A rare pulmonary malformation in a very preterm infant

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Morphometry of the Human Lung

by

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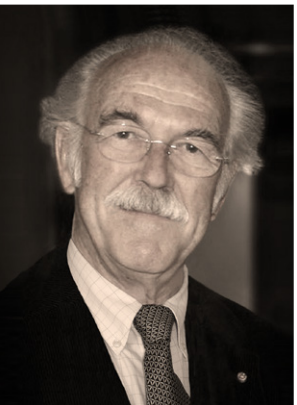

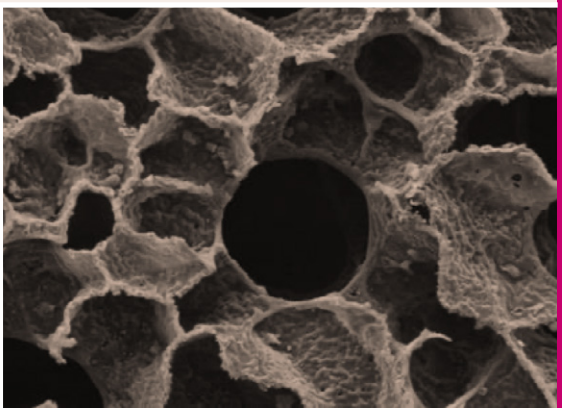

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Title figure:
In 1959, Ewald R. Weibel (1929–2019), was invited by Noble laureate André F. Cournand to join his group at Columbia University in New York with the mandate to "do anything on the structure of the lung that is of interest to physiology"; 4 years later, Weibel's now famous book „Morphometry of the Human Lung" was published.

INTRODUCTION

Fetal interstitial lung tumors (FLITs) are rare, solid to microcystic congenital tumors. FLITs are located intraparenchymally. Immature appearing airspace-like structures with widened septae are characteristic. The interstitium consists of a uniform population of immature round to ovoid clear-celled, mesenchymal cells. These cells resemble the cells observed at 20 to 24 weeks of gestation (canalicular phase of lung development). In contrast, the non-affected pulmonary lobes are developed according to the gestational age. The tumor may be surrounded by a fibrous interface separating it from the normally developed lung tissue. Usually, FLITs are limited to one pulmonary lobe (1). Infants suffering from FLITs mostly present with mild to severe respiratory distress within the first five days of life (1 – 4). FLITs can be cured by lobectomy or resection of the affected lung. So far, neither recurrence nor malignant degeneration have been described in the literature (1 – 5).

We report on a male premature infant born to a 29-year-old P1/G1 at 29 3/7 weeks of gestation. Initial antenatal care was provided in an obstetrics outpatient clinic in Basel. Bilateral pathological changes of the lung tissue were first seen on routine ultrasound at 21 3/7 weeks of gestation. Suspected diagnoses included congenital pulmonary airway malformation (CPAM) or congenital high airway obstruction syndrome (CHAOS).

For further clarification, a fetal MRI was performed at 23 1/7 weeks of gestation. This study revealed bilateral increase in lung volume and signal changes of the parenchyma, three cyst-like lesions and bilateral flattening of the diaphragms. The heart was displaced to the right and ascites was noticed.

Larynx, trachea and esophagus could not be identified. Based on these findings, the mother was referred to the University Hospital of Berne and antenatal steroids were administered prophylactically at 23 3/7 weeks of gestation.

Two weeks later, symptomatic polyhydramnios with shortening of the cervix was diagnosed by ultrasound. Moreover, the pregnant woman presented with premature contractions. A total of 1400 ml of amniotic fluid was drained by amniocentesis at 25 3/7 weeks of gestation. Administration of antenatal steroids was repeated at that time. Genetic testing revealed a

normal karyotype (46, XY) and an unremarkable microarray.

For ongoing antenatal care and delivery, the mother was referred close to home to the Department of Obstetrics at the University Hospital of Basel. Another fetal ultrasound examination at 28 2/7 weeks of gestation confirmed the findings reported by the colleagues in Berne (Fig. 1, 2). A fetal MRI, previously performed at 23 1/7 weeks of gestation, was re-evaluated in an attempt to either confirm or rule out CHAOS. However, larynx, trachea and esophagus again could not be identified. Based on the uncertainty of the antenatal diagnosis and impossible prediction of the outcome, the interdisciplinary team recommended to provide maximum care in case of preterm delivery.

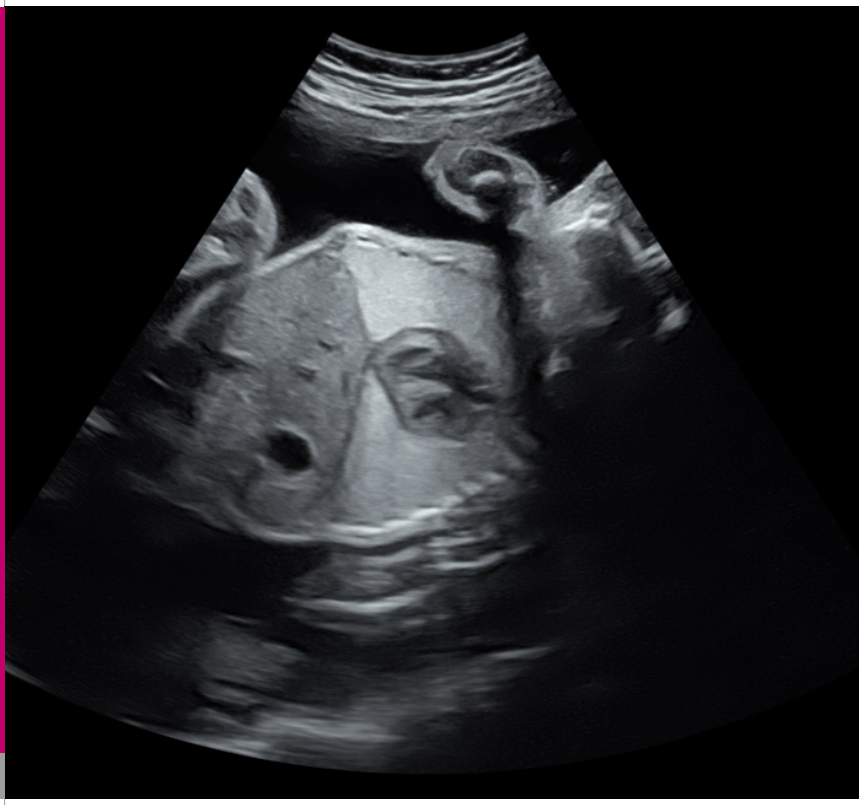

Fig. 1

Fetal ultrasound examination (sagittal section of chest and abdomen): Hyperechogenic, enlarged lung parenchyma with a bilateral diaphragmatic flattening.

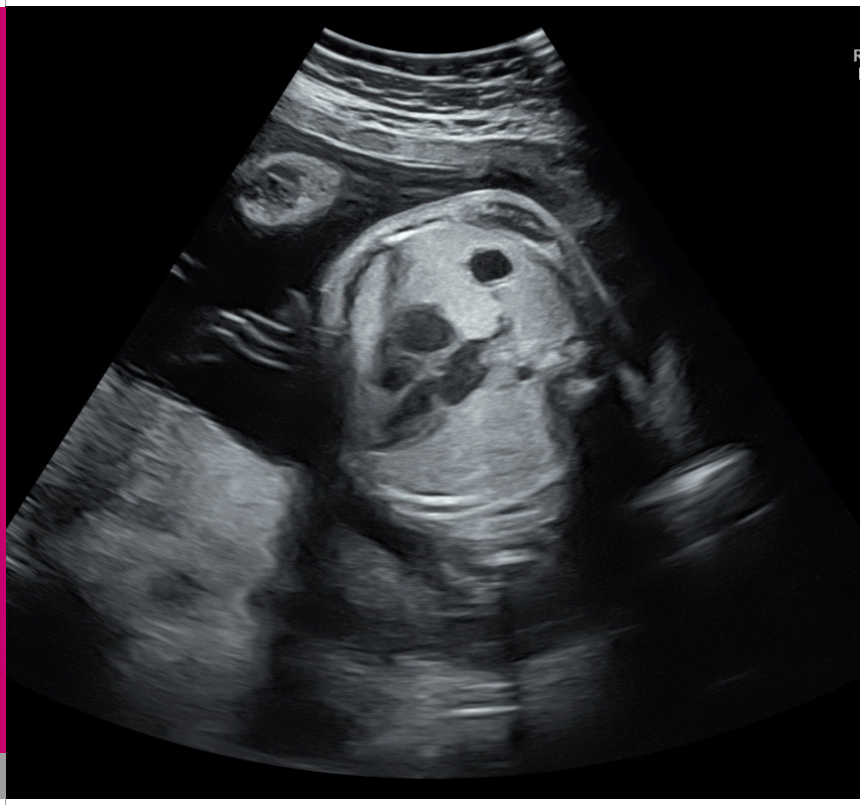

Fig. 2

Fetal ultrasound examination of the chest at the level of the four-chamber-view of the heart (transverse section): Bilateral hyperechogenic lung parenchyma with a hypoechogenic cystic lesion measuring 9 × 10 × 14 mm on the right.

The mother-to-be presented to the Emergency Department with premature rupture of membranes at 29 2/7 weeks of gestation. The infant was delivered by urgent Cesarean section due to fetal bradycardia and suspected partial abruption of the placenta at 29 3/7 weeks of gestation. In the delivery room, the infant required intubation for severe respiratory distress. Intubation was unproblematic at the first attempt with the epiglottis, the vocal cords and the esophagus clearly visible.

Soon after intubation, the infant required an FiO_2 of 1.0 and high peak inspiratory pressures (PIPs) up to 50 cmH_2O. Surfactant was administered at 10 minutes of life and repeated at 30 minutes of life (165 mg/kg in total). Following admission to the NICU, the infant was ventilated using synchronized intermittent positive pressure ventilation (SIPPV) with PIP/PEEP of 28/5 cmH_2O and an FiO_2 of 1.0. Postductal oxyhemoglobin saturation (SpO_2) was 85 % at 45 minutes of life. The chest X-ray demonstrated almost complete bilateral lung opacification with residual aeration of the left upper lobe and the right lower lobe (Fig. 3).

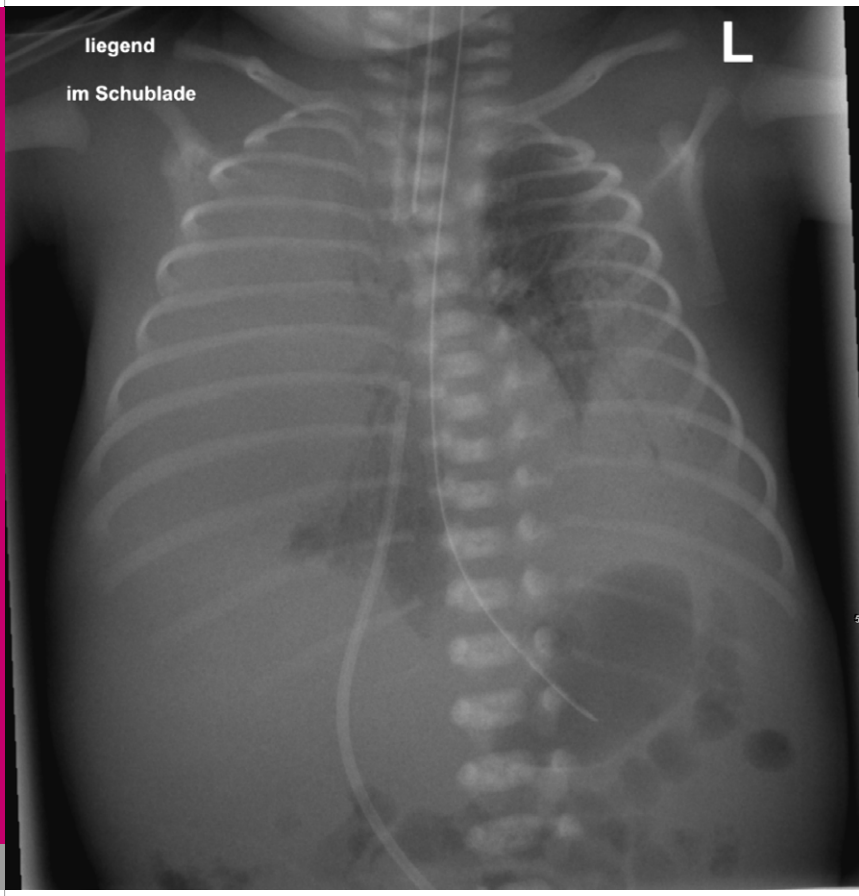

Fig. 3

Chest X-ray following initial stabilization: Almost complete opacification of both lungs with residual aeration of the left upper lobe and the right lower lobe.

Despite the administration of surfactant and an FiO_2 of 1.0, SpO_2 remained in the low 80s. Therefore, the mode of ventilation was changed to high-frequency oscillatory ventilation (HFOV) at 65 minutes of life. In addition, inhaled nitric oxide was started at 20 ppm for suspected persistent pulmonary hypertension of the newborn (PPHN) at two hours of life (later confirmed by echocardiography). Subsequently, the FiO_2 could be reduced to as low as 0.4 with SpO_2 around 90 %.

Unfortunately, from the age of 12 hours of life, the baby boy became increasingly hypoxemic. Despite a third dose of surfactant (100 mg/kg) administered at 16 hours of life, the infant's oxygen requirements gradually increased back to an FiO_2 of 1.0, and he became bradycardic. In view of the unfavorable situation and with parental consent, care was redirected. The patient died shortly after extubation at the age of 41 hours.

Postmortem examination revealed bilateral fetal lung interstitial tumors (FLITs). The tumors caused enlargement of the right upper lobe with hypoplasia of the middle and lower lobe. On the left side, the tumors lead to an enlarged lower lobe and hypoplasia of the upper lobe (Fig. 4).

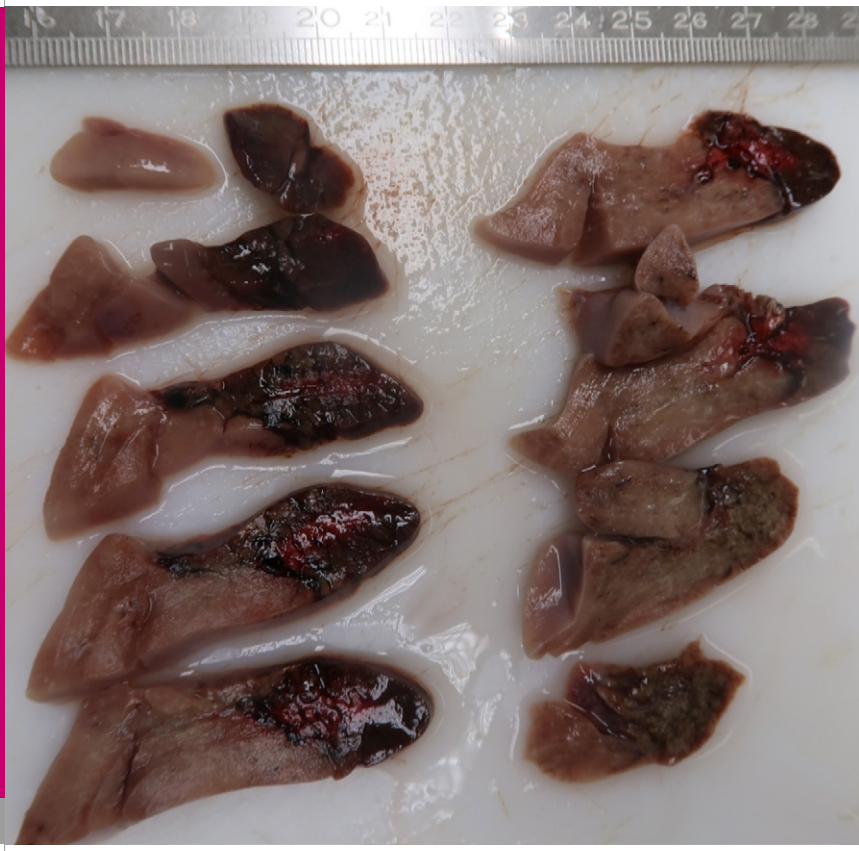

Fig. 4

Sagittal sections of both lungs: cut surfaces revealing solid appearing bilateral tan-colored masses of the lower lobes and right middle lobe of up to approximately 5.5 × 3 × 3 cm; both upper lobes appeared hypoplastic and hemorrhagic

On microscopy, widening of the interalveolar septae was observed with bilateral clear cell interstitial round cell to spindle cell proliferation (Fig. 5, 6). The diagnosis of FLIT was confirmed by immune histochemistry with vimentin-positive staining (vimentin is an intermediary filament of the cytoskeleton of all mesenchymal cells) (Fig. 7). There was no particular PAS positivity (as can be seen in pulmonary interstitial glycogenosis).

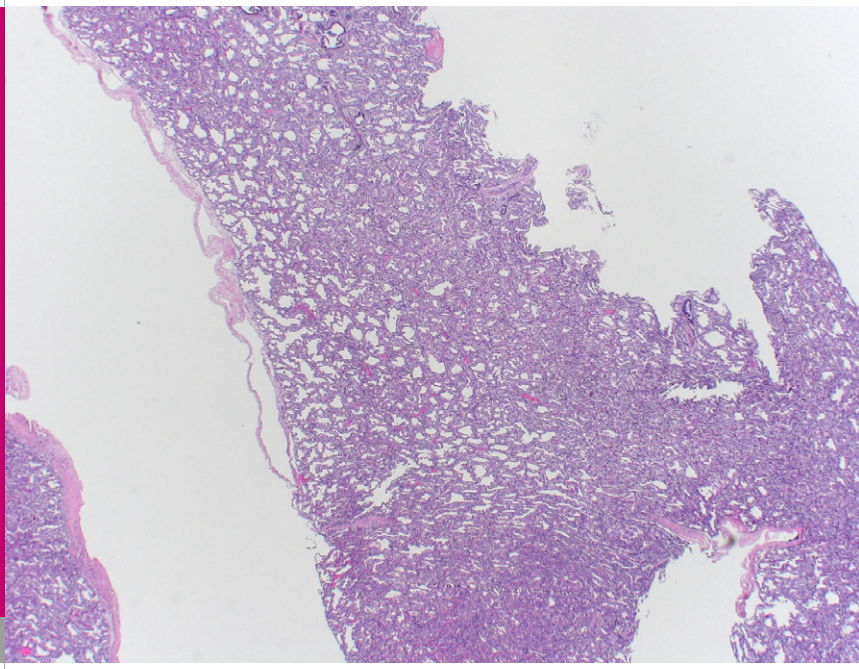

Fig. 5

Scanning magnification showing widened saccular and alveolar septae as well as partly collapsed/obliterated saccular and alveolar spaces (H&E × 40).

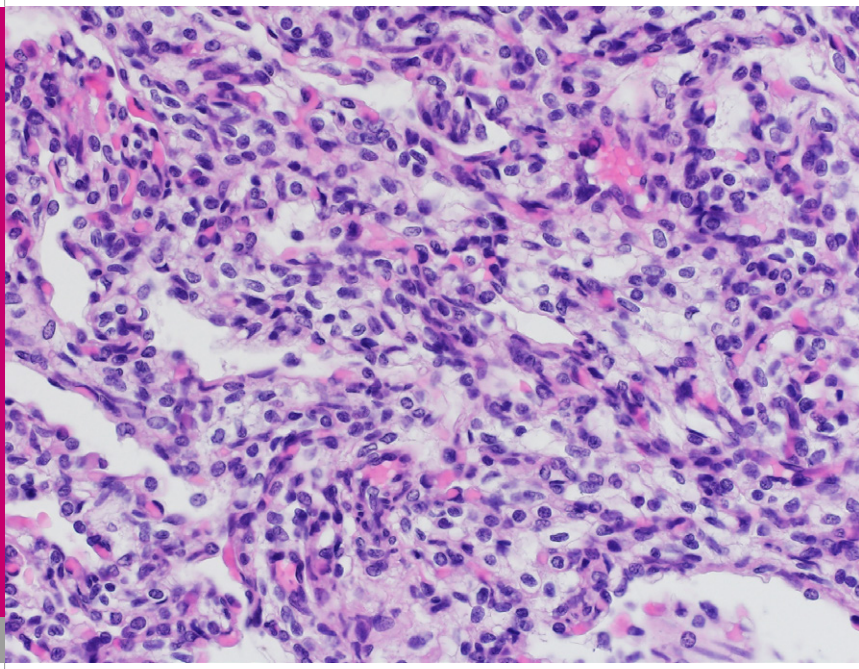

Fig. 6

Upon higher magnification, interstitial proliferation of round cells and spindle cells with ample clear, PAS-negative cytoplasm can be identified (H&E × 400).

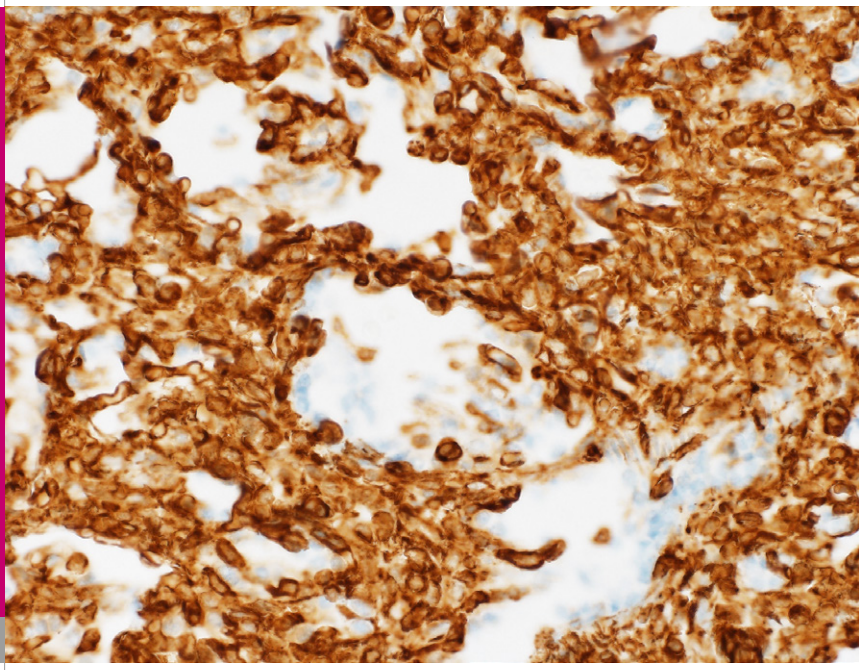

Fig. 7

Immunohistochemistry for Vimentin highlights the spindle cell proliferation of the widened saccular and alveolar septae.

Immune histochemistry with thyroid transcription factor 1 (TTF-1), used to demonstrate normal saccular or alveolar epithelial cells (Fig. 8, 9), revealed that the remaining lung tissue was in the saccular stage of lung development consistent with the patient's gestational age. There was no evidence of pulmonary hyperplasia as reported in CHAOS, and no cyst formation as would be typical of CPAM, and the remaining autopsy findings were normal according to age. Specifically, trachea and esophagus were normal without any evidence of obstruction.

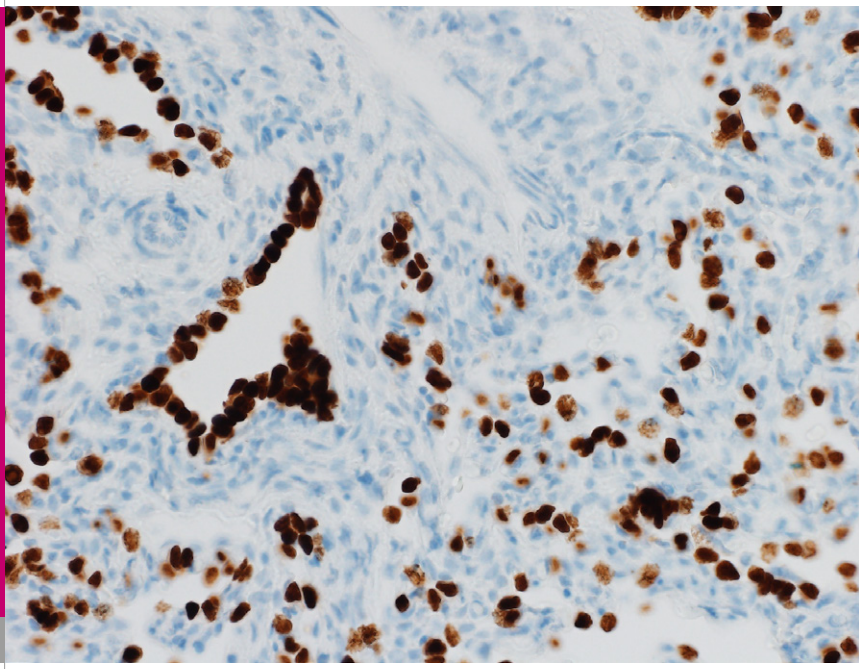

Fig. 8

Immunohistochemistry for TTF-1 (thyroid transcription factor 1) highlights the remaining saccular/alveolar epithelial cells while the mesenchymal interstitial cells remain negative.

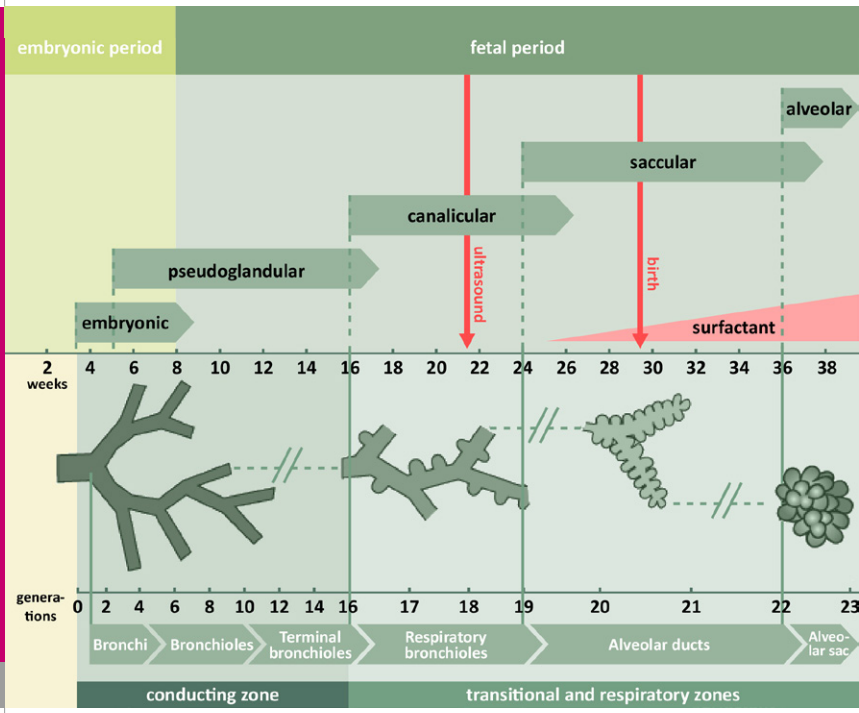

Fig. 9

Stages of lung development (Reference: www.embryology.ch; adapted and reprinted with permission).

DISCUSSION

Most fetal lung lesions can be identified on antenatal ultrasound from 22 weeks of gestation onwards (6 – 8). However, only three out of thirteen reported cases of FLITs were diagnosed antenatally (1 – 5). The earliest antenatal detection of a FLIT was reported at 26 weeks of gestation (3). Another case of FLIT, diagnosed as a solid lung mass, was detected late in pregnancy at 36 6/7 weeks of gestation (5).

On imaging, FLITs usually present as circumscribed and solid tumors (9). In all cases reported thus far, FLIT was limited to one pulmonary lobe. Tumor sizes of approximately 2 – 9 cm have been described in the literature (1 – 5).

We are only aware of case reports of full-term and late preterm infants (1 – 5). The late preterm infant was twin B of a monochorionic-diamniotic twin gestation. Circumscribed lung pathology was detected antenatally. The baby was delivered by Cesarean section following preterm labor (3). One full-term infant was born via elective Cesarean section performed with an EXIT procedure, including resection of the pulmonary tumor at 37 1/7 weeks of gestation (5). To the best of our knowledge, no case reports of very preterm infants with FLIT have been published.

Most patients present within the first five days of life with symptoms ranging from mild to severe respiratory distress (1 – 5). Rarely, respiratory deterioration occurs

later (1,4). The latest reported detection of a lung lesion, later diagnosed as a FLIT, was made by chest X-ray at the age of three months in a patient suffering from respiratory syncytial virus bronchiolitis (1).

The prognosis of FLIT is favorable. All reported patients were successfully treated with lobectomy or wedge excision. The tumors were treated at different time points, but no later than the age of five months (1). During follow-up (in one case up to 15 years), there were no recurrences and no cases of metastatic disease (1 – 5). In two cases, complete resection of the tumors was not possible, but recurrence or metastatic disease did not occur (1). So far there is no other reported case of a FLIT leading to death.

In our case, lung pathology was detected very early at 21 3/7 weeks of gestation. In contrast to the cases reported in the literature, the tumor was not detected as a classic circumscribed tumor. Both ultrasound examination and MRI demonstrated that the entire lung tissue was hyperechogenic/hyperintense and enlarged without normal lung tissue detectable. These findings were compatible with an imaging diagnosis of CHAOS. In addition, observed diaphragmatic flattening, fetal ascites and rightward displacement of the heart were also characteristic signs of CHAOS (10). Finally, the antenatal differential diagnosis of CHAOS was supported by the fact that larynx, trachea and esophagus could not be visualized on fetal MRI.

CPAM was also considered as another potential differential diagnosis due to bilateral cystic lung lesions, even though bilateral CPAM only occurs in less than four percent of the cases (11 – 13). The cysts themselves were compatible with microcystic CPAM (Stocker type II) while the remaining lung sections resembled solid CPAM (Stocker type III) on imaging (12).

CONCLUSION

Postmortem examinations were consistent with FLIT. This case is unique for three different reasons: it is the first case report of a preterm infant diagnosed with FLIT, the first case with bilateral occurrence and the first case with a fatal outcome.

REFERENCES

1. Dishop MK, McKay EM, Kreiger PA, et al. Fetal lung interstitial tumor (FLIT): A proposed newly recognized lung tumor of infancy to be differentiated from cystic pleuropulmonary blastoma and other developmental pulmonary lesions. Am J Surg Pathol 2010;34:1762 – 1772 *(Abstract)*

2. Waelti SL, Garel L, Soglio DD, Rypens F, Messerli M, Dubois J. Neonatal congenital lung tumors – the importance of mid-second-trimester ultrasound as a diagnostic clue. Pediatr Radiol 2017;47:1766 – 1775 *(Abstract)*

3. Phillips J, Blask A, DiPoto Brahmbhatt A, et al. Fetal lung interstitial tumor: prenatal presentation of a rare malignancy. J Neonatal Perinatal Med 2019;12:473 – 477 *(Abstract)*

4. Yoshida M, Tanaka M, Gomi K, Iwanaka T, Dehner LP, Tanaka Y. Fetal lung interstitial tumor: the first Japanese case report and a comparison with fetal lung tissue and congenital cystic adenomatoid malformations/congenital pulmonary airway malformation type 3. Pathol Int 2013;63:506 – 509 *(Abstract)*

5. Lazar DA, Cass D, Dishop MK, et al. Fetal lung interstitial tumor: a cause of late gestation fetal hydrops. J Pediatr Surg 201;46:1263 – 1266 *(Abstract)*

6. Kunisaki SM, Barnewolt CE, Estroff JA, et al. Large fetal congenital cystic adenomatoid malformations: growth trends and patient survival. J Pediatr Surg 2007;42:404 – 410 *(Abstract)*

7. Adzick NS, Harrison MR, Crombleholme TM, Flake AW, Howell LJ. Fetal lung lesions: management and outcome. Am J Obstet Gynecol 1998;179:884 – 889 *(Abstract)*

8. Crombleholme TM, Coleman B, Hedrick H, et al. Cystic adenomatoid malformation volume ratio predicts outcome in prenatally diagnosed cystic adenomatoid malformation of the lung. J Pediatr Surg 2002;37:331 – 338 *(Abstract)*

9. Orman G, Masand P, Hicks J, Huisman TAGM, Guillerman RP. Pediatric thoracic mass lesions: beyond the common. Eur J Radiol Open 2020;7:100240 *(Abstract)*

10. Mong A, Johnson AM, Kramer SS, et al. Congenital high airway obstruction syndrome: MR/US findings, effect on management, and outcome. Pediatr Radiol 2008;38:1171–1179 *(Abstract)*

11. Ortac R, Diniz G, Yildirim HT, Aktas S, Karaca I. Retrospective evaluation of children with congenital pulmonary airway malformation: A single center experience of 20 years. Fetal Pediatr Pathol 2016;35:143–148 *(Abstract)*

12. Stocker JT, Madewell JE, Drake RM. Congenital cystic adenomatoid malformation of the lung. Classification and morphologic spectrum. Hum Pathol 1977;8:155–171 *(Abstract)*

13. Wilson RD, Hedrick HL, Liechty KW, et al. Cystic adenomatoid malformation of the lung: reviwe of genetics, prenatal diagnosis, and in utero treatment. Am J Med Genet A 2006:140:151–155 *(Abstract)*

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