

# Fetal Lung Interstitial Tumor: Clinicopathologic Analysis of 4 Cases From China

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## Research

**Keywords:** infant, fetal lung interstitial tumor, ALK, AFP, pathology

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## **Fetal lung interstitial tumor: clinicopathologic analysis of 4 cases from China**

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### **Abstract**

**Background:** The fetal lung interstitial tumor (FLIT) is a newly identified tumor and is extremely rare, with only five reports published in English. Here, we report 4 cases of FLITs in China and present a literature review, aiming to explore this rare tumor.

**Methods:** The clinical and histological findings, immunophenotype, and ALK FISH of these 4 FLIT cases were evaluated, with a detailed review of the literature.

**Result:** The 4 cases comprised 2 male and 2 female infants. Two cases had a lung or intrathoracic mass during pregnancy, as early as 28 gestational weeks, and tachypnea and groaning shortly after birth. The other two cases received clinical attention because of jaundice and weakness at 3 days and 10 minutes after birth.

The two female patients had a high serum AFP level. CT showed a well-

circumscribed solid-cystic mass in the lung. Surgical removal was performed at 6 days, 11 days, 18 days and 5 days respectively. Grossly, the tumor was a well-circumscribed, solid-to-spongy cut surface, and the largest diameter was 5.5-6.1 cm. Histological examination revealed an immature airspace and interstitium resembling fetal lung tissue at the canalicular stage (20-24 weeks of gestation). The epithelial cells coexpressed CK, EMA, TTF-1 and b-catenin, while the interstitial cells were strongly and diffusely positive for vimentin, with variable degrees of desmin, SMA, MSA and b-catenin. There was no ALK positivity among the four cases. One of the four cases had an ALK gene fusion by FISH. All four cases were in good condition after surgery.

**Conclusions:** The FLIT is a recently reported type of congenital lung lesion with distinct pathological morphology. Some of the FLIT cases have high AFP levels, which represents an ALK gene fusion and may be related to ALK-positive tumors. The FLIT prognosis is good, and surgery is the preferred treatment. The differential diagnosis should include congenital pulmonary airway malformation (CPAM), pleuropulmonary blastoma (PPB), congenital inflammatory myofibroblastic tumor (CIMT) and pulmonary interstitial glycogenosis (PIG).

**Keyword:** infant, fetal lung interstitial tumor, ALK, AFP, pathology

## **Introduction**

Congenital lung lesions include a variety of diseases, such as congenital cystic adenomatoid malformation (CCAM)/congenital pulmonary airway malformation (CPAM), pleuropulmonary blastoma (PPB) and inflammatory myofibroblastic tumor (IMT). Fetal lung interstitial tumor (FLIT) is a newly identified congenital lung lesion that was first reported by Dishop et al. [1] in 2010 and is characterized by its unique gross and microscopic features. This lesion is extremely rare; to date, only five articles have been published in English. Here, we report 4 Chinese patients with FLITs, including 2 patients with a high AFP level. We also discuss several related congenital lung lesions and compare their features to those of FLITs.

## **Methods**

### ***Clinical data***

From 2016 to 2019, four patients were diagnosed with FLIT in the pathology department of Beijing Children's Hospital. Three of the four cases (cases 2, 3 and 4) had been referred for consultation at another children's hospital. Clinical history was obtained by review of the medical records, pathology reports and communication with physicians and their parents.

### ***Methods***

- (1) The tissue specimens were fixed in 10% neutral buffered formalin, subjected to conventional dehydration and embedded in paraffin with standard procedures. Tissue sections (4  $\mu$ m) were cut and stained with hematoxylin and eosin (H&E), periodic acid-Schiff (PAS) and PAS with diastase.
- (2) Immunohistochemical analysis was performed on formalin-fixed, paraffin-embedded tissue sections. All antibodies including CK, TTF-1, Vimentin, Ki-67, CD34, MSA, SMA,  $\beta$ -Catenin, Desmin, Myogenin, ALK, EMA, CD68, CD30, S-100, AFP, HMB-45, SYN, CgA, CD56, CD99, CD3, CD20, CD163, GLUT-1, and CD31 were obtained from Zhong shan golden bridge biotechnology company.
- (3) Fluorescence in situ hybridization (FISH) analysis was performed using a Vysis LSI ALK Dual Color Break Apart Rearrangement probe, in accordance with the ISCN 2013 guidelines. FFPE unstained sections were subjected to hybridization with break-apart ALK probes following the manufacturer's instructions. The orange and green probes were hybridized with the 3' and 5' regions of ALK, respectively. The separation of probe signals indicated a chromosomal rearrangement involving ALK. At least 100 cells were counted. The sample was classified as positive when the cells showed break-apart signals with at least a 2-signal diameter apart and/or a single isolated orange signal. A

specimen with more than 15% positive cells was deemed positive for ALK rearrangement.

## **Results**

### ***Clinical presentation***

#### *Case 1*

A 6-day-old male infant presented with respiratory distress and feeding difficulties shortly after birth, and the symptoms worsened when he cried. CT showed a large heterogeneous mass in his left lung, inside of which there were multiple cysts (Fig. 1a). Congenital lesions, such as CCAM, were initially considered. His mother had an ultrasound performed at 22 weeks of gestation, and the result was normal; however, at 38 weeks, ultrasound identified a heterogeneous echo, measuring 7.1x5.8x5.3 cm. This infant underwent left upper lobectomy. His serum AFP level was <9 iu/l.

#### *Case 2*

A 1-day-old female infant showed respiratory difficulties at birth. CT confirmed a mass in her right middle lobe, and the mass was solid-cystic, measuring 6.6x4.8x6.1 cm in size. A lobectomy was performed when she was 10 days old, and the actual tumor was quite large, measuring 10x8x6 cm and occupying almost the entire right

middle lobe. Her serum AFP level was higher than 1020 iu/l before the operation.

The review of her mother's pregnancy history revealed that the tumor was noted at 28 gestational weeks (1.4×1.1 cm), and that it became larger every day. A tentative diagnosis of CCAM was made by a radiologist.

### *Case 3*

A 3-day female infant received clinical attention because of jaundice and some weakness without dyspnea or fever. CT revealed a large heterogeneous mass in her right lower lobe. A lobectomy was performed when she was 18 days old. Her serum AFP level was 14903 iu/l before the operation. Her mother's gestation course was good, and her routine inspection results for the second and third trimesters of pregnancy were normal.

### *Case 4*

A 5-day-old male infant exhibited weakness and dyspnea 10 minutes after birth, and sonography and imaging suggested cystic adenomatoid malformation. He underwent a left lower lobectomy when he was 5 days old. His serum AFP level was unknown.

### ***Pathology findings***

- (1) Grossly, the masses that were cut measured 7.5 cm×5.5 cm×2.5 cm, 4.8 cm×4.5 cm×2.5 cm, 6.1 cm×4.8 cm×4.3 cm and 8.5 cm×7.0 cm×5.0

cm respectively. The cut sections showed a single mass. The border between the mass and the adjacent seemingly normal lung tissue was characterized by a fibrous interface. The cuts of the masses were tannish-pink, soft and spongy. (Fig. 1b)

- (2) Microscopic examination revealed a well-circumscribed tumorous lesion confirmed by the presence of a fibrous border, and the capsule was complete or incomplete (Fig. 2a). The lesion consisted of immature airspace-like structures. Part of each cyst had ducts, which resembled terminal bronchioles and alveolar ducts. The walls of the cysts and the septa were covered by epithelium. The lining epithelium was low cuboidal or flat with clear or pale cytoplasm, and the borders between cells were not clear. The nuclei were inconspicuous. The septa displayed variations in thickness and were composed of immature round-to-ovoid, clear-to-pale eosinophilic mesenchymal cells without nucleoli (Fig. 2b and c). Mitosis was observed occasionally in case 1 (Fig. 2d), and a bundle of spindle cells could be seen in each of the cases. There were foci of cartilage in case 4 (Fig. 2e). Inflammatory cells, such as neutrophils and eosinophils, were scattered among mesenchymal cells, and the number of inflammatory cells was much higher in case 1. Focal interstitial hemorrhage, hemosiderin-laden macrophages and even necrosis were noted in all cases (Fig. 2f). Thin and thick wall vessels were identified in the septa areas.
- (3) Immunohistochemistry showed that the lining epithelial cells were positive for CK (Fig. 3a), EMA, TTF-1 and  $\beta$ -catenin. Mesenchymal cells showed diffuse positivity for vimentin and focal positivity for SMA,

$\beta$ -catenin (cytoplasmic staining) and MSA. Case 1 was negative for desmin (Fig. 3b), but cases 2 and 3 showed diffuse positivity for desmin (Fig. 3c). None of the interstitial cells showed positive staining for Myogenin (Fig. 3d), ALK (Fig. 3e), CD31, CD34, GLUT-1, SYN, CgA, CD56, HMB-45, S-100, or CD99. The stroma was rich in capillaries, which were positive for CD31 or CD34.

- (4) Histochemical staining revealed that the cytoplasm of the epithelial and interstitial cells contained PAS granular positivity that was diastase digestible, consistent with glycogen.
- (5) Electron microscopy showed that case 1 had lung cells that were Type I or II epithelial cells. Below these cells were oval or irregular cells, and the cytoplasm of these cells was rich in organelles, with a few dense patches and dense bodies, which showed features of differentiation toward the fibroblast lineage. However, the glycogen granules were not obvious, and we speculate that this phenomenon was related to fixation in 10% formalin for more than 5 days.
- (6) FISH was performed in all four cases. Break-apart ALK rearrangement probes revealed that in case 1, most the tumor cells showed split signals (Fig. 3f). We speculated that the fusion was present in case 1. However, the results of the other three cases were negative.

## **Discussion**

The FLIT was first reported and named by Dishop et al. [1]. This tumor was

previously considered to be an atypical pulmonary airway malformation or type I pleuropulmonary blastoma [1, 2]. The prognosis of FLIT is invariably good, complete resection of the lesion is needed, and there are no recorded local recurrences or metastases to date. It is very important to identify and diagnose this lesion. The FLIT is considered to be a special subtype of congenital lung lesion because of its unique characteristics: it is isolated, is circumscribed, has a spongy or cystic/solid mass, and occurs in fetuses or infants. Histologically, FLITs closely resemble fetal lung tissue at the canalicular stage (20-24 weeks of gestation), including immature airspaces and interstitium, and both epithelial and interstitial cells contain abundant cytoplasmic glycogen. The FLIT is a rare disease, and to date [1-5], only 14 cases in 5 studies have reported. It is difficult to identify FLIT from CPAM (especially type III or IV CPAM) and other rare congenital lung tumors, such as PPB (type I) or IMT.

In terms of clinical features, FLIT has no unique symptoms. (A summary of clinical data is shown in Table 1) It is usually discovered at third trimester of pregnancy by ultrasound or shortly after birth because of dyspnea, apnea, feeding difficulty or fever in the newborn. Our review of the literature (including our four cases) revealed 18 cases of FLIT, that the mass was initially discovered as early as 28 weeks gestation, and that the oldest patient in which a mass was discovered was a 3-month-old infant, with the discovery being due to bronchiolitis. All the patients underwent lobectomy or wedge resection before or at 5 months of age, and one of the infants underwent ex utero intrapartum surgical resection when he was a fetus.

Among the four cases reported here, the mother of case 1 had an even gestational course, and the result of the 22-gestational-week ultrasound was normal. The mass was found at 38 weeks of gestation. Although the mass was large, the conditions of the fetus and his mother were good. The patient showed tachypnea as soon as he was born, and imaging studies revealed a well-circumscribed solid-cystic mass. He underwent lobectomy when he was 6 days old. In case 2, prenatal ultrasonography revealed a hyperechoic nodule on her right lobe at 28 gestational weeks, with polyhydramnios. The infant had a severe degree of respiratory difficulties and underwent lobectomy when she was 11 days old. In case 3, the female infant was born after an even pregnancy course and had some weakness. At 3 days of age, she was noted because of severe choleplania. CT revealed the mass. The serum AFP level was obviously higher than normal in both cases 2 and 3. In case 4, the male infant received attention because of weakness and dyspnea ten minutes after he was born. To date, there have been no case records of AFP abnormalities in FLITs, and the reason for this is unknown. Clinical and imaging studies cannot definitively diagnose the disease, and the diagnosis relies on pathology. As previously reported, there were more males than females (9 to 4 cases, with one unknown), and the mass could occur in any lobe of the lung, though it occurred more often in the right lobe than in the left lobe (8 to 6) [1-5]. There were four cases in our report, namely, 2 males and 2 females, and the tumor locations were the left upper lobe, right middle lobe, right lower lobe and left lower lobe. Regarding morphologic features wherein a

FILT resembled the fetal lung at 20 to 24 weeks of gestation, we speculate that the FLIT occurred later than 20 weeks of gestation and that the early-term examination of pregnant women could not provide any information on the mass.

### ***Pathologic features***

Until now, the reported cases were limited to a single lobe, with masses measuring 2~7 cm and having an obvious capsule, with a mass pushing the adjacent normal parenchyma, and with lung proximity to the mass. The fibrous capsule was or was not complete, and the mass was composed of immature air-space-like structures with septa of varying thickness, resembling the fetal lung at 20 to 24 weeks of gestation (canalicular stage) [1]. The cells lining the surface of the air space were flattened or columnar epithelium cells with pale-to-clear cytoplasm, and these cells were developing pulmonary cells [3, 6]. The septa of the airspace was widened to various levels of thickness by round-to-ovoid immature interstitial cells with pale-to-clear cytoplasm and small nuclei. It has been proven that the epithelium and interstitial cells contain glycogen in the cytoplasm. Some characteristics of these cells resemble those of fibroblast cells. Mitosis and even necrosis can be seen in many cases, and we cannot diagnose malignant or malignant potential based on their presence. Additionally, eosinophils are scattered among these cells.

Extramedullary hematopoiesis can be seen in some cases. Although the structure of the FLIT resembles that of the fetal lung at the canalicular stage, the interstitial cells

of the normal fetal lung cannot contain glycogen at any developmental stage [7].

There were no specific immunochemical markers. The immature interstitial cells showed diffuse positivity for vimentin and showed different extents of positivity for SMA, desmin, MSA and  $\beta$ -catenin and negativity for S-100, Myogenin and CD34. One case was positive for ALK, without inflammatory cell infiltration, and this case was proven to be an ALK rearrangement, namely, A2M-ALK [4]. ALK with infiltration of inflammatory cells, as in the other cases. The lung cells on the surface were positive for TTF-1, CK and EMA. The Ki-67 index in the mass was higher than that in the adjacent normal lung, ranging from 15%-25% among both interstitial cells and epithelial cells. Expression of  $\beta$ -catenin was different among the case.

Both interstitial cells and epithelial cells were PAS positive and diastase labile, indicating that glycogen existed in the cytoplasm.

Electron microscopy examination revealed that the lung cells were pulmonary cells and that lamellar bodies could be seen in the cytoplasm, indicating type II alveolar cell differentiation. Glycogen was shown in the cytoplasm of the epithelium and interstitial cells [1]. Case 1 in our report showed type I and II alveolar cells, and the interstitial cells resembled the features of myofibroblast cells, but there was no obvious glycogen in the cytoplasm, which contradicted the histopathology.

In our review of the literature, six cases (6/18 cases) underwent ALK gene FISH examination. (The cases with ALK FISH data are summarized in Table 2) Two of the cases (2/6 cases) showed an ALK gene rearrangement, and the other three

cases were negative for the rearrangement. It seems that there were no morphological factors that could predict whether or not there was an arrangement.

**Table 2 IHC and FISH of ALK**

	Sex	ALK (IHC)	ALK (FISH)
Onoda et al. [4]	M	+	+
Tanaka et al. [8]	F	-	-
Present	M	-	+
	F	-	-
	F	-	-
	M	-	-

M, male; F, female

### ***Differential diagnosis***

FLIT is a rare lung lesion, and the differential diagnosis includes pulmonary tumors or tumor-like lesions as follows.

- (1) PPB is an embryonal malignant tumor of the lung that appears to primarily affect young children. It is classified as type I (cystic), type II (cystic and solid) and type III (solid). Type II and type III PPB usually occur after 12 months of age. Type I PPB is the most common cystic malignant tumor of the infantile lung; most cases occur before 2 years of age, and some of them are found by ultrasound during gestation [9, 10]. The gross pathology and histopathology of PPBs are similar to those of FLITs. PPB shows primitive mesenchymal cells beneath a benign respiratory epithelium forming a superepithelial cambium layer of rhabdomyoblasts. Unlike those in FILTs, the small mesenchymal cells in PPBs are obviously atypical, with nuclear enlargement and hyperchromatism, and are positive for Myogenin. Sometimes we can see that primitive mesenchymal cells show rhabdomyoblastic

differentiation or some primitive cartilage nodules.

(2) CPAM is a hamartomatous lesion of the lung and a common congenital cystic lesion in infants, which is the major reason for infant lung biopsy.

CPAM can be separated into five types based on clinical and pathologic features. However, it was reported that there were cases of CPAM type 1 that were in conjunction with PIG [11]. Here, we emphasize types 3 and 4, which need to be distinguished from FLITs.

1) CPAM type 3, originally known as CCAM, involves an entire lobe or even an entire lung; grossly, the mass is comprised of cysts, most of which are smaller than 0.2 cm in diameter, so the cut mass appears to be solid or slit-like. Microscopically, the lesion shows an adenomatoid appearance, and irregular bronchiole-like structures are separated by dilated alveolus-like structures, all of which are lined by cuboidal epithelial cells. There are no immature interstitial cells beneath the epithelial cells. Most CPAM cases can be noticed earlier than 22 weeks of gestation [12]. The prognosis of this type is poor due to its large size.

2) In CPAM type 4, most of the tumor involves a single lobe, and it is usually at the periphery of the lobe. Gross examination shows a large, thin and air-filled cyst, with many translucent cyst walls inside.

Macroscopically, the cyst walls are composed of loose mesenchymal tissue, with flattened epithelial cells coving above them. The cells

involved in the mesenchymal system are attenuated and mature, and when the number of cyst walls is too high and the cells are rich in mesenchymal cells, differential diagnosis is necessary.

- (3) Pulmonary interstitial glycogenosis (PIG) was first proposed in 2002 [7], and it is a rare neonatal lung disease. Macroscopic examination reveals uniform expansion of the interstitium by spindle-shaped cells containing abundant glycogen. PIG appears to be a selective dysmaturity of interstitial cells, and lining type 2 or endothelial cells are normal. It is proposed to be a developmental abnormality rather than an inflammatory or reactive course. Although it seems to be a transient abnormality, it usually has a favorable prognosis with or without treatment [7, 11, 13]. However, there are several reported cases of death due to serious complications. The etiology and pathogenesis of PIG are unknown. Unlike FLITs, PIG presents as overinflated lungs on chest radiographs and may occur in conjunction with other growth abnormalities rather than a single well-defined nodule, and the lung epithelial cells are normal without glycogen in their cytoplasm [11].
- (4) Although the IMT is the most common tumor of the lung in children, congenital IMTs are rare [14, 15]. Grossly, IMTs tend to be firm and circumscribed masses, although without an obvious fibrous capsule, and the cut is gray and solid. Macroscopically, the tumor is composed

of spinal cells with pale eosinophilic cytoplasm and small nucleoli. The spinal cells are arranged in a fascicular or storiform pattern. There is infiltration of many chronic inflammatory cells, including lymphocytes, plasma cells and histocytes. When the IMT appears to be papillary with epithelial cells entrapped, it resembles a FLIT in some aspects.

Notably, some of the reported IMT cases presented the same ALK gene rearrangement [8].

- (5) Previously, sclerosing pneumocytoma was named sclerosing hemangioma, which is a benign tumor of pneumocytic origin with female predominance. It occurs mostly in middle-aged adults. A review of the diagnostic history in our hospital from 2010 to 2017 shows that only 1 case, a 17-year-old male, was diagnosed as pulmonary sclerosing hemangioma. Grossly, the tumor is a well-circumscribed mass that is solid and gray-tan to yellow on cutting. Microscopically, it contains four types of histological structures: papillary, sclerotic, solid and hemorrhagic regions. Tumor cells contain both cuboidal surface cells and stromal round cells. However, neither cell had a pale cytoplasm with glycogen. The immunohistochemical profiles resemble some aspects of FLITs; for example, the surface cells are positive for CKpan; otherwise, the stromal cells are negative for CKpan. Both of these cells are positive for EMA and TTF-1, which is unlike FLIT.

### ***Gene and molecular***

Gene and molecular analyses have proposed that FLITs, PPBs, and CPMTs share the same mechanism as the growth abnormalities of pulmonary interstitial cells [1].

The etiology and pathogenic mechanism remain unknown. Cutz et al. [11] proposed that the FLIT may be a congenital lung lesion within the congenital lobar emphysema spectrum. It has been documented that the ALK gene rearrangement occurs in some FLIT cases [4]. Consistent with the literature, we had a case of ALK rearrangement in a male infant, which was different from the case in our patient, who had many infiltrating inflammatory cells. Although the ALK gene rearrangement is not a change that is unique to the FLIT, we support the notion that the FLIT is a real tumor rather than a pure pulmonary disorder or reactive disease.

### ***Treatment and prognosis***

Surgery is the most important treatment, and there are no recurrence or metastatic diseases in reported cases, with the longest follow-up being 182 months [1]. The four cases reported here were disease free after excision of the masses, and they grew well, with intervals of 48 months, 27 months 23 months and 15 months; additionally, the AFP levels of two cases of the cases decreased daily.

In summary, FLITs are benign tumors with an excellent prognosis, and local sections are sufficient. Some of them may be desmin positive, so it is important to

differentiate FLITs from PPBs. In addition, some cases of the FLITs have an ALK gene fusion.

### ***List of abbreviations***

FLIT: fetal lung interstitial tumor; CPAM: congenital pulmonary airway malformation; PPB: pleuropulmonary blastoma; CIMT: congenital inflammatory myofibroblastic tumor; PIG: pulmonary interstitial glycogenosis; FISH: fluorescence in situ hybridization; CCAM: congenital pulmonary adenomatous malformation; IHC: Immunohistochemistry

### ***Declarations:***

The authors declare that they have no conflict of interests.

### ***Ethics approval and consent to participate***

All patient samples and clinical data using were approved by the Ethics Committee of the Beijing Children's Hospital Affiliated to Capital Medical University, and the exemption from informed consent was approved as well.

***Consent for publication***

Not applicable.

***Availability of data and materials***

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

***Competing interests***

The authors declare that they have no competing interest.

***Funding***

Not applicable.

***Authors' contributions***

Zhi-juan Deng contributed to study design, reviewed the slides, analyzed the data and wrote the manuscript. Nan Zhang contributed to review the slides and read the manuscript. Xing-feng Yao helped with electron microscopy and read the manuscript. Chao Jia and Meng Zhang helped with FISH and read the manuscript. Le-jian He designed the study, reviewed the slides, analyzed the data and finalized the manuscript. All authors read and approved the final manuscript

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**Table 1. Clinical data**

Refs	Publication time	Number	Sex	Age at presentation	Symptoms	Tumor location	Tumor size (cm)	Age of operation
1 Dishop et al. [1]	2010	10	F	1 d	Lesser degrees of respiratory difficulties with low grade fever	Left upper lobe	3.3	3 d
			M	0 d	Lesser degrees of respiratory difficulties with low grade fever	Right upper lobe	4	5 m
			F	0 d	Moderate-to-severe respiratory distress	Right lower lobe	NA	5 d
			M	36 gestational weeks		Right lower lobe	5	37 gestational weeks
			M	3 m	Respiratory syncytial virus bronchiolitis	Right lower lobe	2	5 m
			F	2 m	Lesser degrees of respiratory difficulties with low grade fever	Right lower lobe	NA	2 m
			F	5 d	Lesser degrees of respiratory difficulties with low grade fever	Left upper lobe	6.6	6 w
			M	2 d	Mild respiratory and feeding difficulties	Right middle lobe	4	11 w
			M	0 d		Left lower lobe	7	7 d
			M	0 d	Moderate-to-severe respiratory distress	Major fissure of right lobe	6.5	2 d
2 Lazar et al. [3]	2011	1	M	36 gestational weeks		Right lower lobe	5.7	36 gestational weeks
3 Yoshida et al. [2]	2013	1	F	7 d	Respiratory distress	Left lower lobe	5	13 d
4 Onoda et al. [4]	2014	1	M	4 d	Mild apnea	Left lower lobe	2.6	11 d

5 de Chadarévian et al. [5]	2011	1	NA	0 d	Na	Left lower lobe		
6 Present		4	M	38-week gestation	Respiratory distress and feeding difficulties	Left upper lobe	5.5	6 d
			F	28-week gestation	Respiratory difficulties	Right middle lobe	4.8	11 d
			F	3 d	Jaundice, weakness	Right lower lobe	6.1	18 d
			M	1 d	Respiratory difficulties	Left lower lobe	8.5	5 d

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M, male; F, female; d, day; w, week; m, month; NA, not available.

## Figure legends

**Fig. 1a.** CT showed a large heterogeneous mass in his left lung.

**Fig. 1b.** The cut of the mass.

**Fig. 2a.** There was a fibrous capsule between the tumor and the adjacent lung (HE×100).

**Fig. 2b.** The thickness of the immature airspace varied (HE×100).

**Fig. 2c.** The immature mesenchymal cells were round-to-ovoid, clear-to-pale eosinophilic mesenchymal cells (HE×200).

**Fig. 2d.** Neutrophils were scattered among mesenchymal cells, and mitosis was evident (HE×400).

**Fig. 2e.** A focus of cartilage can be seen (HE×100).

**Fig. 2f.** Necrosis is evident on the left side (HE×200).

**Fig. 3a.** Lining epithelial cells positive for CK (×100).

**Fig. 3b.** Interstitial cells that are negative for Desmin (×200).

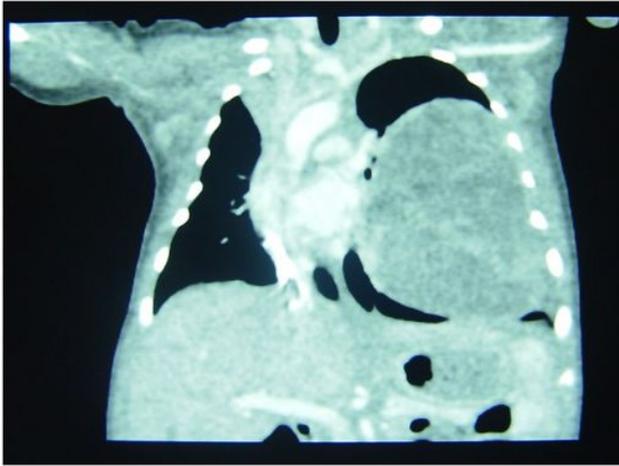
**Fig. 3c.** Interstitial cells that are positive for Desmin (×200).

**Fig. 3d.** Interstitial cells that are negative for Myogenin (×200).

**Fig. 3e.** Interstitial cells that are negative for ALK (×200).

**Fig. 3f.** FISH results showing split signals for the ALK gene.

# Figures



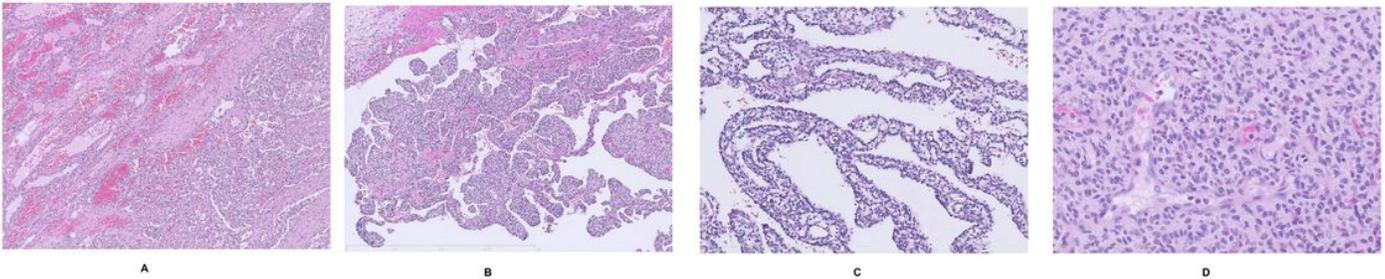
A



B

## Figure 1

1a. CT showed a large heterogeneous mass in his left lung. 1b. The cut of the mass.

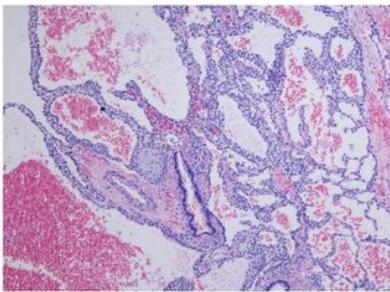


A

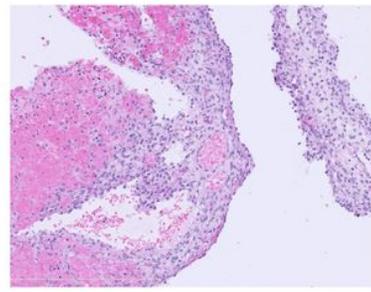
B

C

D



E

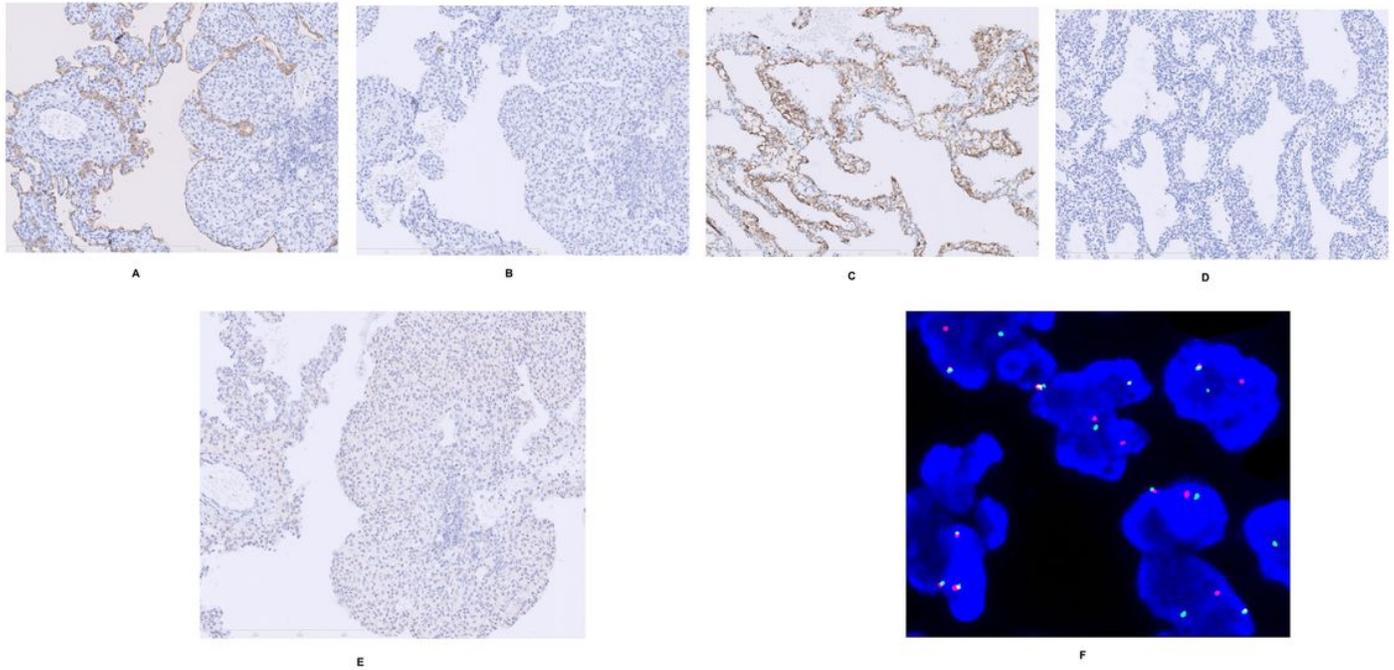


F

## Figure 2

2a. There was a fibrous capsule between the tumor and the adjacent lung (HE×100). 2b. The thickness of the immature airspace varied (HE×100). 2c. The immature mesenchymal cells were round-to-ovoid, clear-

to-pale eosinophilic mesenchymal cells (HE×200). 2d. Neutrophils were scattered among mesenchymal cells, and mitosis was evident (HE×400). 2e. A focus of cartilage can be seen (HE×100). 2f. Necrosis is evident on the left side (HE×200).



**Figure 3**

3a. Lining epithelial cells positive for CK (×100). 3b. Interstitial cells that are negative for Desmin (×200). 3c. Interstitial cells that are positive for Desmin (×200). 3d. Interstitial cells that are negative for Myogenin (×200). 3e. Interstitial cells that are negative for ALK (×200). 3f. FISH results showing split signals for the ALK gene.