

# What you inhale can kill you



@smlungpathguy

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Cleveland Clinic

# Disclosure information

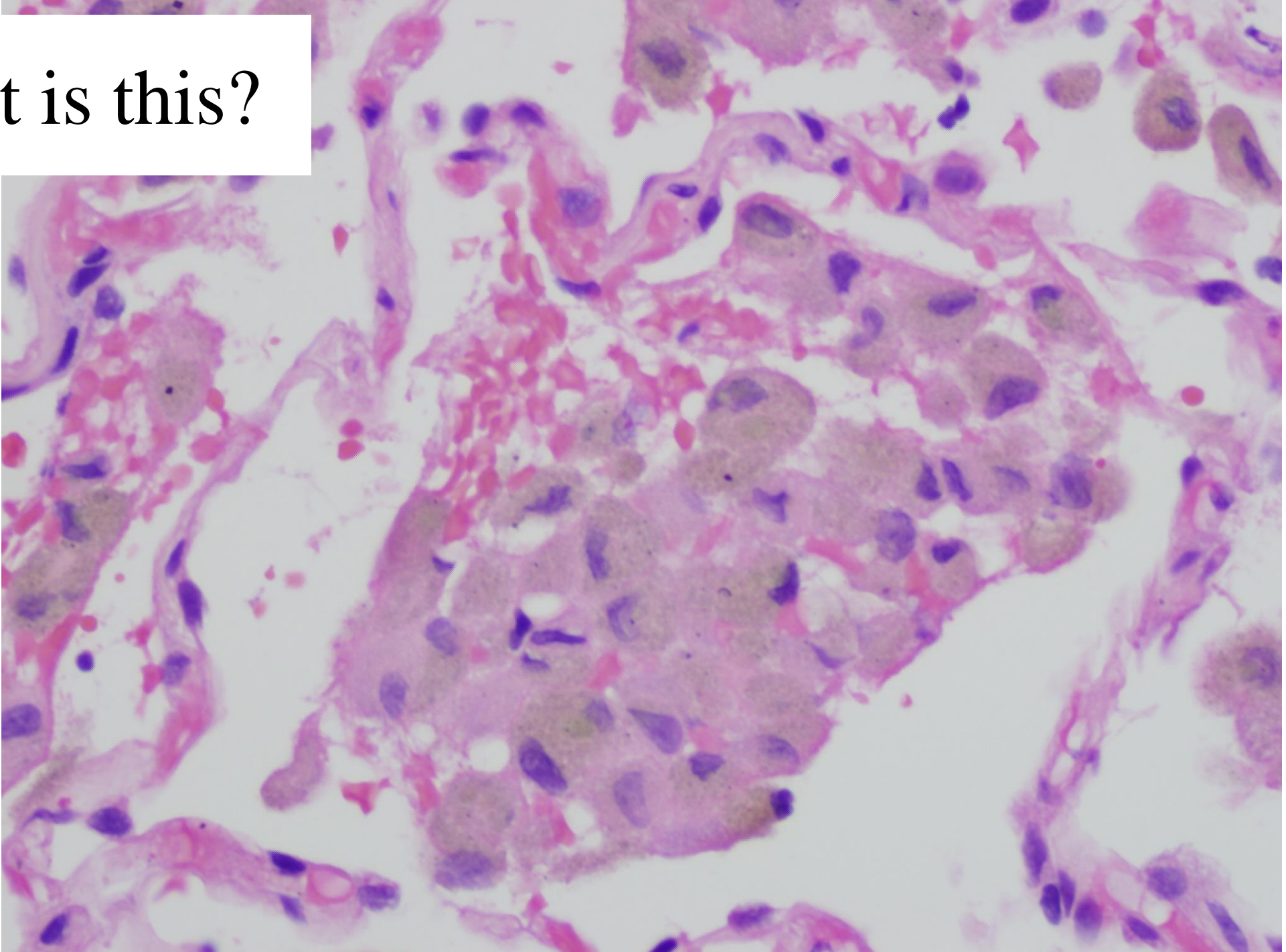
Sanjay Mukhopadhyay, MD

I have no financial relationships pertinent to this presentation

# PART 1: SMOKING

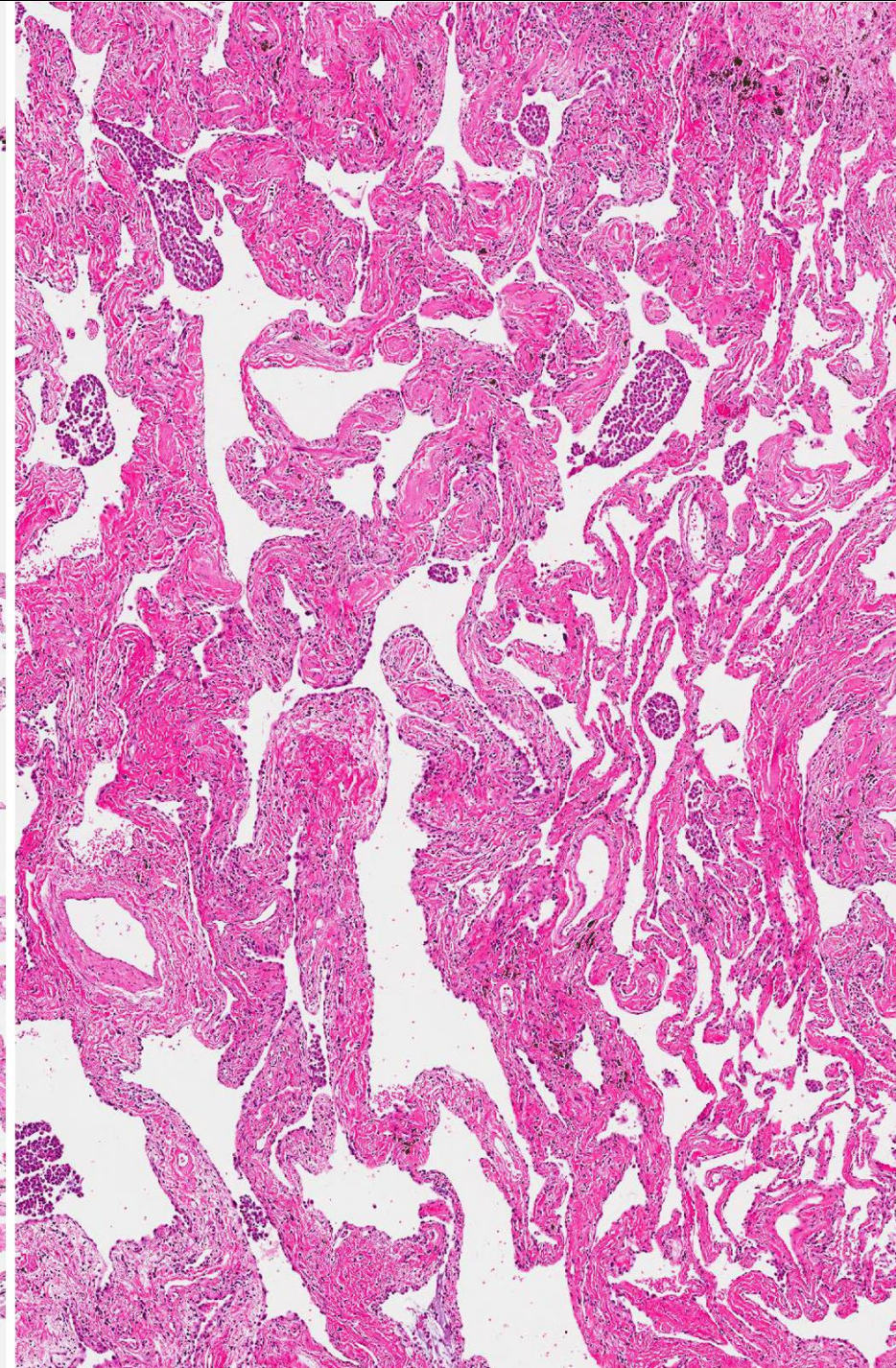
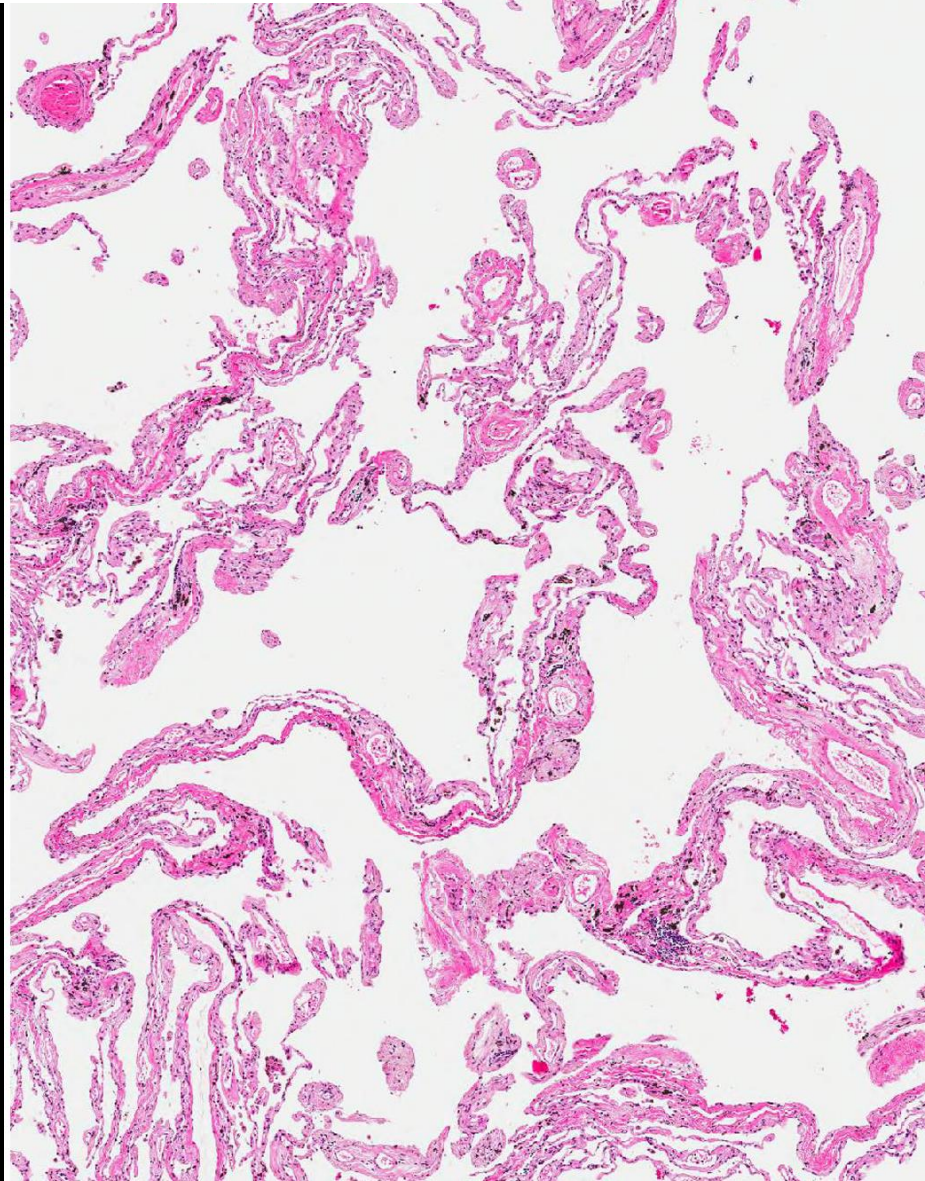


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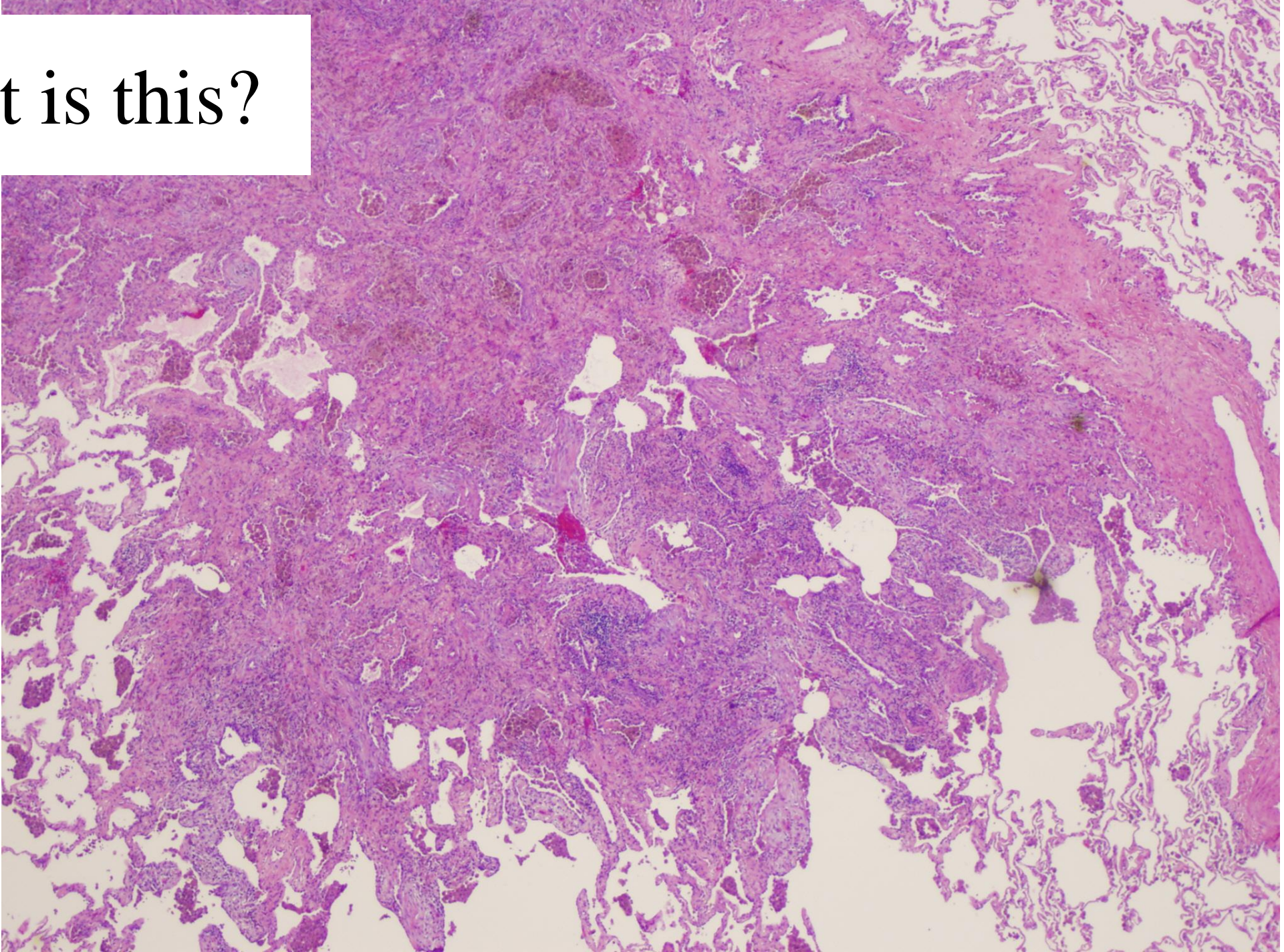


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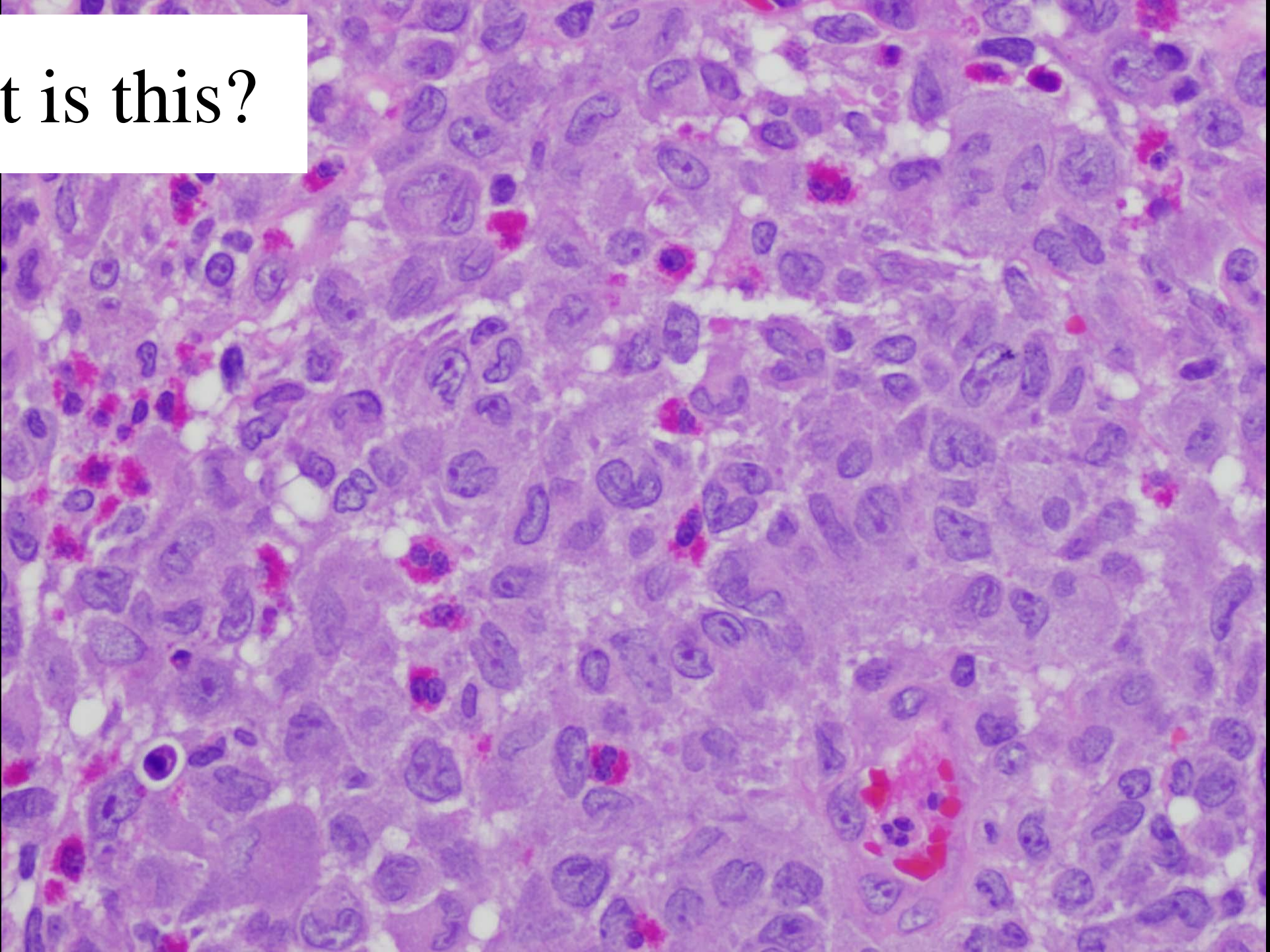


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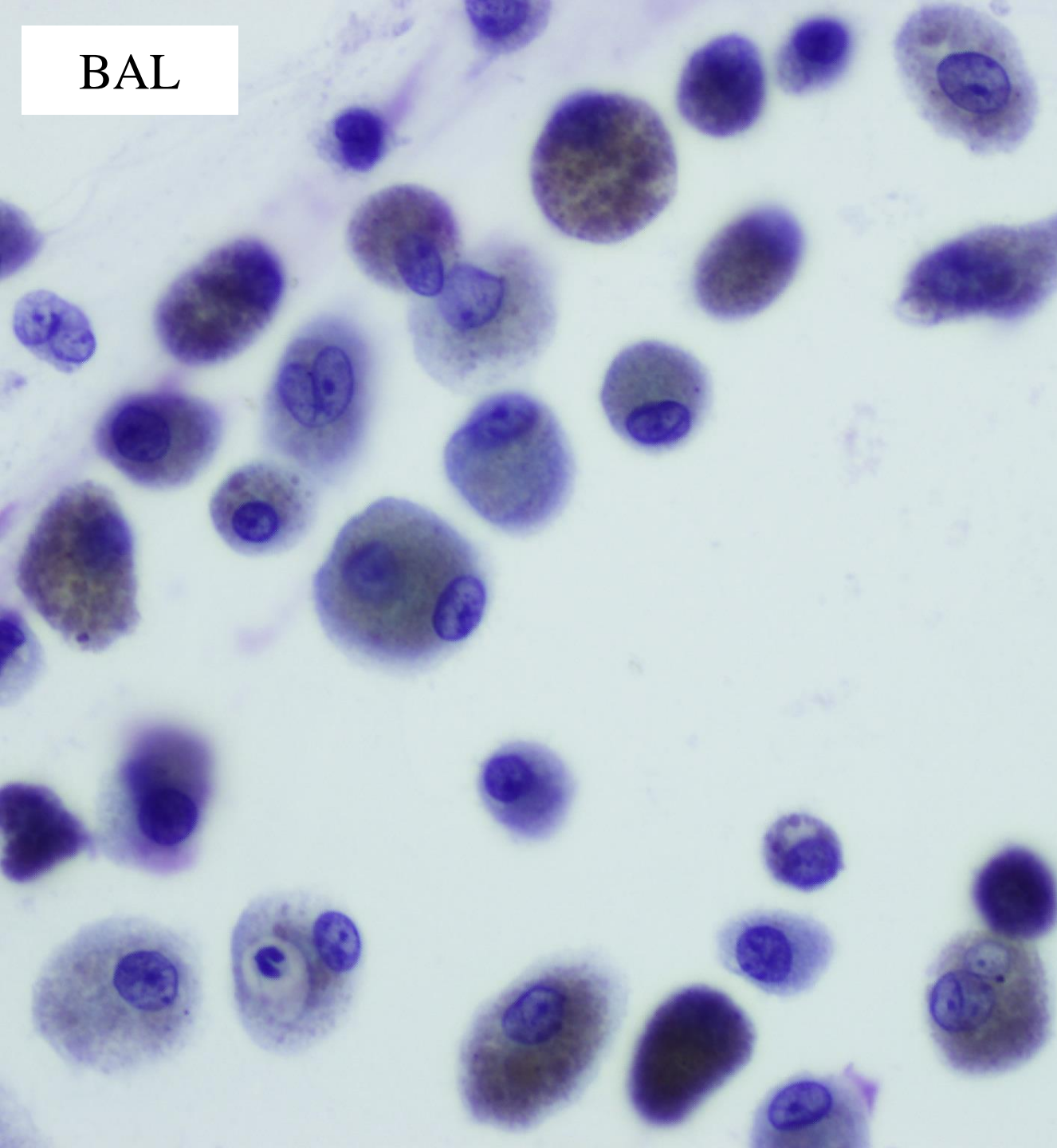


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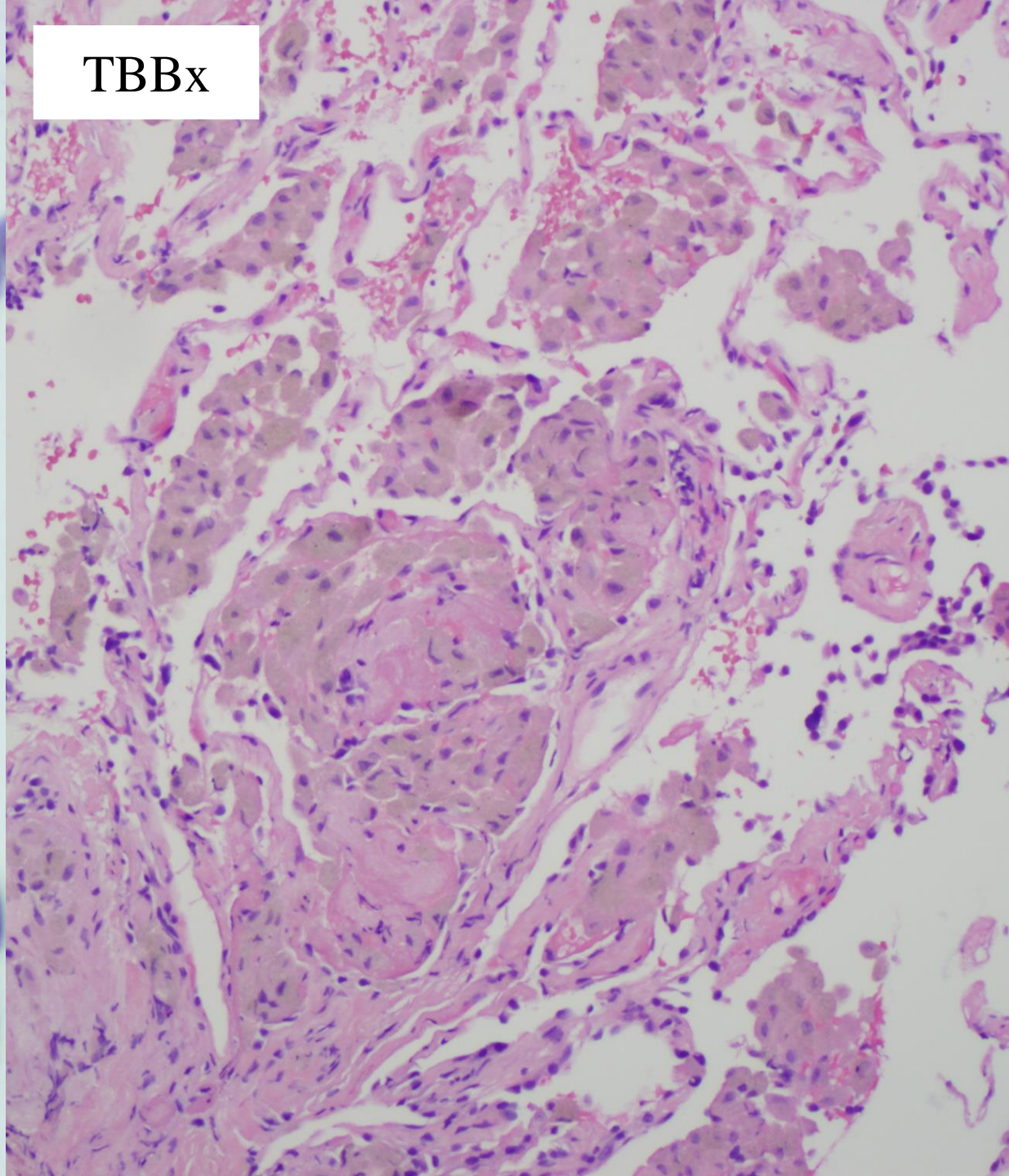




BAL



TBBx





# Cytoplasmic Inclusions in Pulmonary Macrophages of Cigarette Smokers

ARNOLD R. BRODY, PH.D., AND JOHN E. CRAIGHEAD, M.D.

*Department of Pathology, University of Vermont College of Medicine, Burlington, Vermont 05401*

Alveolar and bronchiolar spaces in the lungs of cigarette smokers usually contain numerous macrophages with pigmented cytoplasmic granules. By electron microscopy the pigmentation appears to be due, at least in part, to increased numbers of lysosomes and phagolysosomes. Within these cytoplasmic organelles, structures are found which we designate "smokers' inclusions," since they are observed ex-

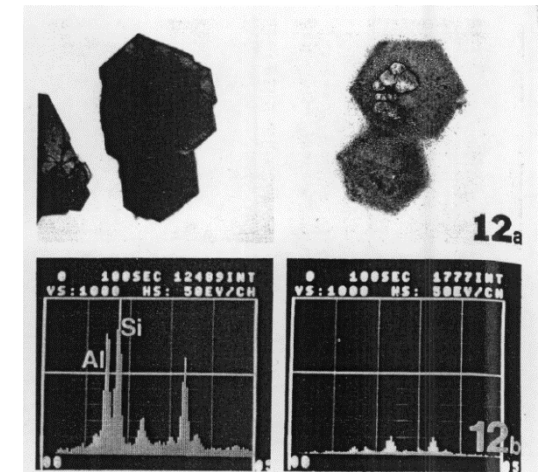
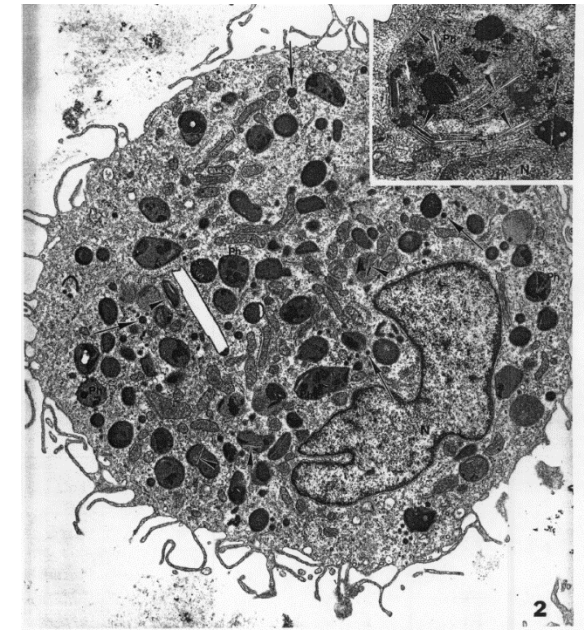


FIG. 12. a, Kaolinite crystals from tobacco digestates of two brands of cigarettes. b, x-Ray analysis of crystals observed in digestates of cigarette tobacco. The presence of aluminum (Al) and silicon (Si) is demonstrated (left). Analysis of areas of the grid adjacent to the crystals demonstrated no appreciable amounts of the two elements (right). Figure 12a,  $\times 12,500$ .

# PATHOLOGIC CHANGES IN THE PERIPHERAL AIRWAYS OF YOUNG CIGARETTE SMOKERS

DENNIS E. NIEWOEHNER, M.D., JEROME KLEINERMAN, M.D. AND DONALD B. RICE, M. DIV.

**Abstract** The lungs of young smokers and controls of comparable age from a population of sudden non-hospital deaths were systematically studied to determine the relation between cigarette smoking and pathologic changes in peripheral airways. The characteristic lesion observed was a respiratory bronchiolitis associated with clusters of pigmented alveolar macrophages and was present in the lungs of all smokers studied but rarely seen in nonsmokers

( $p < 0.002$ ). The lungs of smokers also showed small but significant increases in mural inflammatory cells and denuded epithelium in the membranous bronchioles as compared to controls ( $p < 0.05$ ). We postulate that this respiratory bronchiolitis is a precursor of centriacinar emphysema and may be responsible for the subtle functional abnormalities observed in young smokers. (N Engl J Med 291: 755-758, 1974)

THE association between chronic obstructive pulmonary disease and cigarette smoking has been documented by numerous studies.<sup>1-5</sup> Many years of cigarette smoking usually precede the appearance of anatomic emphysema and the onset of clinical obstructive disease. Little is known about the effects of cigarette smoking on the lung during this early preclinical period. The

ed an index of the subject's exposure to air pollution by relating his home residence for the last five years to isopleths of ambient sulfur dioxide concentrations and particulate counts supplied by governmental sources.

A single lung from each subject was endobronchially inflated and fixed in 20 per cent neutral buffered formalin at a pressure of 25 cm of water for 48 hours. The lungs were cut into 1-cm parasagittal slices and carefully examined for the presence of

From the Division of Pathology Research, Saint Luke's Hospital, Department of Medicine, University Hospitals, and the departments of Pathology and Medicine, Case Western Reserve University (address reprint requests to Dr. Niewoehner at the Saint Luke's Hospital, Division of Pathology Research, 11311 Shaker Blvd., Cleveland, OH 44104).

Supported by a research grant (HL 16542-01) from the National Heart and Lung Institute and a grant (ES00264-07) from the National Institute of Environmental Sciences.

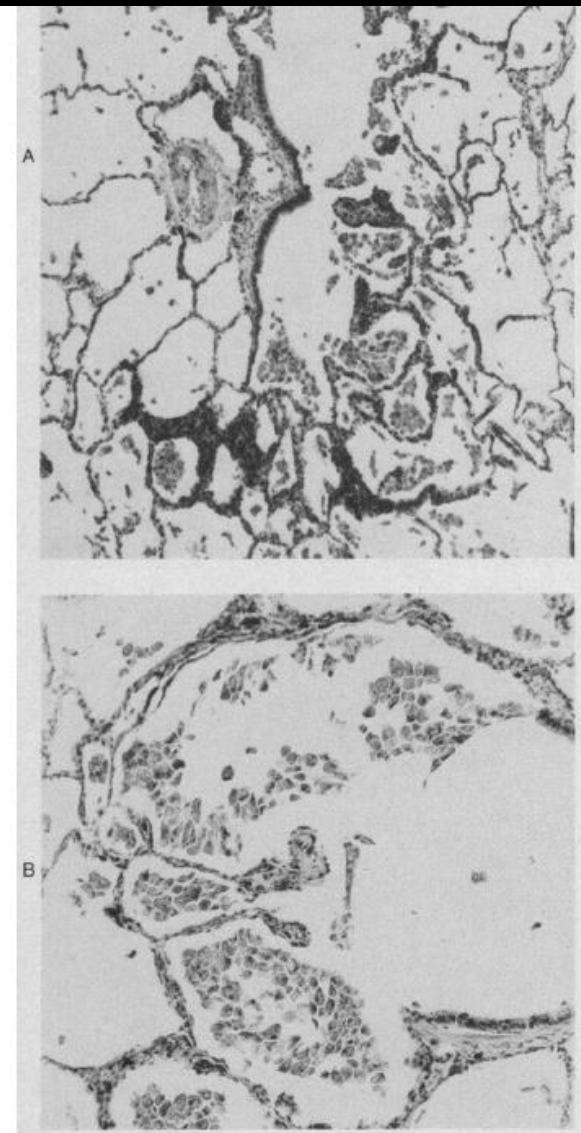


Figure 2. Section through the Junction of a Terminal Membranous and Respiratory Bronchiole from a Smoker (A), Showing Severe Respiratory Bronchiolitis ( $\times 80$  before Reproduction).

# Respiratory Bronchiolitis

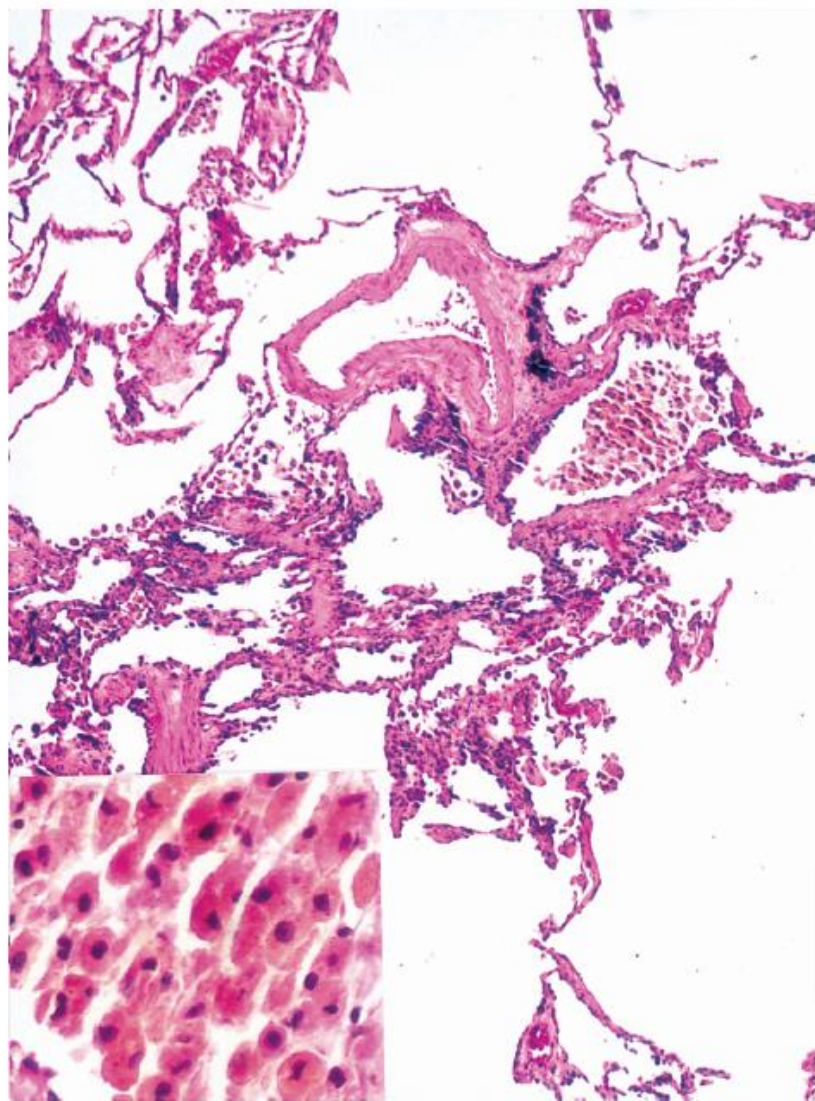
## A Clinicopathologic Study in Current Smokers, Ex-Smokers, and Never-Smokers

Mostafa Fraig, M.D., Udaya Shreesha, M.D., Dana Savici, M.D., and Anna-Luise A. Katzenstein, M.D.

The clinical and pathologic features of 109 cases of respiratory bronchiolitis (RB) identified from review of 156 consecutive surgical lung biopsy specimens were studied. A total of 107 of the 109 cases (98%) occurred in smokers, including all 83 current smokers and 24 of 49 ex-smokers (49%). RB persisted in some patients for many years after stopping smoking, occurring in one third of patients 5 years after quitting, and in one patient 32 years afterwards. A correlation was found between degree of cytoplasmic pigmentation of macrophages and number of pack-years smoked and also between the presence of peribronchiolar fibrosis and number of pack-years. No correlation was found between pulmonary function test results and pathologic findings. A desquamative interstitial pneumonia-like reaction was observed in six individuals. One patient each with a desquamative interstitial pneumonia-like reaction and

Respiratory bronchiolitis (RB) is a common inflammatory lesion of respiratory bronchioles that occurs mainly in cigarette smokers. It was first described in 1974 by Niewoehner et al.<sup>10</sup> in an autopsy study of 39 patients dying of nonpulmonary causes. The histologic appearance is characterized by the accumulation of pigmented macrophages within respiratory bronchioles and surrounding airspaces with minimal associated mural inflammation. Although a relationship of RB and cigarette smoking is well established, questions remain about the sensitivity and specificity of this finding as a marker for cigarette smoking, the occurrence of RB in ex-smokers, the time course of its disappearance after stopping smoke-





**FIG. 1.** Characteristic microscopic appearance of RB with pigmented macrophages filling a respiratory bronchiole and spilling into surrounding airspaces (hematoxylin and eosin, magnification  $\times 48$ ). **Inset.** A higher magnification view showing the pigmented macrophages (hematoxylin and eosin, magnification  $\times 360$ ).

**TABLE 1.** Summary of findings in 156 patients

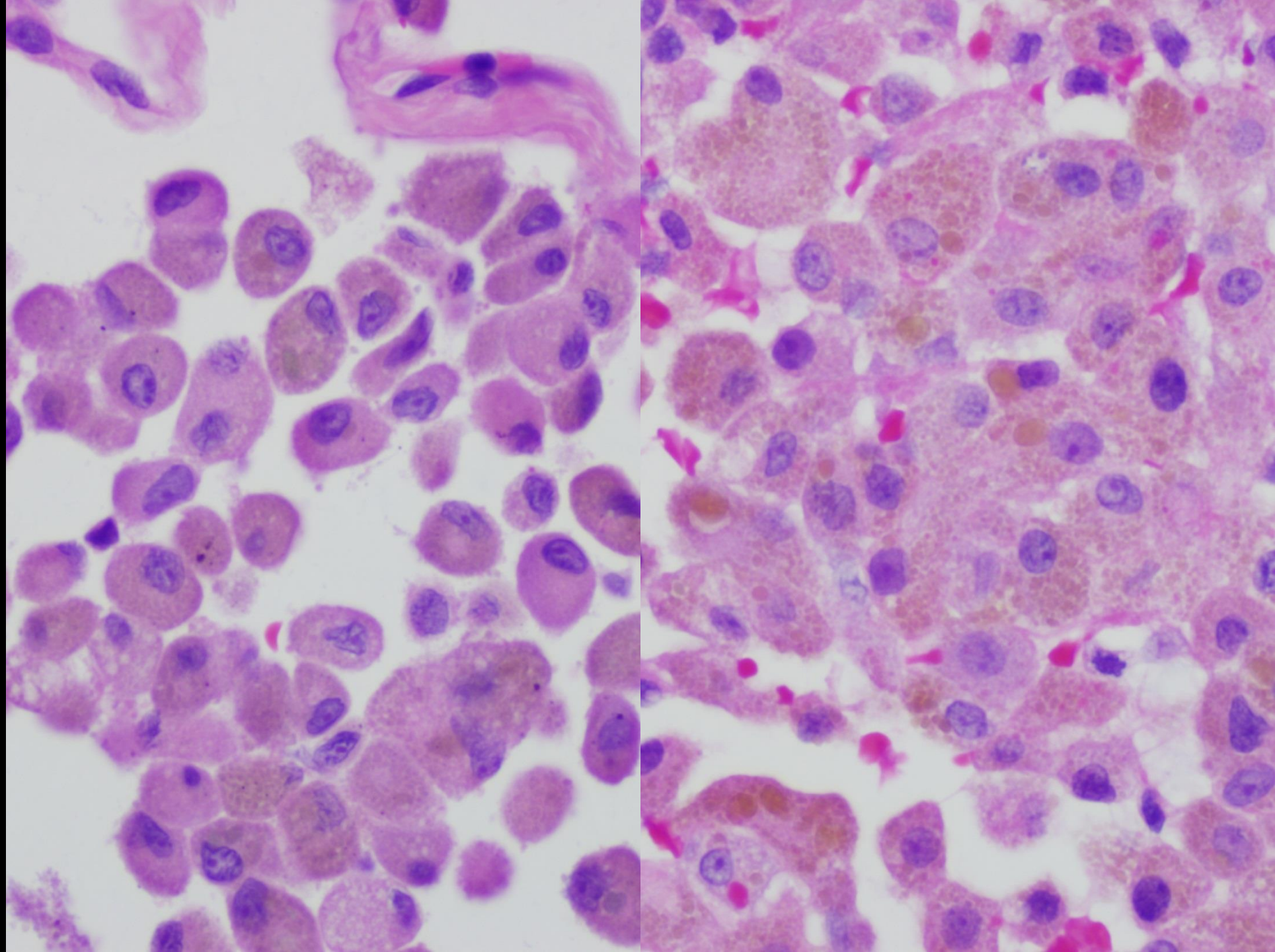
	Current smokers	Ex-smokers	Never smokers	Total
RB present	83	24	2	109
RB absent	0	25	22	47
Total	83	49	24	156

RB, respiratory bronchiolitis.

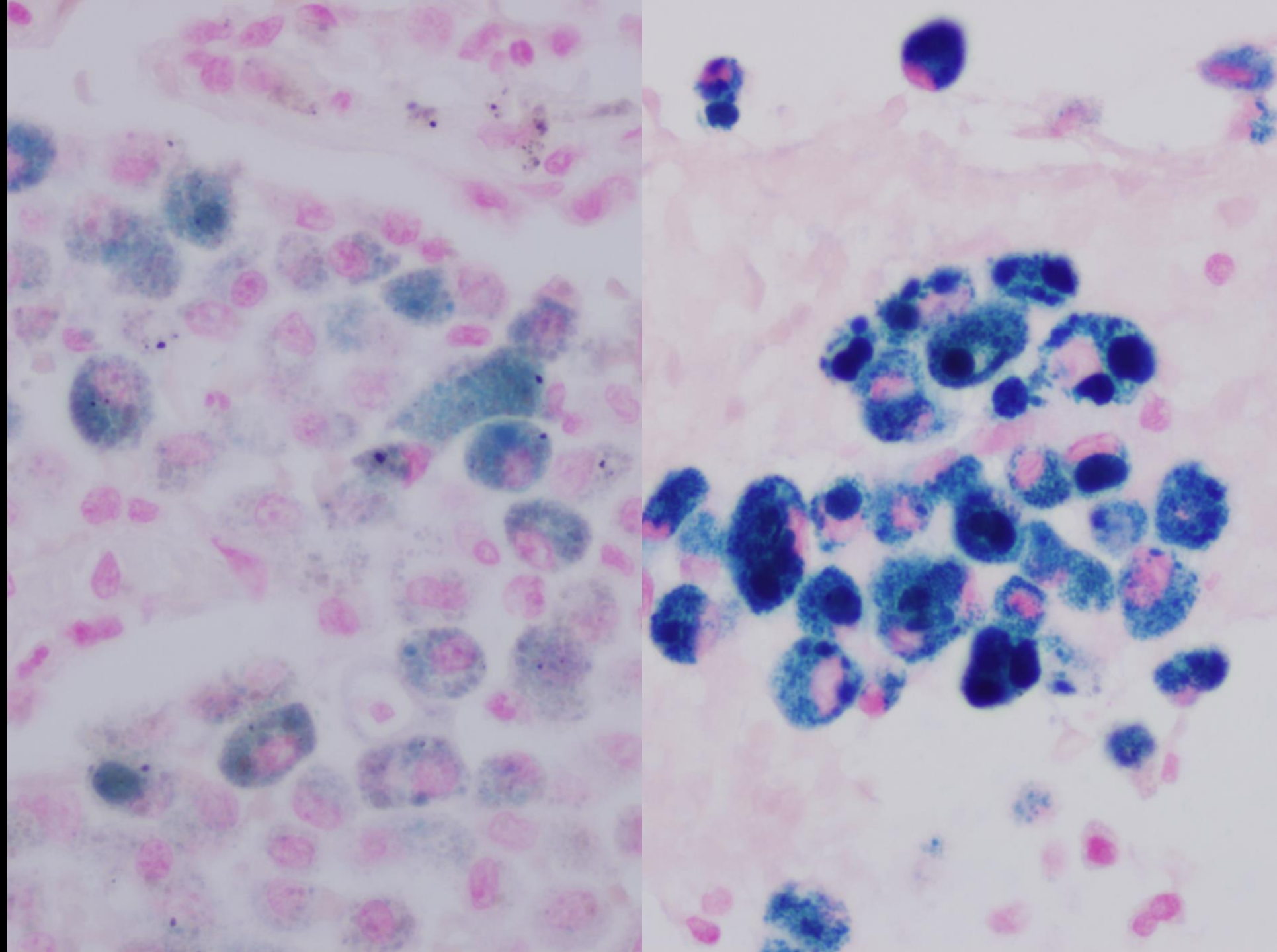
## RESULTS

There were 102 men and 54 women ranging in age from 7 to 83 years (median 61 years). RB (Fig. 1) was found in 109 of the 156 patients, of whom 107 (98%) had a history of smoking (cigarettes in 104 and pipe in three) (Table 1). Eighty-three of the 156 patients were current smokers and all had RB, whereas 49 were ex-smokers, of whom 24 (49%) had RB. RB was additionally found in two of 24 apparent never-smokers (8.3%). One, a 77-year-old man, had a history of intermittent smoking from 1942 to 1945 but none since. Because the smoking history was so short and so long ago (54 years), he was considered a never-smoker. He worked as a mechanic where he was exposed to diesel smoke and fiberglass. The other never-smoker with RB was a 77-year-old woman who was heavily exposed to second-hand smoke from her father, husband, and two sons. Although she denied smoking herself, there is a note in the chart that her daughter stated that she "smoked some." Variant RB (Fig. 2), a lesion differing from RB only in that the intraluminal macrophages lack









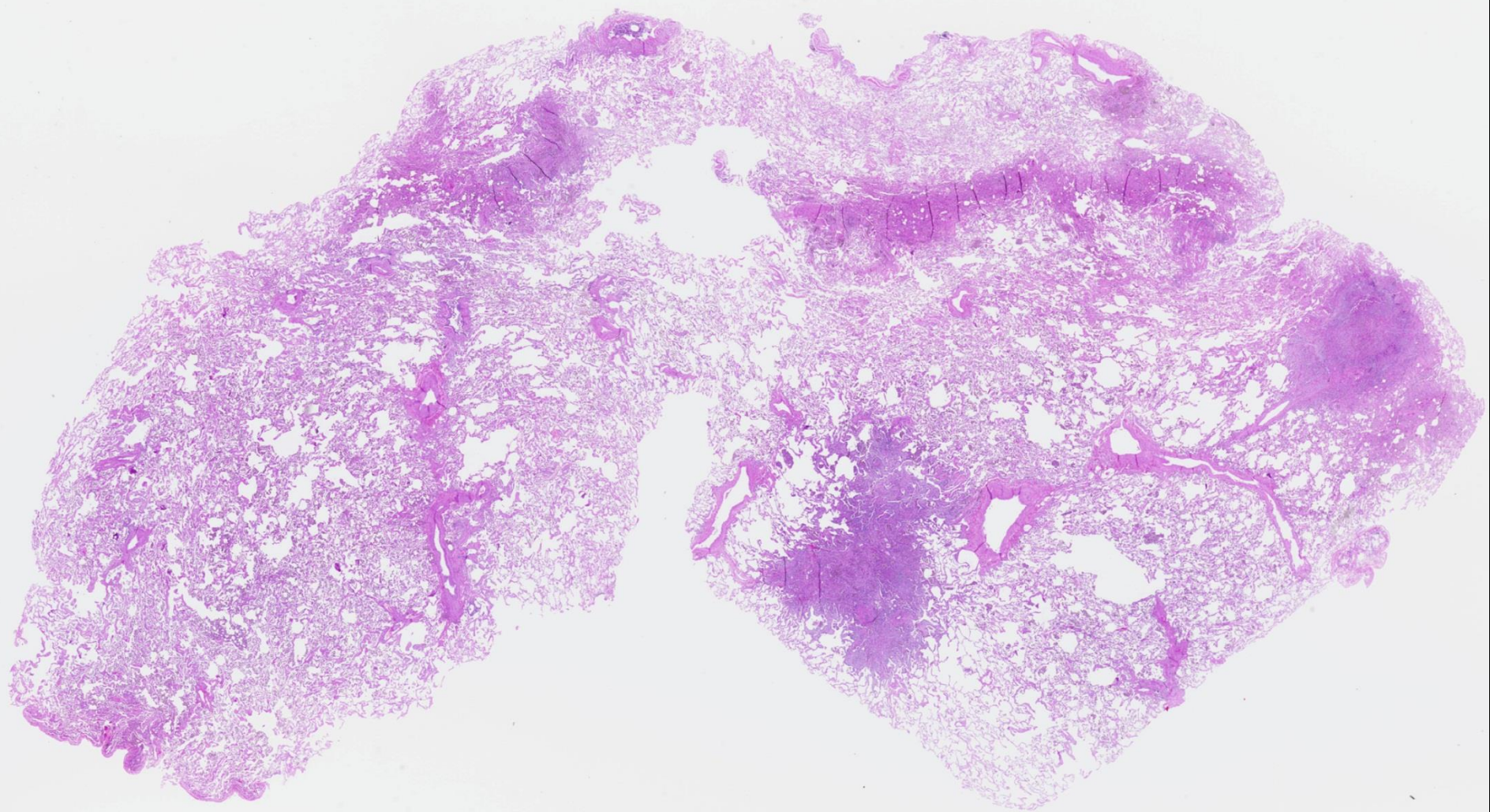
# Pigmented airspace macrophages, smoking-related

- This finding has been given a confusing and misleading term: “respiratory bronchiolitis”; sounds like “inflammation of the bronchioles”
- “itis” refers to macrophages!
- Respiratory bronchiole is not the only structure involved

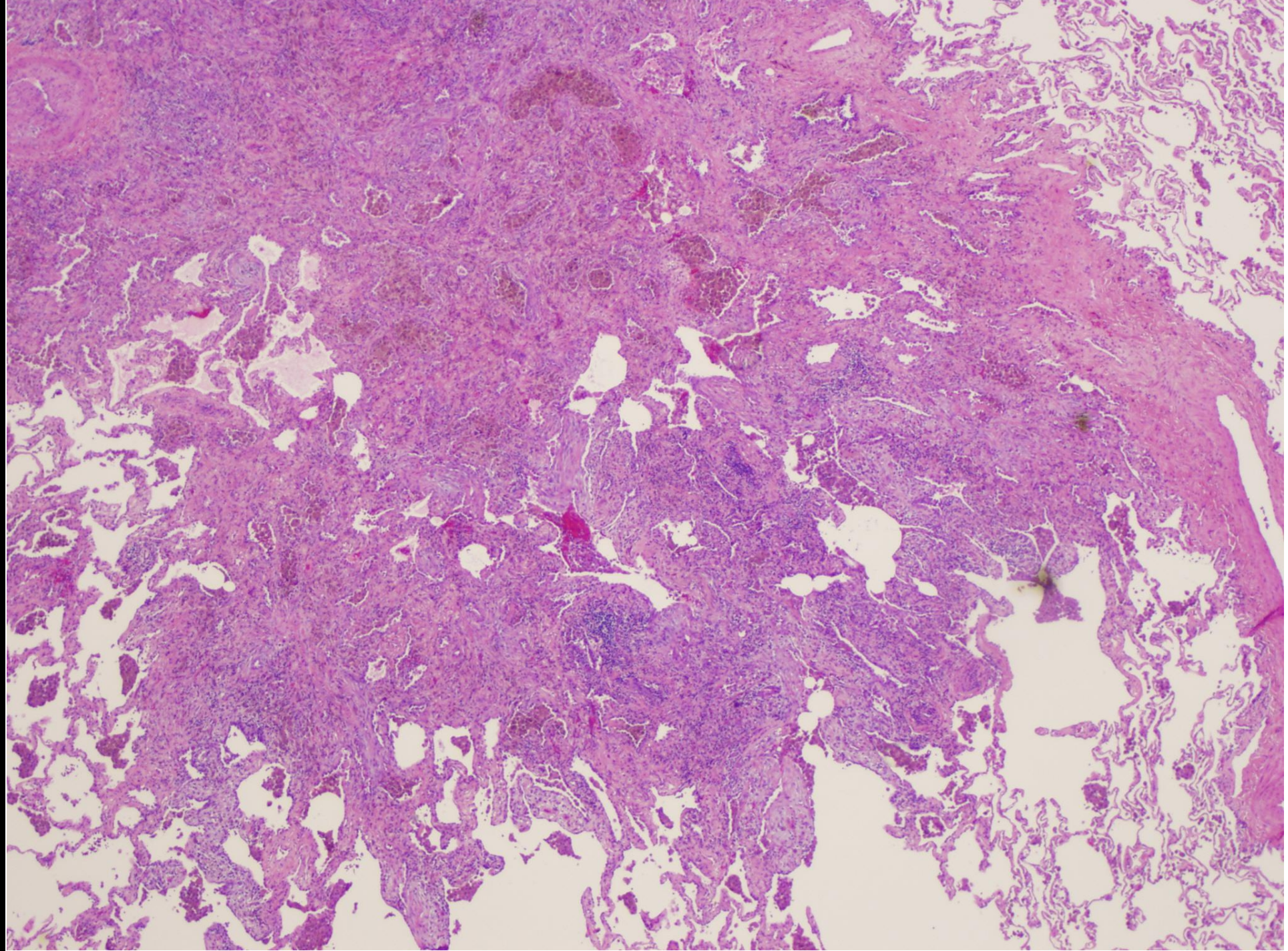
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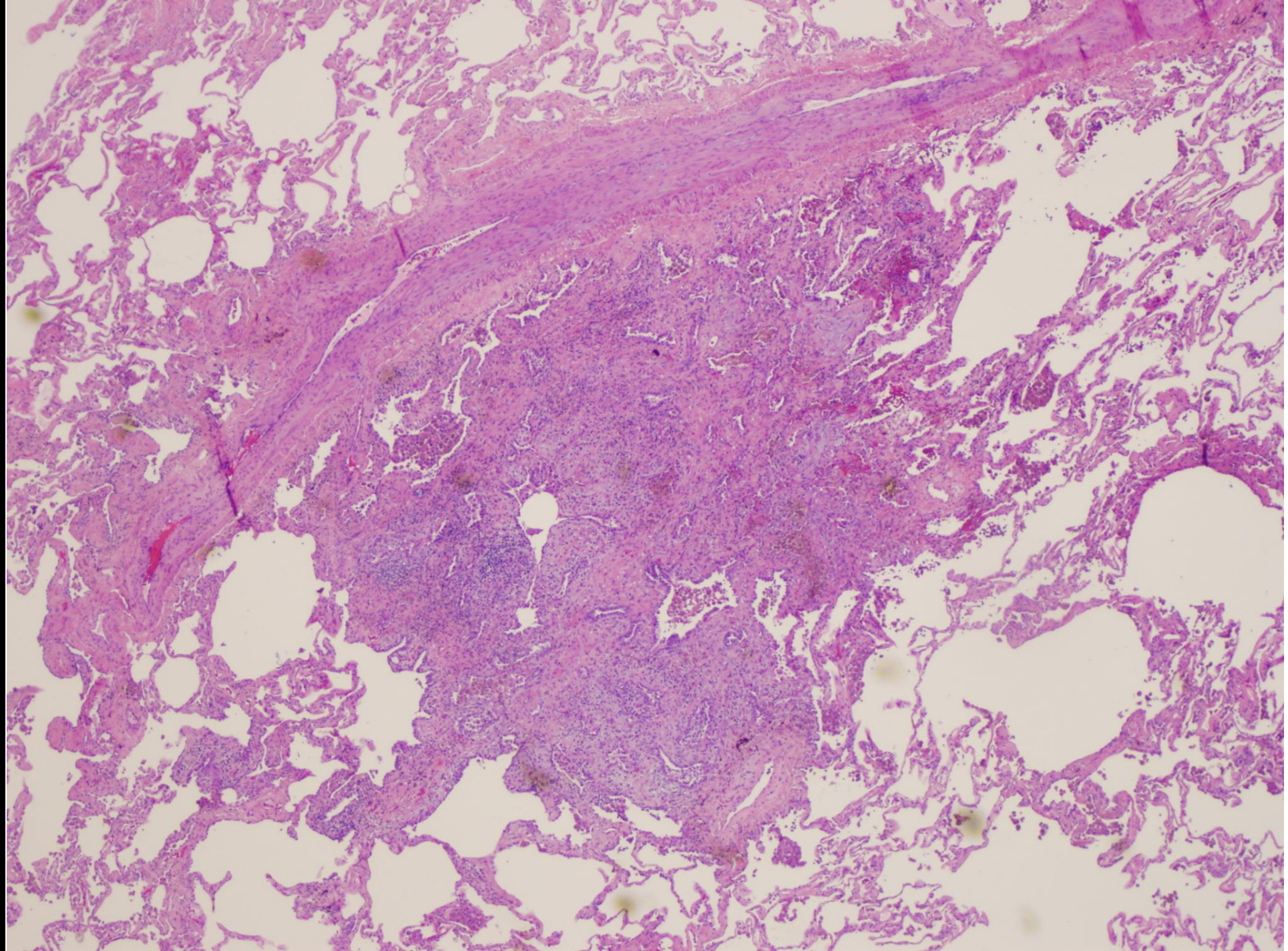




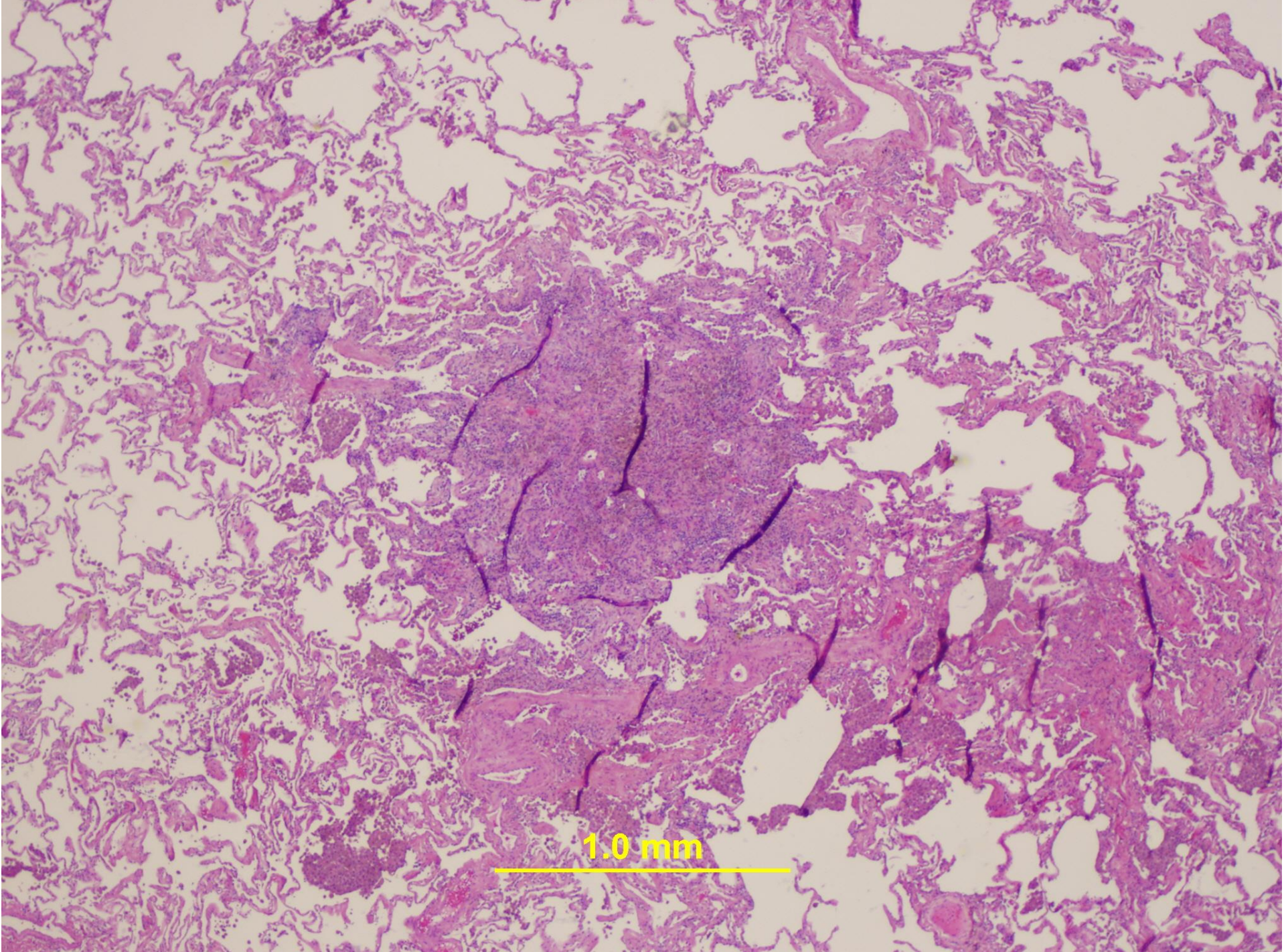




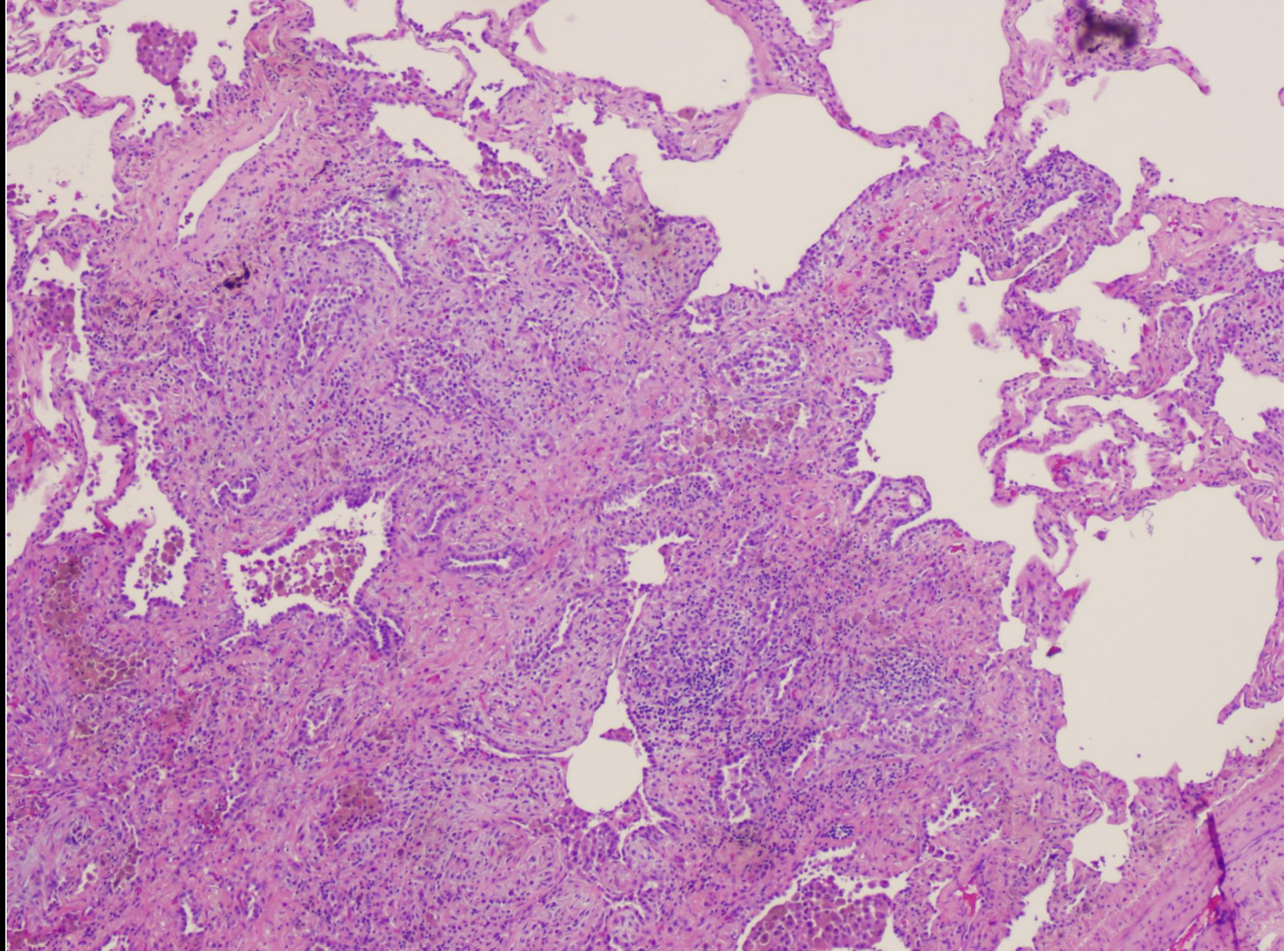




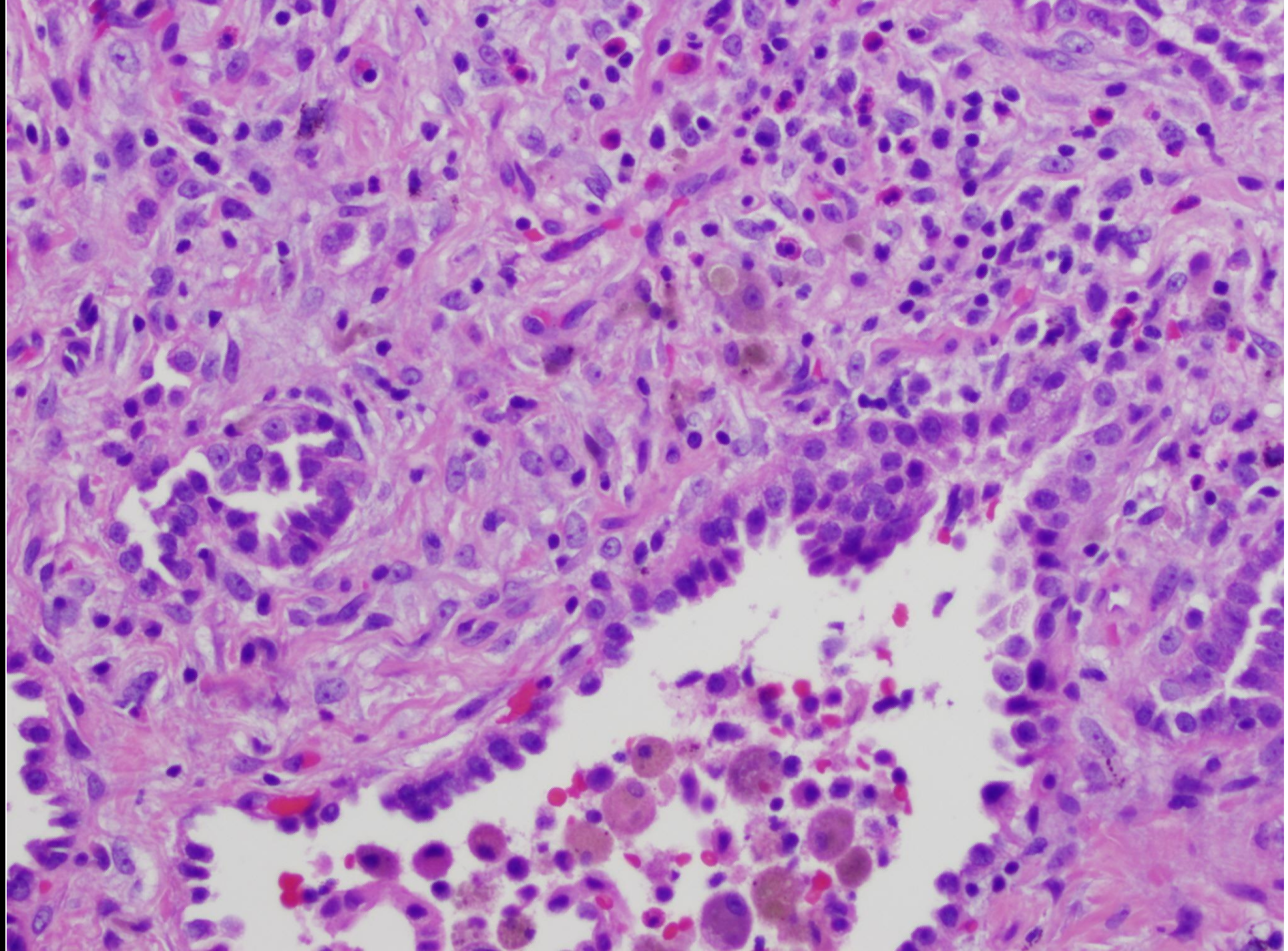




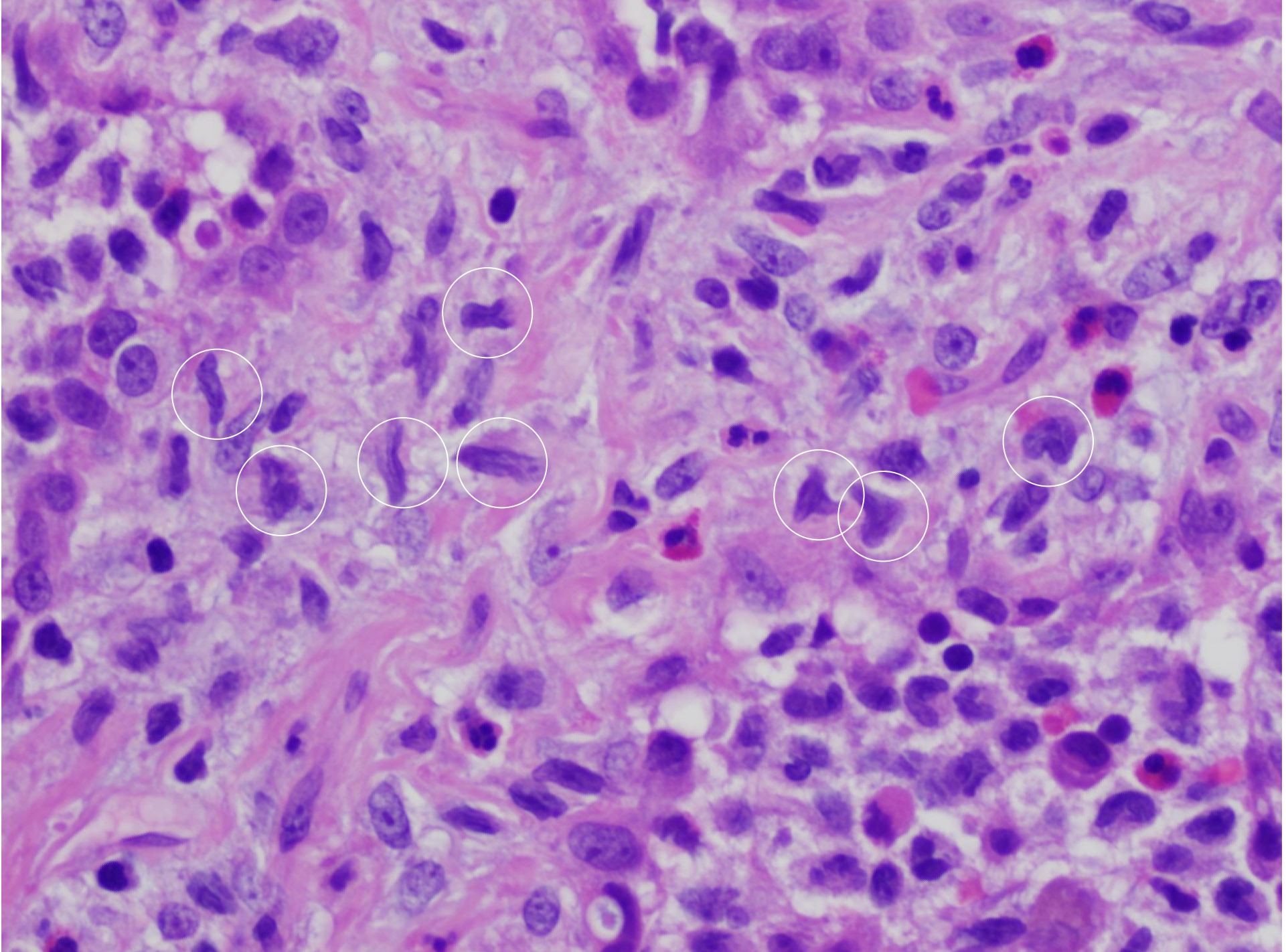




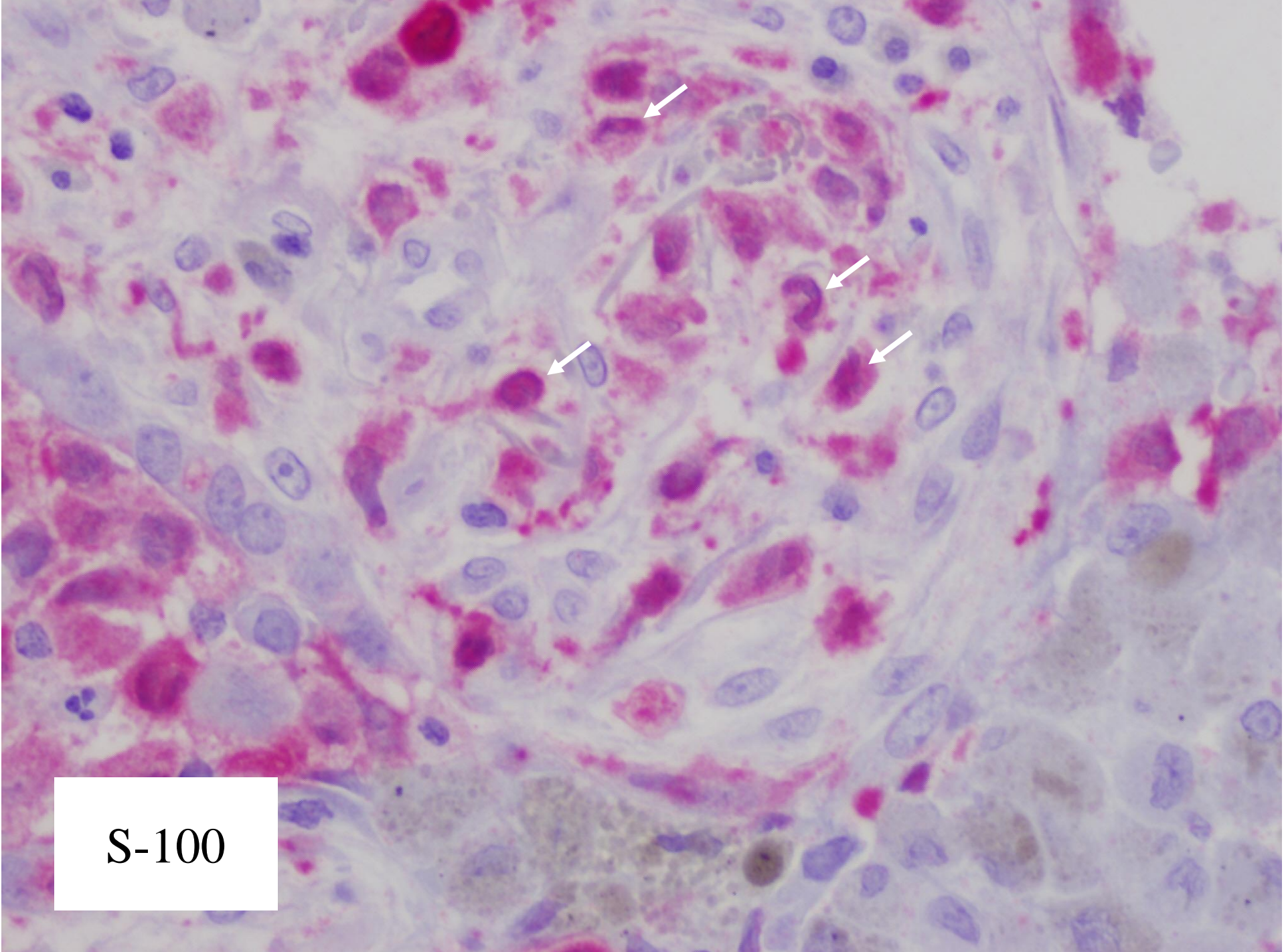






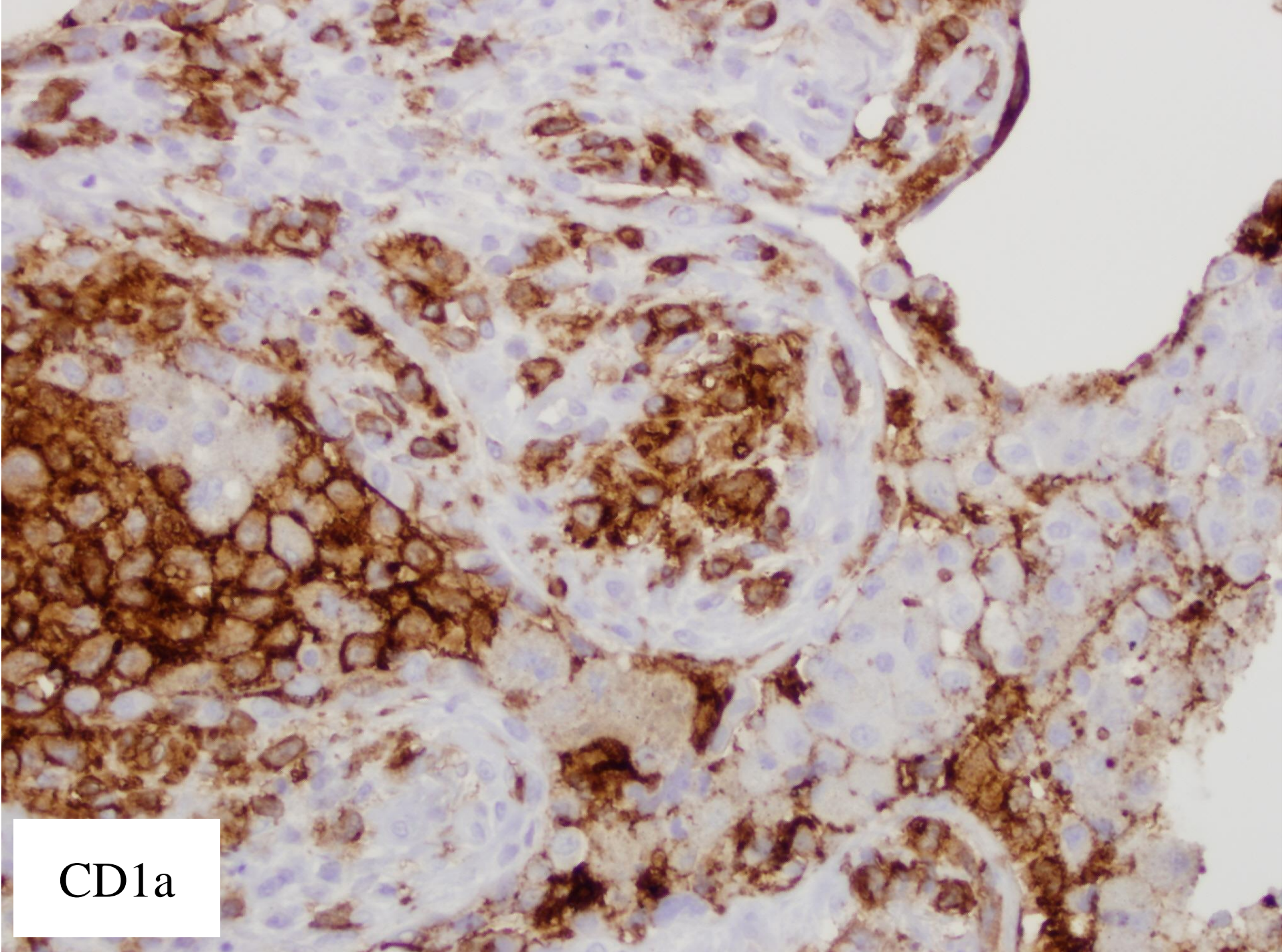






S-100



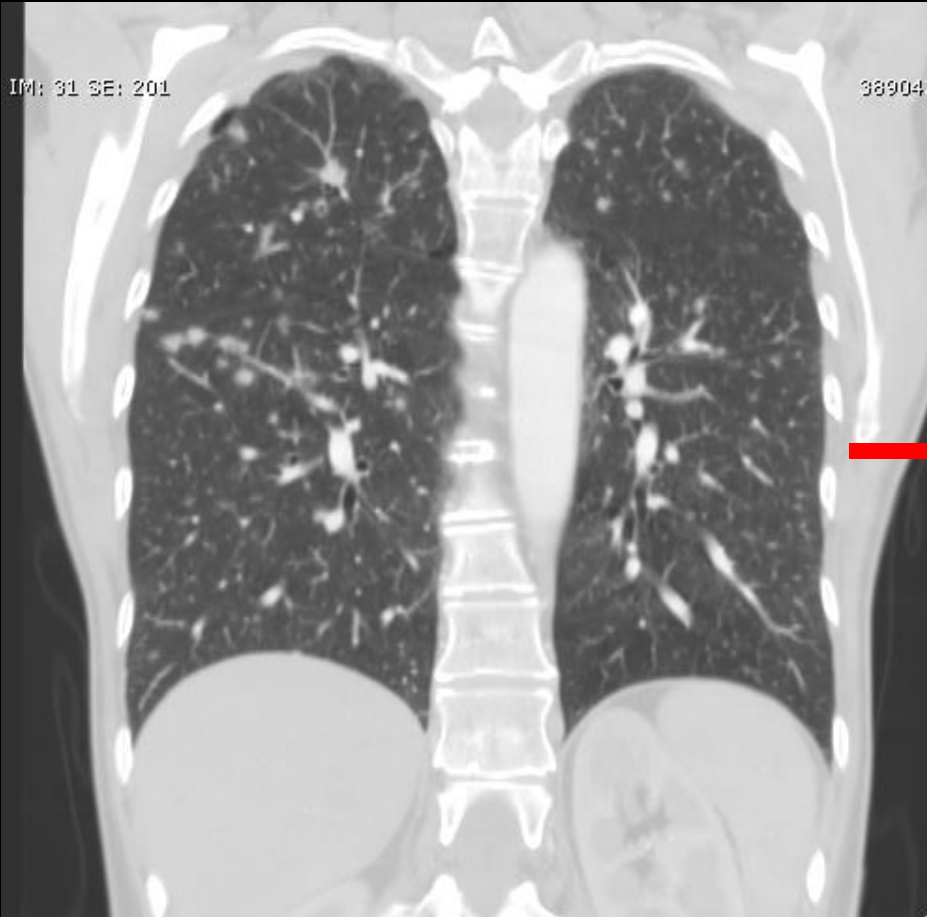


CD1a



10/2009

6/2010



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# Pulmonary Langerhans cell histiocytosis



Paul Langerhans, German pathologist











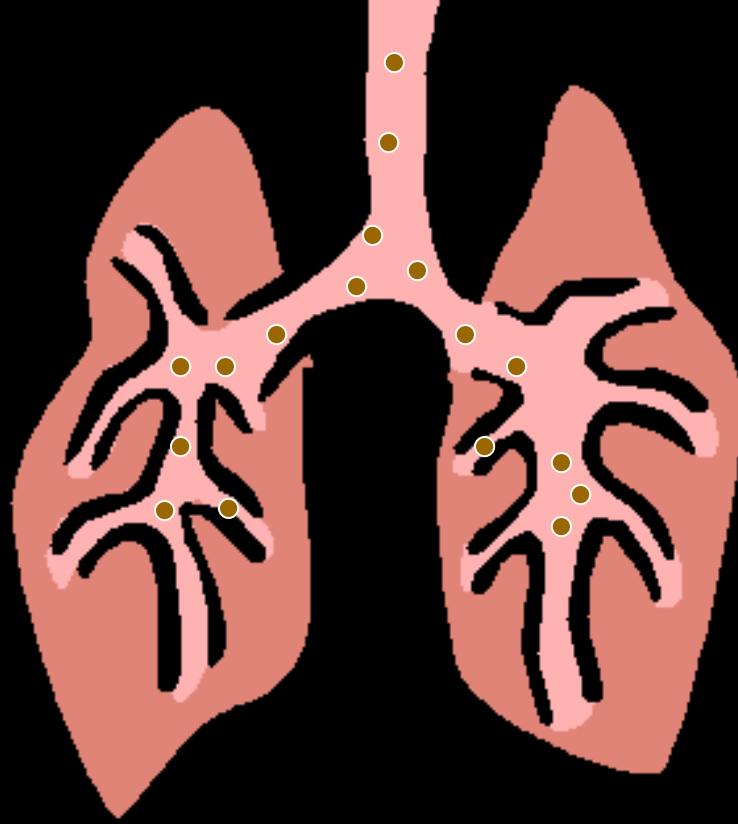






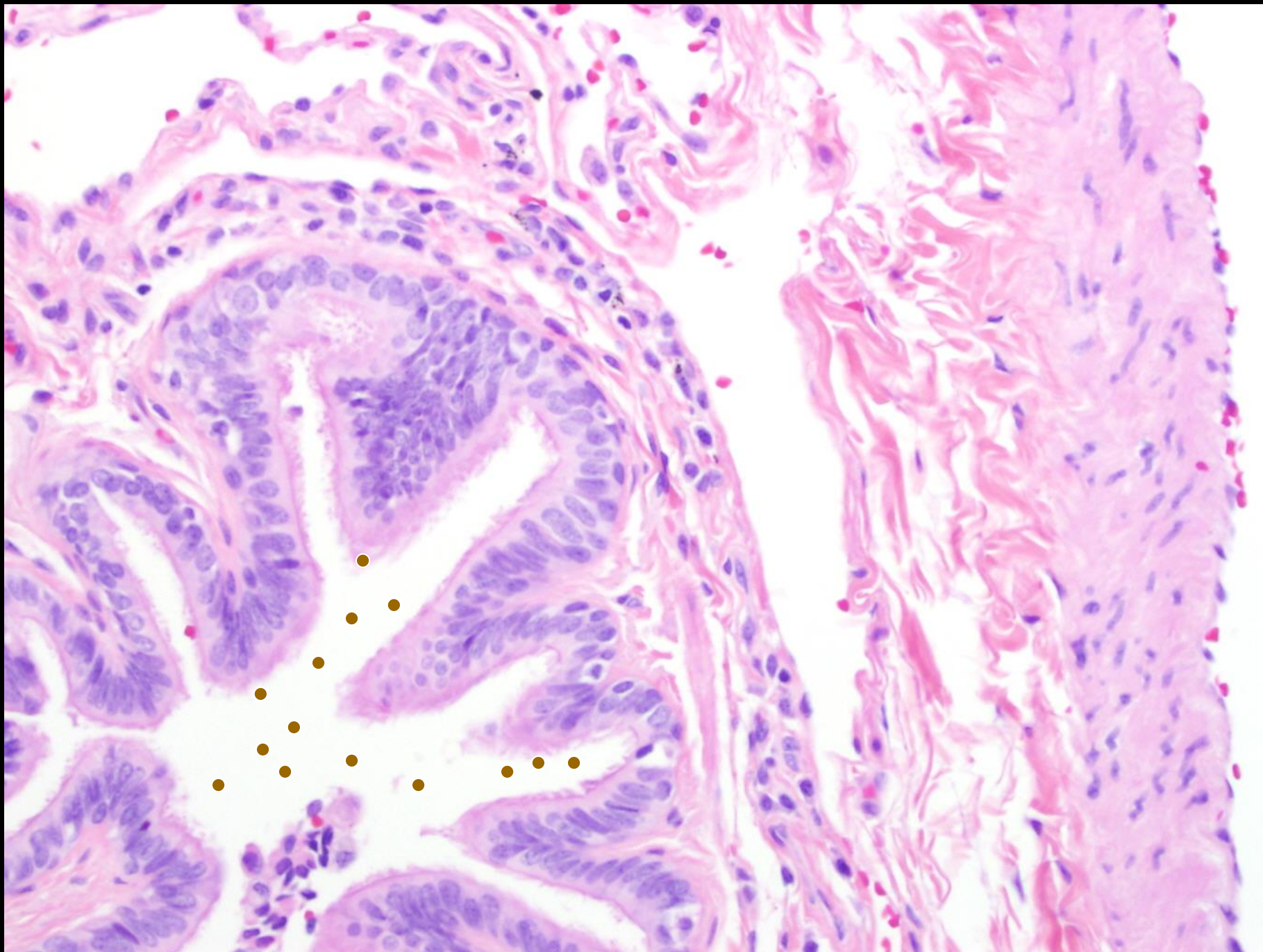




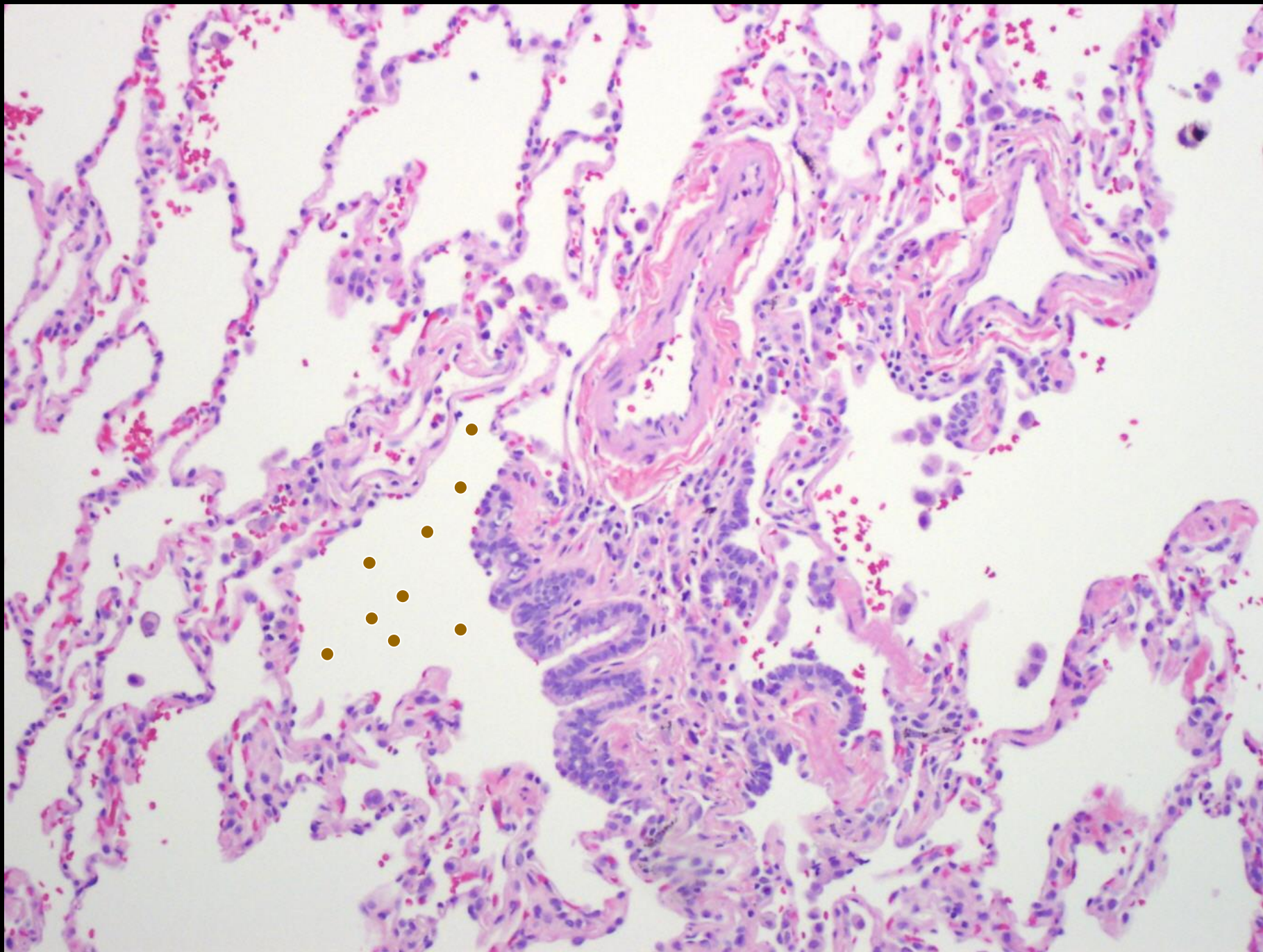




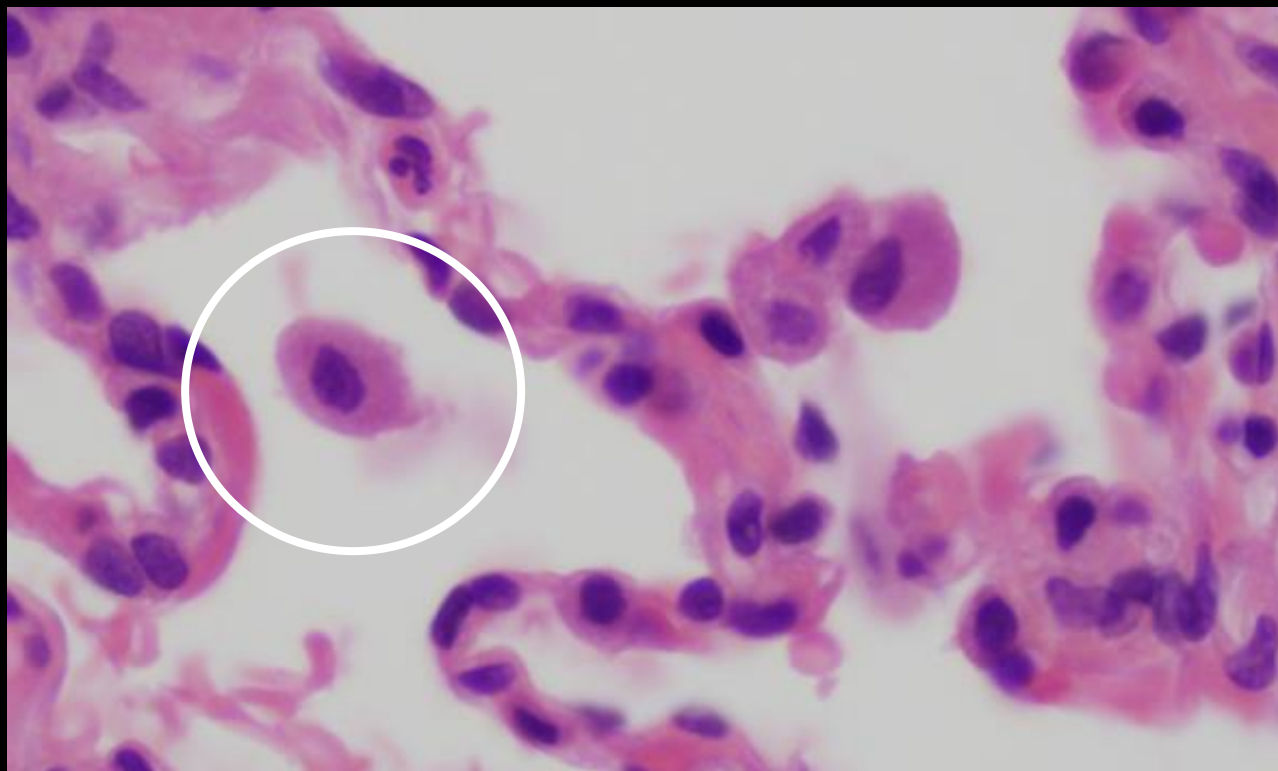


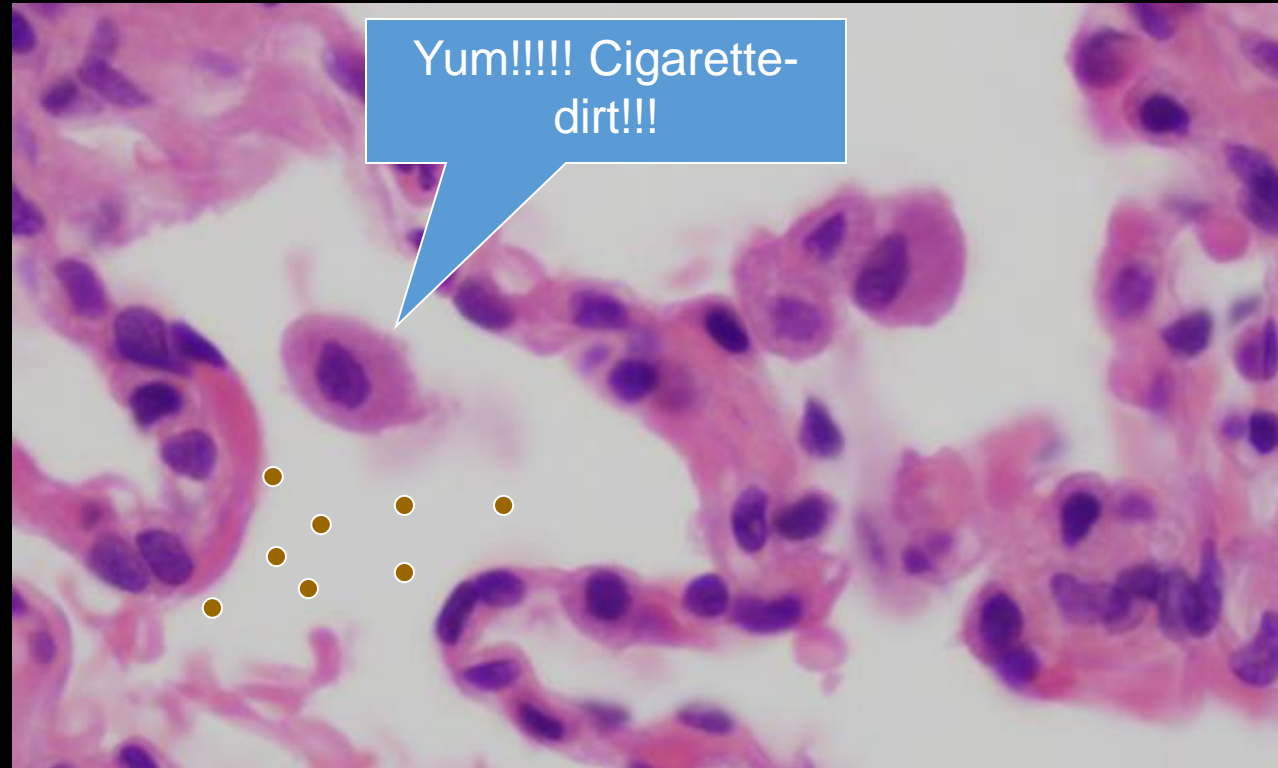




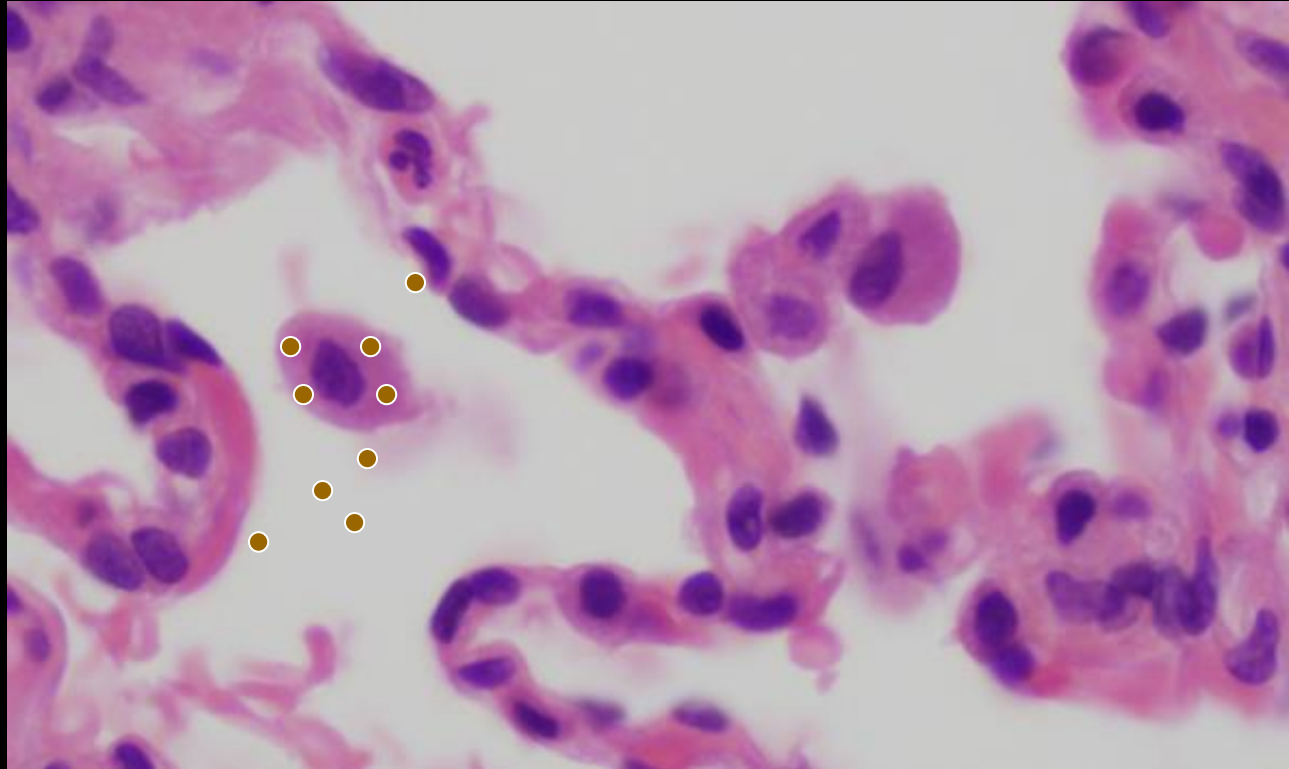


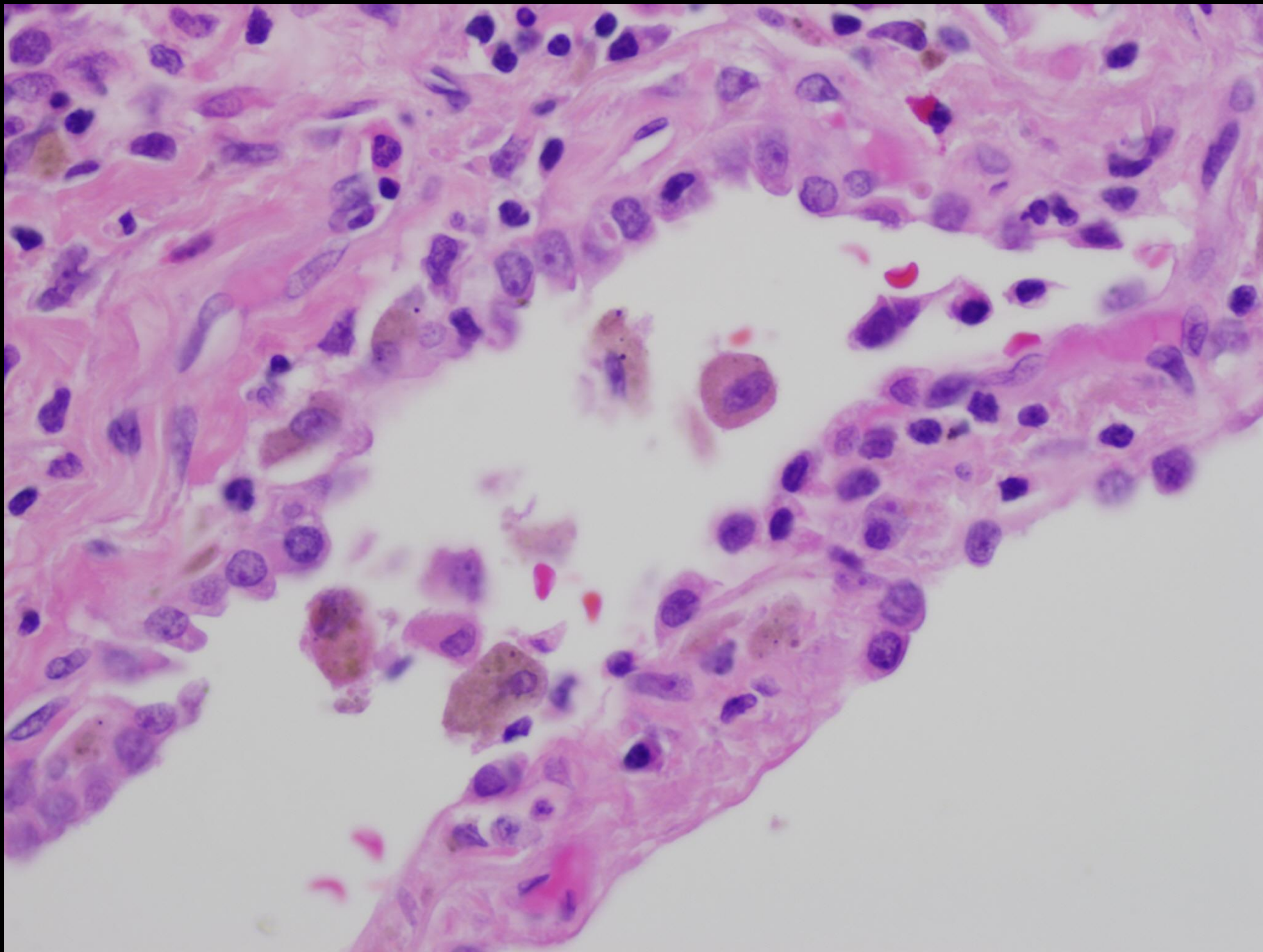




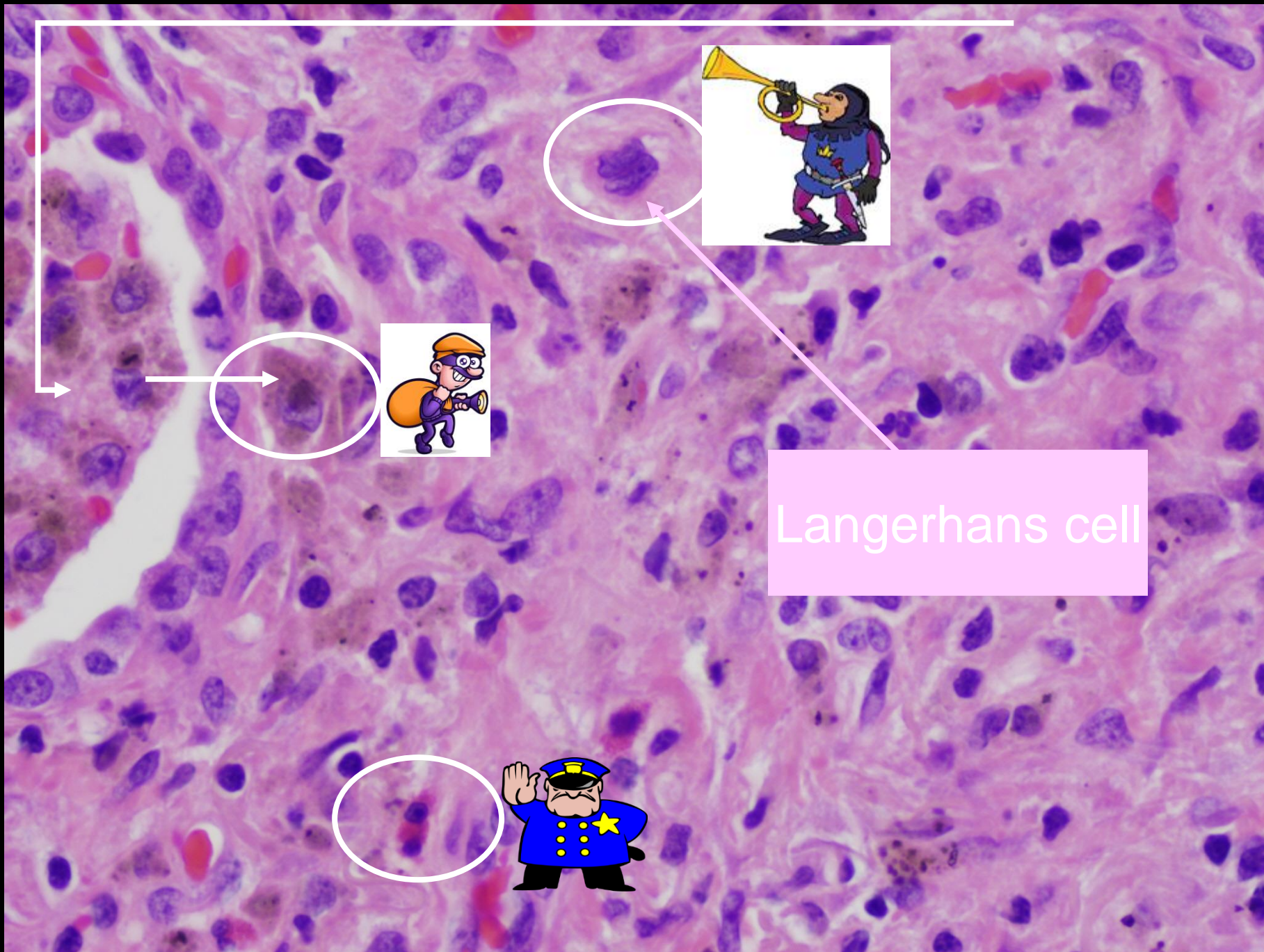






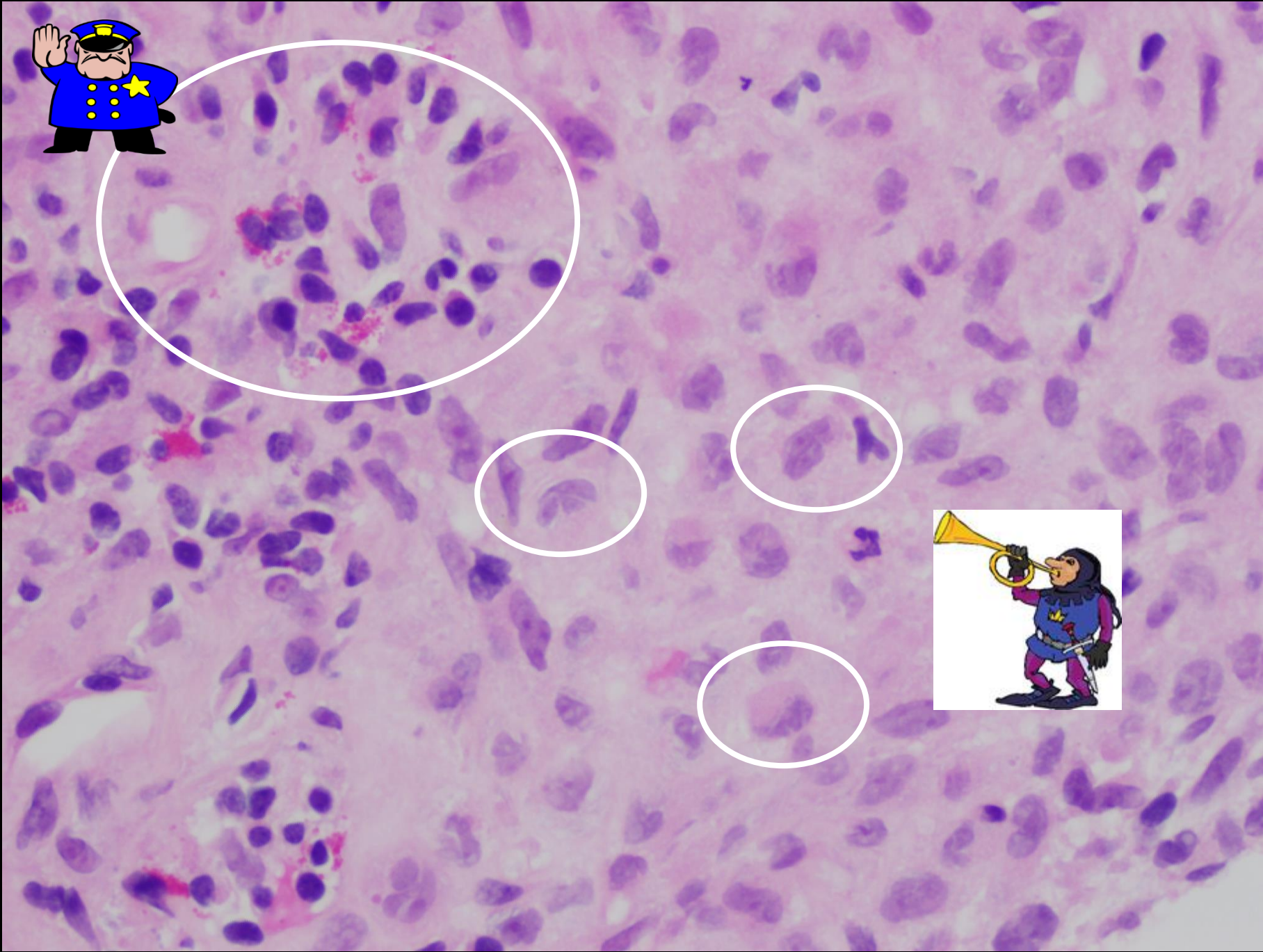




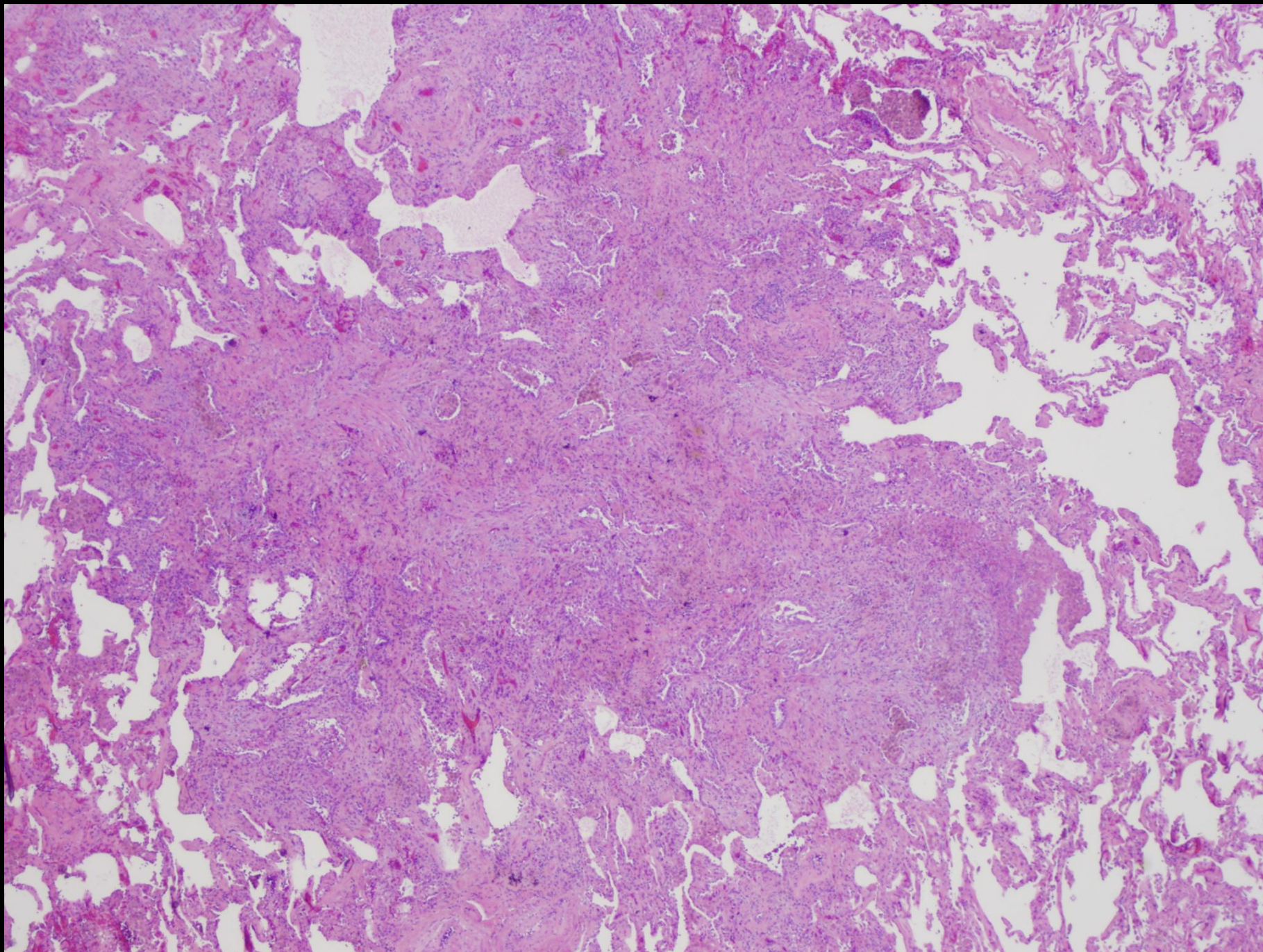


Langerhans cell







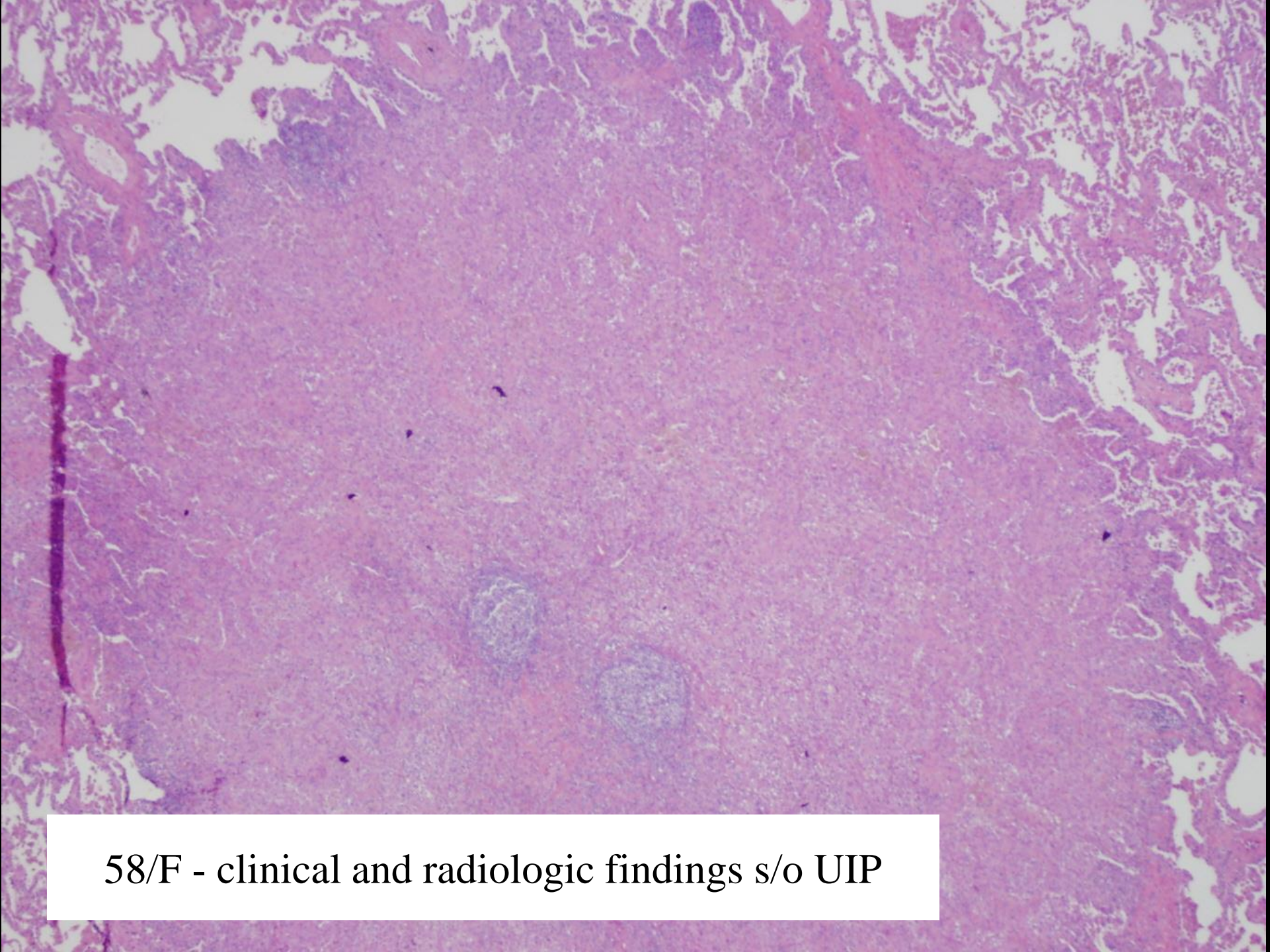






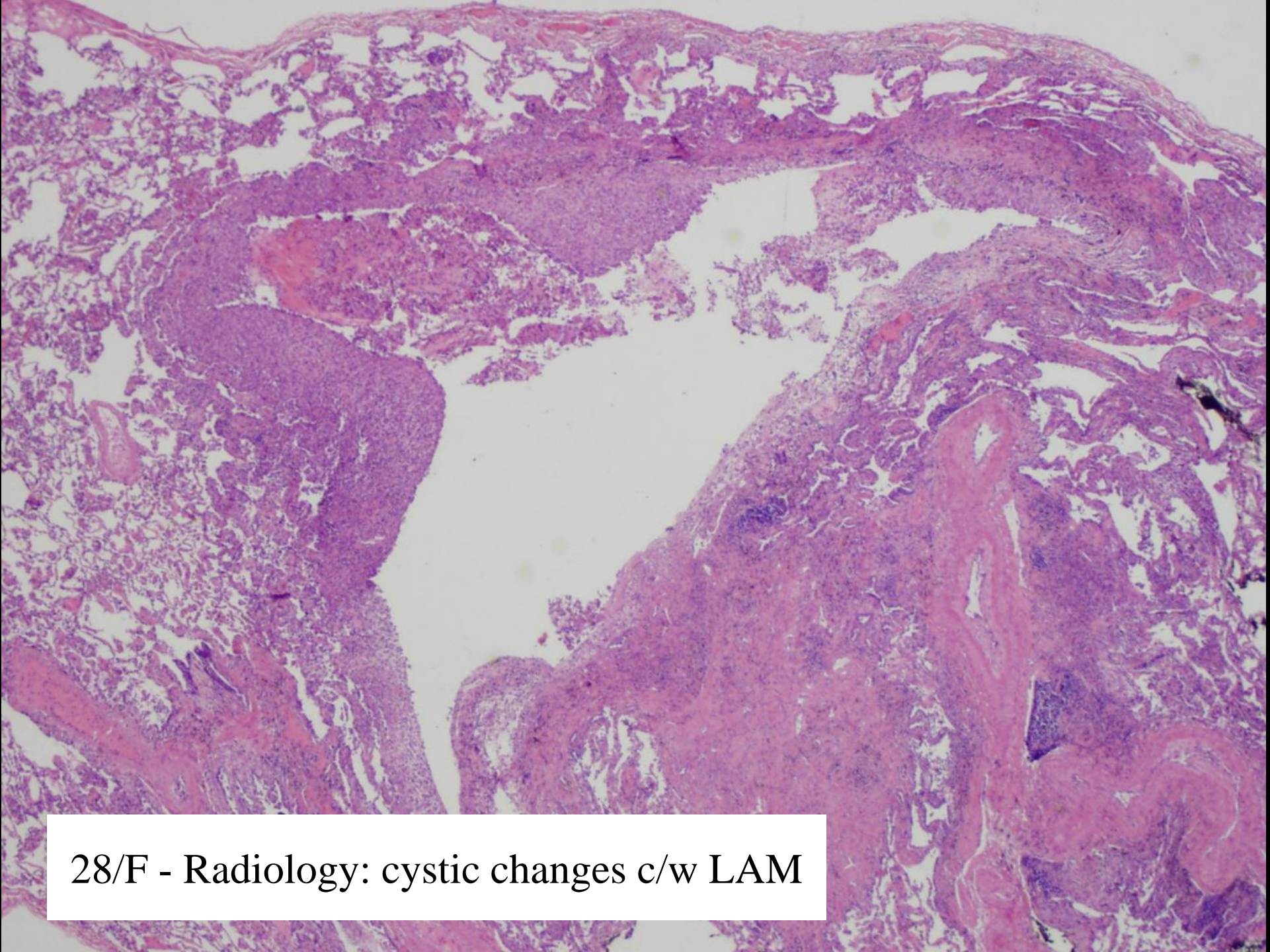






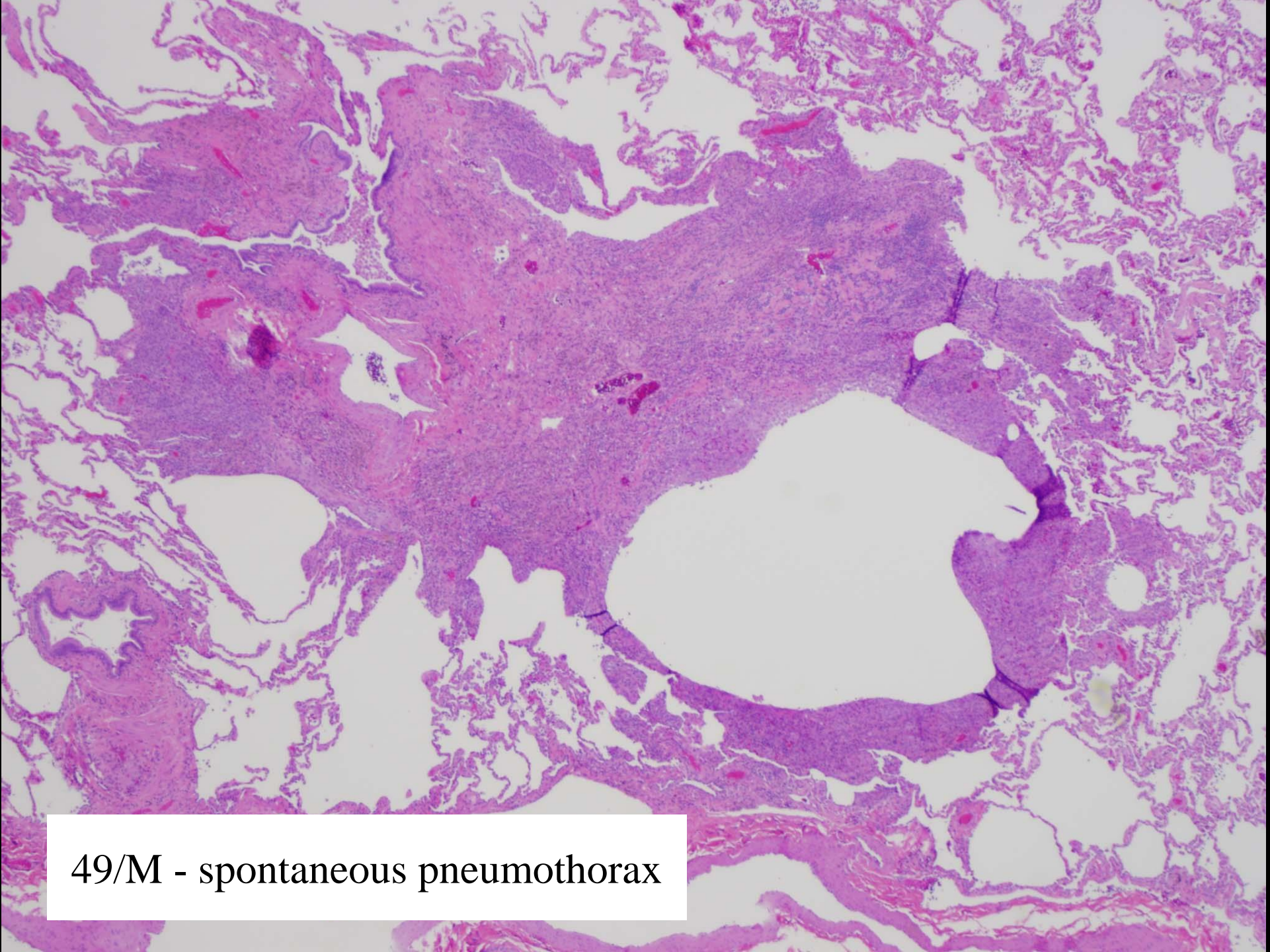
58/F - clinical and radiologic findings s/o UIP





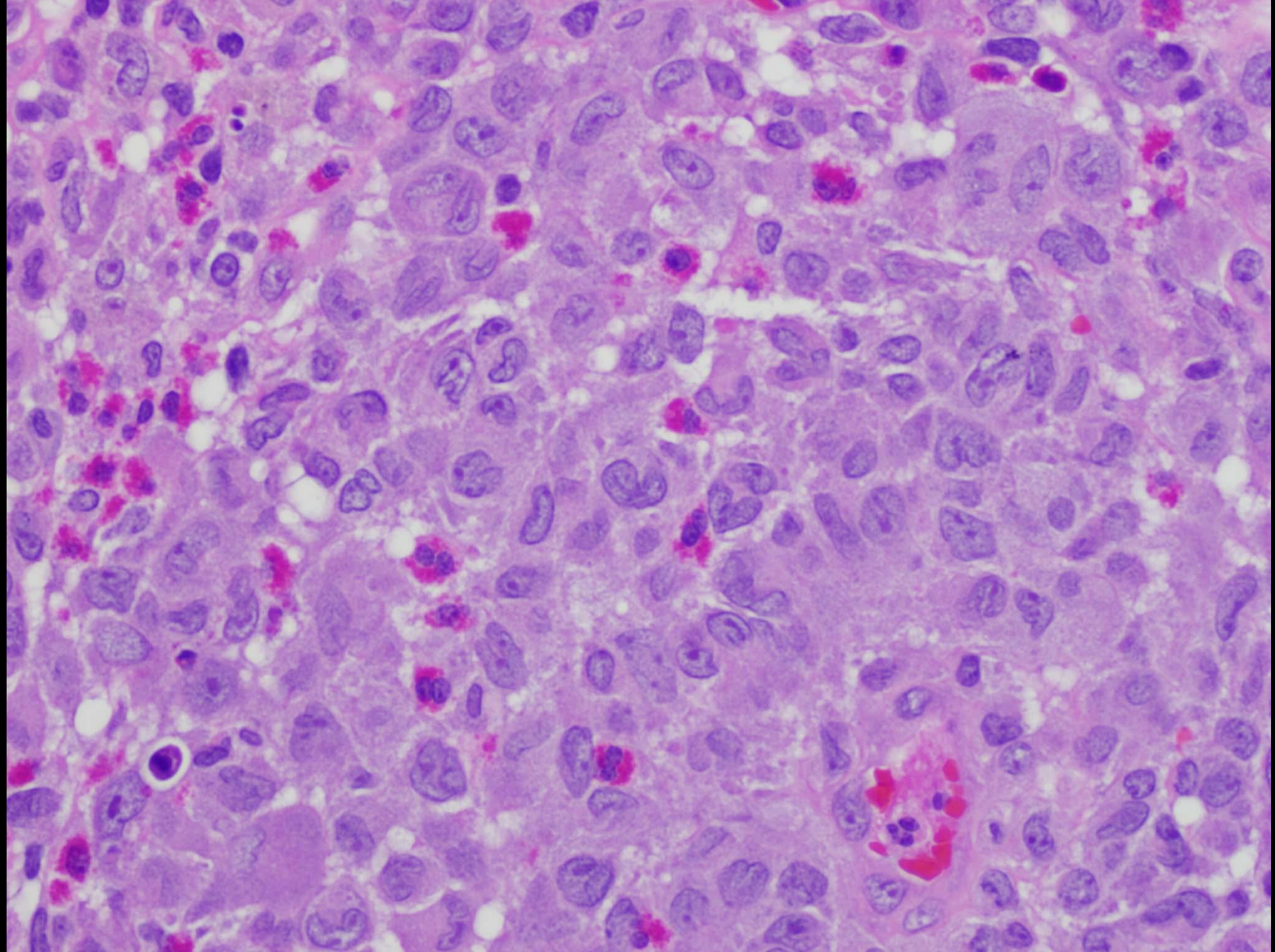
28/F - Radiology: cystic changes c/w LAM



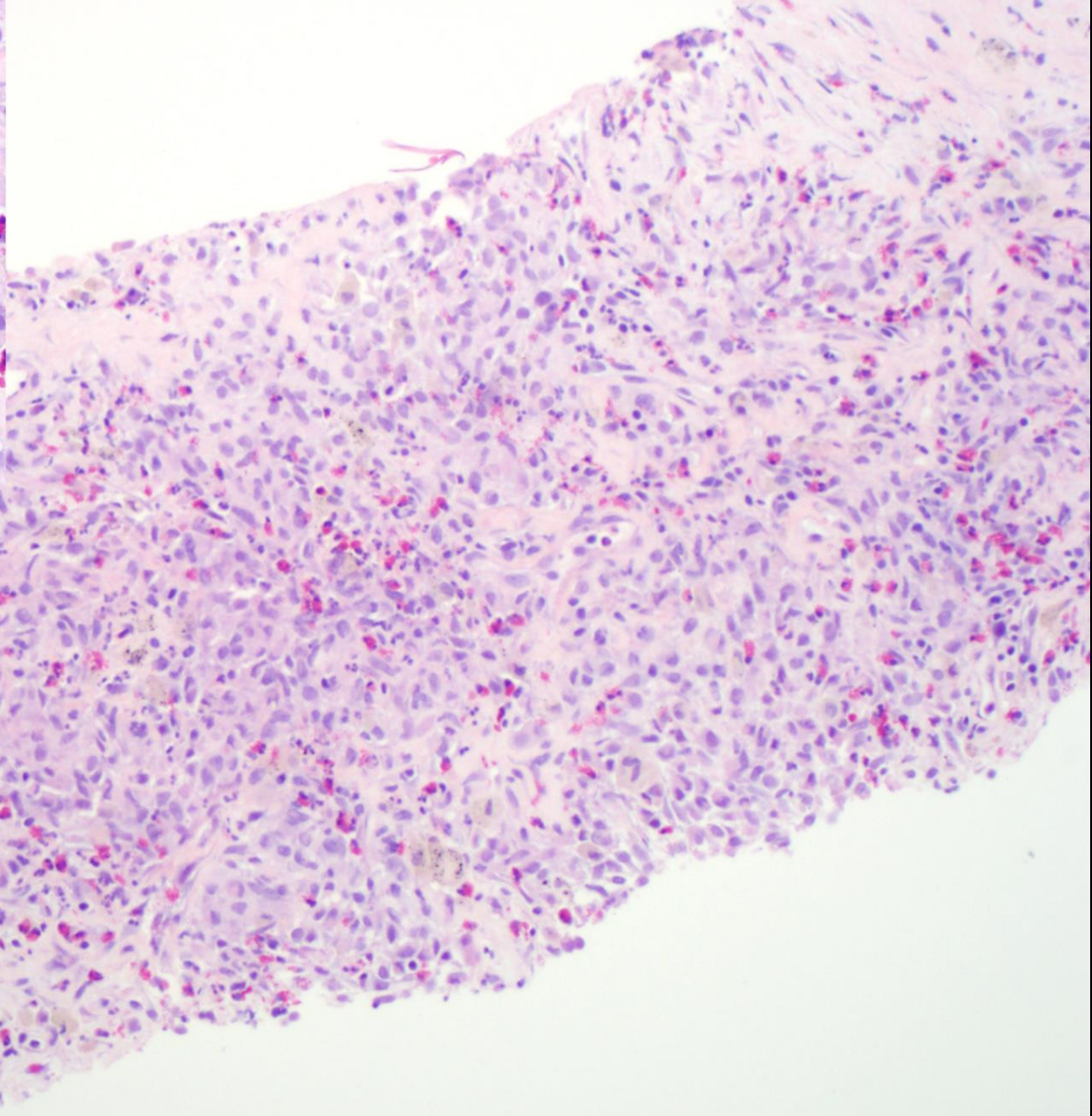
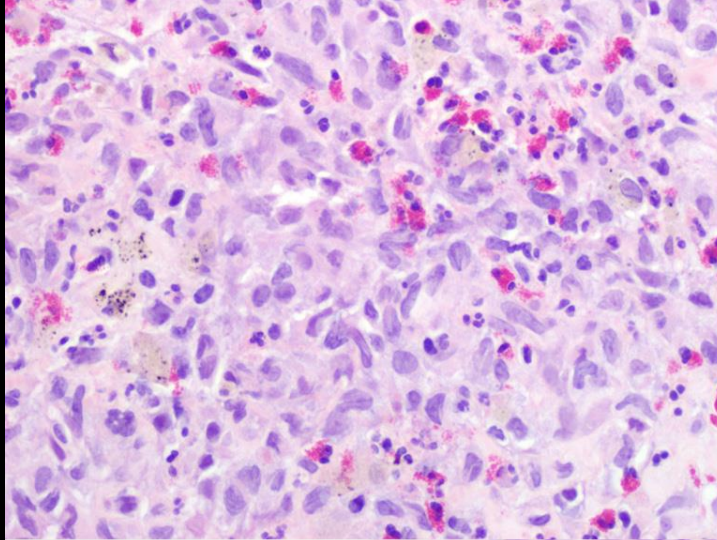


49/M - spontaneous pneumothorax









## Diagnosis of pulmonary Langerhans cell histiocytosis by CT-guided core biopsy of lung: a report of three cases

Sanjay Mukhopadhyay,<sup>1</sup> Shea M Eckardt,<sup>2</sup> Ernest M Scalzetti<sup>3</sup>

### ABSTRACT

A pathological diagnosis of pulmonary Langerhans cell histiocytosis (PLCH) usually requires a surgical lung biopsy. To date, diagnosis of PLCH by core needle biopsy has not been reported. Three cases are presented of PLCH diagnosed by CT-guided core biopsy in adult female smokers found to have multiple small bilateral lung nodules. The nodules biopsied were 5 mm, 7 mm and 1 cm in size, and showed interstitial expansion by Langerhans cells and eosinophils. CT-guided core biopsy should be considered as one of the less invasive techniques by which a pathological diagnosis of PLCH can be established.

### CASE 1

A 68-year-old female 30 pack-year active smoker

noted (figure 3). Pulmonary function tests demonstrated moderate obstruction. The FEV<sub>1</sub>/FVC (forced expiratory volume in 1 s/forced vital capacity) ratio was 0.58 and the DL<sub>CO</sub> (diffusing capacity for carbon monoxide) was 49% of predicted. A metastatic malignancy was suspected. A bone scan performed to evaluate for metastases was negative. CT-guided biopsy of the 1 cm right upper lobe nodule was performed. Cultures were not obtained.

### PATHOLOGICAL FINDINGS

Pathological findings were similar in all three cases, showing expansion of fibrotic pulmonary interstitium by Langerhans cells along with pigment-laden histiocytes and scattered eosinophils (figure 1–3). Focal necrosis was additionally

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<sup>2</sup>Department of Medicine, State University of New York Upstate Medical University, Syracuse, New York, USA

<sup>3</sup>Department of Radiology, State University of New York Upstate Medical University, Syracuse, New York, USA

Correspondence to: Sanjay Mukhopadhyay, Department of Pathology, State University of New York Upstate Medical University, 750 E. Adams St., Syracuse, NY 13210, USA; mukhopas@upstate.edu

63/F - h/o SLE, RA, multiple nodules, all <1 cm, some cavitory



# Pulmonary Langerhans cell histiocytosis

- A form of **smoking-related** interstitial lung disease
- Nearly 100% of cases occur in smokers!
- Think of this if you get a surgical lung biopsy in a patient with multiple bilateral lung nodules: your clinician will suspect mets or infection!

3







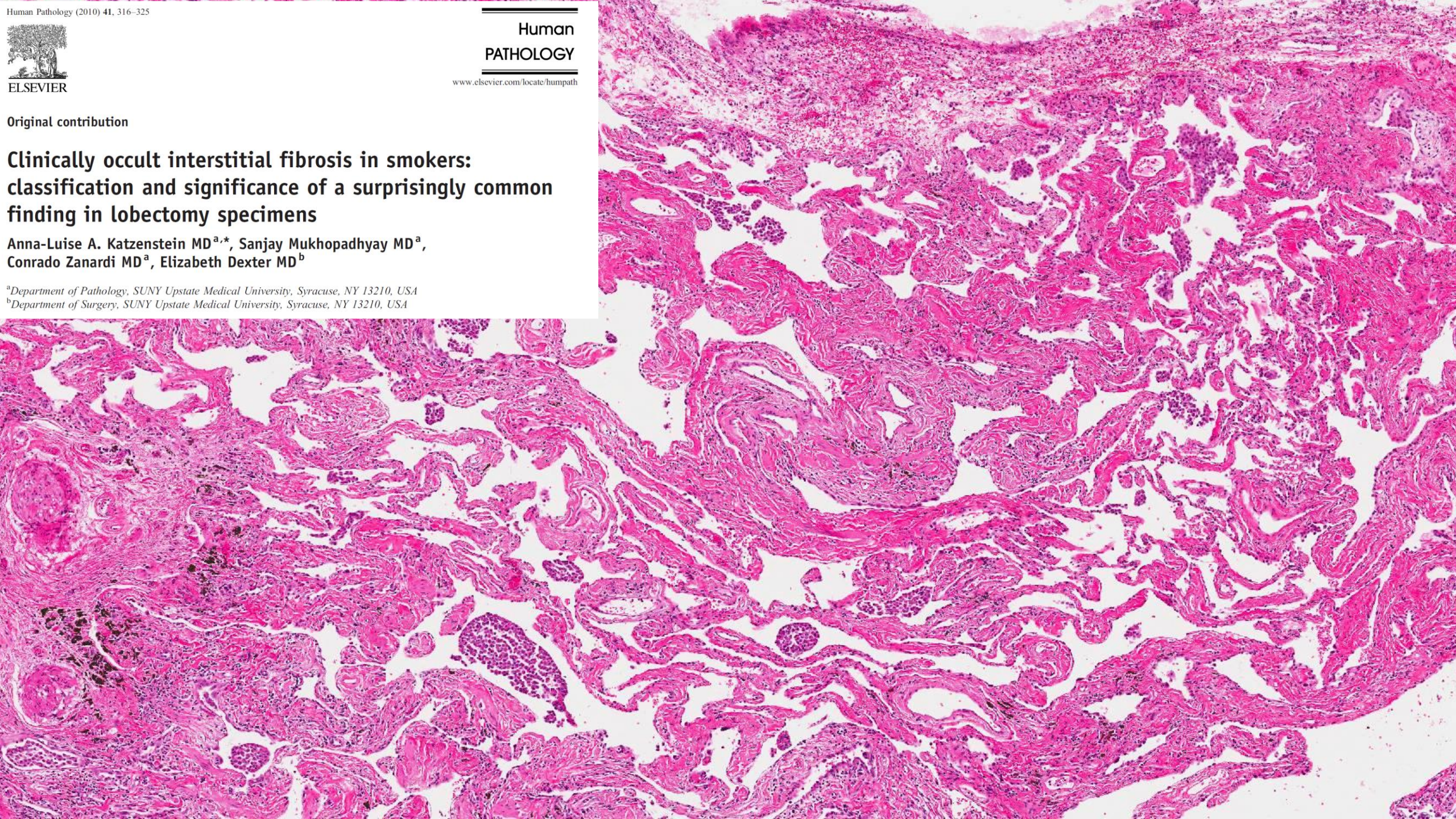
Original contribution

# Clinically occult interstitial fibrosis in smokers: classification and significance of a surprisingly common finding in lobectomy specimens

Anna-Luise A. Katzenstein MD<sup>a,\*</sup>, Sanjay Mukhopadhyay MD<sup>a</sup>,  
Conrado Zanardi MD<sup>a</sup>, Elizabeth Dexter MD<sup>b</sup>

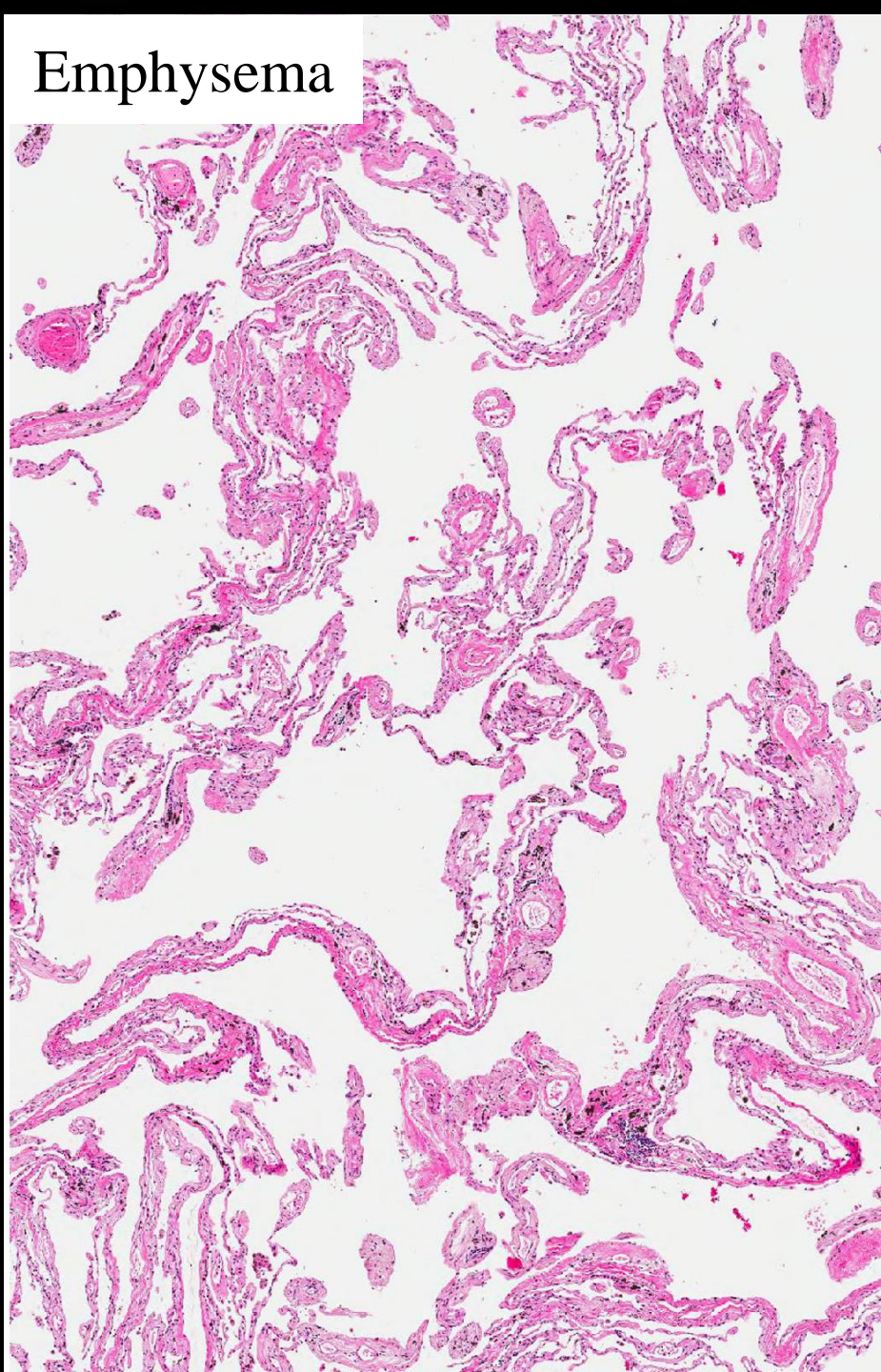
<sup>a</sup>Department of Pathology, SUNY Upstate Medical University, Syracuse, NY 13210, USA

<sup>b</sup>Department of Surgery, SUNY Upstate Medical University, Syracuse, NY 13210, USA

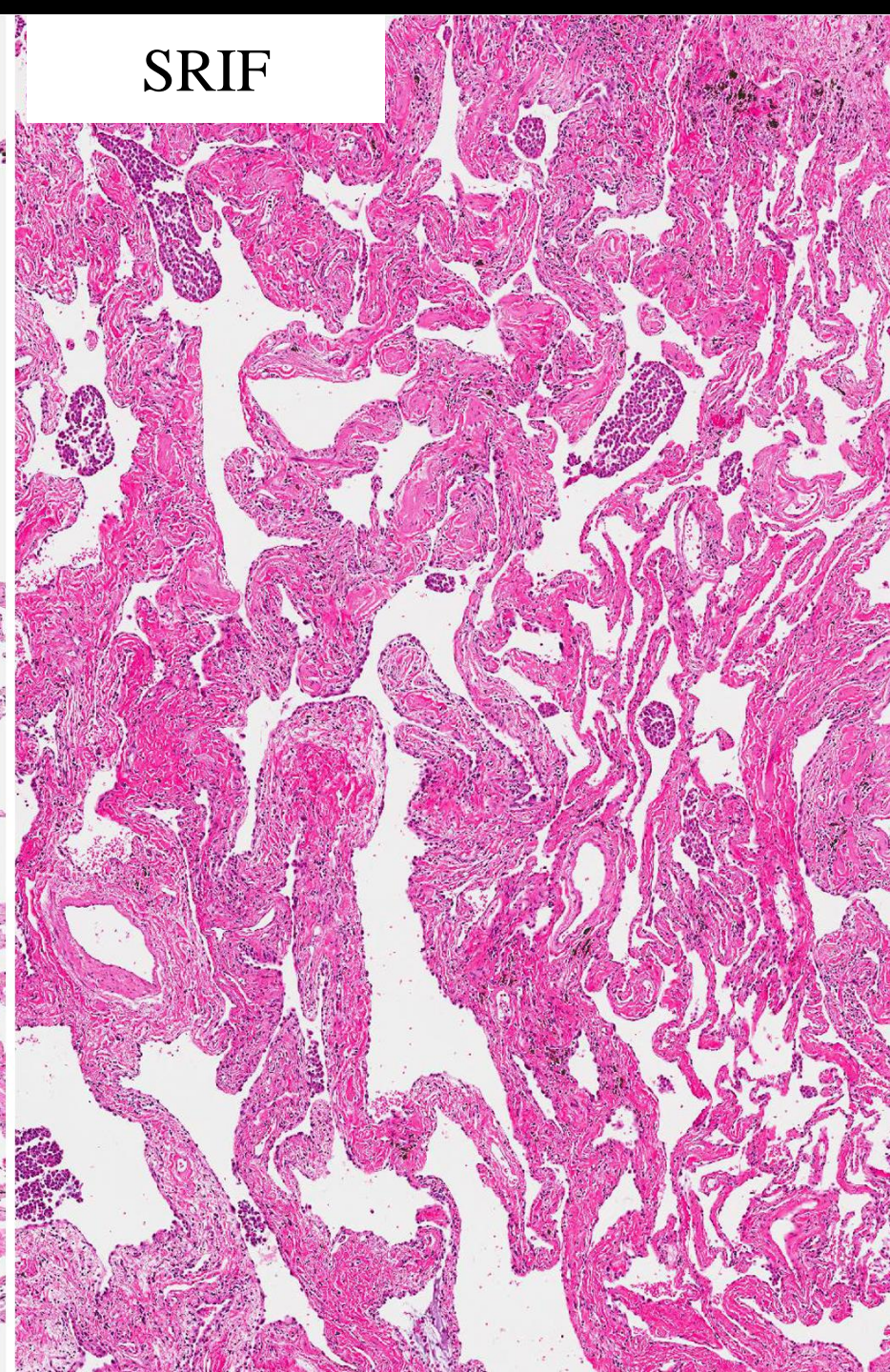




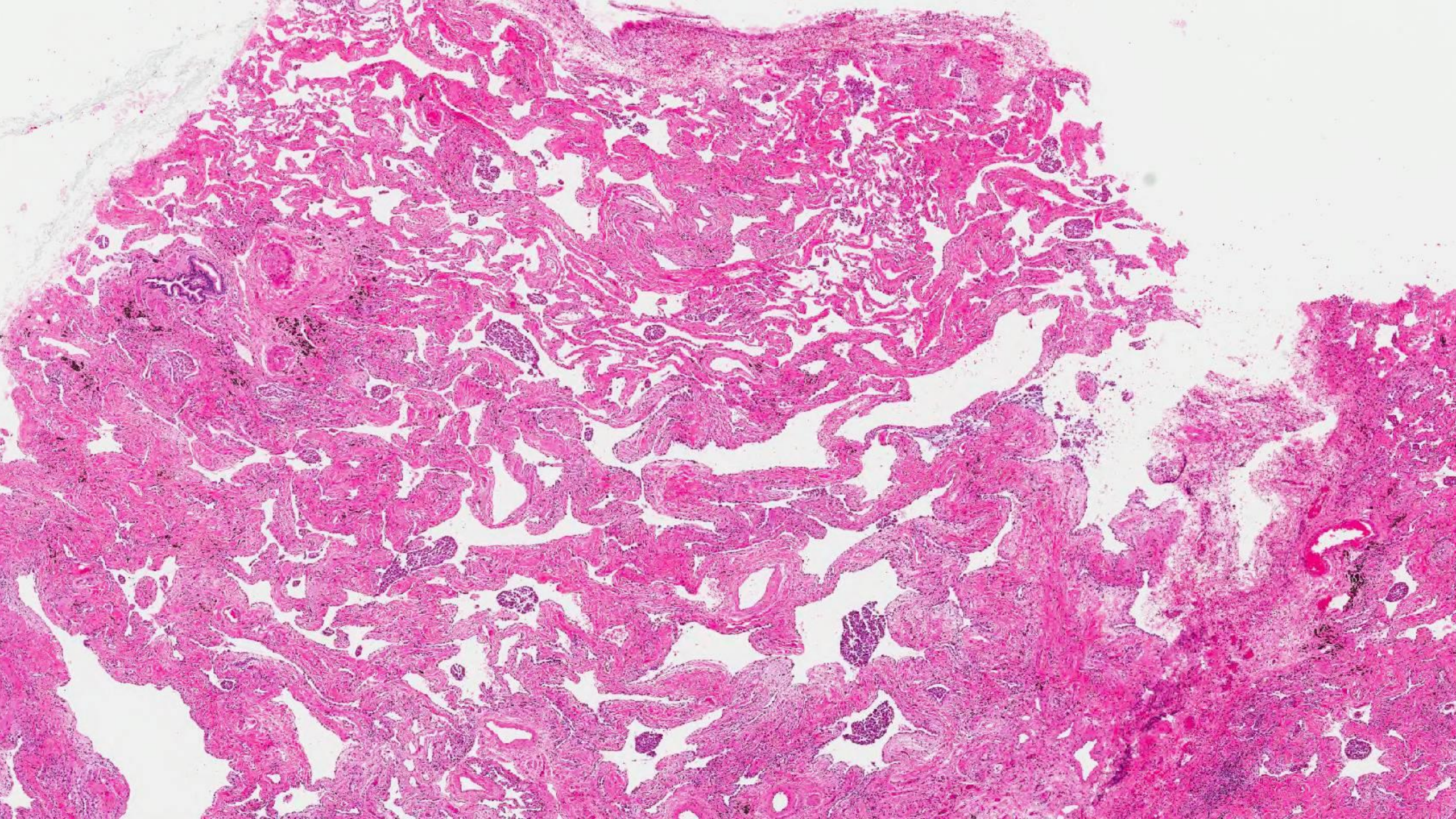
Emphysema



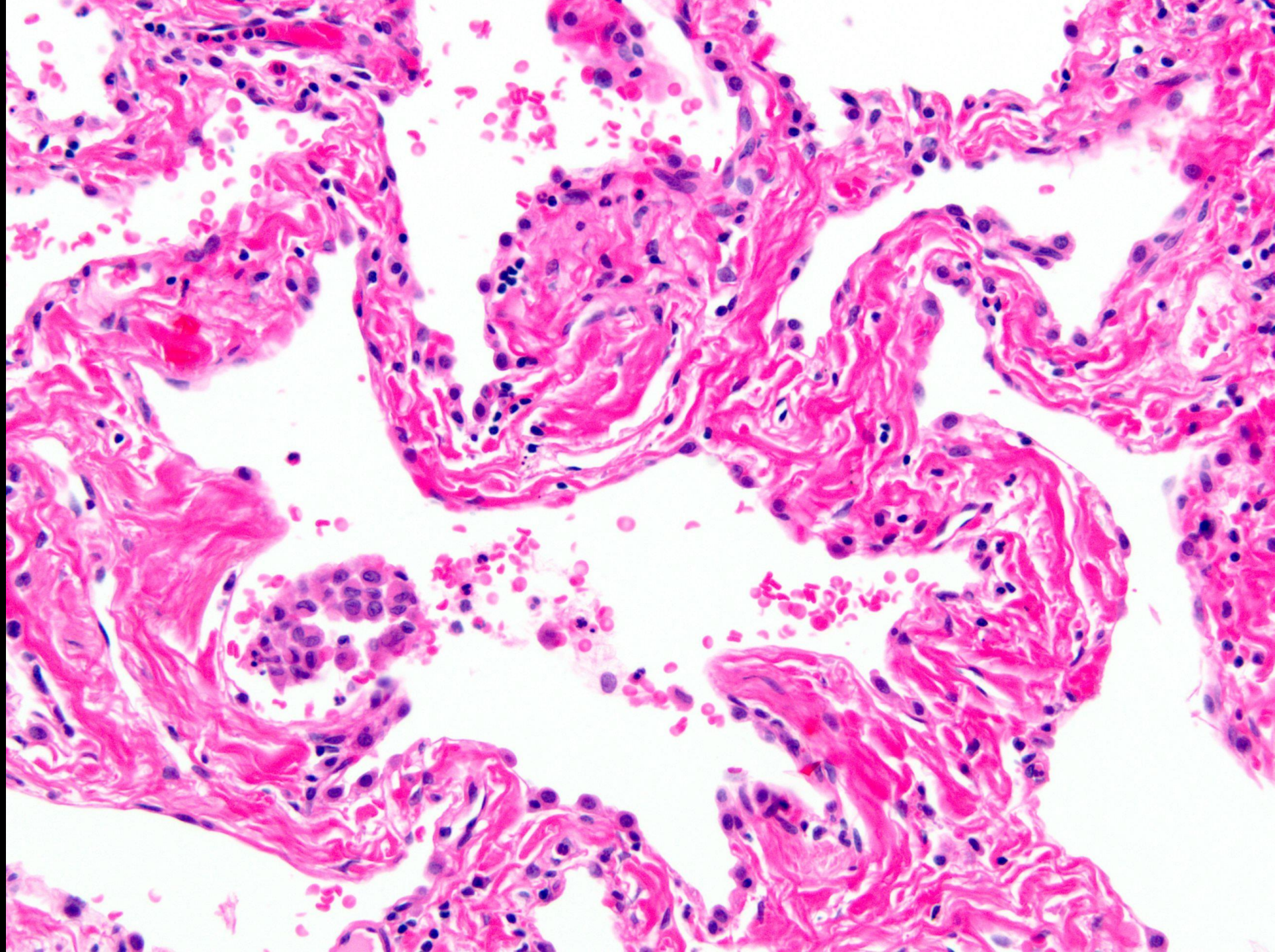
SRIF



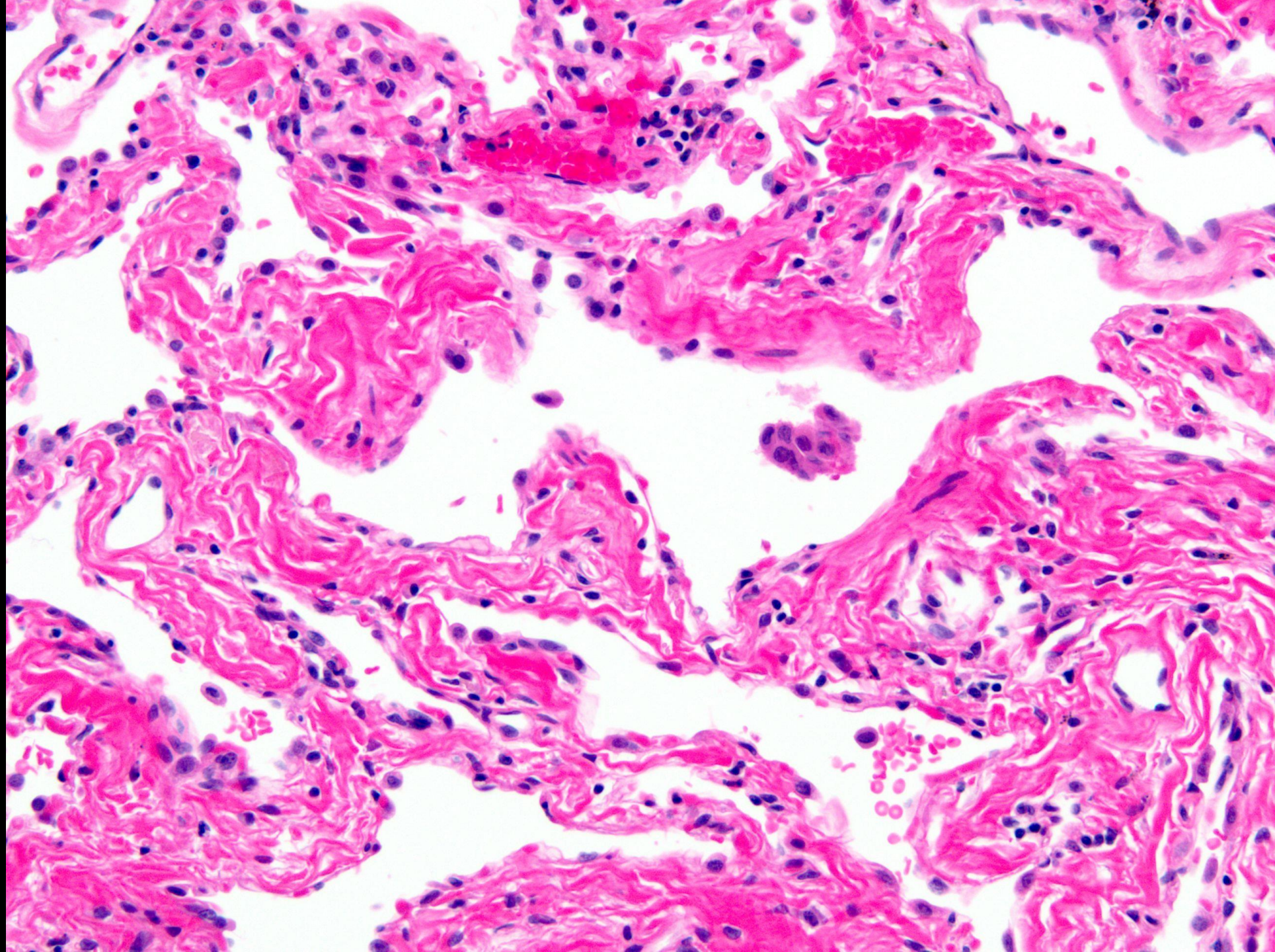




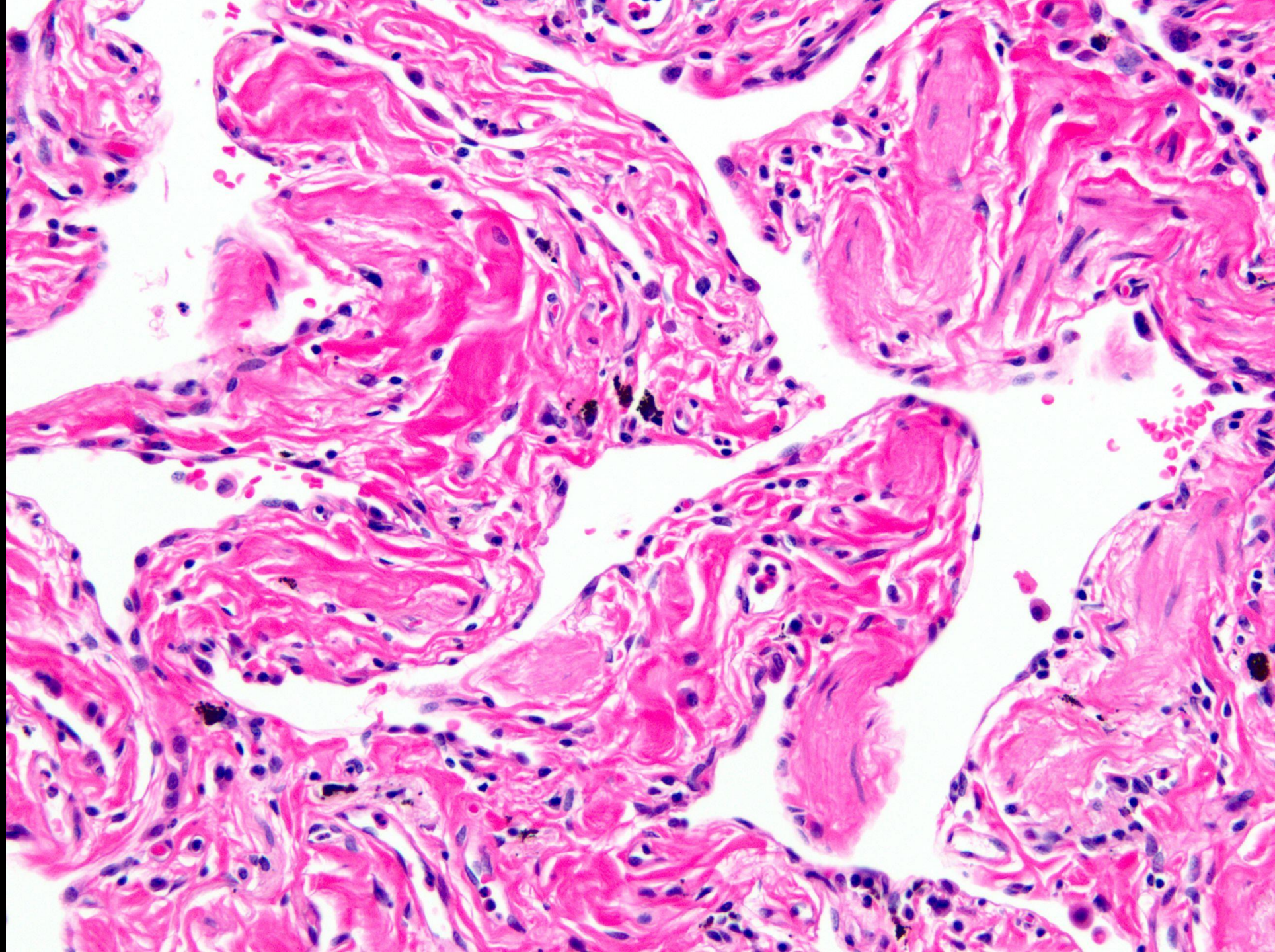














# Smoking-related interstitial fibrosis (SRIF)

- A recently described form of smoking-related interstitial lung disease
- Pathognomonic triad = “ropy” alveolar septal fibrosis + emphysema + pigmented airspace macrophages
- Highly specific for smoking
- Often misdiagnosed as NSIP, HP, UIP, RBILD/DIP, etc.



# PART 2: VAPING





**Vape** (verb): To inhale the aerosol generated by a handheld battery-powered electronic **vaporizer**

**E-cigarette/ENDS**

Contents of vapor:

Nicotine

Propylene glycol-  
vegetable glycerin  
("PG-VG")

Flavorings



**Weed vaporizer  
(vape pen)**

Contents of vapor:

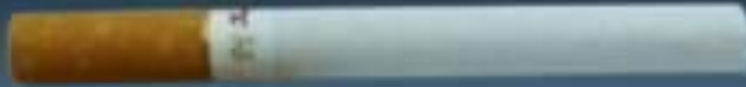
Tetrahydrocannabinol  
(THC)

+/- vitamin E acetate  
in illicit, off-the-street  
cartridges



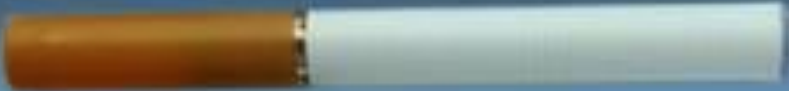
# 2006-2007

E-cigarettes  
introduced  
in United  
States



Cigarette

8.5(D)\*89(L)mm



KR-808A

8.5(D)\*98(L)mm



KR-808

9.2(D)\*110(L)mm



KR-308

9.2(D)\*110(L)mm



KR-308

9.2(D)\*110(L)mm



KR-308

9.2(D)\*119(L)mm



KR-208

9.2(D)\*153(L)mm



KR-108



# 2018



## Debut of Honey Cut



# 2019



## From 'Veronica Mars' to toxic vapes: The rise and fall of Honey Cut

By Marissa Wenzke, with David Downs

November 8, 2019

### Trademark, incorporate, sell sell sell

By the spring of 2019, Honey Cut's success apparently made the company's founder think about protecting his assets. "Just in the first four months of 2019, we had more sales than all of 2018," [Honey Cut's website stated](#). So Temple filed an [application with the US Patent and Trademark Office \(USPTO\)](#) on March 8 to trademark the Honey Cut logo. On the application, the Honey Cut founder listed the same email as he did on his old IMDB Pro account back in his acting/casting days.

Three days later, Temple [registered Honey Cut Labs](#) as a limited liability corporation with the State of California.

Temple described Honey Cut in the USPTO application as an "electronic cigarette liquid (e-liquid) comprised of flavorings in liquid form." He stated it contained propylene glycol and vegetable glycerin, compounds widely used in vaping products. Nowhere on the application were the words "vitamin E acetate" mentioned.

On June 19, Honey Cut posted to [Instagram a video of boxes and boxes of amber glass jugs](#) filled with the thickener prepped for shipping. The operation was pumping.



# 2019



## From 'Veronica Mars' to toxic vapes: The rise and fall of Honey Cut

By Marissa Wenzke, with David Downs

November 8, 2019

### What made Honey Cut so popular?

Honey Cut took off because it made illicit vape cartridge makers a lot of money. The product fooled consumers into thinking they bought something pure. Honey Cut's color and thickness closely resemble that of pure THC oil. It's available online and does not affect the appearance or flavor of THC oil. As such, it fooled consumers performing what's known as the "[bubble test](#)."

Pure THC extract is a thick amber oil, and traditional THC oil cutting agents thin the oil. In response, customers learned to detect cut oil by flipping over vape cartridges to see how the air bubble moves inside the tank—much like the bubble in a carpenter's level. A fast-moving bubble means the oil had been thinned with a cutting agent and wouldn't deliver the high THC potency a consumer desires.

### Related

[Journey of a tainted vape cartridge: from China's labs to your lungs](#)

Tocopheryl-acetate defeats the bubble test by cutting THC oil without thinning it. For years, THC oil had been mixed with the common additives propylene glycol or vegetable glycerin, used to allow the oil to flow and contact the vape pen's heating device. Instead of 10% or 15% propylene glycol cuts, vape cartridge makers could cut THC oil by up to 80%, Honey Cut promised, and consumers would never know.

The chemical created huge profit margins for Honey Cut. Temple could import raw vitamin E acetate for \$8.50 to \$42.60 a liter (converted from gallons), re-package it, and mark it up to between \$1,100 and \$1,350 a liter. That's about a 1,300% markup on every liter.

Even with the import markup, illicit THC vape cartridge fillers who spent \$1,000 on a liter of Honey Cut could fool consumers by stretching their supplies of THC oil and pocket an extra \$5,000 in profit.

Vitamin E acetate also remains perfectly legal to sell in any form. Illegal THC vape cartridge makers shoulder all the legal risk.



# September 6, 2019

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin — Preliminary Report

Jennifer E. Layden, M.D., Ph.D., Isaac Ghinai, M.B., B.S., Ian Pray, Ph.D.,  
Anna Kimball, M.D., Mark Jensen, M.D., Mark Tenforde, M.D., Ph.D.



2019



E-cigarette or Vaping product use Associated Lung Injury = EVALI

Images courtesy of Teresa Candler

# September 13, 2019 (around peak of outbreak)

TABLE. CDC surveillance case definitions\* for severe pulmonary disease associated with e-cigarette use — August 30, 2019



Case classification	Criteria
Confirmed	Using an e-cigarette (“vaping”) or dabbing <sup>†</sup> during the 90 days before symptom onset
	AND
	Pulmonary infiltrate, such as opacities on plain film chest radiograph or ground-glass opacities on chest computed tomography
	AND
	Absence of pulmonary infection on initial work-up: Minimum criteria include negative respiratory viral panel, influenza polymerase chain reaction or rapid test if local epidemiology supports testing. All other clinically indicated respiratory infectious disease testing (e.g., urine antigen for <i>Streptococcus pneumoniae</i> and <i>Legionella</i> , sputum culture if productive cough, bronchoalveolar lavage culture if done, blood culture, human immunodeficiency virus-related opportunistic respiratory infections if appropriate) must be negative
	AND
	No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process).



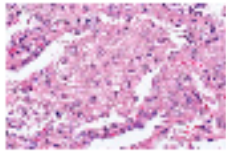
October 2, 2019

CORRESPONDENCE

## Pathology of Vaping-Associated Lung Injury

Y.M. Butt and Others

This letter describes findings in 17 patients with a history of vaping who had lung biopsies after presenting with symptoms and bilateral pulmonary opacities that led to a clinical diagnosis of vaping-associated lung injury. The lung histopathology is described, along with some preliminary insights into the pathogenesis of acute lung injury.



FREE

OCT 02

HEALTH

The New York Times

## Lung Damage From Vaping Resembles Chemical Burns, Report Says

Doctors at the Mayo Clinic examined samples of lung tissue from 17 patients, all of which looked as if the people had been exposed to toxic chemicals, the researchers said.



The lung damage in some people who have become ill after vaping nicotine or marijuana products looks like that seen in people exposed to some chemical weapons, a

October 17, 2019

# **Lung Biopsy Findings in Severe Pulmonary Illness Associated With E-Cigarette Use (Vaping)**

## **A Report of Eight Cases**

Sanjay Mukhopadhyay, MD,<sup>1</sup> Mitra Mehrad, MD,<sup>2</sup> Pedro Dammert, MD,<sup>3,4</sup> Andrea V. Arrossi, MD,<sup>1</sup> Rakesh Sarda, MD,<sup>5</sup> David S. Brenner, MD,<sup>4</sup> Fabien Maldonado, MD,<sup>6</sup> Humberto Choi, MD,<sup>7</sup> and Michael Ghobrial, MD<sup>7</sup>

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From the <sup>1</sup>Department of Pathology and <sup>7</sup>Respiratory Institute, Cleveland Clinic, Cleveland, OH; <sup>2</sup>Department of Pathology, Microbiology and Immunology and <sup>6</sup>Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN; <sup>3</sup>Kent Pulmonary Associates, Dover, DE; <sup>4</sup>Bayhealth Medical Center, Dover, DE; and <sup>5</sup>UnityPoint Health—Meriter Hospital, Madison, WI.

**Key Words:** Vaping; Vaping-associated pulmonary illness; Electronic cigarettes; E-cigarettes; Dabbing; Lung pathology; Lung biopsy; Diffuse alveolar damage; Organizing pneumonia; Acute lung injury

*Am J Clin Pathol* 2019;XX:1–10

DOI: 10.1093/AJCP/AQZ182



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DOCTORS SHOW HOW VAPING THC DAMAGES LUNGS, AS ILLNESSES RISE NATIONWIDE

VAPING

Doctors show how vaping THC damages lungs, as illnesses rise nationwide

The CDC now reports more than 1,600 cases of vaping-related lung injuries nationwide.

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WCVB Boston

4 hours ago

More for vaping

Outbreak of Lung Injury Associated with E-Cigarette Use, or ...

https://www.cdc.gov > basic\_information > e-cigarettes > severe-lung-disease

Food and Drug Administration (FDA), state and local health departments, and other clinical and public health partners are investigating a multistate outbreak of lung injury associated with use of e-cigarette, or **vaping**, products. If you have questions about CDC's investigation ... HAN · Quick Facts on the Risks of E ... · Severe Pulmonary Disease · For the Public

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5 Vaping Facts You Need to Know | Johns Hopkins Medicine

https://www.hopkinsmedicine.org > health > wellness-and-prevention > 5-t...

Smoking electronic cigarettes is often considered safer than regular smoking. Learn facts about **vaping** and why you should rethink taking it up.

Electronic cigarette

An electronic cigarette or e-cigarette is a handheld battery-powered vaporizer that simulates smoking and provides some of the behavioral aspects of smoking, including the hand-to-mouth action of smoking, but without burning tobacco. Using an e-cigarette is known as "vaping" and the user is referred to as a "vaper." Wikipedia

Vape companies

Reynolds American

Vapor Group

Turning Point Brands

Kush Bottles

Healthier Choices Manage...

Vape ingredients

Carabao

Juice

Candy

Vanilla

Strawberry

Oct. 24, 2019, 1:50 PM EDT / Updated Oct. 24, 2019, 8:35 PM EDT

By Erika Edwards

The number of life-threatening lung illnesses linked to e-cigarettes has risen to 1,604 nationwide, according to the Centers for Disease Control and Prevention.

Most cases involve THC, the psychoactive ingredient in marijuana that produces a high. However, a minority of patients have reported vaping only nicotine.

Thursday, the CDC updated its count of confirmed and probable cases of what it now calls EVALI, short for "e-cigarette or vaping product use associated lung injury."

Meanwhile, state health departments tell NBC News they've either confirmed or are investigating more than 2,100 cases. Alaska remains the only state without any reported cases.

Two more vaping-related deaths were confirmed Thursday, one in Tennessee and another in Washington, DC. That brings the total number of deaths so far to 36. Other deaths are under investigation.

As the search for a definitive cause continues, a small study published last week in the American Journal of Clinical Pathology provided a closer look at the damage to lung tissue caused by vaping THC.

Researchers at the Cleveland Clinic analyzed lung tissue biopsies taken from eight patients who'd been treated either in Ohio or in other states. All are men, and all mainly vaped THC. One of those patients died.

A microscopic view of the tissue revealed two different patterns of lung injury. One is called organizing pneumonia, which is when tiny airways and air sacs become inflamed. Others had damaged alveoli, the tiny air sacs responsible for allowing oxygen into the blood and carbon dioxide out.

Some patients had a combination of the two.

"This is one more layer of evidence that this is a practice that is causing lung damage," Dr. Sanjay Mukhopadhyay, director of pulmonary pathology at the Cleveland Clinic, said. "That's the major advantage of having a microscopic study."

Table 1

Clinical Features of Patients With Vaping-Associated Pulmonary Illness

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age, y/sex	35/M	22/M	61/M	20/M	21/M	28/M	19/M	28/M
Main symptoms	Fever, night sweats, weight loss, dyspnea, cough, nausea, vomiting	Fever	Dyspnea, cough, chest heaviness, nausea, fever, dizziness	Dyspnea, cough, nausea, vomiting, diarrhea, fever	Cough, flare of inflammatory bowel disease	Dyspnea, cough, fever, nausea	Nausea, weight loss, abdominal pain, fever	Cough, dyspnea, fever, weight loss, night sweats
Substance vaped	90% THC	THC (brand: “Dank”) and nicotine; recent refill of cartridge with 90% THC	THC/marijuana (vaping) and marijuana wax (dabbing)	THC (cannabis oil)	Purified THC	THC	THC, nicotine	93% THC
Approximate time between vaping and symptom onset	Not known	Switched to “Dank” brand a few weeks prior to admission	2 years (vaping) 2 months (dabbing)	2 weeks	Simultaneous	3 weeks	14 months	Not known
Approximate time from symptom onset to presentation	2 days	1 week	3 days	2 weeks	2 weeks	1 week	6 months	3-4 days
Initial total leukocyte count, /μL	19,900	9,320	9,000	44,900	12,400	20,000	15,000	13,340
ESR, mm/h	72	102	Not available	123	23	Not available	89	Not available
CRP, mg/dL	29.5	35.4	Not available	284	31	Not available	20	Not available
Imaging (chest CT)	Bilateral GGO and consolidation, peripherally located	Bilateral GGO and consolidative opacities in mid to lower lung fields	Diffuse bilateral GGO	Diffuse bilateral GGO and basilar	Diffuse bilateral GGO	Bilateral GGO, somewhat patchy	Diffuse bilateral GGO and nodular	Diffuse bilateral GGO with solid nodular densities
Therapy	IV methylprednisolone	IV methylprednisolone	High-dose IV corticosteroids	Corticosteroids	Oral prednisone	Oral prednisone	Antibiotics	Antibiotics and methylprednisolone
Outcome	Alive; discharged home on room air on day 3 of steroids	Alive; discharged home on day 3 of treatment	Died on day 31 of admission	Alive; discharged home on day 7	Alive; discharged home on day 8	Alive; discharged home on day 4	Alive; discharged on room air on day 4	Alive; discharged on room air after 3 days of intravenous methylprednisolone



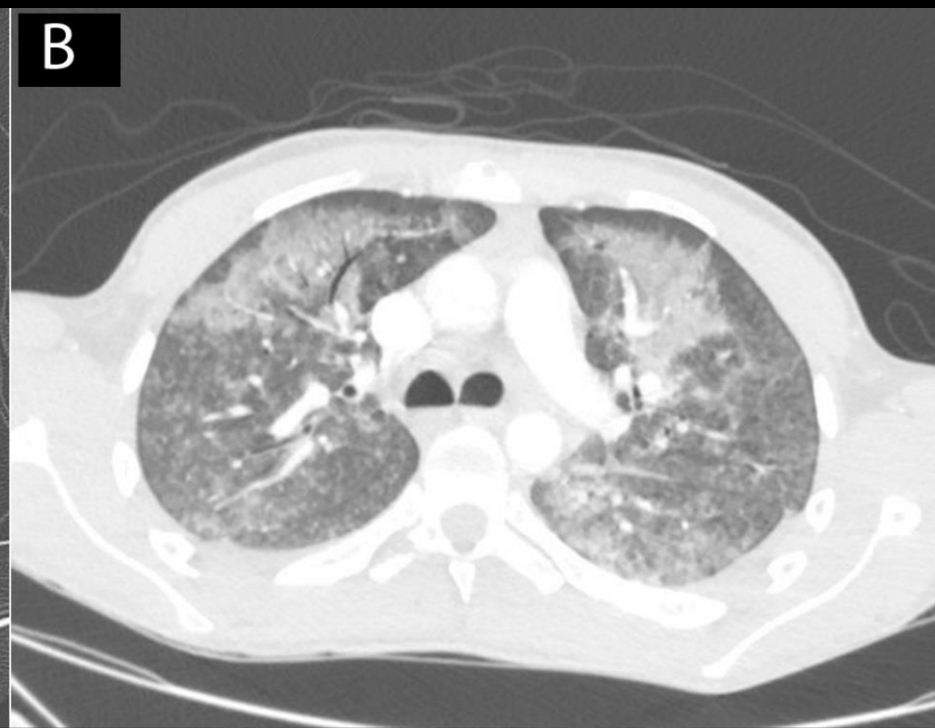
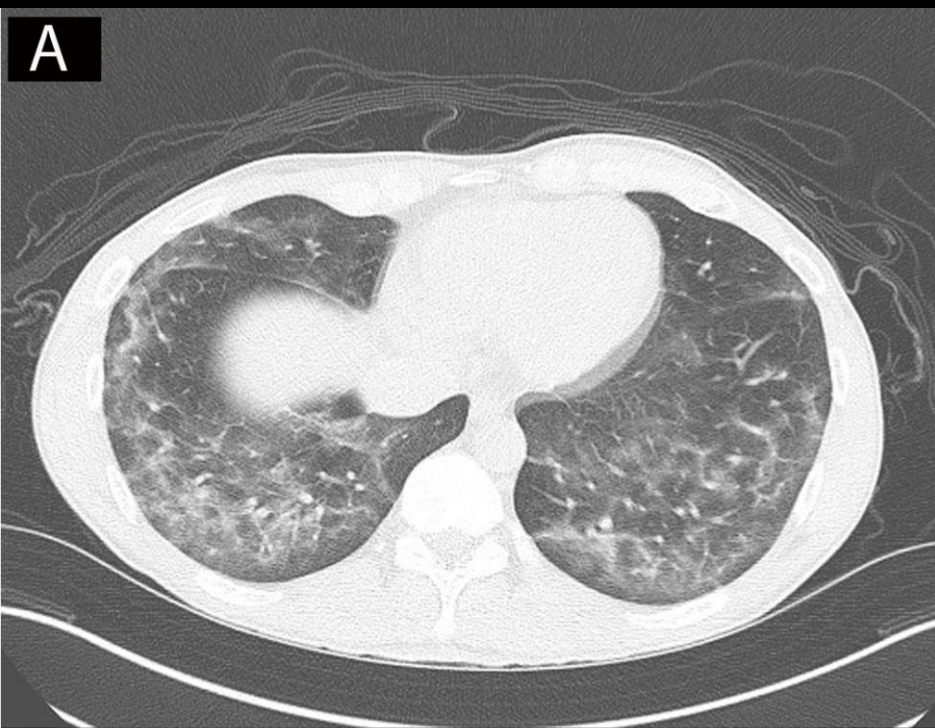
**Table 2**

**Pathologic Findings in Vaping-Associated Pulmonary Illness**

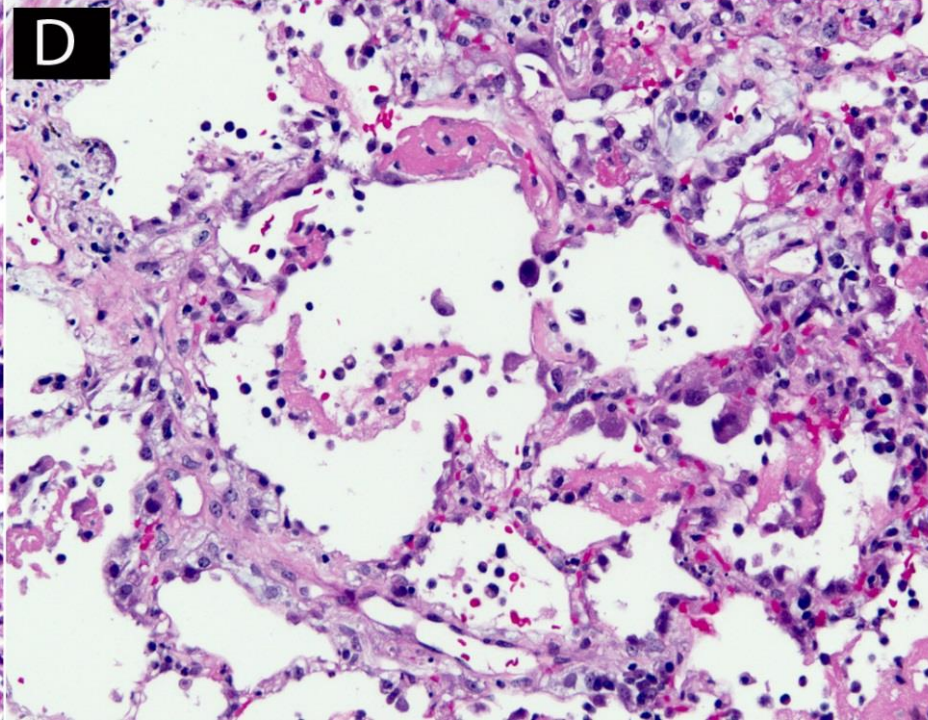
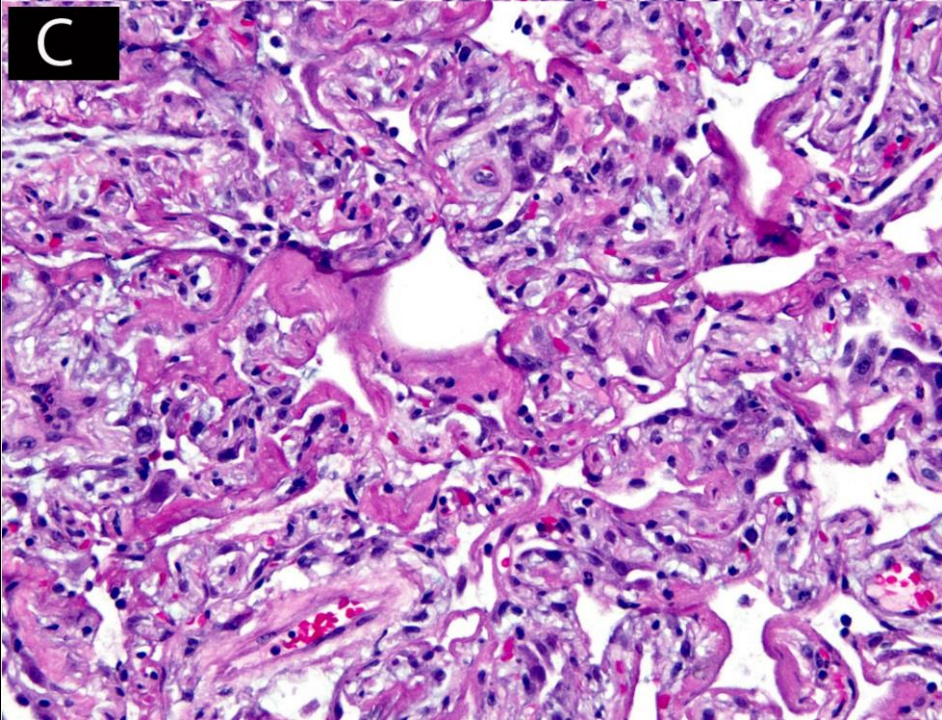
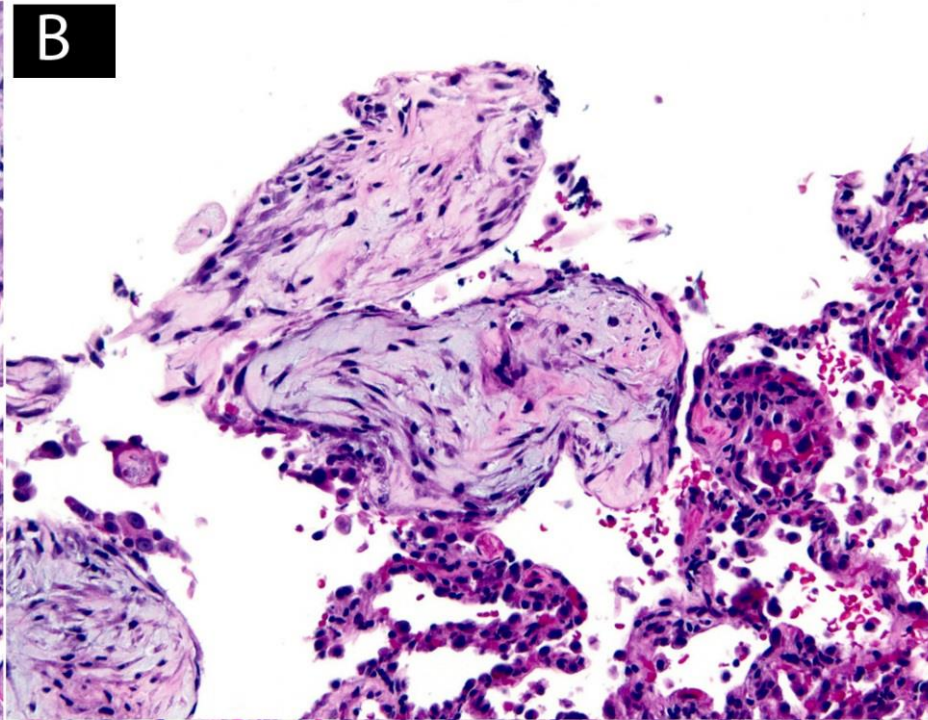
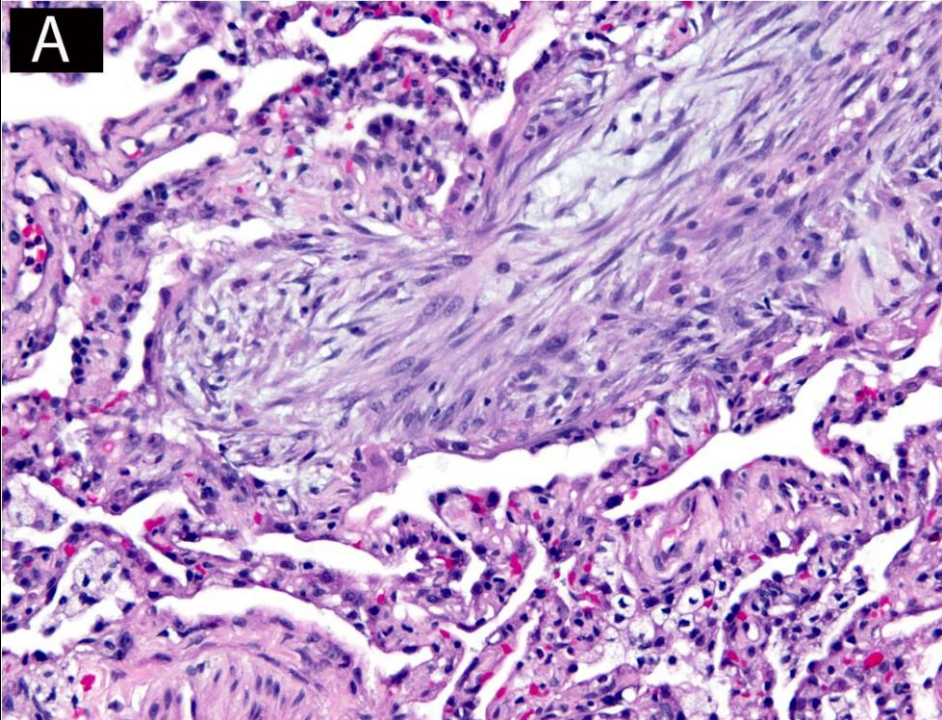
Case No.	Biopsy Type	Biopsy Site	Major Histologic Finding	Macrophages in Biopsy Specimen	BAL	Other Histologic Findings
1	TBBX	Right middle lobe, right lower lobe	Diffuse alveolar damage, acute and organizing	Present within airspaces; no evidence of exogenous lipoid pneumonia	BAL cytology: macrophage predominant	Fibrinous exudates in airspaces, interstitial chronic inflammation, rare eosinophils; AFB and GMS negative
2	TBBX	Lingula and left lower lobe	Organizing pneumonia	Present within airspaces; no evidence of exogenous lipoid pneumonia	No BAL cytology	Fibrinous exudates in airspaces, interstitial chronic inflammation, rare eosinophils; GMS negative
3	Surgical (open) lung biopsy	Right middle lobe, right lower lobe	Diffuse alveolar damage (acute and organizing) and organizing pneumonia	Present within airspaces; no evidence of exogenous lipoid pneumonia	No BAL cytology	Organizing fibrinous exudates, squamous metaplasia
4	TBBX	Right lung	Organizing acute lung injury	Few; no evidence of exogenous lipoid pneumonia	Lipid-laden macrophages, oil red O positive	Fibrinous exudates in airspaces, interstitial chronic inflammation, AFB and GMS negative
5	TBBX	Right lung	Organizing pneumonia	Present (foamy); no evidence of exogenous lipoid pneumonia	Lipid-laden macrophages, oil red O positive	Interstitial chronic inflammation, AFB and GMS negative
6	TBBX	Right lower lobe	Organizing acute lung injury	Present (foamy); no evidence of exogenous lipoid pneumonia	Lipid-laden macrophages, oil red O positive	Fibrinous exudates in airspaces, interstitial chronic inflammation, AFB and GMS negative
7	TBBX	Right lower lobe	Organizing pneumonia	Present (foamy); no evidence of exogenous lipoid pneumonia	Macrophage predominant	Fibrinous airspace exudates, GMS and AFB negative
8	TBBX	Right lower lobe	Organizing pneumonia	Present (foamy); no evidence of exogenous lipoid pneumonia	Macrophage predominant	Interstitial inflammation, focal acute inflammation in airspaces, AFB and GMS negative

AFB, acid-fast bacteria; BAL, bronchoalveolar lavage; GMS, Grocott methenamine silver; TBBX, transbronchial biopsy.

Mukhopadhyay S, et al.  
*Am J Clin Pathol* 2020





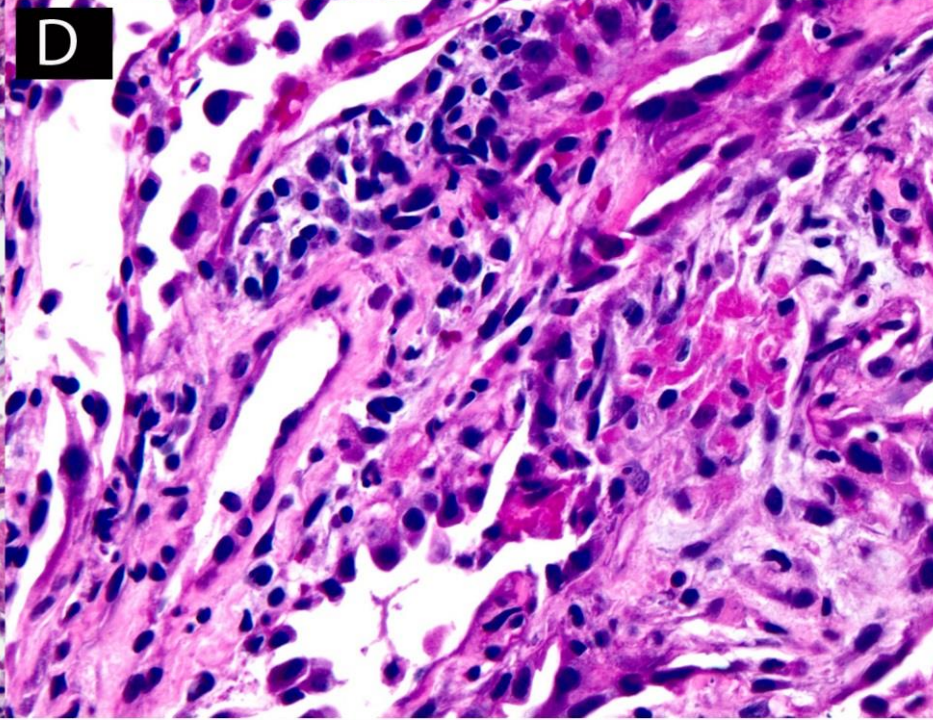
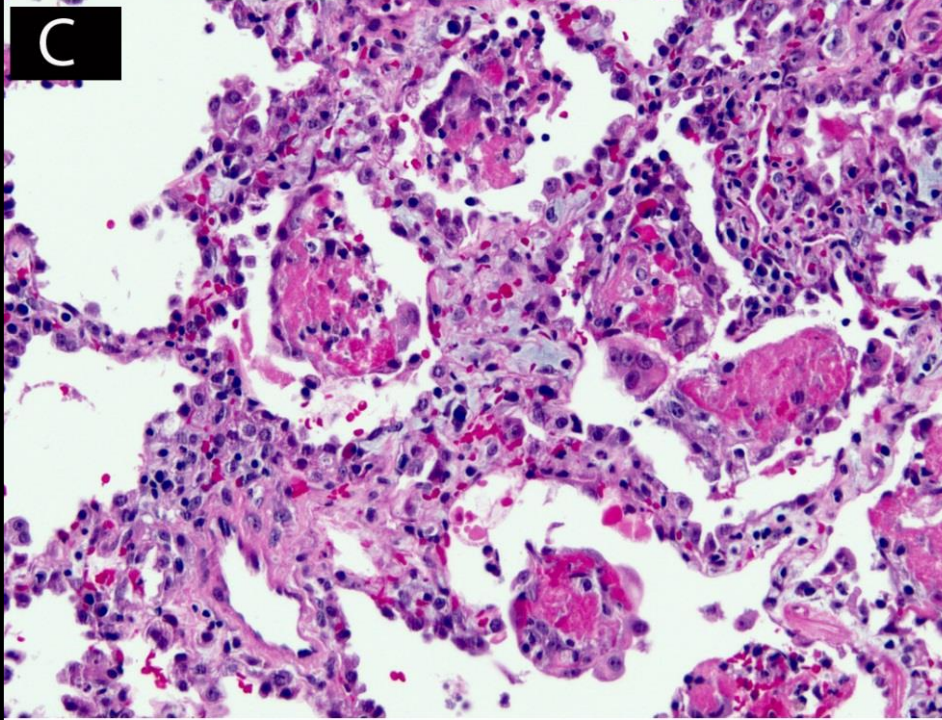
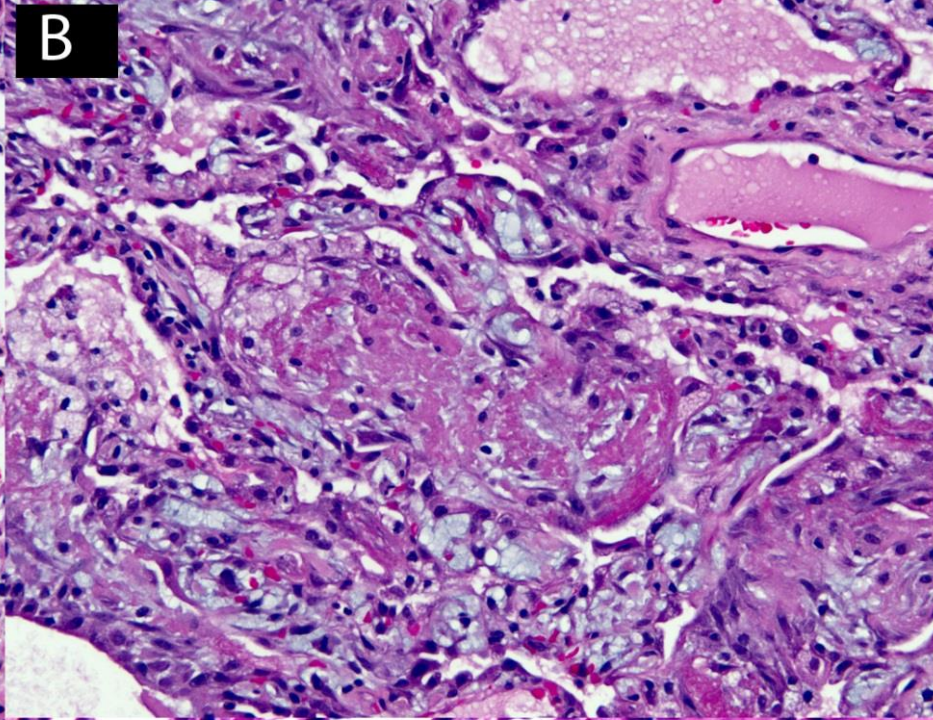
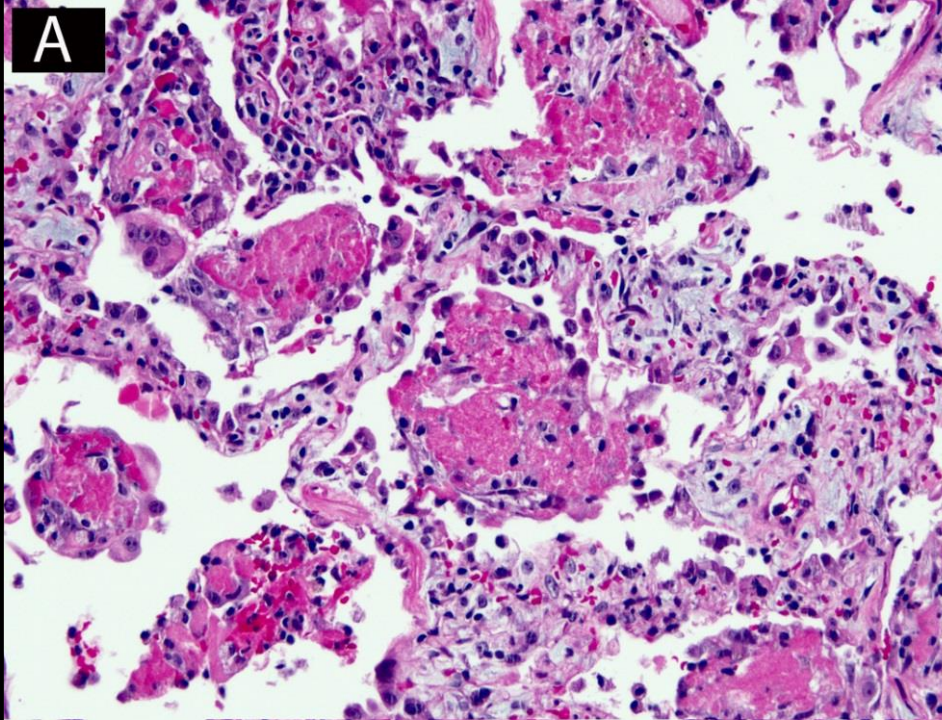


Organizing  
pneumonia

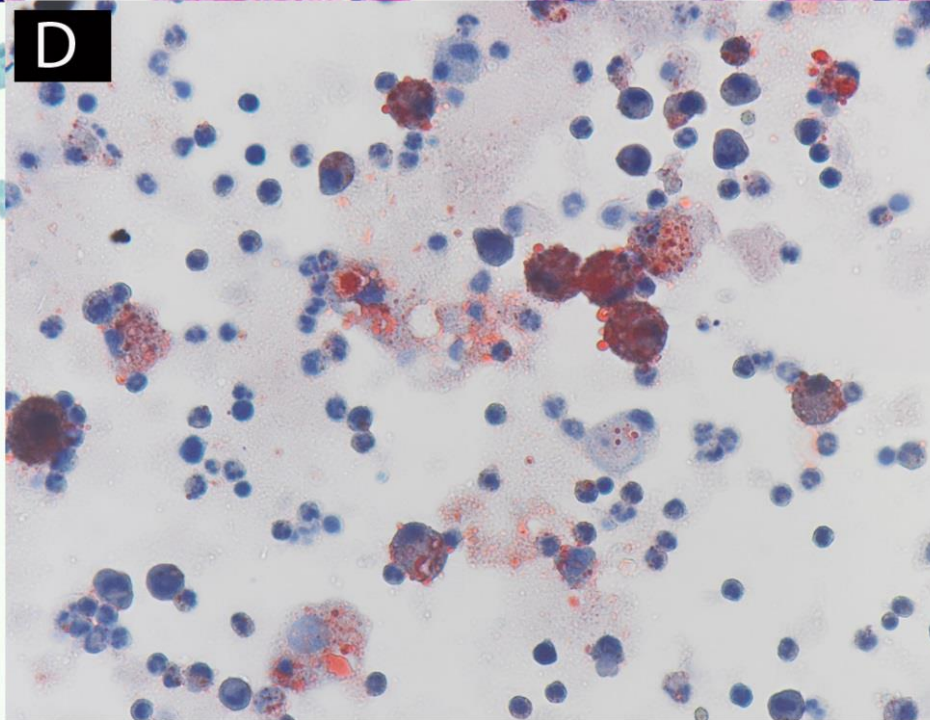
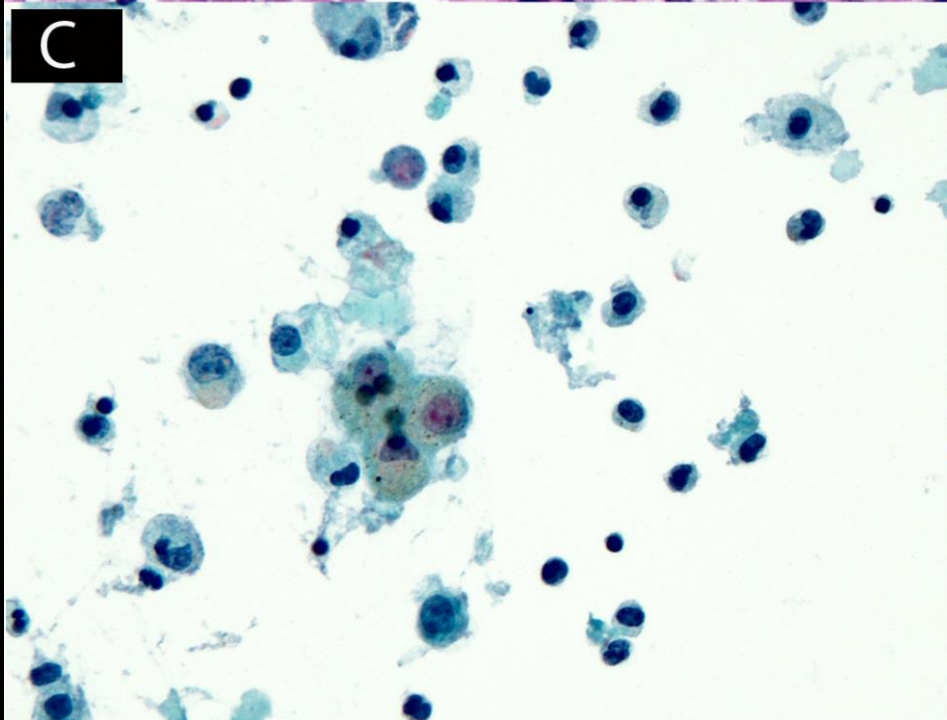
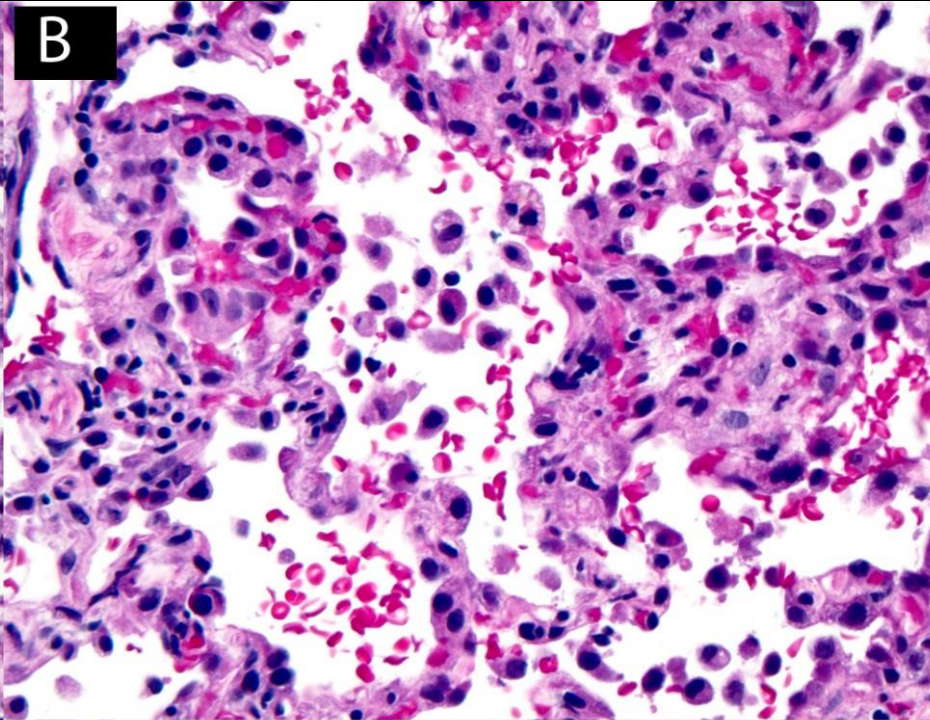
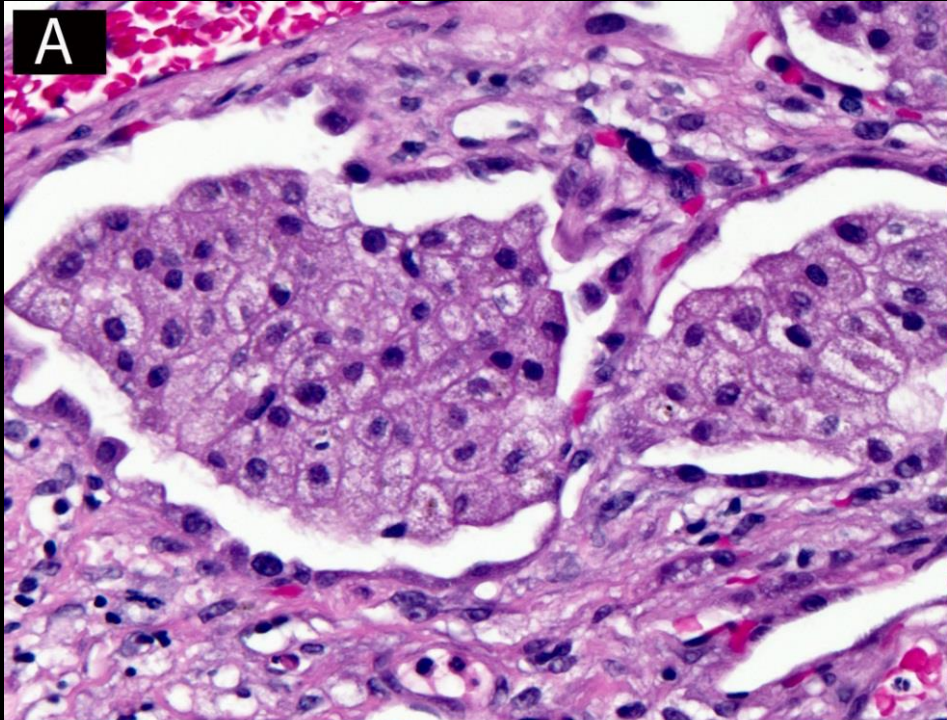
Diffuse alveolar  
damage

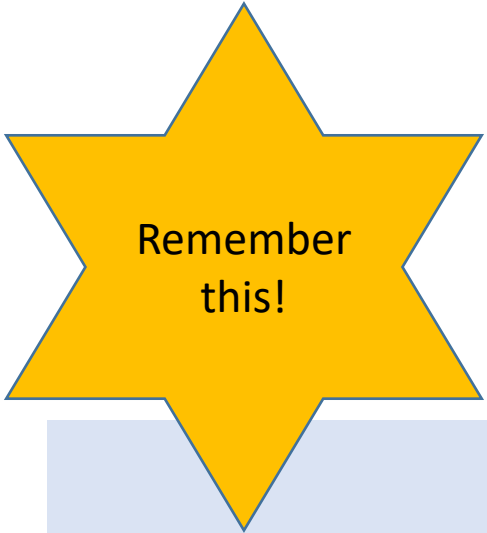
Mukhopadhyay S, et al.  
*Am J Clin Pathol* 2020









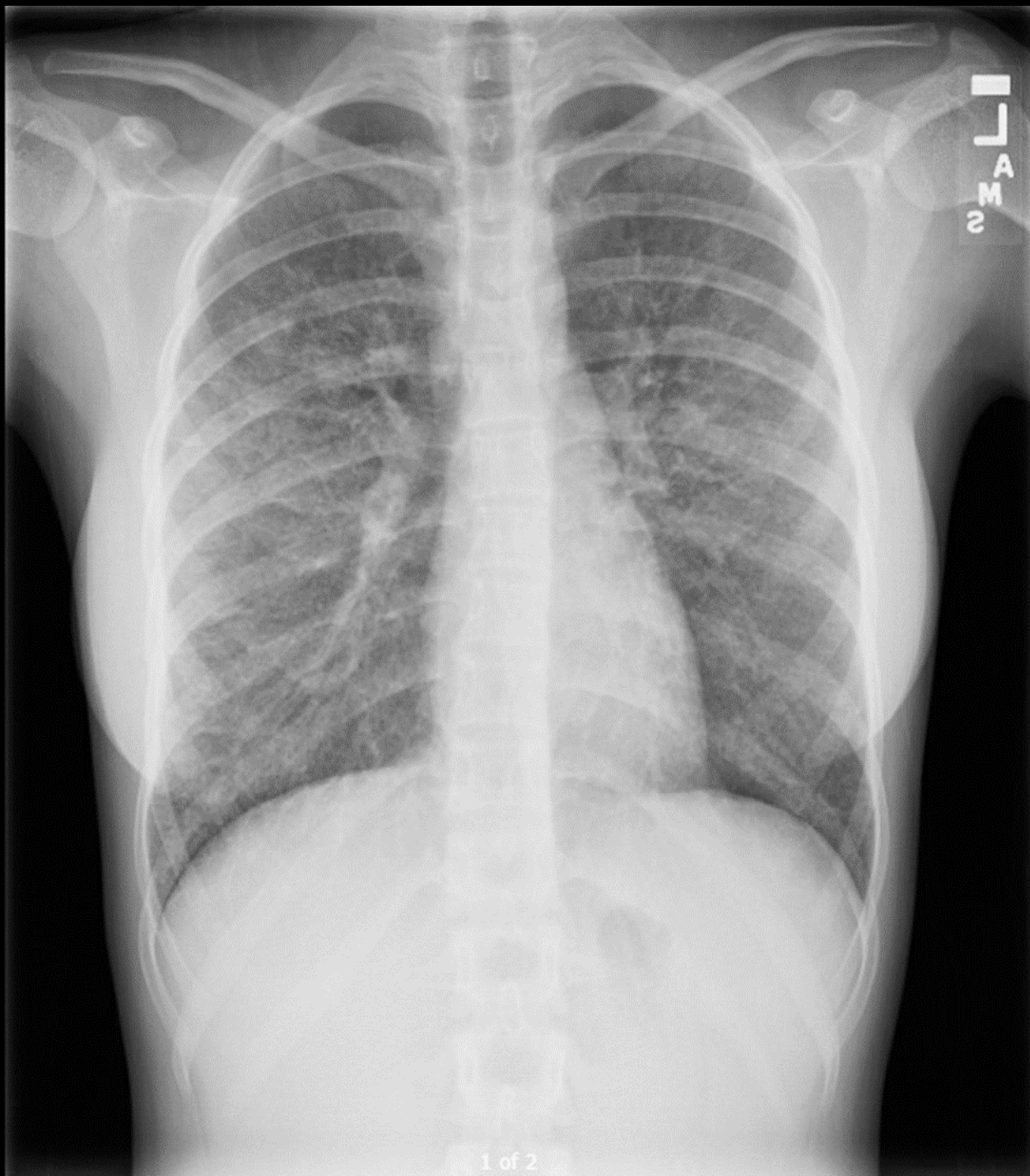


Remember  
this!

Pathology of vaping  
=  
Acute lung injury (DAD, OP)



Can EVALI be diagnosed without  
BAL or lung biopsy?



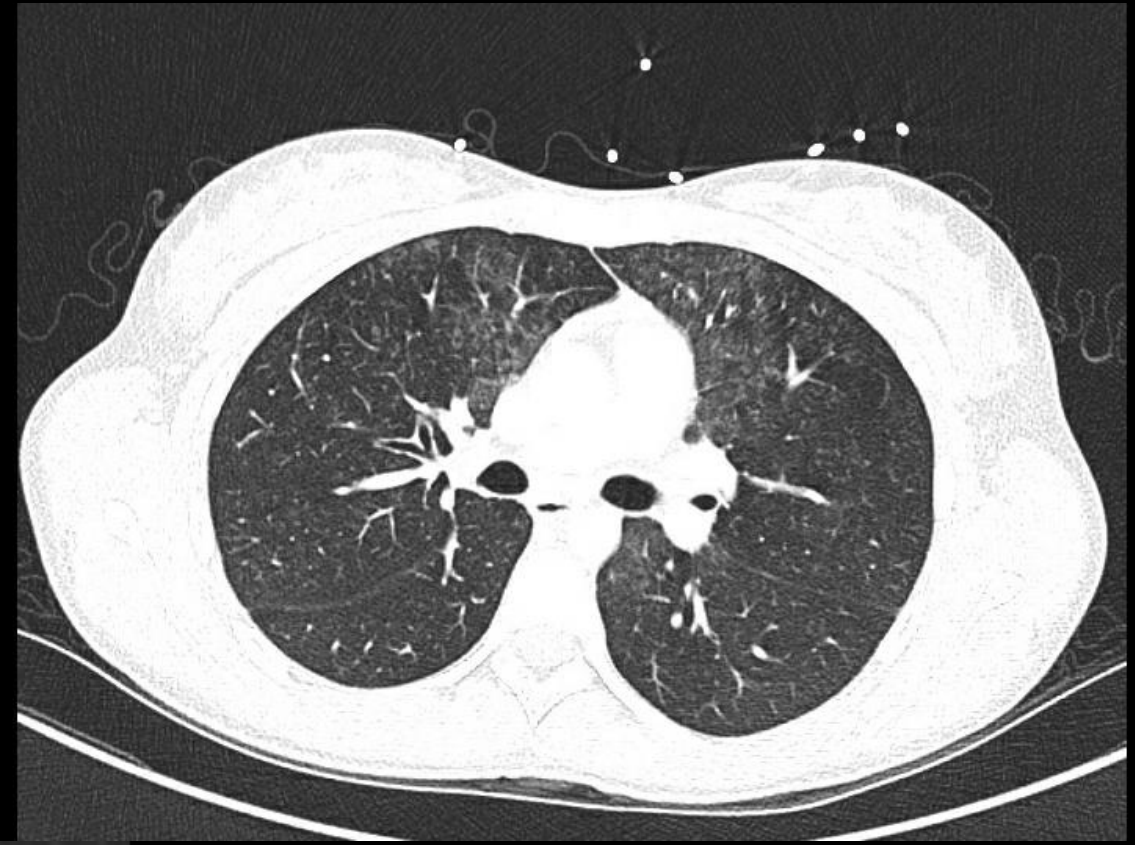
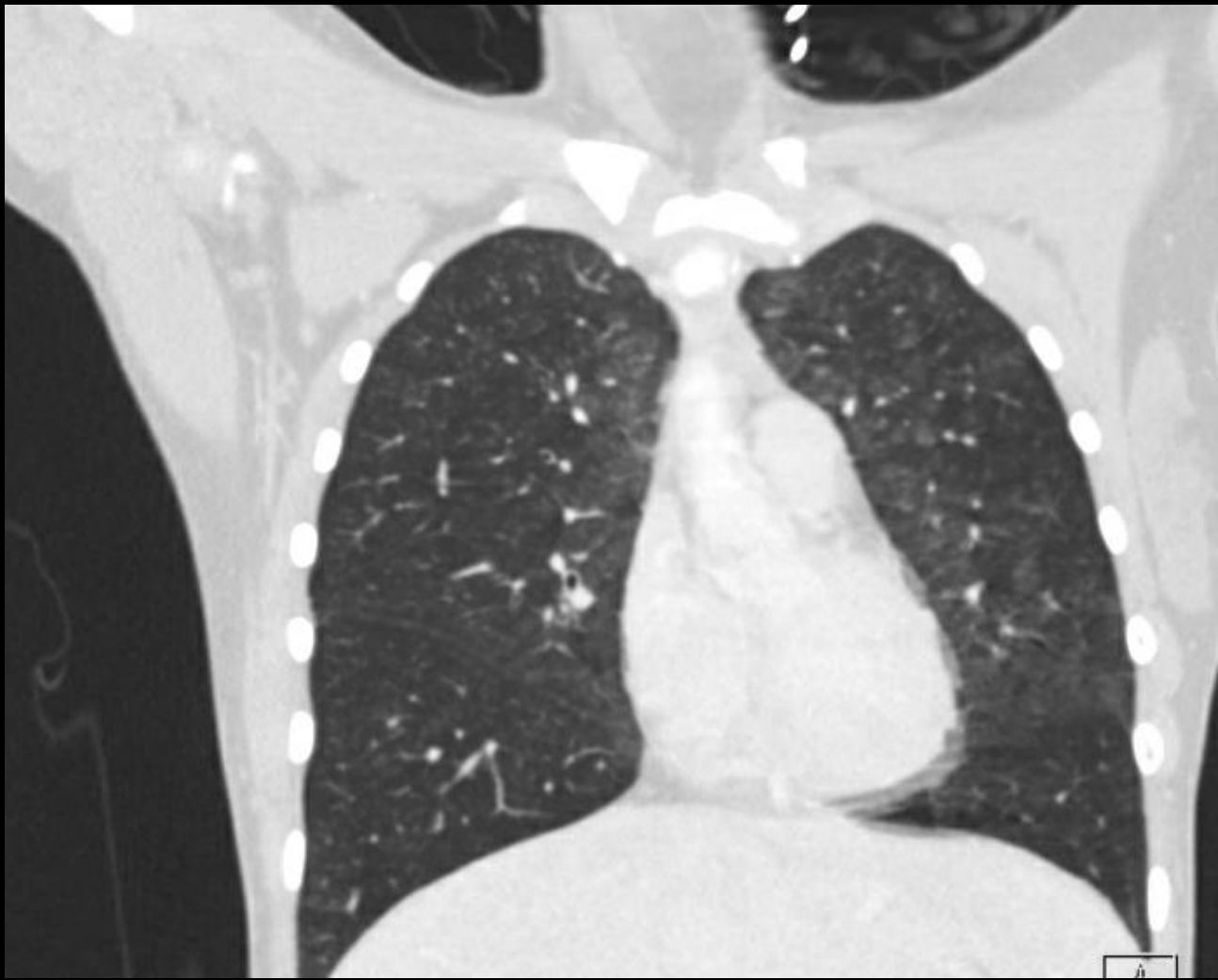
16/F, h/o reactive  
airway disease

Chest pain, cough,  
dyspnea, fever

10d prior, admission  
for abdominal pain and  
diarrhea

Slides courtesy of Blanca Gonzalez, MD





Leukocytosis, elevated C-reactive protein  
Started on ceftriaxone. Infectious disease consult

# Bronchoscopy performed: Negative *Legionella*, PJP and cultures

	1	2
	8/29/2019 0528	8/29/2019 0526
<b>ROUTINE ANALYSIS</b>		
Color, BA Lavage	Colorless	SLIGHT YELLOW
Supernatant Color,...	Colorless	Colorless
Supernatant Clarit...	Clear	Clear
Clarity, BA Lavage	Slightly turbid	Slightly turbid
RBC, BA Lavage	323 *	915 *
Total Nucleated Ce...	570 *	690 *
Neut%, BA Lavage	35	55
Lymph%, BA Lavage	9	3
Macro%, BA Lavage	55	42
Eosin%, BA Lavage	1	
Slide Number BA La...	1,910,107	1,910,106
BAL Comment	SEE COMMENT *	SEE COMMENT *
BAL Review	SEE COMMENT *	SEE COMMENT *





# Diagnosis = EVALI. No lung biopsy required

TABLE. CDC surveillance case definitions\* for severe pulmonary disease associated with e-cigarette use — August 30, 2019



Case classification	Criteria
Confirmed	Using an e-cigarette (“vaping”) or dabbing <sup>†</sup> during the 90 days before symptom onset
	AND
	Pulmonary infiltrate, such as opacities on plain film chest radiograph or ground-glass opacities on chest computed tomography
	AND
	Absence of pulmonary infection on initial work-up: Minimum criteria include negative respiratory viral panel, influenza polymerase chain reaction or rapid test if local epidemiology supports testing. All other clinically indicated respiratory infectious disease testing (e.g., urine antigen for <i>Streptococcus pneumoniae</i> and <i>Legionella</i> , sputum culture if productive cough, bronchoalveolar lavage culture if done, blood culture, human immunodeficiency virus-related opportunistic respiratory infections if appropriate) must be negative
	AND
	No evidence in medical record of alternative plausible diagnoses (e.g., cardiac, rheumatologic, or neoplastic process).





EVALI is a diagnosis of exclusion

There is no confirmatory  
diagnostic test

Vape fluids in EVALI are  
mostly THC oils

Oil = lipid

Oil deposits in lung and  
causes damage

Hence, "acute lipoid  
pneumonia"

How to prove this?

Oil red O stain on BAL fluid

Oil red O stain = pos

Theory proved!



**Table 3.** Frequency of Detection of Priority Toxicants in EVALI Case Patients and in Healthy Comparators.\*

Toxicant	EVALI Case Patients (N = 51)	Healthy Comparators			
		Nonusers (N = 52)	E-Cigarette Users (N = 18)	Cigarette Smokers (N = 29)	All Comparators (N = 99)
		<i>number/total number (percent)</i>			
Vitamin E acetate	48/51 (94)	0/52	0/18	0/29	0/99
Medium-chain tri- glyceride oil	0/49	0/34	0/11	0/18	0/63
Coconut oil	1/48 (2)	0/34	0/11	0/18	0/63
Plant oil	0/49	0/34	0/11	0/17	0/62
Squalane	0/38	0/52	0/17	0/29	0/98
Squalene	0/38	0/52	0/17	0/29	0/98
$\alpha$ -Pinene	0/39	0/52	0/17	0/28	0/97
$\beta$ -Pinene	0/39	0/52	0/17	0/28	0/97
3-Carene	0/39	0/52	0/17	0/28	0/97
Limonene	1/39 (3)	0/52	0/17	0/28	0/97
Petroleum distillates	0/12	0/52	0/17	0/29	0/98

\* The listed toxicants were detected in bronchoalveolar-lavage fluid obtained from 51 patients with EVALI in 16 states from August through December 2019 and in 99 healthy comparators.

September 6, 2019

CORRESPONDENCE

## Pulmonary Lipid-Laden Macrophages and Vaping

[Appendix](#)). A notable and consistent feature of the cases we report is the presence of lipid-laden macrophages seen with oil red O staining in BAL samples that are not attributable to aspiration of exogenous lipid material. In addition, the diffuse parenchymal opacities seen on CT scans did not have low attenuation (in Hounsfield units) consistent with classic lipoid pneumonia.<sup>2</sup> Although the pathophysiological significance of these lipid-laden macrophages and their relation to the cause of this syndrome are not yet known, we posit that they may be a useful marker of this disease.<sup>3-5</sup> Further work is needed to characterize the sensitivity and specificity of lipid-laden macrophages for vaping-related lung injury, and at this stage they cannot be used to confirm or exclude this syndrome. However, when vaping-related lung injury is suspected and infectious causes have been excluded, the presence of lipid-laden macrophages in BAL fluid may suggest vaping-related lung injury as a provisional diagnosis.

Sean D. Maddock, M.D.

Meghan M. Cirulis, M.D.

Sean J. Callahan, M.D.

Number of pathologists in study = 0



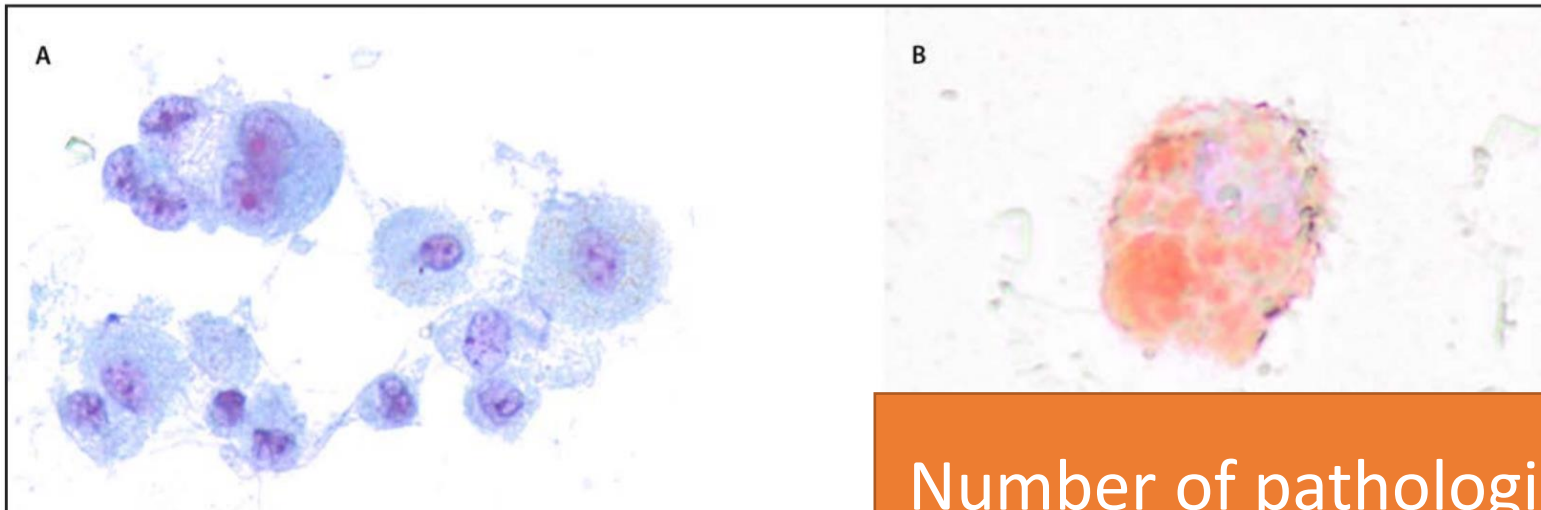
September 13, 2019

## Outbreak of Electronic-Cigarette–Associated Acute Lipoid Pneumonia — North Carolina, July–August 2019

Kevin Davidson, MD<sup>1</sup>; Alison Brancato, MS<sup>1</sup>; Peter Heetderks, MD<sup>1</sup>; Wissam Mansour, MD<sup>1</sup>; Edward Matheis, MD<sup>1</sup>; Myra Nario, MS<sup>1</sup>; Shrinivas Rajagopalan, MD, PhD<sup>2</sup>; Bailey Underhill, MS<sup>1</sup>; Jeremy Wininger, MS<sup>1</sup>; Daniel Fox, MD<sup>1</sup>

Morbidity and Mortality Weekly Report

FIGURE 2. Microscopy of a bronchoalveolar lavage sample (Papanicolaou stain [A]\* and oil red O stain [B]<sup>†</sup>) from a patient with acute lung injury associated with vaping — North Carolina, July–August 2019



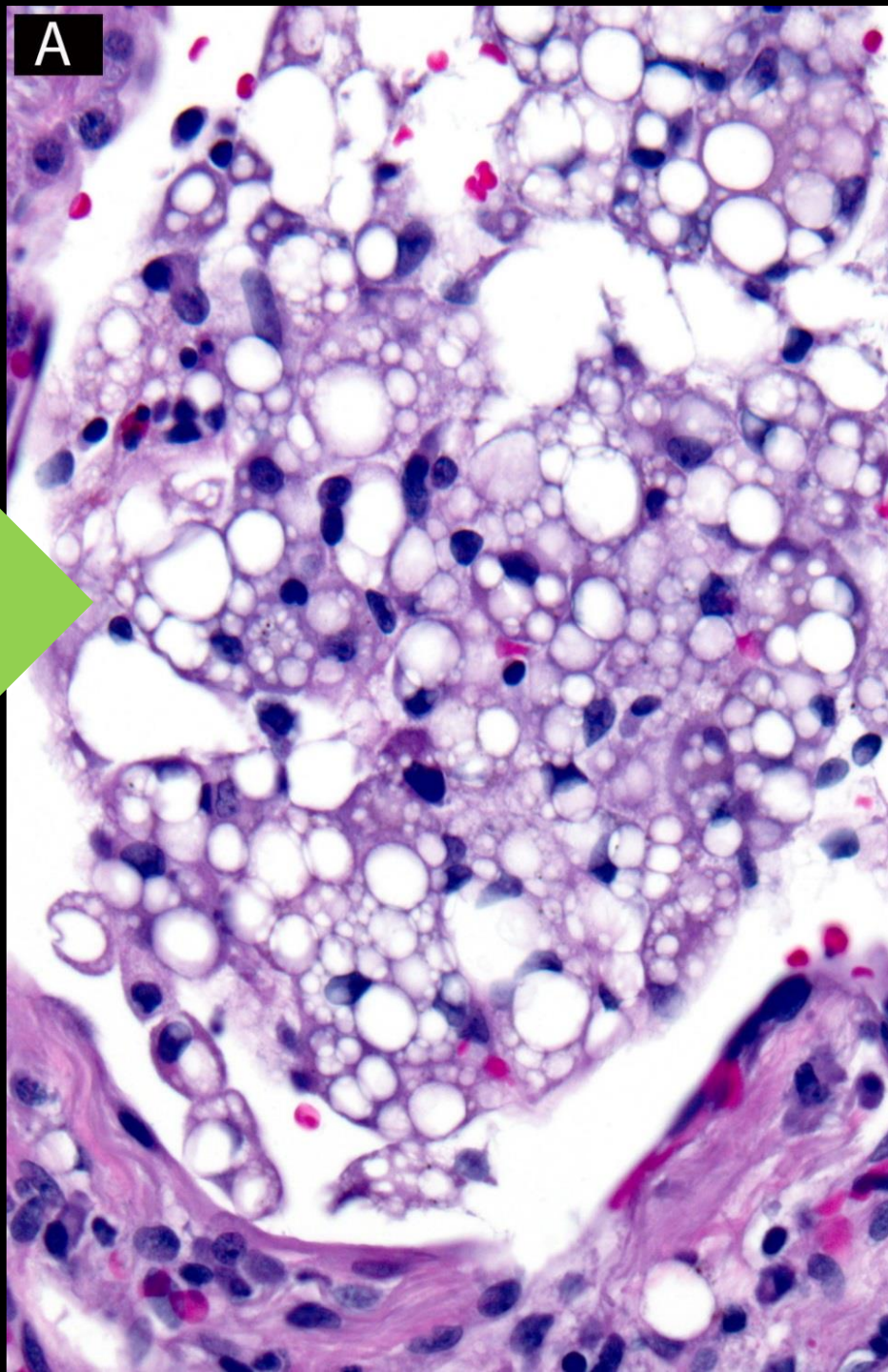
\* Papanicolaou stain demonstrating alveolar macrophages laden with vacuoles.

<sup>†</sup> Oil red O stain showing lipid deposits staining red (400x magnification).

Number of pathologists in study = 1

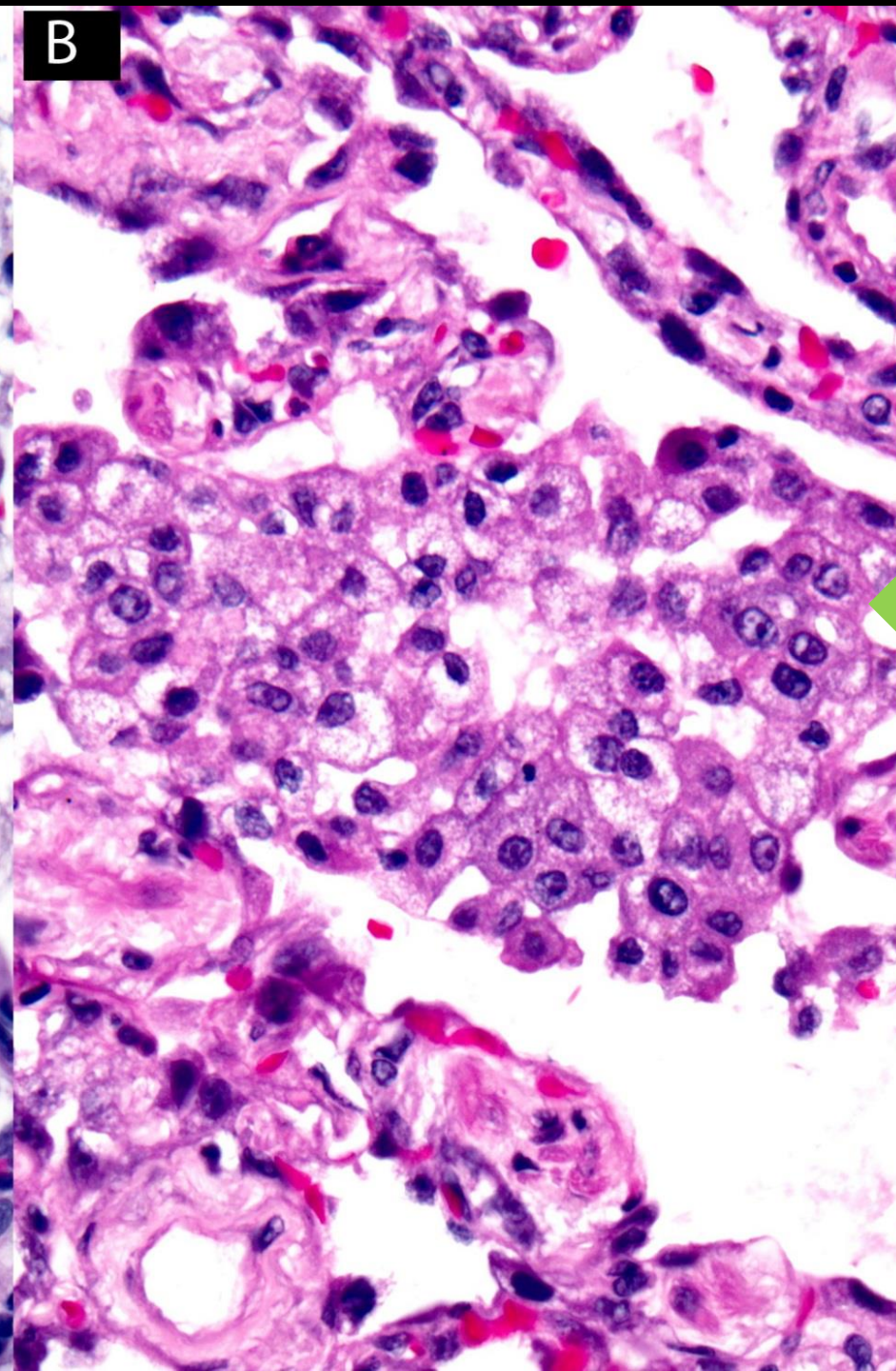


A



EXOGENOUS  
LIPOID  
PNEUMONIA

B



VAPING





# The Washington Post

*Democracy Dies in Darkness*

up 100 percent,” said Dr. Sean Callahan, a University of Utah Health lung specialist who has treated vaping illness patients.

Callahan was among doctors who have described the illness as lipoid pneumonia.

But with new information coming in, he said he is ready to stop using the term lipoid pneumonia because it implies the patient inhaled fats.

“Lipoid pneumonia”?

## TO THE EDITOR

The national outbreak of vaping-associated lung injury has affected 2172 patients and led to 42 deaths, but its causes remain incompletely understood.<sup>1</sup> In their letter, Butt et al. reported on 17 patients from this outbreak who underwent lung biopsy. The biopsy specimens from all 17 patients were fixed in formalin and embedded in paraffin before examination. However, this histologic technique masks and washes away oils and lipids within the specimen, obscuring some characteristic findings of this disease entity. Given the positive cytologic staining for lipids in bronchoalveolar lavage (BAL) fluid, lipids should also be present in lung biopsy specimens.<sup>2,3</sup> Analysis of BAL specimens alone might suffice to establish a diagnosis of vaping-associated lung injury, but if biopsy is performed, analysis of frozen sections or work with fresh tissue is recommended by CDC guidelines to avoid this confounding laboratory artifact.<sup>4</sup> Classic lipoid pneumonia occurs with aspiration of larger droplets of oil; however, a new variant of lipoid pneumonia may be seen with vaporization of tiny oil microparticles from vaping. We continue to suspect that the presence of lipid in BAL fluid is more than an incidental marker and could be the primary signature of lung disease within this outbreak.

Kevin R. Davidson, M.D.

Daniel L. Fox, M.D.

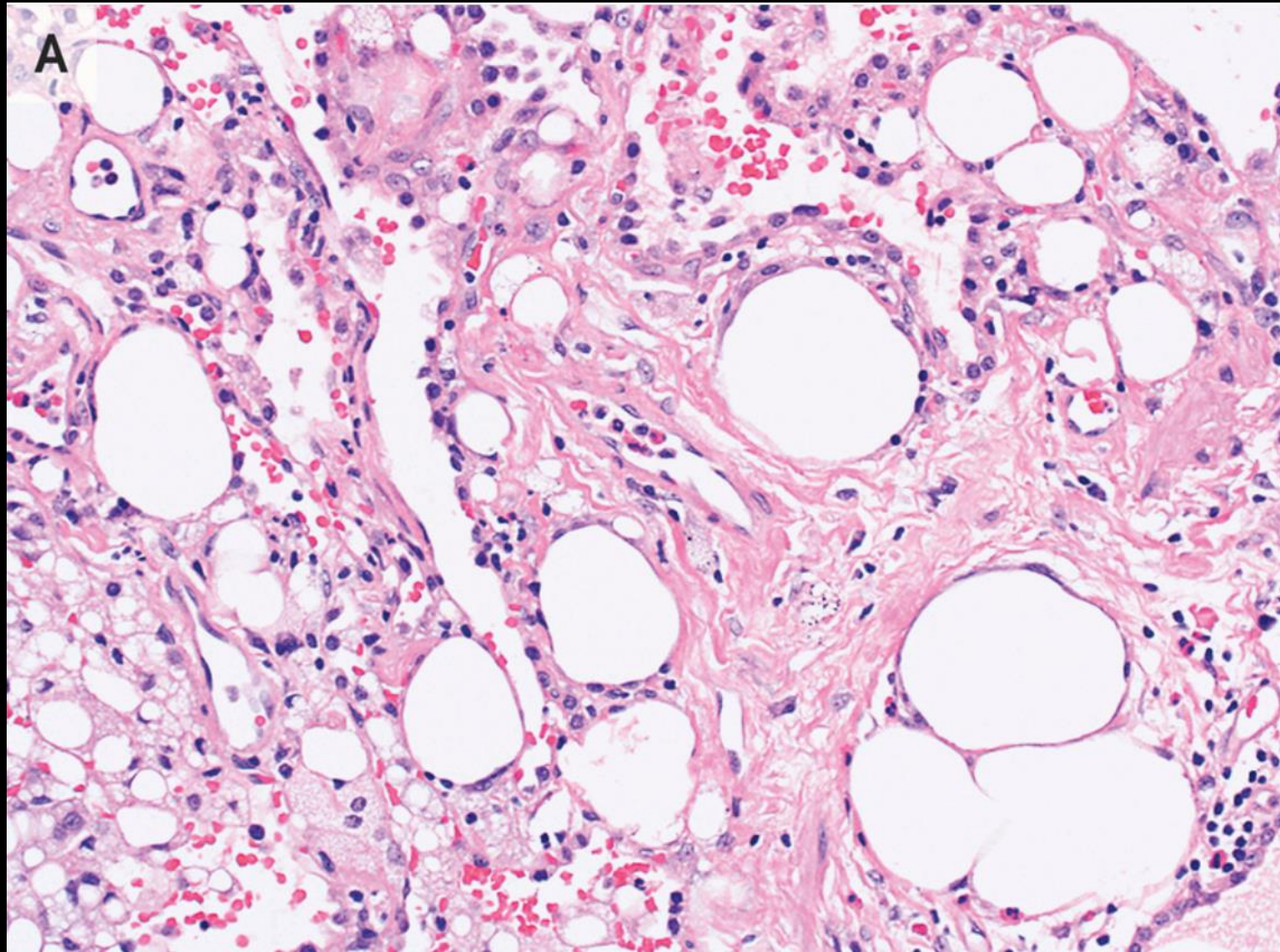
WakeMed Health and Hospital, Raleigh, NC

[kdavidson@wakemed.org](mailto:kdavidson@wakemed.org)

Number of pathologists = 0

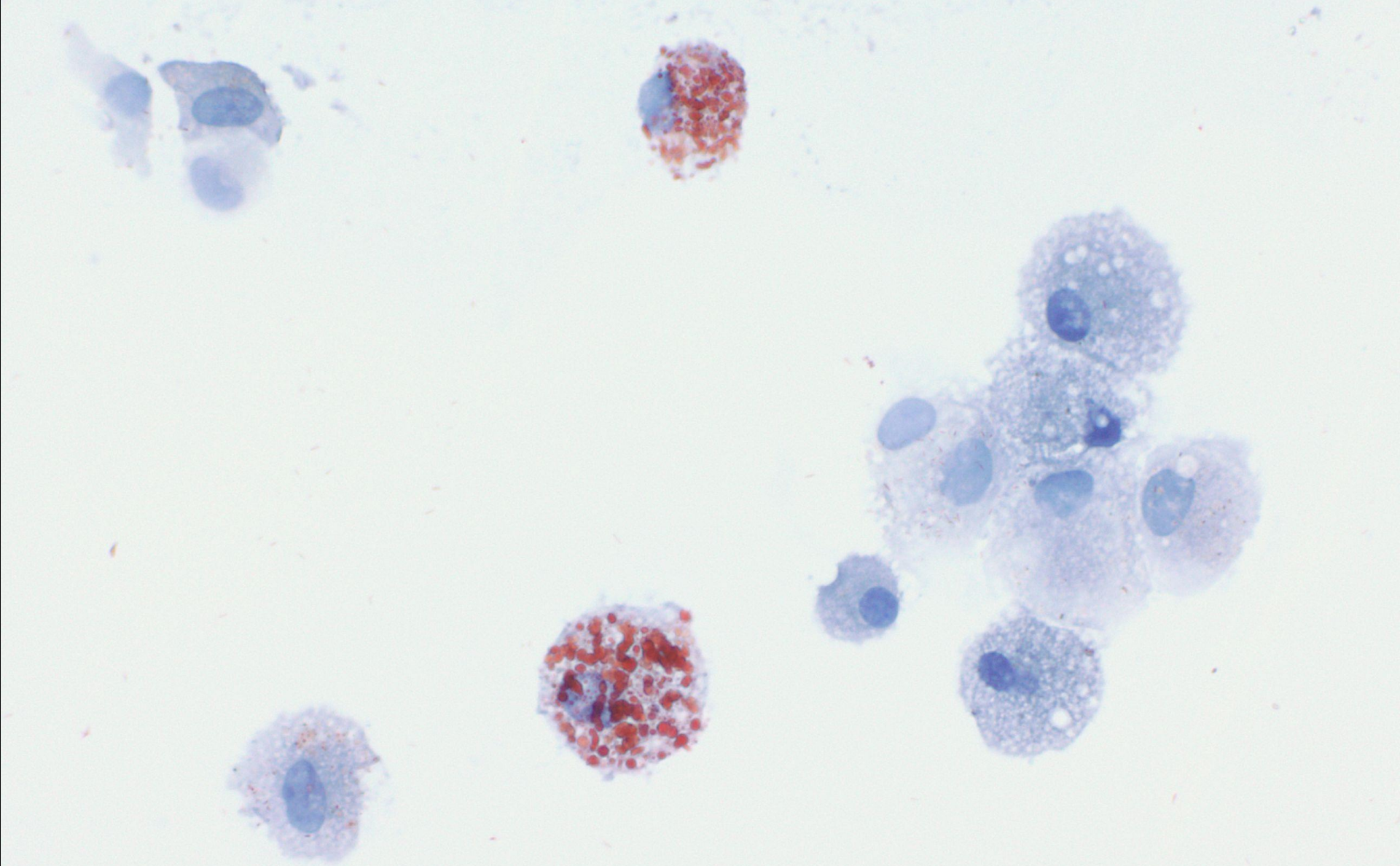


Although it is correct that tissue processing dissolves lipid, we disagree that this masks exogenous lipoid pneumonia histologically, as any surgical pathologist will readily attest (Figure 1). Regardless of whether “oil microparticles” from vaping explain the BAL findings, it should be remembered that the value of a laboratory test is directly related to its sensitivity, specificity, and reliability. Lipid-laden macrophages are frequently seen in infection, aspiration, drug reactions, and autoimmune disorders, often in high numbers.<sup>3,4</sup> They accumulate from any cause of epithelial injury and engulf cellular debris, surfactant, and endogenous lipids from cell membranes — all of which are substances



Number of pathologists = 3

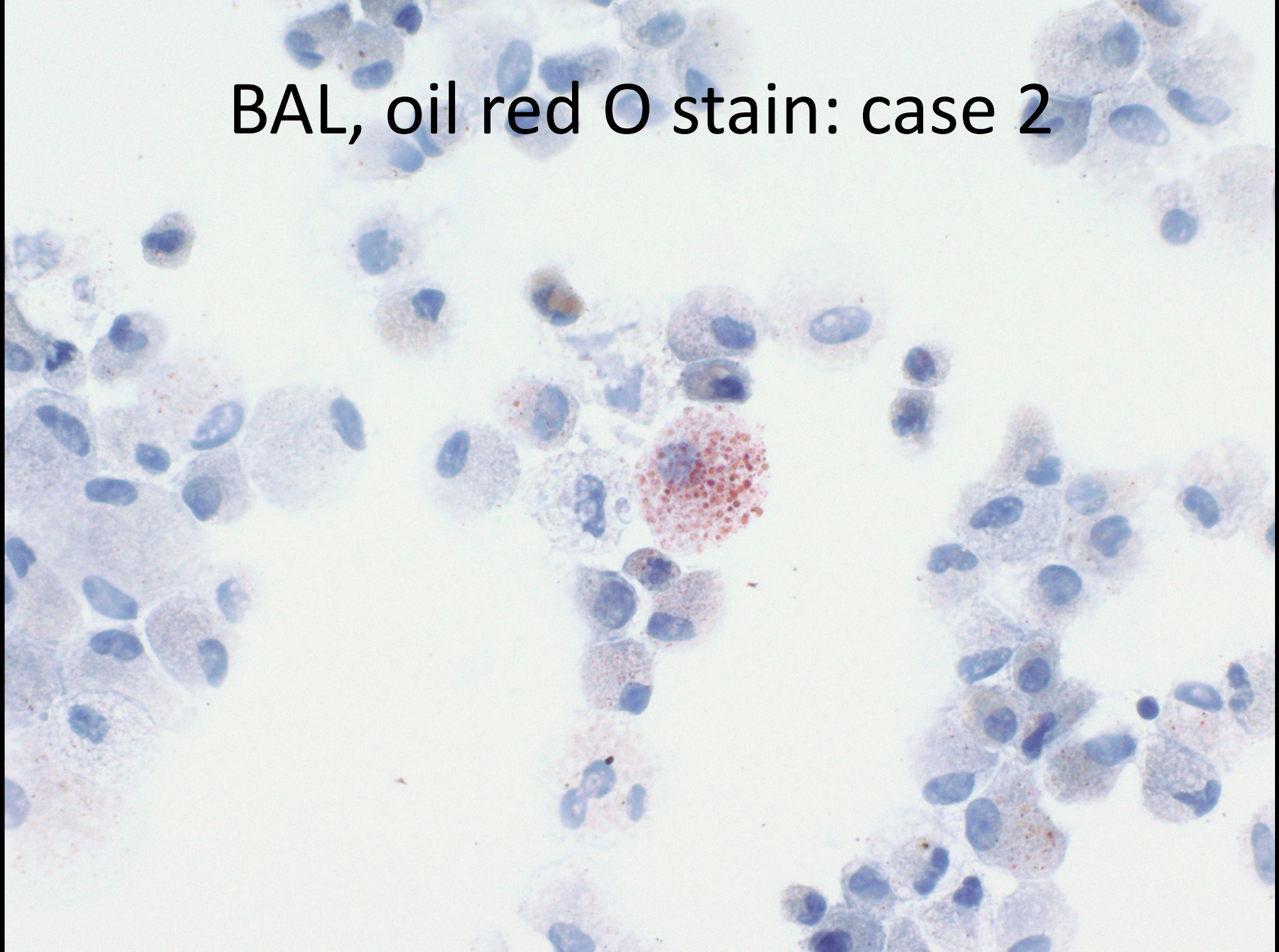




BAL, oil red O stain: case 1

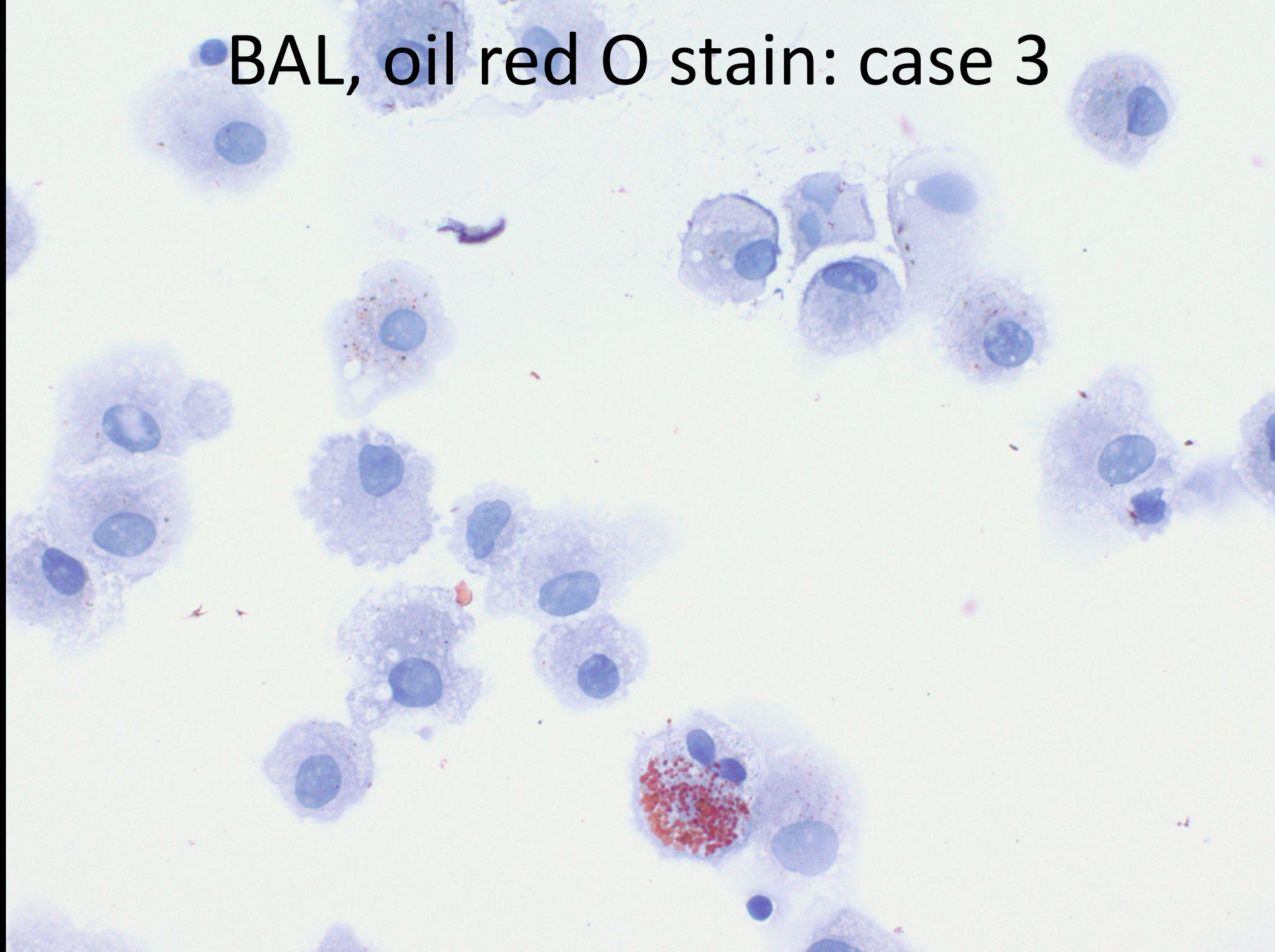


BAL, oil red O stain: case 2



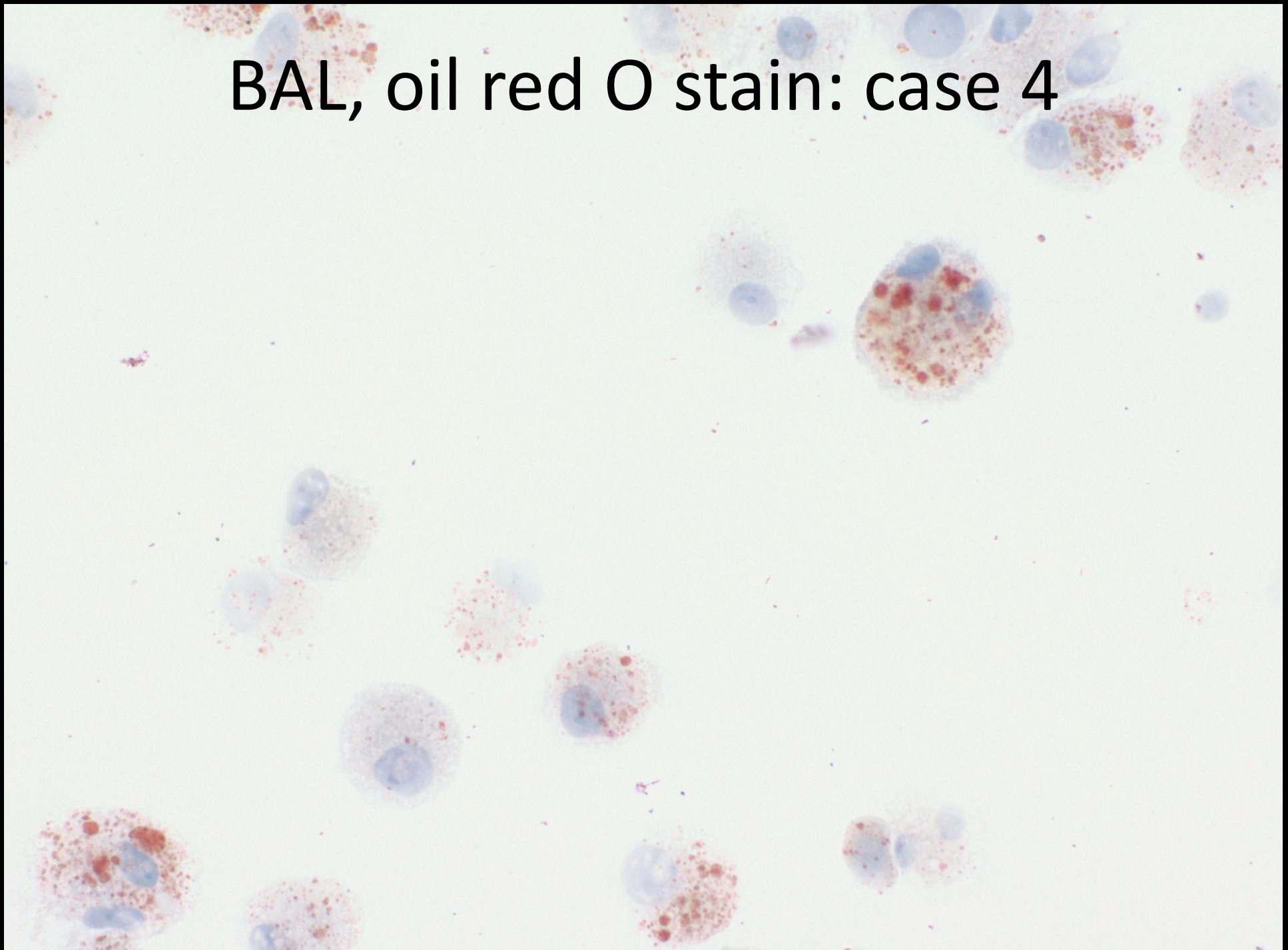


BAL, oil red O stain: case 3



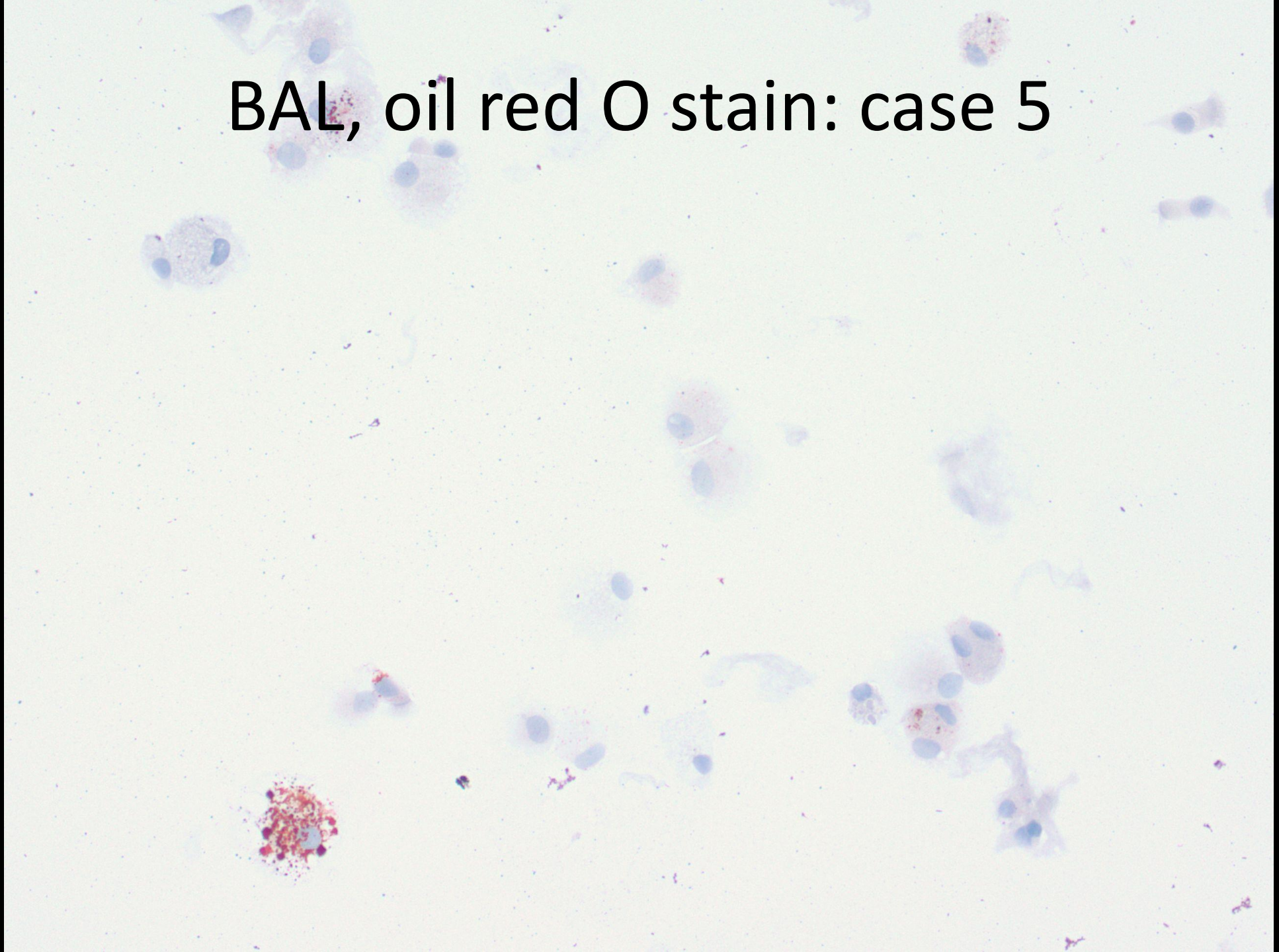


BAL, oil red O stain: case 4





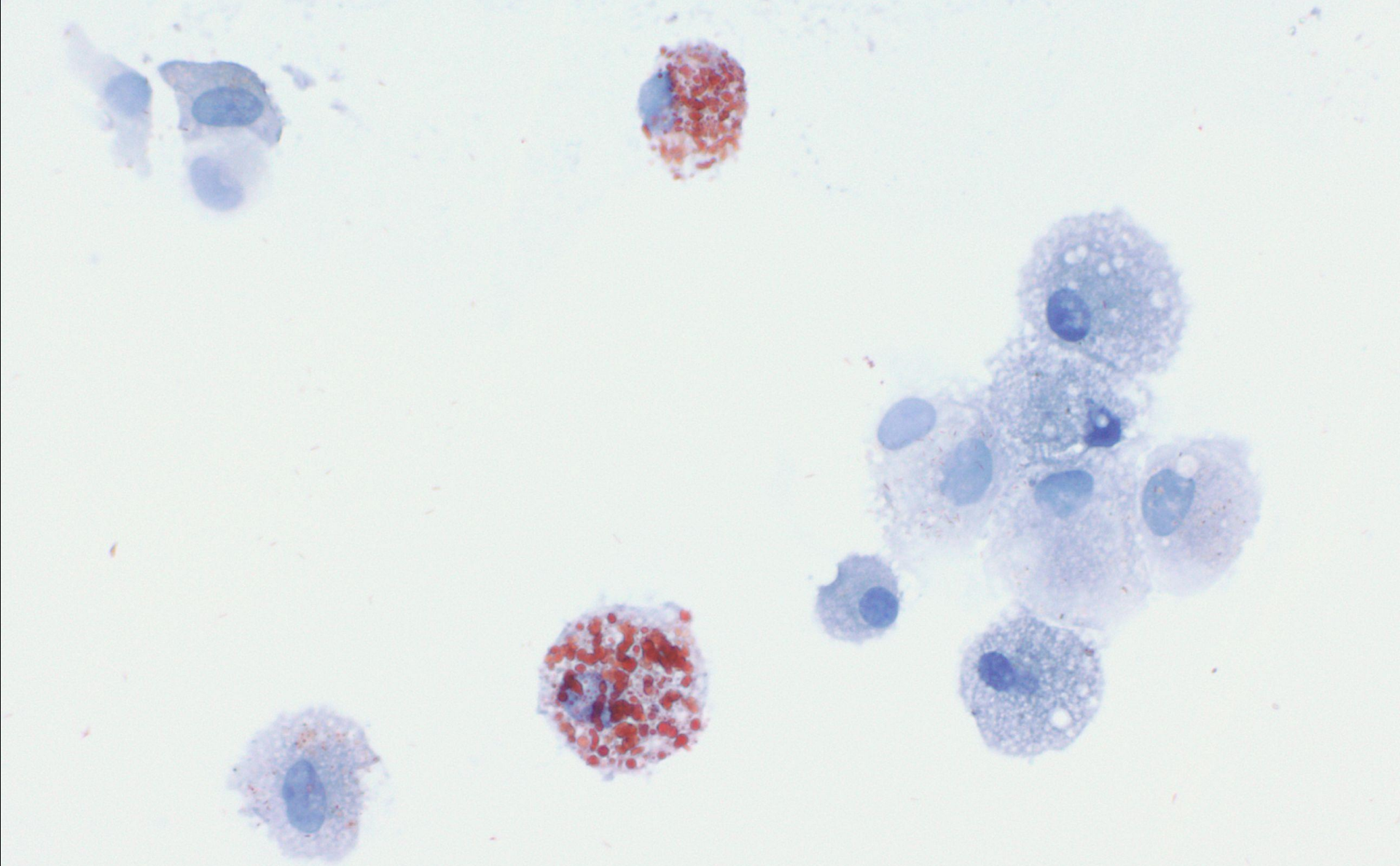
BAL, oil red O stain: case 5





Surprise!

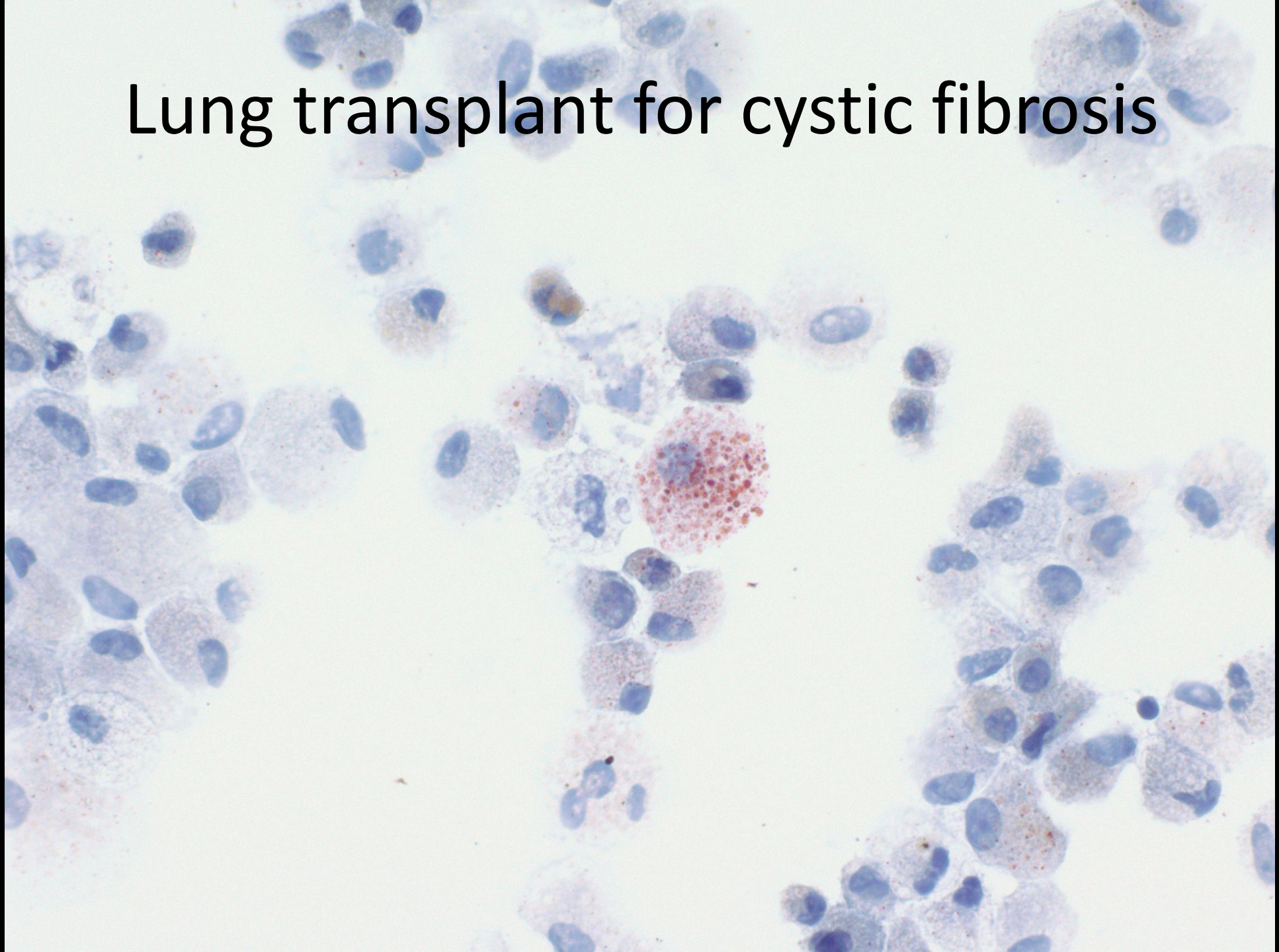
None of these BALs were from  
patients who vaped.



Asthma

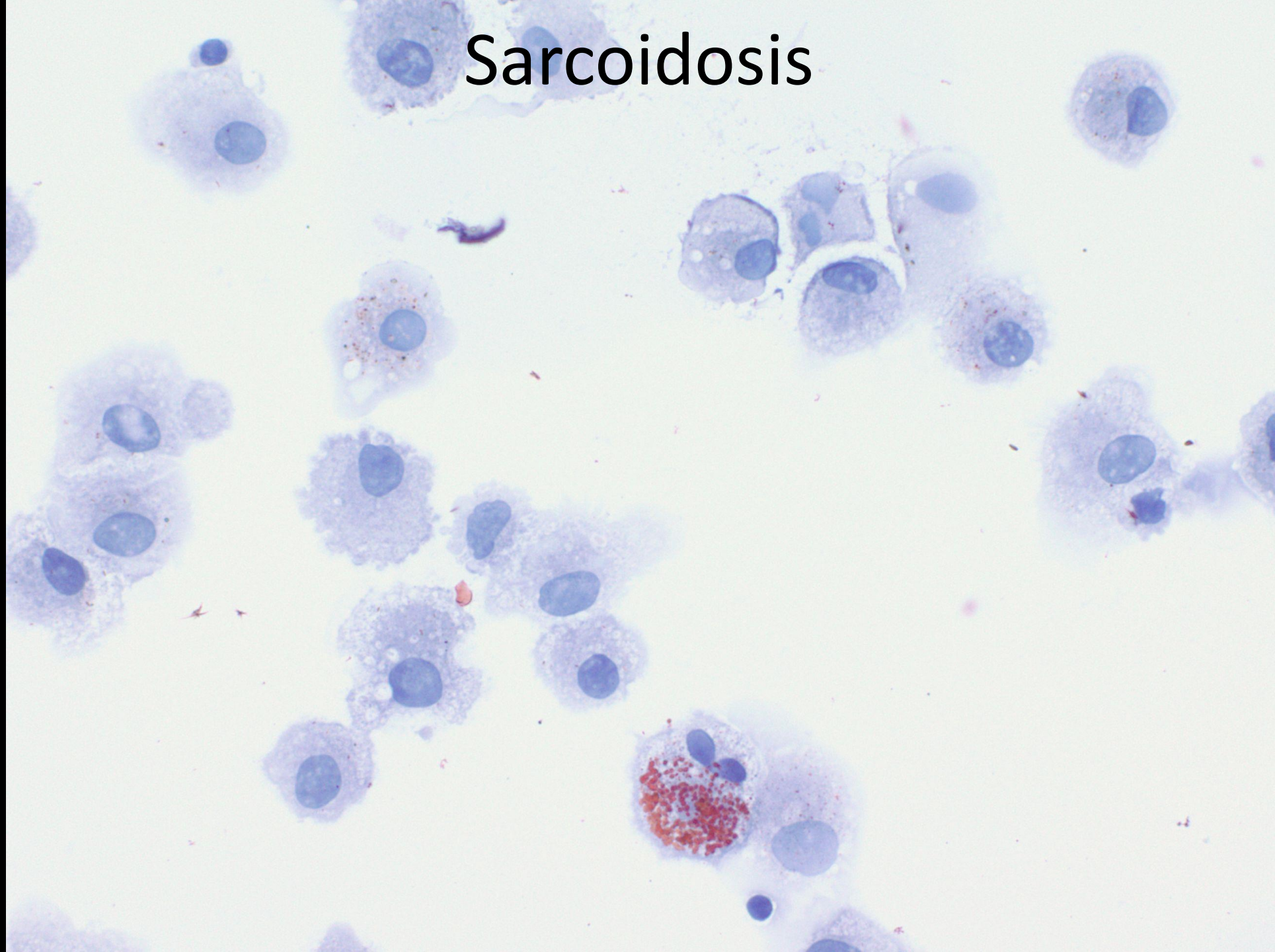


# Lung transplant for cystic fibrosis



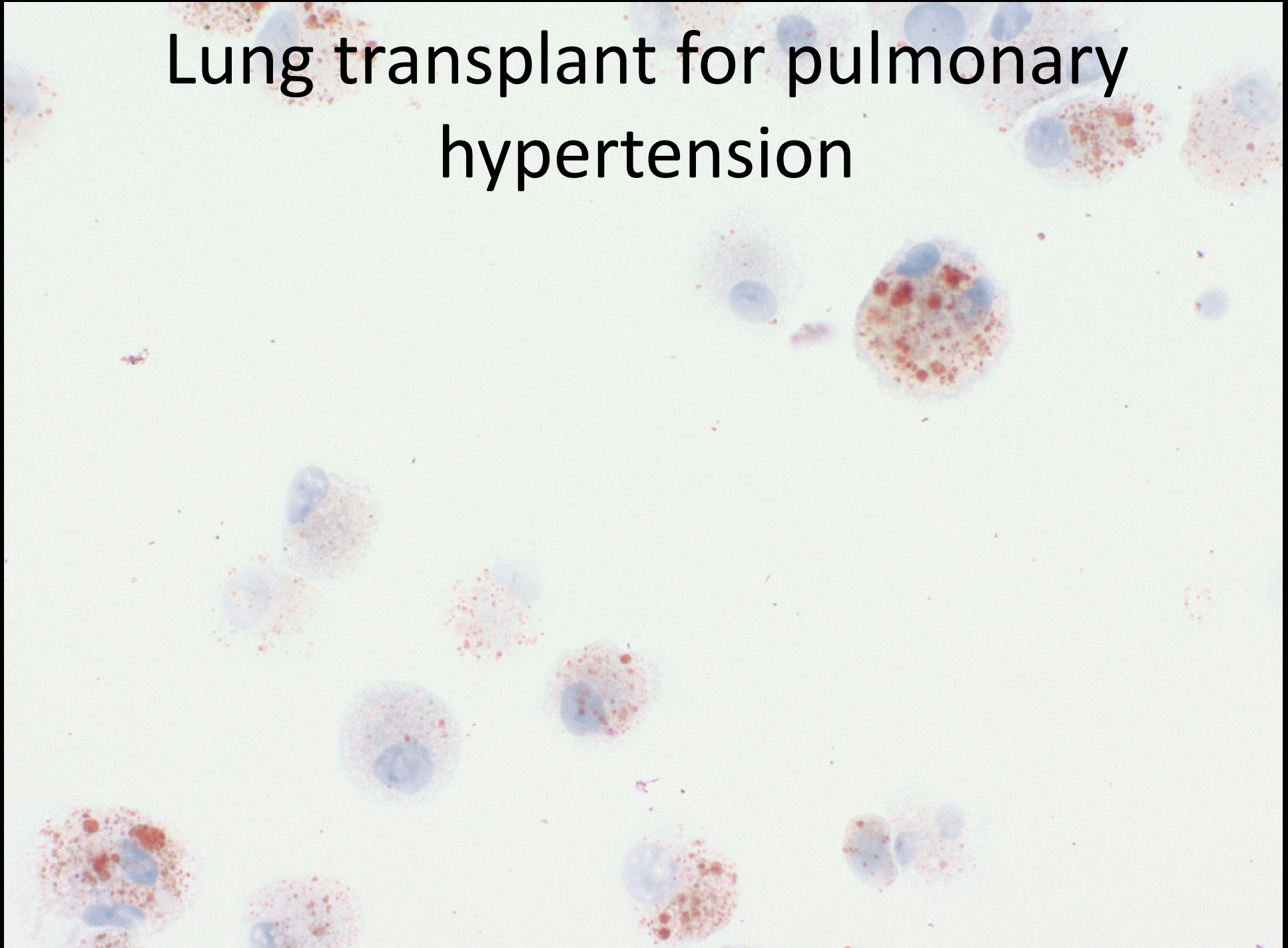


# Sarcoidosis



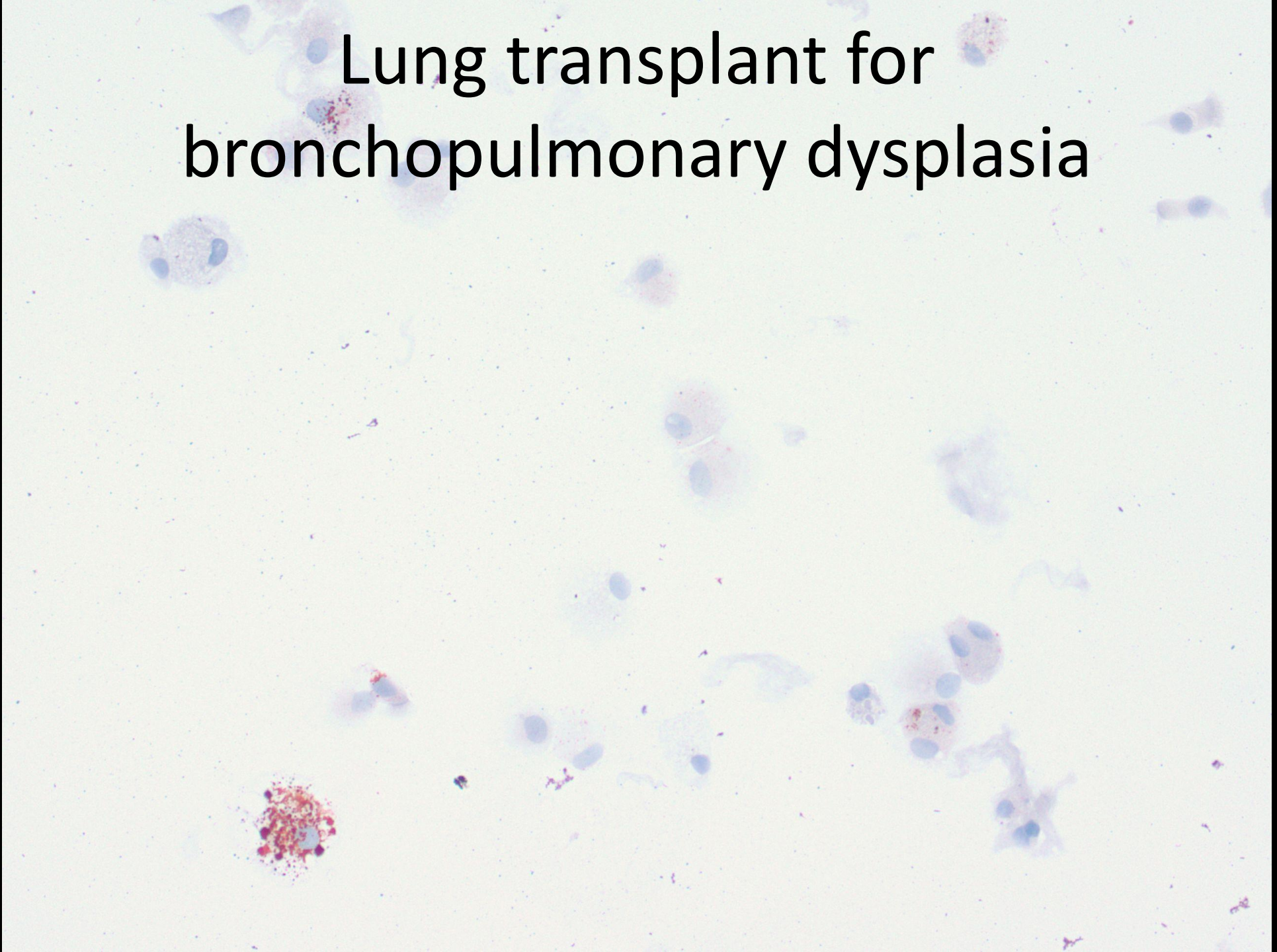


# Lung transplant for pulmonary hypertension






# Lung transplant for bronchopulmonary dysplasia







Remember  
this!

Oil red O is not specific for vaping,  
and is not required for the  
diagnosis of EVALI

Mukhopadhyay S, et al. *Am J Clin Pathol* 2020;153(1):30-39. PMID 31621873

Cecchini MJ, et al. *Arch Pathol Lab Med* 2020; PMID 32401055

# EVALI

(final CDC update, Feb 18, 2020)

2,807 hospitalized cases

68 deaths

82% THC-containing

152 THC-containing brands





Sanjay Mukhopadhyay  
@smlungpathguy



Let's see if we can all agree on a few things about vaping and lung injury:

- 🔥 Vaping with illicit THC carts is associated with the vast majority of acute lung injury
- 🔥 Children and young people should NEVER vape
- 🔥 If you don't smoke, don't vape

AJCP

American  
Journal of  
Clinical  
Pathology

January 2020

Lung Biopsy Findings in Severe  
Pulmonary Illness Associated With...  
[academic.oup.com](http://academic.oup.com)

# Thank You! Questions?

