Lung Transplantation for Bronchopulmonary Dysplasia in Adults: A Clinical and Pathological Study of Three Cases

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Abstract

Background: Bronchopulmonary dysplasia (BPD) is usually seen in premature infants who require mechanical ventilation and oxygen therapy for acute respiratory distress. Although most patients wean from oxygen therapy by the ages of two to three, re-hospitalization for respiratory problems is common in these patients in adulthood. There have been few studies that document the long-term outcomes of BPD survivors and information about pulmonary function and radiographic findings of adult BPD are scarce. Data on pathologic features of adult BPD are essentially non-existent.

Method: Three adult patients who underwent recent lung transplantation for BPD from two institutions were identified. Clinical data including clinical presentation, chest radiographic images, pulmonary function tests (PFT), cardiac catheterization, and echocardiography were retrieved from the electronic medical records. Hematoxylin & eosin (H&E) stained sections of the explant lungs were examined.

Results: All three cases had similar clinical and radiological features including history of prematurity and long-term mechanical ventilation after birth, hyperexpanded lungs with air-trapping and mosaic attenuation on chest CT scan, severe obstructive changes on PFT, and pulmonary hypertension. Pathologic examination showed common features including peri-bronchial, sub-pleural, and interlobular septal fibrosis, narrowing/obliteration of the small airways by muscular hypertrophy, thickening of venous walls by fibromuscular hyperplasia, chronic bronchiolitis, and emphysematous changes. Cholesterol granulomas were seen in two cases.

Conclusion: The common pathological findings in the lungs explain the clinical and radiological findings. Future studies are warranted to further characterize the clinical and pathological features of adult BPD in order to develop optimal management strategies for these patients.

Keywords: bronchopulmonary dysplasia, lung transplantation, pulmonary hypertension

Introduction

Bronchopulmonary dysplasia (BPD) is a chronic lung disease in infancy and is usually seen in premature infants who require mechanical ventilation and oxygen therapy for acute respiratory distress (1, 2). The overall incidence of BPD in ventilated newborns is about 20% (2). Other risk factors of BPD include the following: presence of patent ductus arteriosus (PDA), maternal smoking, chorioamnionitis, and placental insufficiency (3).

BPD was first characterized clinically in 1967 by Northway and colleagues (3, 4). The traditional definition of BPD includes persistent respiratory signs and symptoms, the need for supplemental oxygen due to hypoxemia, and an abnormal chest radiograph at or after 36 weeks gestational age (3). Due to changes in treatment, BPD is divided into "old" and "new" BPD based on radiographic and pathologic findings (3). The former is due to increased oxygen treatment and ventilator injury (3, 5). Oxygen toxicity leads to increased production of free radicals and release of pro-inflammatory and anti-inflammatory cytokines (5, 6). The resulting inflammation and severe airway injury to the immature lung and repair of the damage lead to the radiologic and pathologic changes of old BPD, which center on fibrosis, thickening of alveolar septa, and smooth muscle proliferation (5). "New BPD" is due to changes in management in the mid 1990s, which has transformed from aggressive oxygen and ventilator treatment to administration of exogenous surfactant and prenatal steroids (2). The main changes of "new" BPD are thought to be due to impairment of alveolarization and vascularization; pathologic findings are described as alveolar simplification and enlargement, with less inflammation and fibrosis (3, 5).

In most infants with BPD, pulmonary function gradually improves along with lung growth and remodeling (7, 8). Most patients wean from oxygen therapy by age 2-3 years (2, 5). However, re-hospitalization is common in these patients and children with these histories have a greater incidence of asthma and wheezing (1, 5). These patients also experience an increased use of respiratory medications, and studies have found that they are less likely to be responsive to beta-agonists (9). Long-term pulmonary impairments include: asthma, emphysema, pulmonary hypertension, and more frequent infections (1, 5). In rare cases with severe pulmonary insufficiency, lung transplantation is indicated.

There have been few studies that document the long-term outcomes of BPD survivors who continue into adulthood, and there have not been any comprehensive longitudinal studies that follow patients into adulthood (3, 10). As a result, most cases of BPD are described in premature infants or children. There are few data on the pulmonary function and radiographic findings of BPD in adult patients (1). Data on pathologic findings of adult BPD are non-existent except for a single case report from Korea in 2015 (1). In this study, we describe the clinical, radiographic and pathologic findings in three adult patients with BPD who recently underwent lung transplantation.

Material and Methods

A diagnostic review of all lung transplants performed at Indiana University Health and the University of Michigan between November 1, 1990 and December 31, 2017 in search of patients receiving a lung transplant for a diagnosis of BPD revealed three lung recipients; two at Indiana University Health and one at the University of Michigan. Patient demographics, medical history, and pre-operative wait-list diagnostic studies were gathered from the respective institutions' electronic medical records. Hematoxylin and eosin (H&E) slides of the lung explants for all patients were reviewed independently by four pathologists (OC, AL, CZ). This study received institutional review board (IRB) approval.

Results

Patient 1

A 34-year-old Caucasian female regularly saw a pulmonologist since May 2011 for acute bronchitis flares. She had a history of prematurity, and a PDA repair at the age of one. The patient was on home mechanical ventilation until five years of age. A tracheostomy was in place until age six; an unhealed stoma was surgically closed at age eight. She was regularly followed by a pediatrician during her childhood and these visits were discontinued when her symptoms started to improve. Starting at the age of 28, she required treatments of prednisone and antibiotics for recurrent respiratory illnesses presumed to be related to acute flares of bronchitis that occurred one to two times per year. Her pre-transplantation pulmonary function tests (PFTs)

showed severe expiratory air flow obstruction, moderate gas trapping, and severe diffusion impairment (Table 1). Cardiac catheterization showed moderate to severe pulmonary hypertension with a normal pulmonary wedge pressure (PCW). Echocardiography showed severe right ventricular dilation and right atrial dilatation with a normal left ventricular cavity size. Her chest CT was reported as "severe pan-lobular emphysematous changes with interposed mosaic attenuation consistent with air trapping." The patient underwent lung transplantation in February 2017. Histopathologic findings of the explanted lungs showed fibrosis surrounding the bronchovascular bundles and extending into the interlobular septa and subpleural areas. Thickening in the walls of the veins by fibromuscular hyperplasia was noted. The arteries showed no significant intimal hyperplasia. Chronic bronchitis and bronchiolitis were present. Lumens of some small bronchioles were narrowed or obliterated due to muscular hypertrophy. Alveolar spaces were enlarged and separated by simplified, thin alveolar septa. Occasional cholesterol granulomas were observed.

Patient 2

A 21-year-old Caucasian male was born prematurely at 28 weeks and received mechanical ventilation for one month. He had a PDA repaired surgically shortly after birth and was dependent on oxygen until the age of four. He experienced respiratory events that were attributed to "asthma attacks" throughout his childhood and adolescence that worsened over time and required repeated courses of antibiotics and corticosteroids in recent years. His sweat chloride test was normal. His pre-transplantation PFTs showed severe expiratory air flow obstruction, severe gas trapping, moderately abnormal distribution of ventilation, and severe diffusion impairment. His cardiac catheterization showed moderately elevated right heart pressures, including PCW, and preserved cardiac output and cardiac index. Echocardiography was described as having normal right and left ventricular size and function. His chest CT showed hyper-expanded lungs with mosaic type attenuation suggestive of air trapping and mild bronchiectasis most notable in the lung bases. He underwent lung transplantation in February 2017. Histopathologic findings of the explanted lungs showed fibrosis surrounding the bronchovascular bundles and extending into the interlobular septa and sub-pleural areas. Thickening in the walls of the veins by fibromuscular hyperplasia was noted. Occasional

bronchiolar lumens were narrowed by muscular hypertrophy. Acute and chronic bronchitis and bronchiolitis were prominent.

Patient 3

A 30-year-old white male was born prematurely at 25 weeks with a diagnosis of BPD and required three months of mechanical ventilation. He had a history of PDA ligation surgery. He was hospitalized multiple times for recurrent respiratory exacerbations, such as bronchitis, asthma, and respiratory infections. This patient used prednisone and antibiotics regularly for treatment of his respiratory symptoms. He was also dependent on chronic home oxygen. His pre-transplantation PFTs showed very severe obstructive lung disease with severe diffusion impairment. His cardiac catheterization showed pulmonary hypertension, biventricular pressure overload, and a high cardiac output. Echocardiography showed normal left and right ventricular systolic function and normal sizes of atria and ventricles bilaterally. His chest CT showed severe diffuse pan-lobular emphysema with mild lower lung cylindrical bronchiectasis. Pathologic findings showed emphysematous changes and patchy peribronchial, sub-pleural and interlobular fibrosis. Thick-walled and dilated veins were present within the prominent interlobular septa. The arteries did not show significant intimal hyperplasia. There was also chronic bronchiolitis with multiple cholesterol granulomas.

All three patients had similar clinical features (Table 1) including history of prematurity, patent ductus arteriosus (PDA) repair, long-term mechanical ventilation after birth. Pulmonary function tests (PFT) showed results consistent with severe air flow obstruction and air-trapping while right heart catheterization revealed moderate to severe pulmonary hypertension. Chest computed tomography (CT) showed hyperexpanded lungs with air-trapping and mosaic attenuation (Figure 1).

Histopathologic examination of the three cases showed some common features (Table 1 and Figure 2), including emphysematous changes (Figure 2A), narrowing/obliteration of the small airways by muscular hypertrophy (Figure 2B), fibrosis surrounding the bronchovascular bundles and within the interlobular septa (Figure 2C) as well as the subpleural areas (Figure 2D); thickening in the walls of the veins by fibromuscular hyperplasia (Figures 2C and 2D), and chronic bronchiolitis. Cholesterol granulomas were noted in two of the three cases (Figure 2E).

Discussion

Bronchopulmonary dysplasia (BPD) is a major cause of morbidity, mortality, and re-hospitalization in premature infants and can also be seen in full-term infants that required ventilator therapy for severe lung disease (1, 3). The overall incidence of BPD has remained the same despite changes in management, such as the use of corticosteroids and surfactant administration (2).

Distinct pathologic findings have been described in pediatric patients with BPD. In old BPD, the main features include bronchiolar hyperplasia, diffuse fibroproliferation, thickening of alveolar septa, hyperinflation, and smooth muscle hyperplasia (1, 3, 5). The remodeling of vessels and narrowing of airways lead to symptoms that are similar to those observed in severe pulmonary hypertension patients (3). In comparison, new BPD shows less severe fibrosis and inflammation (11). Instead, the predominant features are decreased alveolar numbers due to enlarged and simplified alveoli, impaired capillary growth, and decreased smooth muscle hyperplasia (6, 11).

While BPD has been well-studied in the pediatric population, few studies exist concerning the clinical findings in adults with a history of BPD, and even fewer describe the radiographic and pathologic findings of these patients as adults. Northway et al followed their initial 1967 study in 1990 with a study of patients 14 to 23 years old, diagnosed with BPD as infants (10). Clinically, these patients had increased episodes of wheezing and pneumonia; they also had decreased exercise capacity and used respiratory medications more often. Pulmonary function tests showed airway obstruction present in greater than 50% of the patients (10). A study performed by Gough et al in 2013 supported these findings with their conclusion that BPD survivors have "increased respiratory symptoms and impaired lung function which persists well into adulthood." (12) In 2011, Wong et al studied the high-resolution computed tomography (HRCT) scans of the chest in a group of adults with BPD ranging from ages 18 to 33. The main radiological findings were triangular and linear opacities, gas trapping, and emphysema (13). While the first two findings correlated with the HRCTs in children, the last finding was specific to adults (13).

A single case report describing pathologic findings of an adult with BPD was reported in 2015 by Lee et al from South Korea (1). This 29-year-old patient, who was a twin born pre-

maturely with BPD and received mechanical ventilation, presented with 20 days of productive cough (1). Pulmonary function tests performed shortly after admission showed findings consistent with a mild restrictive ventilatory defect (FVC 74% predicted, FEV1 76% predicted) rather than an obstructive pattern. Diffusing capacity was reduced to 57% of the predicted value. A chest CT scan revealed mixed areas of ground-glass and reticular opacities in both lungs (1). In this case, the presence of restrictive pulmonary physiology and ground-glass opacities on the HRCT suggests a differential diagnosis that includes interstitial lung disease, acute alveolar diseases, and opportunistic infections (14). The authors noted that these findings may have been a result of respiratory infections, which BPD patients are predisposed to. Video-assisted thoracoscopic surgery (VATS) lung wedge biopsy revealed small airway damage superimposed on a combination of old BPD and new BPD findings, such as smooth muscle hyperplasia, peri-bronchial fibrosis, and focal emphysematous change (1). Focal cystic dilatation of bronchiolar lumens was noted. The combination of old and new BPD with damage primarily to the small airways supported the authors' comments that the pathological findings would not follow a consistent pattern since the lungs were "damaged to a varying extent." (1) This report is the first and only one that provided a glance into the histopathologic findings of this disease process along with pulmonary physiologic and radiographic findings in an adult with BPD. There have been no other published studies on BPD in adults.

In our study, we report on three patients, ranging from the ages of 21 to 34 years, who were diagnosed with BPD as premature infants and underwent lung transplantation as adults. All patients received PFTs, cardiac catheterization, echocardiography, and chest CT prior to their lung transplantation (Table 1). Our cases showed several similarities to the case study by Lee et al. The history of prematurity and treatment with mechanical ventilation were similar among all patients. The histopathologic findings in all cases had a combination of old and new BPD, as seen with the presence of chronic bronchiolitis with smooth muscle hyperplasia, fibrosis involving the peri-bronchial, sub-pleural, and interlobular septal areas, and emphysematous changes. Major differences in the clinical diagnostic findings also existed between our patients and the Lee et al case study. Ground glass opacities on chest CT were reported in the Lee et al case study, raising the possibility of interstitial lung disease and infectious etiologies. Pulmonary function testing also favored a restrictive rather than the obstructive ventilatory defect seen in our patients, although diffusion impairment was present in all subjects. In contrast, the consistent

radiological findings in our three cases were pan-lobular emphysema and attenuation consistent with air-trapping, which are indicative of chronic obstructive lung disease. Lee et al commented that there would not be a consistent pattern to the histopathology of adult BPD due to varying extent of damage to the lungs. Several patterns were noted among most or all of our three cases. In addition to the common histopathologic findings described above, our three cases also showed thickening in the walls of the veins by fibromuscular hyperplasia. This consistent pattern of histopathologic change may allow us to further speculate about the pathogenesis of this disease that is relatively unknown in adults.

The common findings of bronchiolitis, muscular hypertrophy, and emphysema in our cases explain the clinical symptoms and radiological evidence of chronic obstructive lung disease observed in these patients. Our findings also support the conclusion in the 2010 EPICure study that BPD patients would be at an increased risk of obstructive lung disease, during adulthood (15). The patients in a 2014 study by Gough et al of respiratory health in adult survivors of BPD, reported similar symptoms and significantly reduced FEV_1 values, independent of whether they received BPD treatment before or after the era of aggressive mechanical ventilation and oxygen supplementation (12).

An interesting pathological finding of note in two of our patients was the presence of cholesterol granulomas with a background of chronic bronchiolitis. There are several proposed mechanisms for the formation of cholesterol granulomas and their role in obstructive lung disease. In 1992, Fisher et al speculated that aspiration may have a role in the formation of chronic lung disease in these patients, and thus, the presence of cholesterol granulomas (16). In 2016, Bhandari et al expanded on this speculation by proposing that children with BPD are at a higher risk of other comorbidities, such as neurocognitive developmental delay and swallowing dysfunction. This, in turn, increases the risk of impaired airway clearance and episodes of micro-aspiration in these patients; therefore, there may be a greater risk of infection and continued inflammation (17). Fisher et al proposed that the response of the pulmonary epithelium to this insult sets the stage for the development of fibrosis and continued destruction of lung tissue (16). This causes the release of lipid material, which is phagocytosed by macrophages that accumulate fat and cholesterol (18). Overtime, the combination of extensive fibrosis and macrophages leads to further obstruction, a further increase in foamy macrophages, and the subsequent formation of

cholesterol granulomas (18). Another postulated mechanism for the development of cholesterol granulomas ties in with presence of pulmonary hypertension. In 1968, Glancy et al observed that cholesterol granulomas did not occur outside of the presence of pulmonary hypertension in their group of patients (18). A study by Nolan et al in 1999 reported that as many as 25% of patients in their study had the presence of cholesterol granulomas in conjunction with pulmonary hypertension (19). This suggests that cholesterol granulomas may exaggerate the obstructive changes and have a role in the development of pulmonary hypertension and the severity of the clinical symptoms in two of our three cases. Conversely, Fisher et al suggested that the presence of pulmonary hypertension itself may alter how surfactant is metabolized; in this case, into cholesterol crystals that eventually undergo fibrosis and become cholesterol granulomas (16).

Past studies have shown that there is an increased risk of pulmonary hypertension in patients with obstructive lung disease, specifically emphysema (20). In addition to the proposed mechanism of how cholesterol granulomas lead to an increase in obstructive symptoms and pulmonary hypertension, the interlobular fibrosis and fibrous thickening of venous walls may also explain the pulmonary hypertension reported in the cardiac catheterization results in these patients. One interesting aspect of the pulmonary hypertension in our cases was the fact that the veins were the main vasculature affected as opposed to the arteries. The findings share similarities with one rare sub-group of pulmonary arterial hypertension (PAH): pulmonary veno-occlusive disease (PVOD), which mainly affects the post-capillary venous pulmonary vessels and was described in the past as "obstructive disease of the pulmonary veins." (21, 22) Pathologic similarities between our patients and PVOD include interlobular fibrosis, venous fibrous thickening, and obliteration (22). However, our cases lack the capillary proliferation and hemosiderin deposition commonly observed as a result of venous congestion in PVOD. We suspect that these features are not observed in our cases since the disease process of BPD causes capillaries to develop abnormally. New BPD has been described as having decreased and dysmorphic capillaries compared to normal lung and old BPD (11).

The clinical symptoms exhibited by the three patients in this study were more exaggerated compared to the majority of patients with a past diagnosis of BPD. Our findings suggest that there is a subset of patients in which the disease continues to progress and worsens rapidly into adulthood. The clinical and pathological features of our cases seem to involve

features of both COPD and PVOD but still possess their own unique features. Further studies of adult BPD patients are needed to possibly categorize them into a more specific group of lung diseases, which may expand their treatment options outside of lung transplantation or preserve lung function as a bridge to this procedure. More studies may also bring attention to the severity of disease progression in these patients and lead to more pertinent follow-up recommendations for BPD patients after childhood.

In summary, common histopathologic findings are observed in the lungs of adult patients who developed BPD in childhood and required lung transplantation to improve survival. . These findings explain the common clinical findings of the patients and offer insight into the pathogenesis of the severe form of BPD in adults. With whole explanted lungs at hand, we were able to perform a comprehensive histopathologic examination of BPD in the adult. More studies are needed to further characterize the clinical and histopathologic features of this disease that may lead to development of new prophylactic treatment options and/or improve current therapy for these patients.

Acknowledgment

CZ is the guarantor of the content of the manuscript, including the data and analysis. CZ, NL, OWC and AL performed microscopic examination. CAH and KMC provided patients' clinical data. CZ and NL contributed to data analysis and interpretation. All author contributed to study design and manuscript preparation.

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Table 1. Summary of clinical, radiologic and histopathologic findings.

	Patient 1 (ET)	Patient 2 (JS)	Patient 3 (MC)
Age (years)	34	21	30
Sex	Female	Male	Male
Race	Caucasian	Caucasian	Caucasian
History	Prematurity PDA repaired Dependent on home mechanical ventilation until age 4 or 5	Prematurity at 28 weeks PDA repaired Dependent on home mechanical ventilation Thoracotomy performed for PDA Oxygen use until age 4	Prematurity at 25 weeks PDA repaired Dependent on home mechanical ventilation H/o PDA ligation surgery Dependent on chronic home oxygen
Major Symptoms	Acute bronchitis flares since 2011 Required regular use of prednisone and antibiotics	Asthma symptoms during adolescence Progression to congestion	Recurrent respiratory tract infection and asthma Multiple recurrent hospitalizations for bronchitis, asthma, and respiratory infections Regular use of prednisone and antibiotics
Pulmonary Function Tests (PFTs) (Liters, % predicted)	FVC 1.85 (54%), FEV_1 0.71 (26%), FEV_1/FVC 38, TLC 5.34 (114%), RV 3.45 (278%), DLCO 37%	FVC 1.96 (34%), FEV_1 0.83 (18%), FEV_1 /FVC 43, TLC 7.97 (106%), RV 6.01 (347%), DLCO 45%	FVC 2.20 (45%), FEV_1 0.56 (14%), FEV_1 /FVC 25, TLC 10.32(153%), RV 8.12(461%), DLCO 22%
Cardiac Catheterization (mmHg)	mPAP 41, CI 2.37, PVR 7.4 WU, PCW 11	mPAP 38, CI 2.68, PVR 3.9 WU, PCW 19	mPAP 52, CI 4.91, PVR 4.0 WU, PCW 20
Echocardiography	Left ventricular cavity size normal Severe right ventricular dilation Right atrial dilatation	Left ventricular cavity size normal Normal left ventricular ejection fraction Right ventricle normal in size and function	Normal right and left ventricular systolic function Normal sizes of atria and ventricles bilaterally
Chest CT	Severe pan-lobular emphysematous changes Interposed mosaic attenuation consistent with air trapping	Hyper-expanded lungs Mosaic type attenuation suggestive of air trapping Mild bronchiectasis most notable in lung bases	Severe diffuse pan-lobular emphysema Mild lower lung cylindrical bronchiectasis
Pathologic Findings	Peribronchial, interlobular septal and subpleural fibrosis Fibromuscular thickening of the venous walls Narrowing/obliteration of bronchioles by muscular hypertrophy Emphysematous changes Occasional cholesterol granulomas	Peribronchial, interlobular septal and subpleural fibrosis Fibromuscular thickening of the venous walls Mild smooth muscle hyperplasia of the bronchioles Acute bronchitis/bronchiolitis Patchy emphysema and atelectasis	Patchy subpleural and interlobular fibrosis Prominent interlobular septa with thick-walled and dilated veins Emphysematous changes Chronic bronchiolitis with cholesterol granulomas

FVC= Forced Vital Capacity, FEV1= Forced expiratory volume at 1 second, TLC= total lung capacity, RV= residual volume, DLCO= diffusing capacity lung for carbon monoxide, mPAP= mean pulmonary artery pressure, CI= cardiac index, PVR = pulmonary vascular resistance, WU = Wood units, PCW = pulmonary capillary wedge pressure

Figure 1. Chest CT scans of all three patients are similar, showing severe pan-lobular emphysematous changes and mosaic attenuation consistent with air trapping.

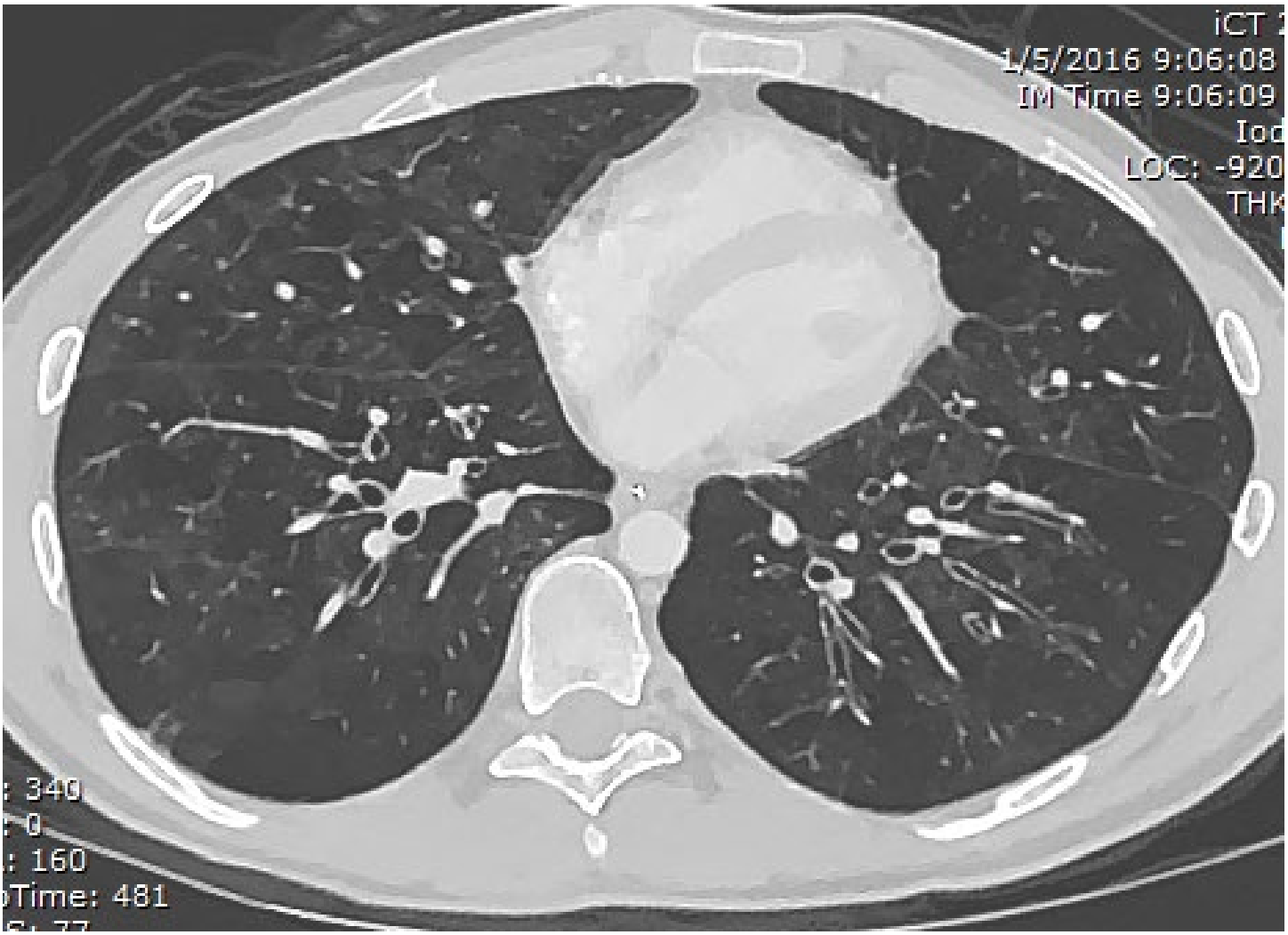
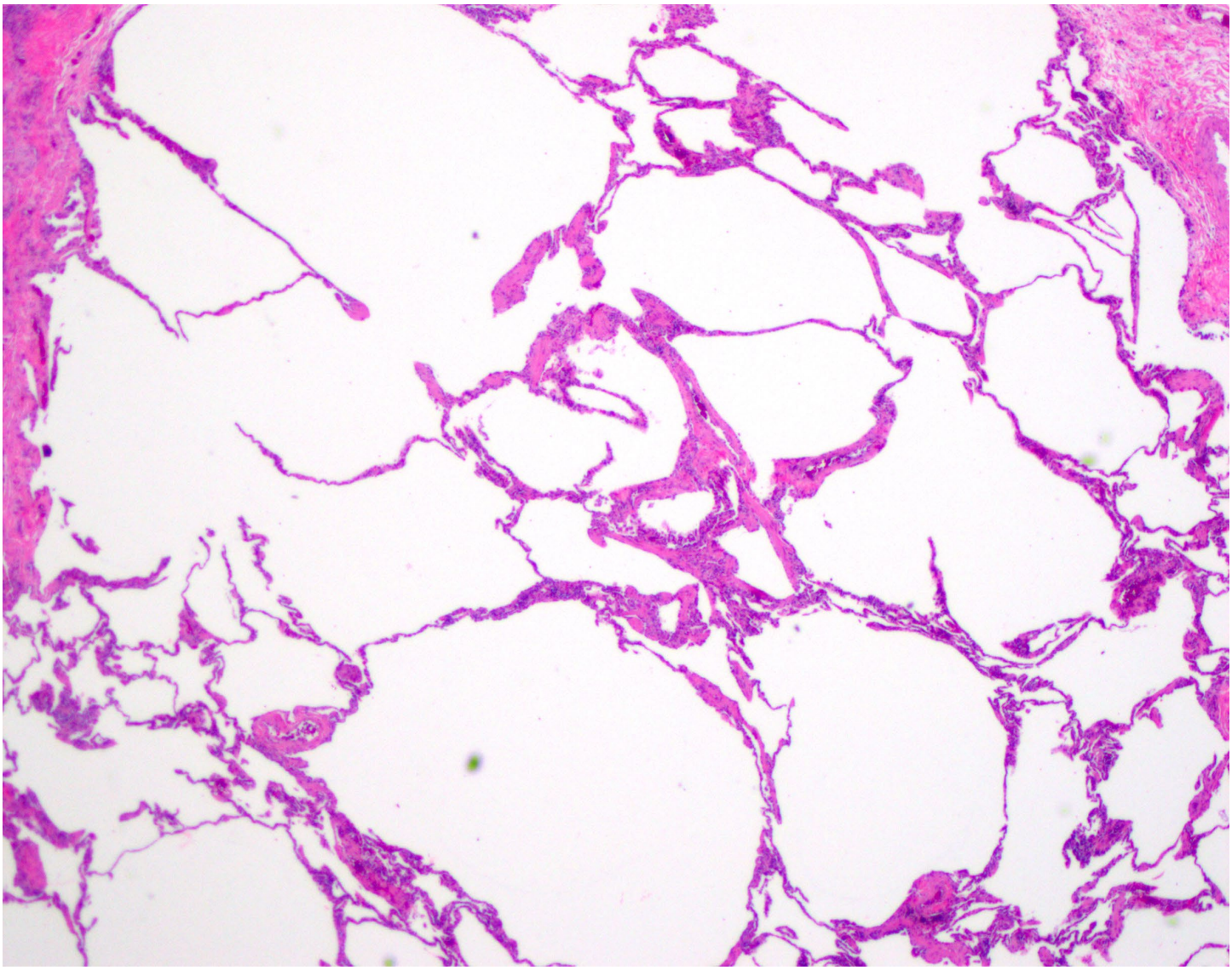


Figure 2. Common pathologic features of the three cases. **A**. Enlarged airspace with thin and simplified alveolar septa (emphysematous change). **B**. Bronchiolar lumen is narrowed with muscular hypertrophy. **C**. Fibrosis of the interlobular septa. Veins within the septa show fibromuscular hyperplasia of the walls. **D**. Subpleural fibrosis and fibromuscular hyperplasia of the veins. **E**. Cholesterol granulomas, aggregates of multinucleated giant cells containing cholesterol crystals/clefts, are present in two patients (#1&3). Magnification: 40X (A, C, D) and 100X (B, E)

2A



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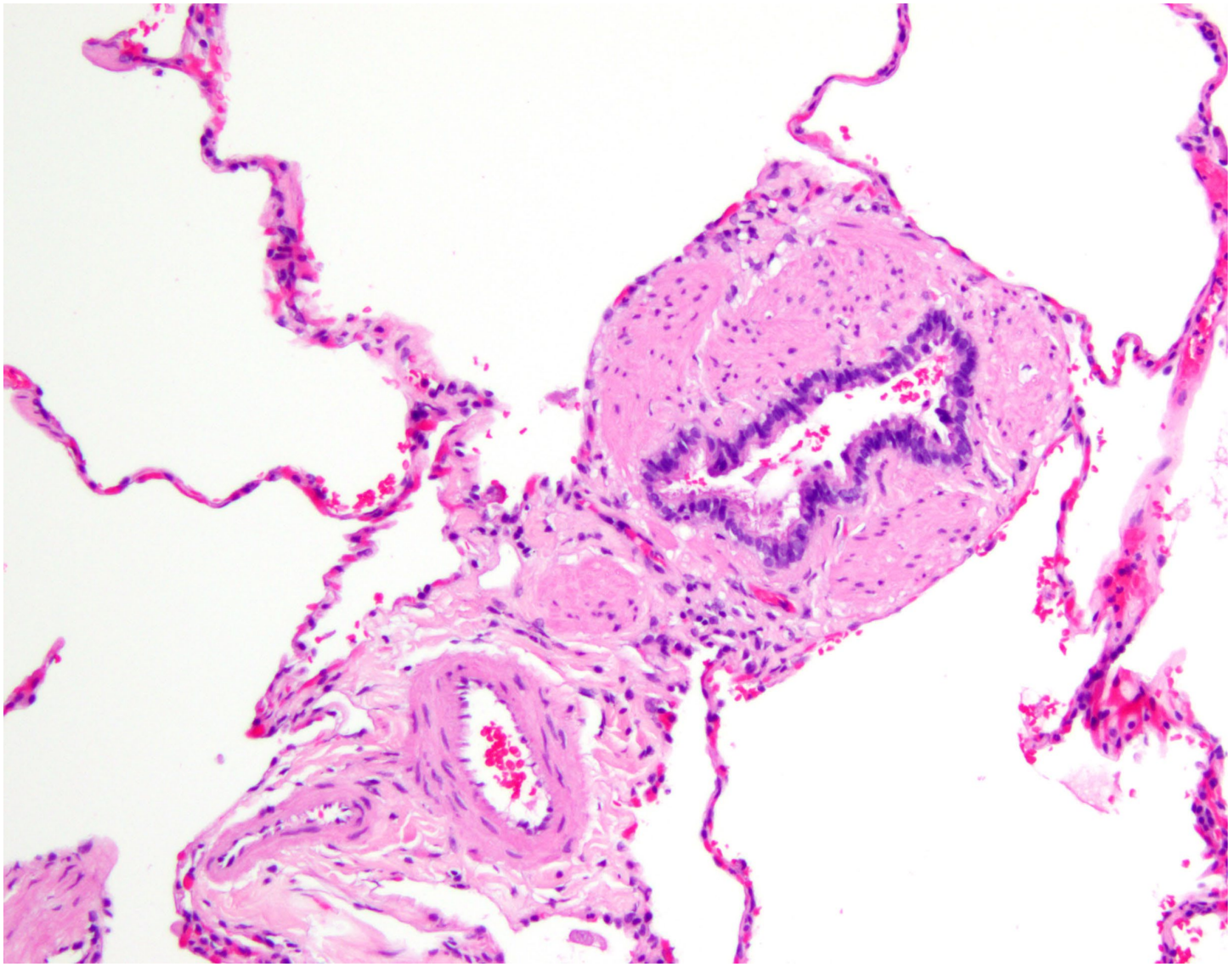

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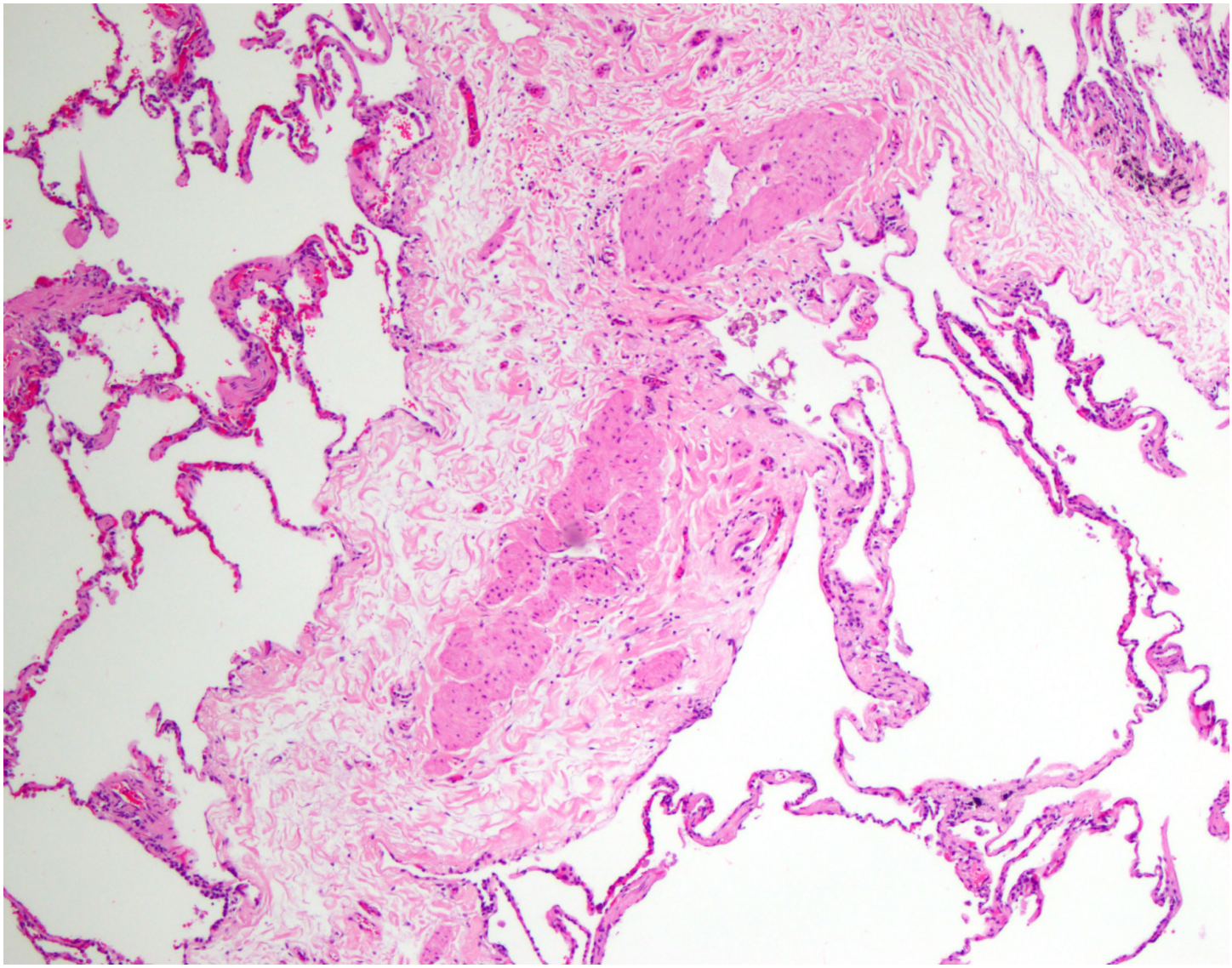
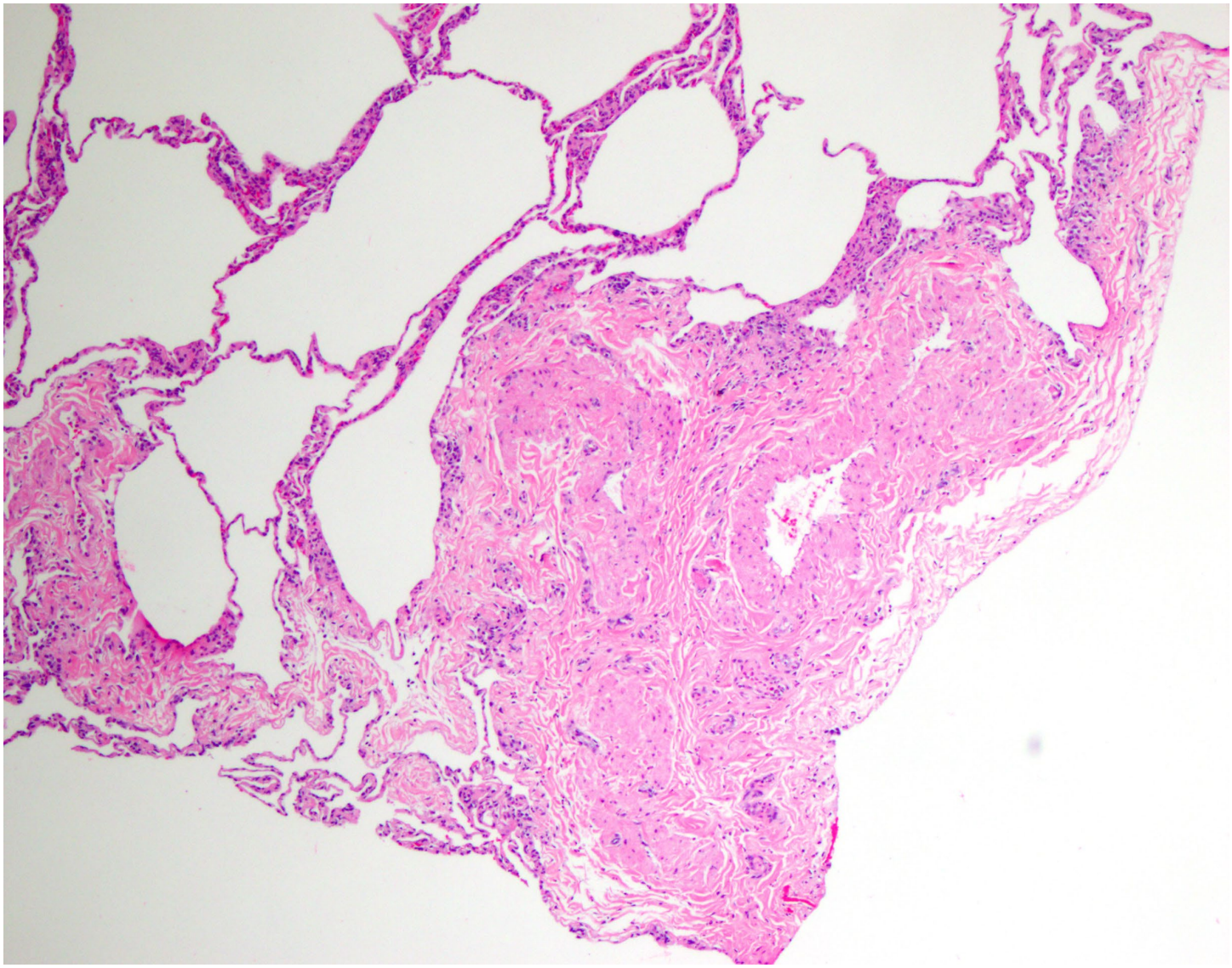


2D



2E