor would a number of my colleagues recommend freezing lung biopsy samples for the purpose of performing lipid stains, which would compromise your ability to evaluate that specimen for other potential causes of acute lung injury. There is no data to support freezing lung tissue instead of submitting it for routine histology. And at this point, in our practice, we continue to submit lung biopsies for routine histology in their entirety. We're not performing lipid stains on these specimens.

So, those would be the two things. Make sure you're doing an infectious disease workup with appropriate special stains, and make sure you're submitting your lung tissue biopsies for routine histology.

**Julie McDowell:**

Finally, it's clear that pathologists play a significant role in both identifying the clinical underpinnings of vaping-associated lung injury, as well as treating patients with this disease. How do you recommend pathologists keep current on research findings, such as study you referenced earlier that's forthcoming from Ireland, and clinical recommendations?

**Dr. Brandon Larsen:**

I think I would keep my attention on the pathology literature. Right now, there's limited information in the pathology literature for general pathologists out in community practice, but that will change shortly. There will certainly be reviews of this problem coming out soon for pathologists to help provide guidance. The other thing to certainly keep your eyes on would be the CDC and their recommendations that are available on the CDC's website, and those are updated based on current information and are changing as we learn more about this problem.

**Julie McDowell:**

Thank you very much, Dr. Larsen, for discussing this important issue with the CAP. The CAP has released the following statement on vaping: The CAP, the world's largest organization of board-certified pathologists, strongly opposes vaping, particularly among children, teens, and young adults who have never smoked. While the CAP acknowledges that vaping may have a role in smoking cessation, we stress the need for improved medical research to inform vaping-related U.S. Food and Drug Administration regulations or guidance.

For more information on this statement, please visit the news and media section on the CAP's website, cap.org. Thank you for listening to this CAPcast. Be sure to listen to our other CAPcasts from the CAP on our SoundCloud channel by downloading the SoundCloud app on your mobile device. And we're also on Apple Podcast, and the Stitcher app. To find this podcast, search for the word CAPcast on these apps. Once you find our podcast, be sure to click the subscribe button so you don't miss new CAPcast episodes.