

When tiny lungs Struggle to breathe; a rare cause of Refractory Primary Pulmonary Hypertension

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Case Report

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Abstract

Alveolar capillary dysplasia with malpositioned pulmonary veins (ACD/MPV) is a lethal congenital lung disorder with a mortality rate of almost 100%. Infants deteriorate within the first 24 hours of life.

Here, we present a 2-day old female child born of full term normal vaginal delivery and cried immediately after birth. The baby presented with Respiratory distress within 6 hours of life and was put on extracorporeal membrane oxygenation. 2-D echo revealed no congenital heart disease. The child continued to have pulmonary hypertension non-responsive to pharmacotherapy and eventually passed away. A post mortem histopathology examination revealed immature lung parenchyma with arrest in the saccular phase, thickened alveolar septae with abnormally positioned pulmonary capillaries. Focally, there were thin-walled vessels invested in the same adventitial sheath as the pulmonary arteries. The pulmonary arterioles exhibited features of pulmonary artery hypertension. Based on this constellation of features, the baby was diagnosed with ACD/MPV. The rarity and the focal nature of this condition make it a diagnostic challenge in terms of awareness of this entity and subsequent interpretation.

Conclusion: This case reiterates the importance of knowing and understanding normal histology. A high degree of clinical suspicion as well as expertise in the field of thoracic pathology is required for appropriate diagnosis.

Background

Alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV) is a rare and lethal disorder of infancy with an abnormal vascular development of the lung. These infants present with refractory pulmonary hypertension and are non-responsive to any intervention. The mortality rate is near 100% and most newborns lose their life within the first 24 hours of life. Clinically, these babies have no significant antenatal history and also cry immediately after birth, having excellent APGAR scores. However, they develop severe respiratory distress within the first 6 hours of life. The babies are then put on supportive care including extra corporeal membrane oxygenation (ECMO). Majority of the babies have associated cardiovascular, gastrointestinal and urogenital defects. Here we describe a newborn with non-classical features of this entity with a brief review of existing literature.

Case presentation

A two- day old female child, born of full term normal vaginal delivery presented to the hospital with respiratory distress since the 6th hour of life. The child was born to parents who had a non-consanguineous marriage. The child had no significant antenatal history and cried immediately after birth. The child had no other congenital abnormalities. The child was initially started on Oxygen by nasal prongs, then was shifted to a tertiary centre where the child was put on a conventional ventilator with maximum settings. Subsequently, a 2-D Echocardiogram was performed to rule out congenital cardiac disease and was normal. The patient was treated with inhaled Nitric oxide at 20 ppm, as idiopathic

pulmonary hypertension was suspected. Despite all efforts, the infant continued to worsen and eventually a lung biopsy was sent post-mortem to our department.

We received a specimen of right middle and lower lobe of lung which were grossly unremarkable. On microscopy, sections showed immature lung parenchyma with arrest in the sacular phase of development with prominent secondary crests (Fig. 1).

There were focal thin-walled blood vessels invested in the same adventitial sheet as that of the pulmonary arteries in the broncho-vascular bundles (Fig. 2). This change was present in less than 10% of broncho-vascular bundles and hence was termed as focal (Fig. 2 and Fig. 3). This finding was ratified by the usage of EVG stain (Fig. 4).

Deficient capillarization was also present which included both paucity of capillaries and centrally located malpositioned capillaries within a thickened inter-alveolar septum (Fig. 5). As like the above finding, these changes were also present focally. There was a variable degree of septal microvascular proliferation (Fig. 6). The medium sized pulmonary arteries and arterioles showed muscularization and medial hypertrophy with occasional non-laminar intimal cellular proliferation and occlusion (Fig. 7).

Some of the alveoli exhibited deposition of eosinophilic amorphous material on alveolar spaces with denuded epithelium (Hyaline membrane formation) (Fig. 8).

Discussion

Alveolar capillary dysplasia usually presents as refractory pulmonary hypertension which is non-responsive to pharmacotherapy. Despite supportive measures, patients usually pass away within the first week of life and most biopsies are received post mortem (Slot E, 2018). The closest differential is persistent pulmonary hypertension of newborn, which is a disease of the pulmonary vasculature and responds well to inhaled nitric oxide (Sankaran D, 2022).

The presence of FOX F-1 mutation has been identified as the main genetic cause of ACD/MPV. The presence of this gene can be identified by conventional Sanger sequencing or newer Next generation sequencing methods (Stankiewicz P, 2009). 10% of the cases occur in siblings and a familial association was suggested (Kitano A, 2020). Apart from lung, the newborns have associated defects such as hypoplastic left heart, intestinal malrotation, genitourinary defects, including posterior urethral valve, ureteropelvic junction obstruction, and hydronephrosis (Sendi P, 2026).

The pathological features of ACD/MPV cases were evaluated using the extent of deficient capillarization as diffuse (all fields are affected with difficulty in identifying any normal capillaries), mixed (when normal capillaries and deficient capillarization are both present) and focal (when majority of the fields exhibit a normal capillarization with focal areas of deficiency); extent of misalignment of pulmonary veins as extensive (If pulmonary veins were present within > 50% of the broncho-vascular bundles), patchy (If the pulmonary veins were present within 10–50% of the broncho-vascular bundles) and focal (If present

within < 10% of the broncho-vascular bundles); and the medial hypertrophy of the pulmonary arteries as mild (mild medial thickening), moderate (significant thickening with still patent lumen) and severe (presence of occlusive lesions). Also noted was the presence/ absence of proliferative microvasculature in the inter-alveolar septum (Alturkustani M, 2021).

ACD/MPV cases were then termed as 'Typical' or 'classical' when they had diffuse capillary deficiency and extensive misalignment of pulmonary veins according to the above-mentioned criteria. Those newborns with patchy or focal deficient capillarization as well as misalignment of veins were termed as 'Atypical' or 'Non-classic' ACD/MPV (Alturkustani M, 2021) (Towe CT, 2018).

Certain features made our case interesting. Our patient had focal deficient capillarization as well as focal misalignment of pulmonary veins putting her under the 'Atypical' or 'Non-classic' category. The focal nature of the disease in this patient also made it a diagnostic difficulty as majority of the capillaries were non-dysplastic and most of the veins were appropriately placed in the inter-acinar septum. A high index of suspicion, awareness of this entity and the aid of special stains such as EVG made it possible to report this case with a high degree of certainty.

Despite the focal malpositioning of veins and dysplasia of capillaries, our case had severe medial hypertrophy with occluded lumina as well as presence of proliferative microvasculature in the inter-alveolar septum. Although the latter two categories were not used by Alturkustani et al or Towe et al to classify the cases into the 'typical' and 'atypical' spectrum, it is interesting to note the discordance in the grades between the former two and latter two features in this patient (Alturkustani M, 2021) (Towe CT, 2018).

Traditionally the histological features of pulmonary artery hypertension in children with congenital cardiac defects are graded using the Heath-Edwards Grading system (Heath D, 1958). One study highlights the presence of a prominent right to left vascular shunt pathway in ACD/MPV cases (Galambos C, 2015). This study notes the presence of intrapulmonary pathways that link systemic and pulmonary circulations and bypass the capillary bed, which is very similar to patients who present with right to left shunts due to congenital cardiac defects. Despite considering the similar pathophysiology, literature where the pulmonary hypertension in ACD/MPV cases were graded using the Heath-Edwards system were extremely sparse. Here, this patient as Grade III (progressive intimal fibrosis with luminal occlusion), as per the above-mentioned grading system (Heath D, 1958). Further studies are need to identify if there are any prognostic implications of using the Heath-Edwards Grading system over the system used by Towe et al and Alturkustan et al.

Studies have reported the presence of lymphangiectasis in many patients with this condition (Semple T, 2022) (Bertolizio G, 2022). However, our case exhibited no features of lymphangiectasis.

One study reported the occurrence of an unusual glomeruloid endothelial proliferation (Kitano A, 2020), however no such finding was noted in our case.

This is the first case in literature where the presence of a Hyaline membrane along with features of ACD/MPV is reported concomitantly. This may be attributed to the usage of a conventional ventilator rather than extra corporeal membrane oxygenation in this patient (Ricard JD, 2003). Hence, the hyaline membranes are likely to represent ventilator associated lung injury rather than acute respiratory distress syndrome and should be interpreted accordingly. This highlights the importance of knowing the full clinical history and stresses the need for clinical and pathological co-relation.

Patients with 'non-classic' or 'atypical' features of ACD/MPV have higher survival rates compared to the 'typical' or 'classic' case due to the presence of normal pulmonary vasculature (Towe CT, 2018) (Licht C, 2004). Despite our patient fitting into the 'atypical' category, the child passed away within 24 hours of life. It is possible that the associated lung injury hastened the process.

Conclusion

ACD/MPV is a rare and lethal condition with near 100% mortality rate. Most newborns die within the first 48 hours of life. Lung transplantation offers a chance for survival. However, this is extremely rare due to practical and logistic considerations.

Imaging modalities including HRCT are non-contributory in diagnosing this condition.

Molecular testing, although useful from an academic perspective, may not be possible in a diagnostic setting especially considering the fact that these tests require outsourcing and also the longer turnaround time for the results.

Histopathology remains the gold standard and also the only feasible way of accurately diagnosing this time sensitive condition.

Abbreviations

ACD

Alveolar Capillary dysplasia

MPV

Misalignment of Pulmonary veins

APGAR

Appearance, Pulse, Grimace, Activity and Respiration

ECMO

Extra corporeal membrane oxygenation

2-D

Two-dimensional

ppm

Parts per million

FOX-F1

Forkhead box F-1 protein
EVG
Elastic Van Geison
HRCT
High resolution Computed Tomography

Declarations

ETHICS DECLARATION: This study was approved by the Institutional Ethics Committee of St John's Medical College, Bangalore, India in accordance with institutional policy drawing from standard frameworks like Declaration of Helsinki and ICMR guidelines, bearing IEC number 274/26.

CONSENT TO PUBLISH DECLARATION: A waiver of consent was applied for and approved by the Institutional Ethics Committee for this case.

AVAILABILITY OF DATA AND MATERIAL: Not applicable.

COMPETING INTERESTS: The authors submit that there is no conflict of interest.

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AUTHOR'S CONTRIBUTIONS: MS prepared the manuscript. DCP and MFB reviewed the manuscript.

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References

1. Alturkustani M. L. D. (2021, January 1). Histopathologic features of alveolar capillary dysplasia with misalignment of pulmonary veins with atypical clinical presentation. *Cardiovascular Pathology*, 50, 107289.
2. Bertolizio G, E. T. Congenital interstitial lung diseases: what the anesthesiologist needs to know. *Pediatr Anesth*. 2022, February;32(2):138–47.
3. Galambos C. S.-L. S. (2015, January 1). Intrapulmonary vascular shunt pathways in alveolar capillary dysplasia with misalignment of pulmonary veins. *Thorax*, 70(1), 84 – 5.
4. Heath D, E. J. The pathology of hypertensive pulmonary vascular disease: a description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. *Circulation*. 1958, October;18(4):533–27.
5. Kitano A. N. M. (2020, May 9). A familial case of alveolar capillary dysplasia with misalignment of the pulmonary veins: the clinicopathological features and unusual glomeruloid endothelial proliferation. *Diagnostic Pathology*, 15(1), 48.
6. Licht C. S. S. (2004, March). Prolonged survival in alveolar capillary dysplasia syndrome. *European journal of pediatrics*. 2004, 163(3), 181-2.

7. Ricard JD. D. D. (2003, August 1). Ventilator-induced lung injury. *European Respiratory Journal*, 22(42, supplementary), 2s-9s.
8. Sankaran D. L. S. (2022, August 1). Pulmonary hypertension in the newborn-etiology and pathogenesis. *In Seminars in Fetal and Neonatal Medicine*, 27(4), 101381.
9. Semple T. W. A. (2022, January 1). Childhood interstitial lung disease: imaging guidelines and recommendations. *Radiologic Clinics*, 60(1), 83–111.
10. Sendi P. M. P. (2026, June 29). Alveolar capillary dysplasia with misalignment of pulmonary veins in neonates: a multicenter cohort study. *Pediatric Research*, 1–7.
11. Slot E. E. G. (2018, August). Alveolar capillary dysplasia with misalignment of the pulmonary veins: clinical, histological, and genetic aspects. *Pulmonary circulation*, 8(3).
12. Stankiewicz P. S. P. (2009, June 12). Genomic and genic deletions of the FOX gene cluster on 16q24.1 and inactivating mutations of FOXF1 cause alveolar capillary dysplasia and other malformations. *The American journal of Human Genetics*, 84(6), 780 – 91.
13. Towe CT. W. F. (2018, March 1). Infants with atypical presentations of alveolar capillary dysplasia with misalignment of the pulmonary veins who underwent bilateral lung transplantation. *The Journal of pediatrics*, 194, 158 – 64.

Figures

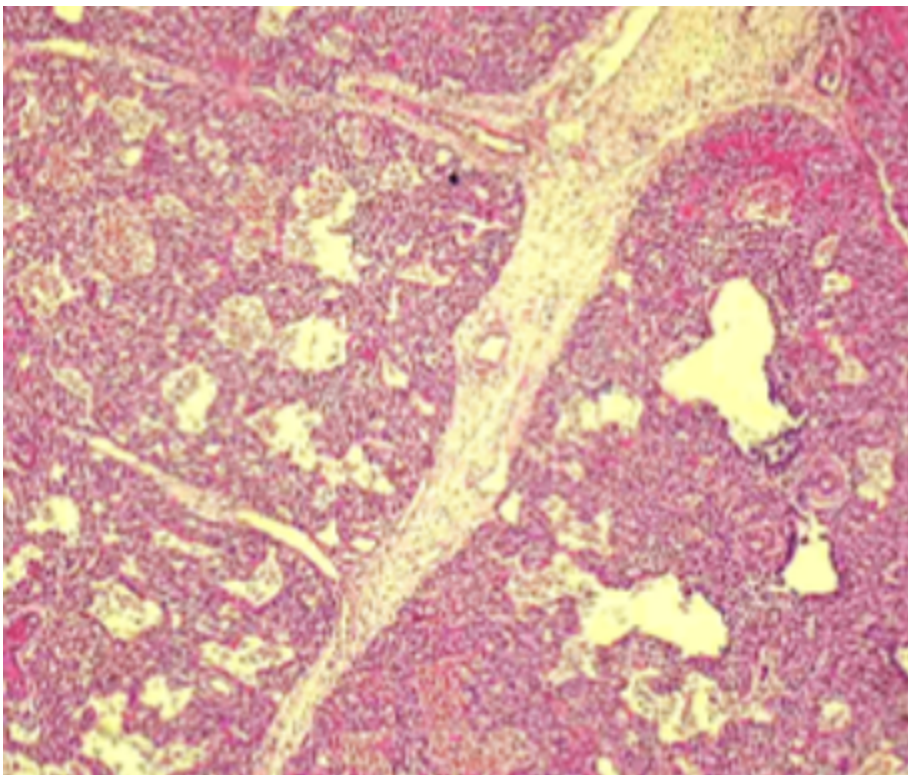


Figure 1

Arrest in the saccular phase of development with secondary crests (H&E stained section 100X)

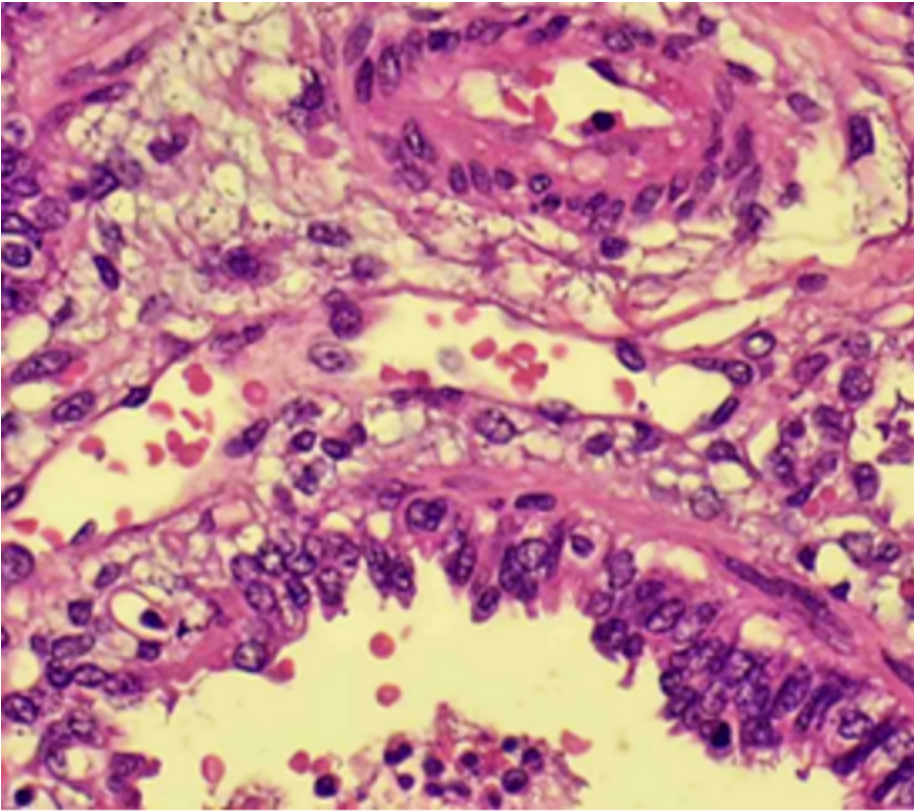


Figure 2

Malpositioned pulmonary vein within the adventitial sheath of the pulmonary artery (H&E stained section 400X). B-Bronchiole A-Artery V- Vein.

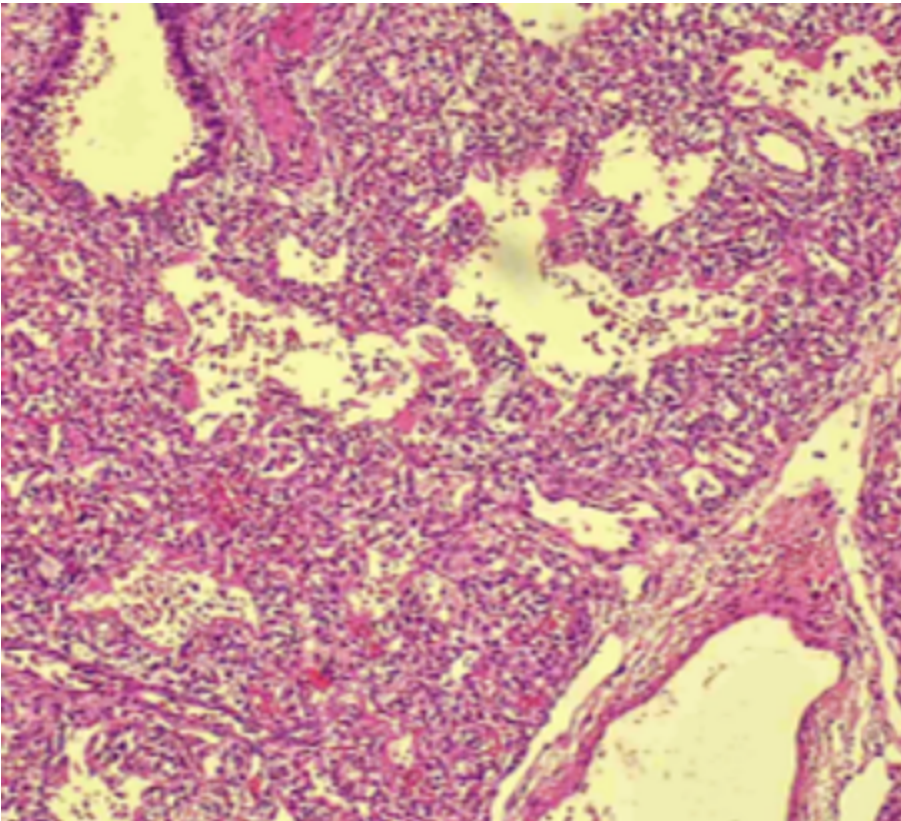


Figure 3

Normally positioned pulmonary vein in the inter-acinar septum (H&E stained section 100X). B-Bronchiole A-Artery V-Vein.

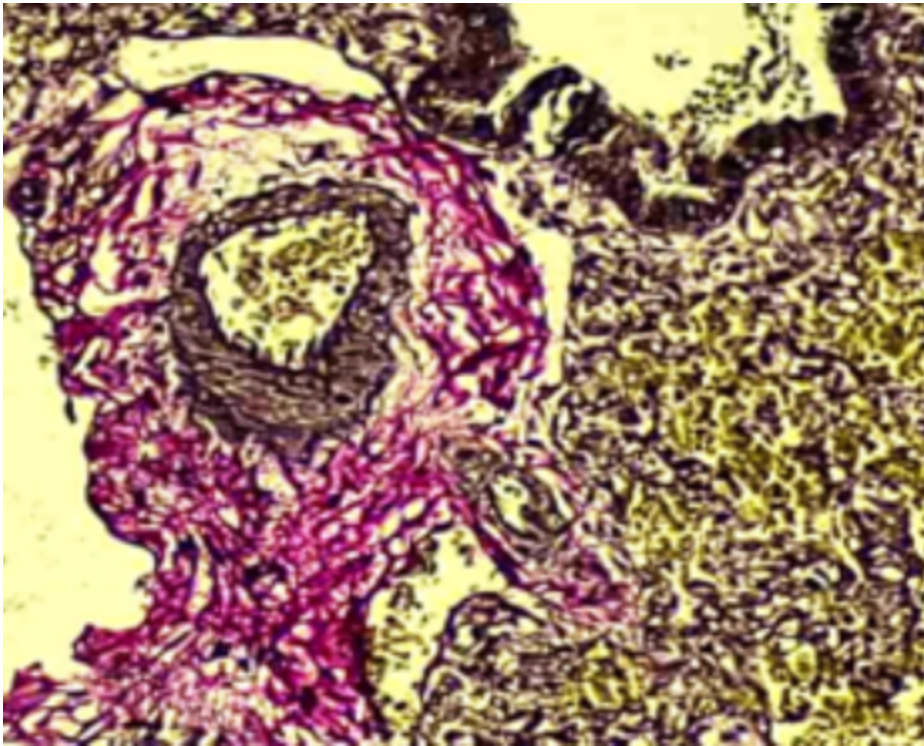


Figure 4

Elastic Van Geison stain highlighting the abnormally placed pulmonary veins (100X). B-Bronchiole A-Artery V-Vein.

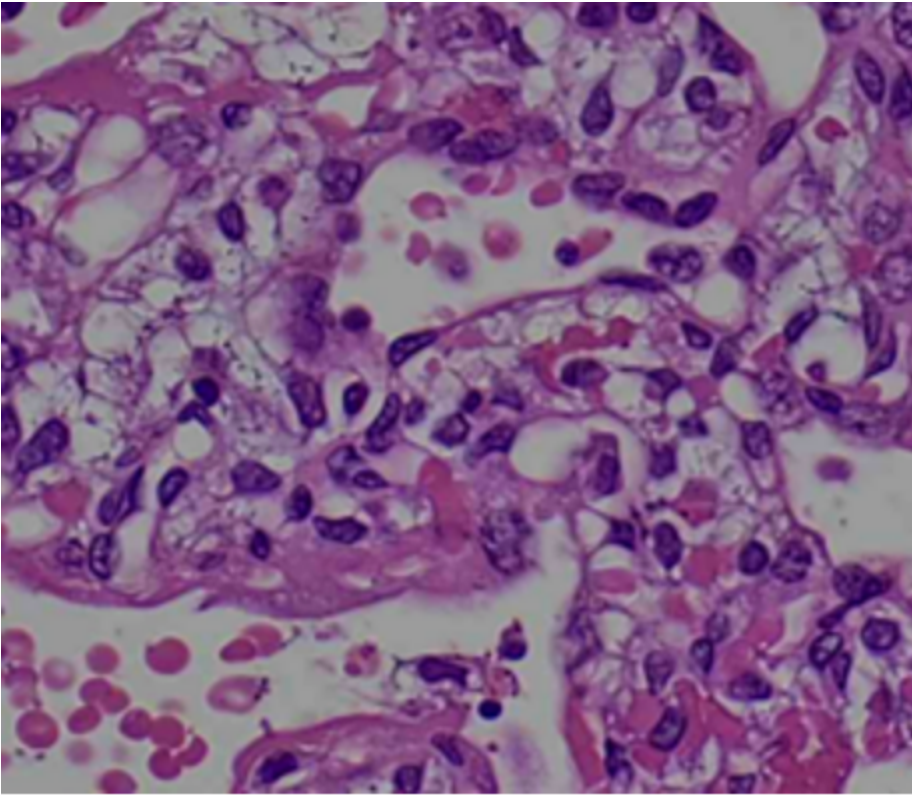


Figure 5

Malposed capillary in the middle of the alveolar septa (H&E stained section 400X). C-Capillary, AL-Alveoli.
Note: The bottom shows a part of an alveoli with RBCs within the space.

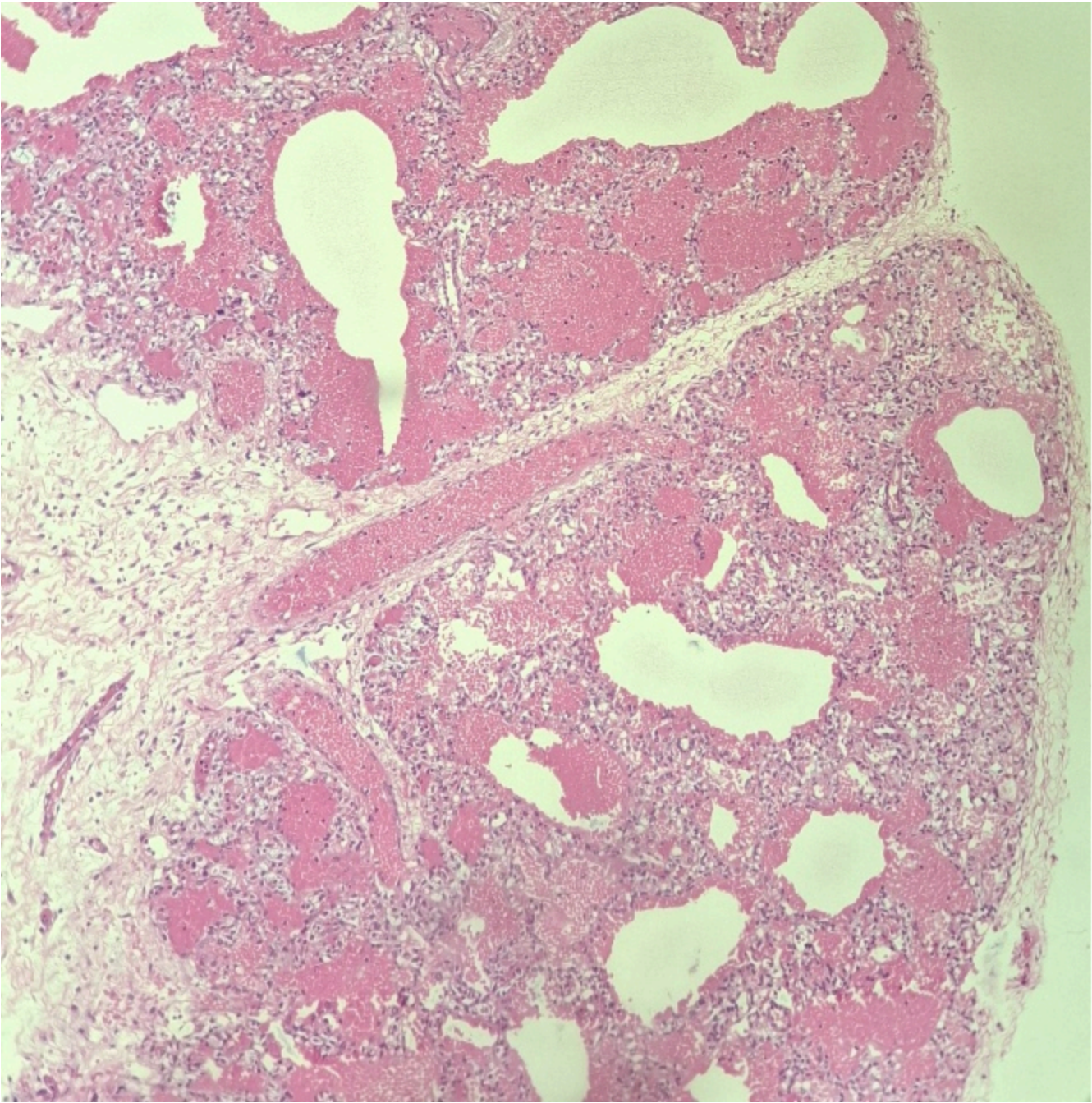


Figure 6

Septal microvascular proliferation (H&E section 100X)

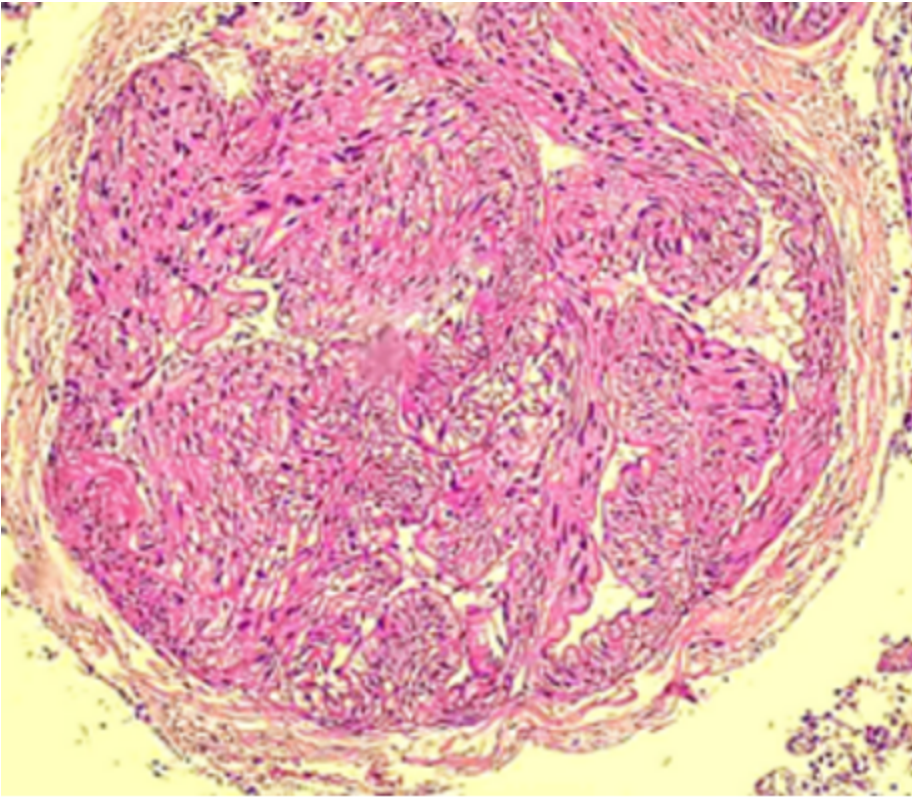


Figure 7

Pulmonary artery showing muscularization and medial hypertrophy with occasional non-laminar intimal cellular proliferation and occlusion (H&E section 100X)

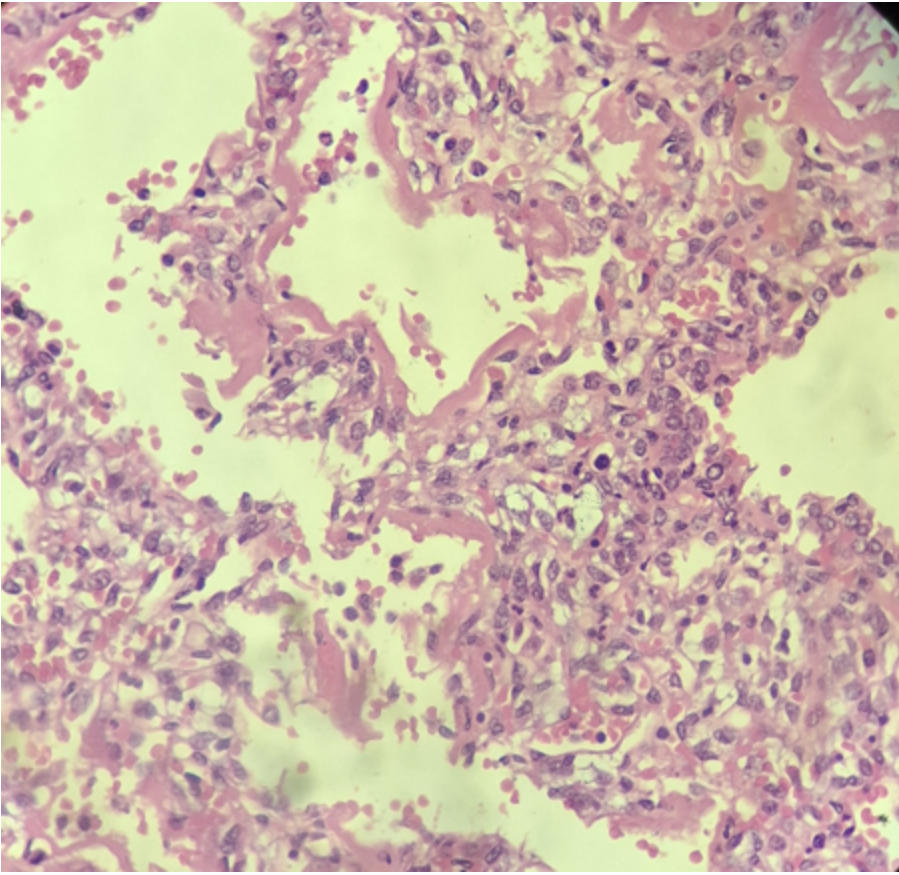


Figure 8

Hyaline membranes lining the alveoli (H&E section 400X)