Pulmonary hypertension associated with veno-occlusive disease in systemic sclerosis: Insight into the mechanism of resistance to vasodilator

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Hayato Tada (MD)[a]*, Tetsuo Konno (MD, FJCC)[a], Motohiko Aizu (MD)[b], Junichiro Yokawa (MD)[a], Toshinari Tsubokawa (MD)[a], Hiroshi Fujii (MD)[b], Kenshi Hayashi (MD, FJCC)[a], Katsuharu Uchiyama (MD)[a], Masami Matsumura (MD)[b], Mitsuhiro Kawano (MD)[b], Masa-aki Kawashiri (MD)[a], Masakazu Yamagishi (MD, FJCC)[a]

[a]Division of Cardiovascular Medicine Kanazawa University Graduate School of Medicine, Kanazawa, Japan

[b]Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

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Address of correspondence: Hayato Tada, MD

Division of Cardiovascular Medicine, Kanazawa University Graduate School of Medicine,

13-1 Takara-machi, Kanazawa, 920-8641, Japan.

Tell: +81-76-265-2000 (2251), Fax: +81-76-234-4251

E-mail: ht240z@med.kanazawa-u.ac.jp

Summary

We report a case with pulmonary veno-occlusive disease (PVOD) associated with systemic sclerosis which exhibits strong resistance to pulmonary vasodilator.

A 55-year-old female with severe pulmonary hypertension was admitted to our hospital to be introduced epoprostenol infusion therapy. She was diagnosed as pulmonary arterial hypertension (PAH) associated with systemic sclerosis at the age of 51. Several aggressive treatments with pulmonary vasodilators, including oral prostaglandin, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors, failed to improve her symptoms. We introduced continuous intravenous epoprostenol therapy from 2 μg/kg/min for her. However, pulmonary edema appeared and worsened dose dependent manner. We made a diagnosis as PVOD clinically at that time. Thereafter, pulmonary edema gradually disappeared in consistent with the reduction of the dose of epoprostenol infusion. She died of renal failure and infection 4 months after the introduction of epoprostenol infusion therapy. A histological examination revealed severe stenosis and occlusions of pulmonary veins as well as pulmonary arteries over a wide area. We suggest that prevalence of veno-occlusive type of disease could be one of the major mechanisms of less responsive or even refractory to pulmonary vasodilator therapies to patients with PH associated with connective tissue disease.

Introduction

Recent advances regarding the treatment for pulmonary hypertension, especially, for pulmonary arterial hypertension (PAH) have improved the prognosis of patients with PAH [1, 2]. Several reports have described that connective tissue diseases such as systemic sclerosis and systemic lupus erythematosus could be complicated by severe PAH which worsens their prognosis [3, 4]. Pulmonary hypertension associated with connective tissue disease has been categorized into PAH. Pulmonary veno-occlusive disease (PVOD) has been described as a relatively rare cause of pulmonary hypertension that affects predominantly post-capillary pulmonary vessels. A major concern with PVOD is the poor responsiveness to available pulmonary vasodilator, especially, the risk of pulmonary edema with continuous intravenous epoprostenol therapy [5, 6]. We recently experienced a case with PVOD associated with systemic sclerosis which exhibited strong resistance to pulmonary vasodilator, including continuous intravenous epoprostenol therapy.

Case report

A 55-year-old female admitted to our hospital for the introduction of epoprostenol infusion therapy. She was diagnosed as systemic sclerosis at the age of 39. And the initial diagnosis of her pulmonary hypertension was made when she was 51 years old. She had been treated with beraprost since then. Thereafter, her symptoms of dyspnea gradually worsened associated with the increase of pulmonary artery pressure in spite of the introduction of sildenafil, ambrisentan and home oxygen therapy during four years of clinical course. Physical examination at the admission revealed a heart rate of 80 bpm, a blood pressure of 90/52 mmHg and a respiratory rate was 20 breaths/min. She had some

signs of fluid overload such as jugular vein distension and lower extremity edema and was in functional New York Heart Association (NYHA) class III. Arterial blood gas analysis revealed hypoxemia (pH 7.41, $PaCO_2$ 35 mm Hg, PaO_2 79 mmHg under O_2 2L/min). The electrocardiogram revealed a sinus rhythm of 80 bpm, and right ventrichlar hypertrophy findings of the tall R waves in right precordial leads with right ventricular strain pattern (Fig. 1A). Chest x-ray (Fig. 1B) demonstrated bilateral hilar enlargement, a prominent medial arch and pulmonary artery trunk. Echocardiography confirmed dilatation of both the right atrium and right ventricle, and normal left ventricular function (left ventricular ejection fraction of 62%) with flattening of ventricular septum (Fig 1C). Trans-mitral flow velocity pattern revealed abnormal relaxation, and the ratio of mitral inflow and mitral annular tissue Doppler imaging velocities (E/e') was within the normal range (8.3). Right heart catheterization demonstrated severe pulmonary hypertension (pulmonary arterial systolic pressure 94 mmHg, pulmonary arterial diastolic pressure 27 mmHg, mean pulmonary arterial pressure 48 mmHg) in contrast to the normal range of pulmonary capillary wedge pressure 14 mmHg. Other important parameters were cardiac output 3.9 L/min, (thermo dilution method) and pulmonary vascular resistance 540 dynes· s· cm^{-5}. After these examinations, epoprostenol infusion therapy was introduced from the dose of 2μg/kg/min. However, pulmonary edema appeared and her oxygenation worsened dose dependent manner. Based on this clinical course, we made a diagnosis as PVOD clinically at the dose of epoprostenol was 12μg/kg/min. Thereafter, pulmonary edema gradually recovered in consistent with the reduction of the dose of epoprostenol infusion. A high-resolution computed tomography (HRCT) of her chest revealed centrilobular ground-glass opacities and septal thickness (Fig 1D). Lung transplantation was proposed as the sole treatment option to

prolong her life, but she declined. The patient died of renal failure and infection 4 months after the introduction of epoprostenol infusion therapy. Histopathological examination of her heart revealed hypertrophy of both ventricles without any apparent pathological interstitial fibrotic change (Fig 2A). In addition to the findings of small pulmonary arteries that revealed pronounced intimal fibrosis as typically seen in PAH (Fig 2B), small pulmonary vein also showed fibrotic occlusive lesions with marked intimal thickening characteristics of PVOD (Fig 2C). The capillaries in the alveolar area showed dilatation like angioma (Fig 2D) as well as the findings of intra-alveolar hemorrhage (Fig 2 E-G). On the basis of these pathological findings and clinic features, the patient was diagnosed as PVOD.

Discussion

Even though PAH and PVOD share many similarities, the clinical classification was modified to change to separate PVOD from other forms of PAH following the Fourth World Symposium on PAH held in 2008 at Dana Point, California [8]. It is currently well established that PAH associated with connective tissue disease such as systemic sclerosis is frequently less responsive or even refractory to pulmonary vasodilator therapies. The likely mechanism is a selective dilatation of the small pulmonary arteries without associated pulmonary venodilatation could cause an increase in trans-capillary hydrostatic pressure. Several papers have described the usefulness of HRCT to predict the presence of PVOD [9, 10]. Our case also showed centrilobular ground-glass opacities and septal thickness; however, the findings of HRCT suggesting the presence of PVOD were obtained after the introduction of epoprostenol infusion therapy. Thus, we could not suspect PVOD until then. Several studies suggested that the frequencies of veno-occlusive types of disease in the

patients with PAH associated with connective tissue disease might be larger than expected, and there is some evidence from histopathological reports to support this hypothesis [5]. However, the current definite diagnosis of PVOD can be made by histopathologically, thus, limiting the estimation for the accurate involvements of this type of disease.

In conclusion, we report a case with PVOD associated with systemic sclerosis which exhibits strong resistance to pulmonary vasodilator. We suggest that prevalence of veno-occlusive type of disease could be one of the major mechanisms of less responsive or even refractory to pulmonary vasodilator therapies to patients with pulmonary hypertension associated with connective tissue disease.

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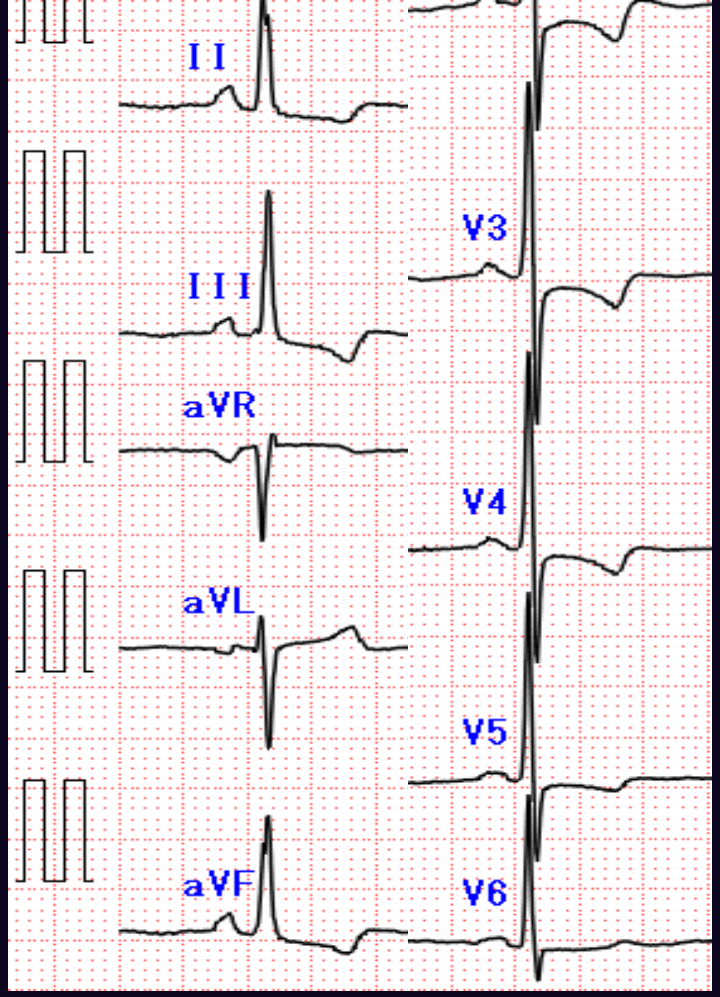
Figure Legends

Figure 1: Imaging of the case

Electrocardiogram at the admission revealed right ventrichlar hypertrophy findings of the tall R waves in right precordial leads with right ventricular strain pattern (A). Chest x-ray demonstrated bilateral hilar enlargement, a prominent medial arch and pulmonary artery trunk (B). Echocardiography revealed dilatation of right ventricle, and normal left ventricular function with flattening of ventricular septum (C). HRCT of her chest revealed centrilobular ground-glass opacities and septal thickness (D, arrow).

Figure 2: Histopathological findings

Macroscopic finding of heart; Transverse section of the heart showing hypertrophy of both the left and right ventricles (A). Small pulmonary artery revealed pronounced intimal fibrosis, as typically seen in PAH (B, Elastica van Gieson stain, ×200). Small pulmonary vein showed fibrotic occlusive lesions with marked intimal thickening characteristics of PVOD (C, Elastica van Gieson stain, ×200). The capillaries in the alveolar area showed dilatation like angioma (D, hematoxylin and eosin stain, ×200). Macroscopic findings of lung; alveolar hemorrhage was observed (E, arrow). Intra-alveolar macrophages were observed (F, arrow, hematoxylin and eosin stain, ×40). Fe-stain revealed the existence of iron in the alveoli (G, arrow, Fe-stain, ×200).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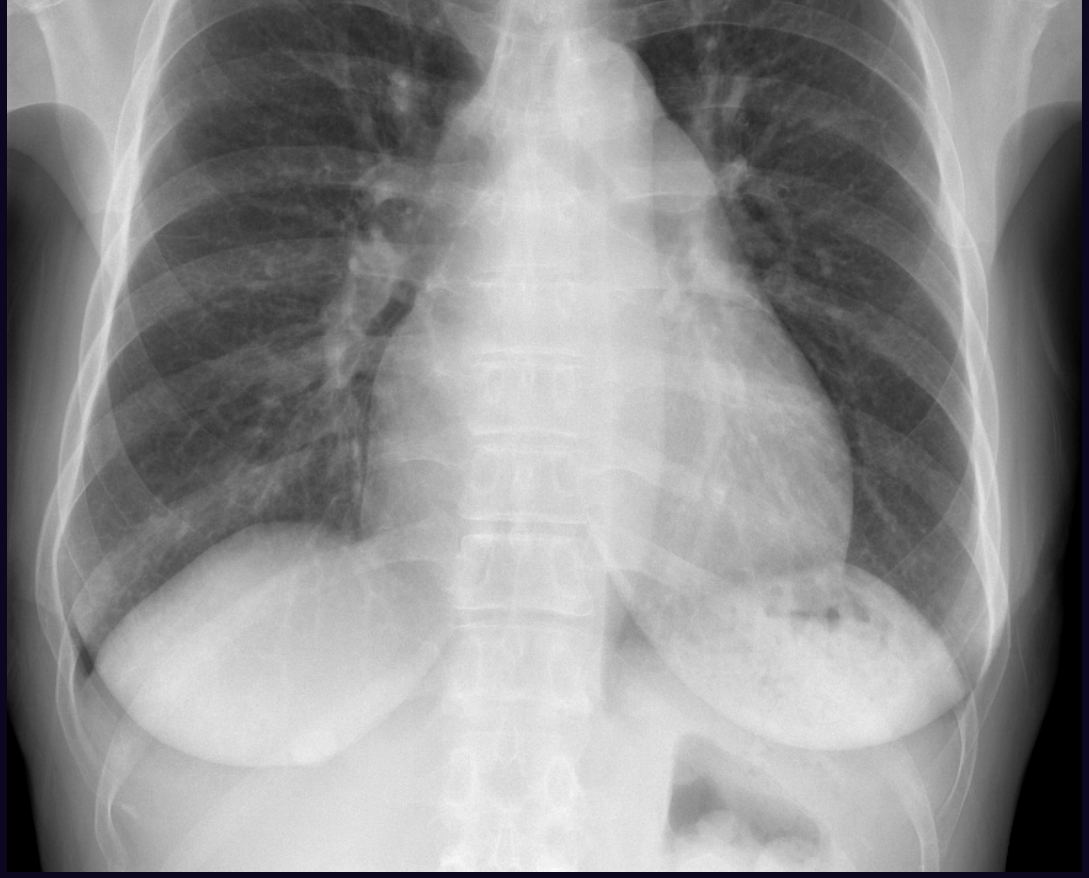

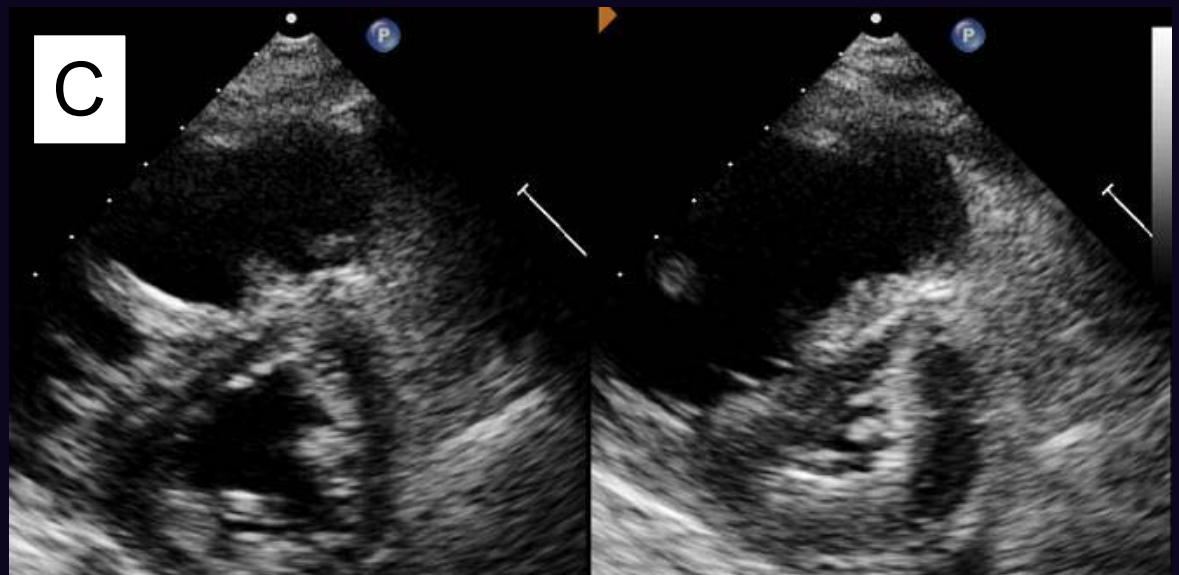
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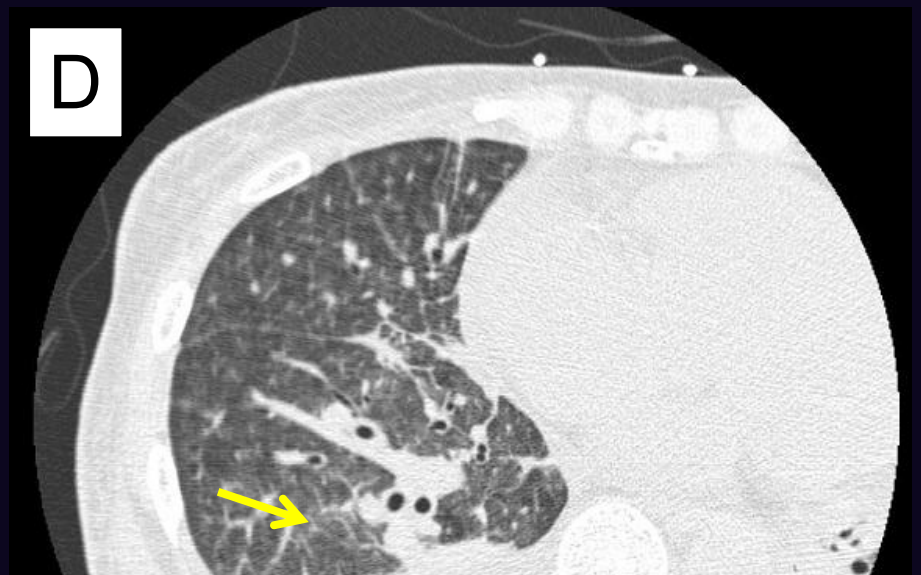
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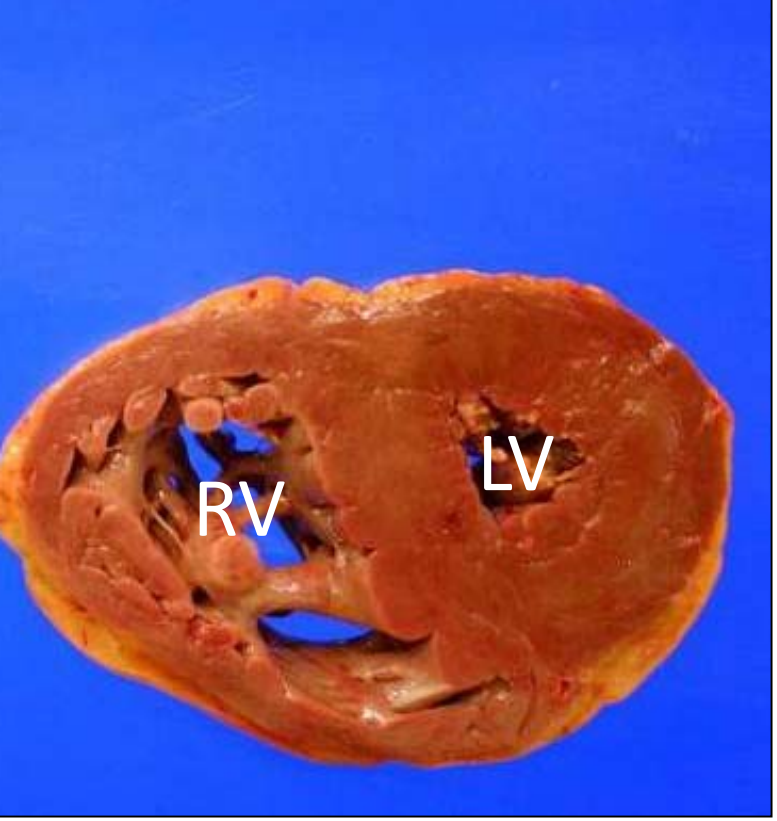
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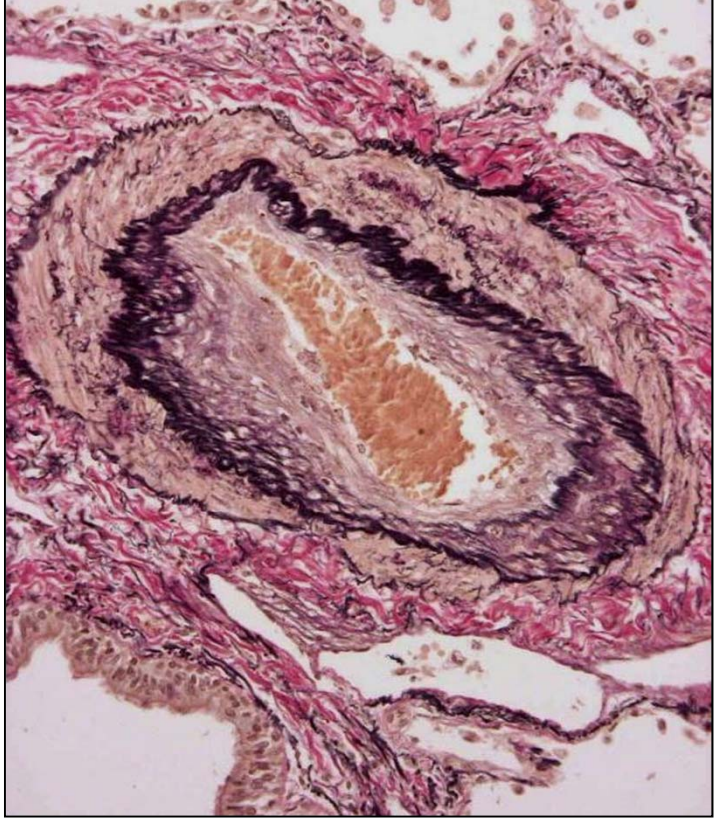

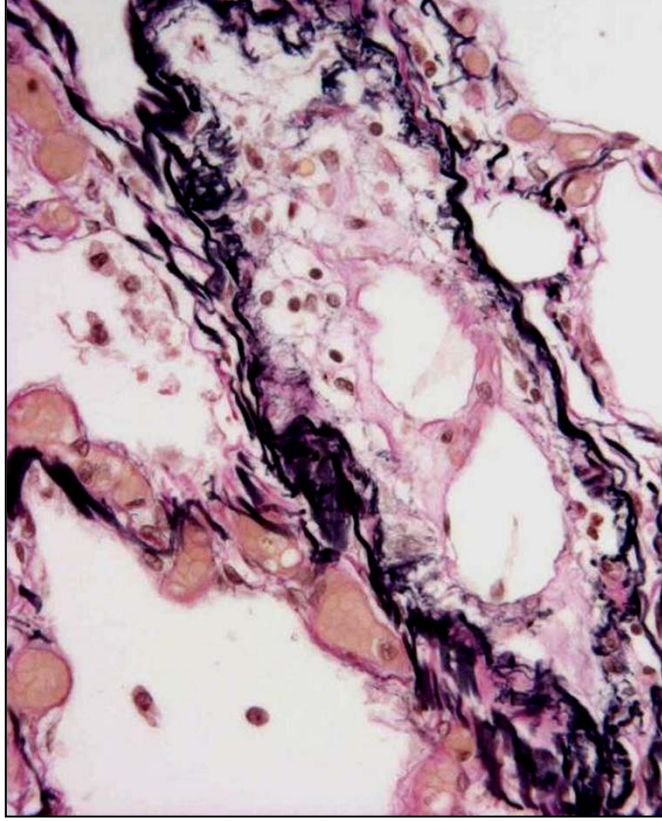

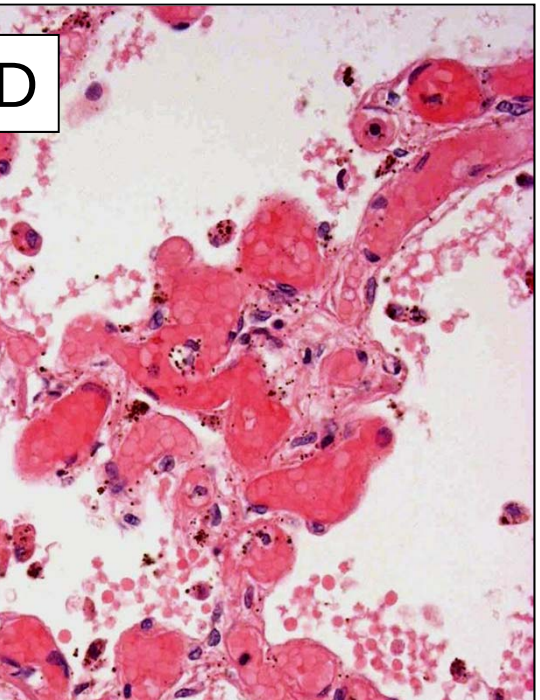
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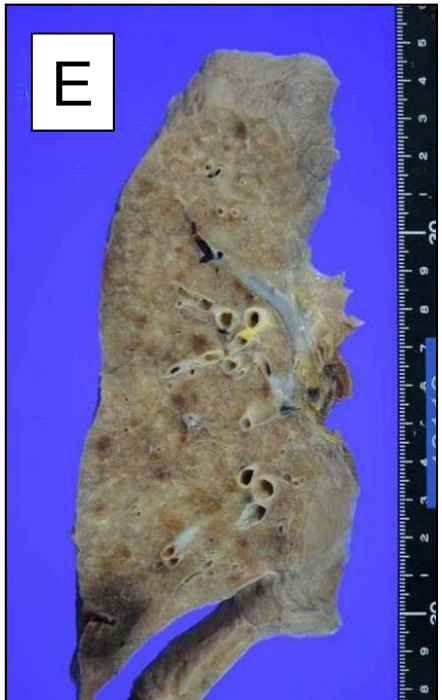
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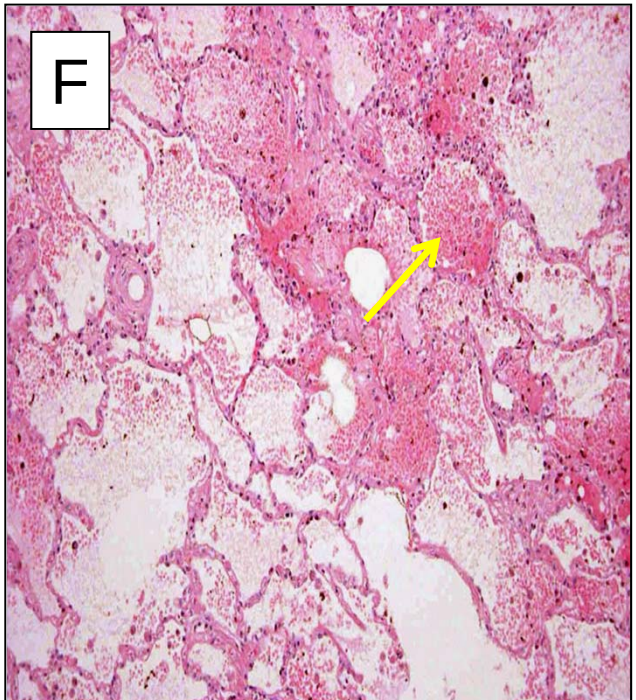
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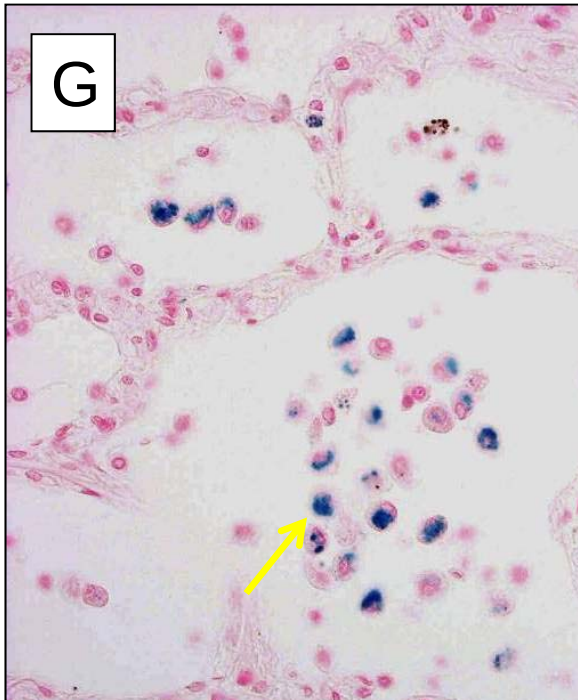
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