Case Report

Fetal lung interstitial tumor: An uncommon pediatric pulmonary neoplasm

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ABSTRACT

Fetal lung interstitial tumor (FLIT) is a rare pediatric lung tumor with radiological features similar to developmental pulmonary malformations and other congenital lung neoplasms. There are about 17 cases of FLIT reported worldwide till date. We report the first case of FLIT in the Indian literature which was diagnosed in the early postnatal period (at the 21st day of life) by pathological examination. The tumor exhibited a novel focal micropapillary architecture, in addition to the previously described microscopic features. We discuss the pathogenesis and differential diagnoses of FLIT and review the literature.

KEY WORDS: Congenital pulmonary airway malformation, fetal lung interstitial tumor, pediatric lung tumor, pleuropulmonary blastoma

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INTRODUCTION

Pediatric pulmonary mass-forming lesions are categorized as developmental malformations and neoplasms. They may present as cystic, solid, or solid-cystic space-occupying lesions radiologically, with no specific diagnostic features on imaging. This mandates surgical resection and pathological evaluation to determine the nature of the mass. Developmental anomalies such as congenital pulmonary airway malformation (CPAM), bronchogenic cyst, pulmonary sequestration, and pulmonary atresia are more common than primary lung tumors such as pleuropulmonary blastomas (PPB), congenital bronchial myofibroblastic tumor, and infantile fibrosarcoma.[1,2] It is, therefore, important to arrive at a correct diagnoses in view of the differences in treatment protocols.

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Fetal lung interstitial tumor (FLIT) is a recently described, rare pediatric lung tumor with an indolent course, characterized by expansion of the interstitial mesenchymal cells. There are 17 reported cases in the literature till date,[1-7] of which ten are part of the first and largest series[3] and the rest are case reports [Table 1].[1,2,4-7] We present the first case of FLIT in the Indian literature to create greater awareness of this uncommon entity.

CASE REPORT

A term neonate diagnosed provisionally with dextrocardia at birth, on further evaluation was found to have an incidental left lung mass. Computed tomography (CT) showed a hypodense solid mass with some cystic changes,

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Table 1: Summary and review of fetal lung interstitial tumor in the literature

Author	Number of cases	Age at presentation	Age at surgery	Gender	Tumor location	Tumor size (cm)	Gross features	IHC and other ancillary studies	Treatment	Outcome
Dishop *et al*., 2010	10	36 weeks of gestation to 3 months postnatal		Male (7) Female (3)	RLL (4); LLL (2); RUL (1); LUL (1); RML (1); major fissure of RL (1)	2-7 (mean of 4.5)	Solid spongy and fleshy circumscribed mass with cystic change in 1 case	Positive stains: Vimentin (diffuse), SMA (diffuse or focal), Desmin and MSA (few cases, focal), Ki 67 10%-25% TTF-1 (epithelium) Negative stains: Myogenin, S100, CD34	Lobectomy (6) Wedge excision (3) Lobectomy during EXIT procedure (1 case)	NER, follow-up varied from 15-182 months
de Chadarévian J-P *et al*., 2011	1	*In utero*	Newborn	-	LLL	-	Cystic spaces ranging from 0.1 to 1 cm	Similar to Dishop *et al*. FISH - Trisomy 8	Lobectomy	NER, 84 months
Lazar *et al*., 2011	1	36 weeks 6 days with fetal hydrops and heart failure	37 weeks 1 day	Male	RLL	5.7	-	-	EXIT procedure with resection of thoracic mass	NER, 60 months
Yoshida *et al*., 2013	1	7th day	13th day	Female	LLL	5	Solid well-circumscribed mass with thick fibrous capsule	Positive stains: Interstitial cells- Vimentin (diffuse), SMA (diffuse), Desmin (focal), Ki-67 <1% Epithelial cells - Cytokeratin, EMA, β-catenin	Lobectomy	NER,180 months
Onada *et al*., 2014	1	0 day	11 days	Male	LLL	2.5	Solid well-circumscribed spongy mass with equivalent cystic areas	Positive stains: Interstitial cells-Vimentin (diffuse), SMA (scattered), Desmin (focal), ALK (cytoplasm), Ki-67 1%-2% Epithelial cells - Cytokeratin, EMA, Cam 5.2 FISH - *t* (2;12) (p23;p13)	Wedge resection	NER, 36 months

Contd...

Table 1: Contd...

Author	Number of cases	Age at presentation	Age at surgery	Gender	Tumor location	Tumor size (cm)	Gross features	IHC and other ancillary studies	Treatment	Outcome
Waelti *et al*., 2017	2	0 day 33 weeks with fetal hydrops	-	Male (2)	LUL RUL	8.5 9.5	Solid homogeneous intraparenchymal mass with microcystic component Solid mass with mediastinal compression	-	Lobectomy with incomplete resection Lobectomy	NER, 36 months
Phillips *et al*., 2019	1	26 weeks of twin gestation with mediastinal shift	20th day	-	LUL	6	Spongiform mass with cystic spaces	-	Lobectomy	-
Present case 2020	1	0 day	21st day	Male	LUL	6.5	Solid soft lobulated intraparenchymal mass with few cystic spaces	Positive stains: Vimentin (diffuse), SMA (focal), Ki 67 8%-20% TTF - 1 (epithelium) Negative stains: Desmin, Myogenin, S100, CD34, β-catenin, ALK	Lobectomy	NER, 12 months

RLL: Right lower lobe, LLL: Left lower lobe, RUL: Right upper lobe, LUL: Left upper lobe, RML: Right middle lobe, SMA: Smooth muscle actin, MSA: Muscle-specific Actin, TTF-1: Thyroid transcription factor-1, EXIT: *Ex utero* intrapartum treatment, NER: No evidence of recurrence, ALK: Anaplastic lymphoma kinase, FISH: fluorescence *in situ* hybridization, EMA: Epithelial membrane antigen, RL: Right lung

compressing the lower lobe of the left lung [Figure 1a and b]. A radiological diagnosis of CPAM was suggested. The mass was excised on day 21 of life because of the unusual imaging findings associated with a mediastinal shift. Grossly, the excised mass was soft, lobulated, tan pink, and predominantly solid with interspersed cystic spaces, and measured 6.5 cm × 6 cm × 2.5 cm. On histology, the pulmonary interstitium was expanded by monomorphic ovoid cells with scant cytoplasm, compressing the maldeveloped air spaces, which were lined by single layer of epithelial cells [Figure 2a and b]. The tumor had a well-defined thick fibrous capsule (interrupted at places) demarcating it from the adjacent normally developed lung parenchyma, and interspersed ectatic thin and thick-walled vascular spaces with hemorrhage [Figure 2c and d]. Furthermore, present were occasional glandular structures resembling immature bronchioles [Figure 2e and f]. The tumor formed papillary projections from the lining of the cystic spaces [Figure 2g-i]. Few bundles of bland spindle cells suggestive of myofibroblasts were present focally [Figure 2k]. Extramedullary hematopoiesis was observed [Figure 2l]. Features of aggressiveness such as nuclear atypia, increased mitoses, tumor necrosis, and immature cartilage were absent. On immunohistochemistry (IHC), the interstitial cells displayed diffuse Vimentin [Figure 3a] positivity. Smooth muscle actin (SMA) [Figure 3b] was positive in the spindled myofibroblast-like cells. The proliferation index (Ki-67) was 8 to 20% [Figure 3c]. Immunostains for desmin, myogenin, beta-catenin, and anaplastic lymphoma kinase (ALK) were negative. Thyroid transcription factor-1 expression was seen in the epithelial cells lining the compressed air spaces [Figure 3d]. The features were most consistent with FLIT as described in the seminal report by Dishop *et al*. The child had no recurrences at 1 year postsurgery and he was lost to follow-up thereafter.

DISCUSSION

FLIT is an infantile tumefactive lung neoplasm first characterized in 2010 by Dishop *et al*., in a retrospective attempt to classify ten similar appearing pediatric lung tumors which were previously diagnosed as atypical PPB or CPAM. These neoplasms showed gestationally inappropriate fetal lung-like morphology with immature interstitial cells which prompted the authors to designate the lesion FLIT.[3] Over the next decade, six reports including seven additional cases were described in the literature.[1,2,4-7] A male predilection was noted (male-to-female ratio of 2.75:1). These lung masses usually came to clinical attention incidentally, in late pregnancy (>33 weeks gestation) on routine imaging or

immediately after birth (within the first week of life). Only one case presented at 26 weeks in one fetus of a twin gestation[7] and two cases were identified at the second and third month of life.[3] Typically, the infants presented with mild breathing/feeding difficulties and had tachypnea with diminished breath sounds.[4] Our patient had mild tachypnea and right-sided heart sounds which warranted radiological evaluation to exclude dextrocardia. This led to the discovery of a mass on the CT scan, and its subsequent excision.

Developmental lung anomalies present early in the second trimester and stop growing thereafter or may involute before delivery. Congenital lung neoplasms, on the contrary, are diagnosed in late pregnancy or early infancy and continue to grow, resulting in complications such as fetal hydrops, and polyhydramnios.[2,4,7] FLIT appears to be a neoplasm rather than a malformation.[2,7] It is mostly described as a lobe-based intraparenchymal solid spongy mass with focal cystic change. It usually has a well-demarcated fibrous capsule and no invasive features. The size can range from 2 cm to 9.5 cm, with a mean of 4.9 cm. When larger, the tumor may cause a mediastinal shift, as was seen in our case. CPAM type III and PPB type I are the main differential diagnoses on imaging. CPAM classically presents in the second trimester (during the canalicular phase of lung development) occupying an entire lobe, unlike FLIT, which mostly occurs in late pregnancy or the immediate postnatal period and is a circumscribed intraparenchymal lesion. PPB is often seen after 1 year of life being multilocular, peripheral, and multifocal in 40% of the cases and typically exhibits invasion, necrosis, and hemorrhage.[3] As these lesions have different biological behavior, surgery is the preferred first line of treatment for proper histological categorization to plan further management.

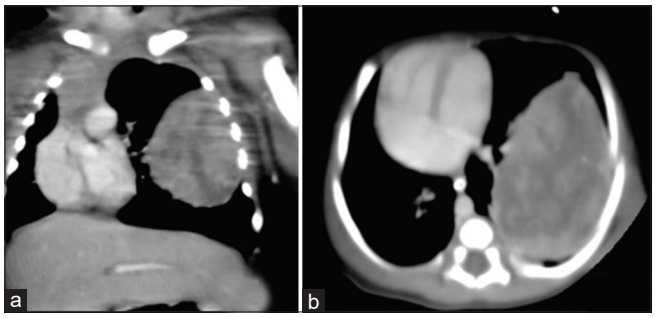

Figure 1: (a and b) Computed tomography scan (coronal and transverse sections) showing a well-circumscribed hypodense left lung mass causing a mediastinal shift

Histologically, FLIT has a well-demarcated fibrous interface from the adjacent nonneoplastic lung parenchyma and is composed of ovoid to spindle mesenchymal cells expanding the interstitium, forming thick and thin septa with interspersed few immature bronchioalveolar structures. Extramedullary hematopoiesis, hemorrhage, hemosiderophages, and occasionally cartilage have been previously described.[3] In addition to the above, the current case possessed cystic spaces lined by micropapillary formations which have not been emphasized in earlier reports. The interstitial cells of FLIT show diffuse strong vimentin positivity with foci of SMA and desmin expression in some cases.

The histologic and pathogenic relationship of FLIT and PPB has been discussed in earlier reports as both appear to originate from interstitial mesenchymal cells. Cystic PPB has rarely been reported in early infancy. In contrast to the bland cells of FLIT, PPB has small atypical undifferentiated

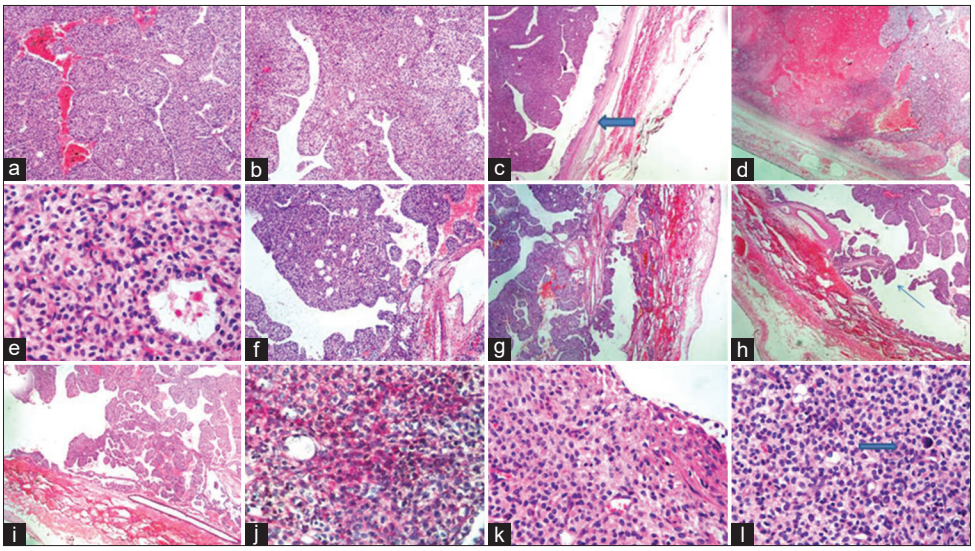

Figure 2: (a-d) Fetal lung interstitial tumor showing broad widened septae comprising bland interstitial cells with interspersed cystic spaces and a well-defined fibrous capsule (arrow). H and E stain. (e) Ovoid bland tumor cells with entrapped glandular structure, H and E stain. (f-i) Micropapillary projections (arrow) in the cystic areas with compressed adjacent lung parenchyma. (j) Cytoplasmic glycogen positivity in tumor cells, periodic-acid Schiff stain. (k) Spindled myofibroblast-like cells beneath the epithelial lining, (l) Megakaryocyte (arrow) representing a focus of extramedullary hematopoiesis, H and E stain

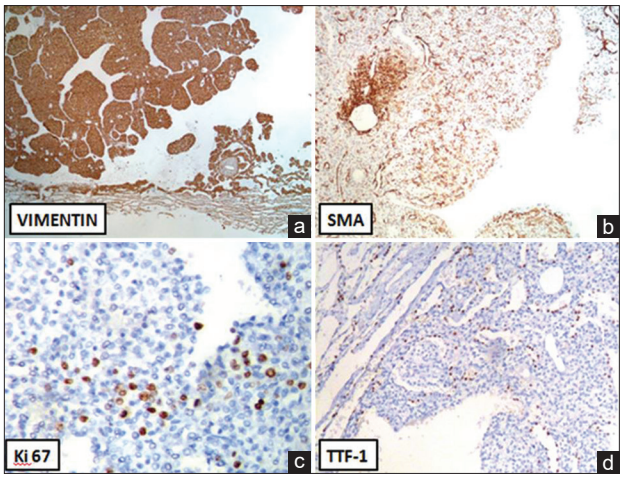

Figure 3: (a) Diffuse vimentin positivity in the interstitial tumor cells, immunohistochemistry stain, ×100. (b) A focus of myofibroblast-like spindle cells with smooth muscle actin positivity, immunohistochemistry stain, ×100. (c) Ki-67 nuclear positivity in few of the interstitial cells, immunohistochemistry stain, ×400. (d) Uniform nuclear Thyroid transcription factor-1 positivity in the cuboidal epithelial cells lining the cystic spaces, immunohistochemistry stain, ×400

interstitial cells with focal rhabdomyomatous or chondroid differentiation, increased mitosis, and areas of necrosis which predict an adverse behavior. In 2011, de Chadarévian *et al*. reported a lung mass in a newborn with morphologic and immunohistochemical features of FLIT associated with trisomy 8. They urged Dishop *et al*. to incorporate fluorescence *in situ* hybridization in their study of ten cases of FLIT, to exclude trisomy 8 and trisomy 2, that have been commonly associated with PPB. However, Dishop *et al*. in response advised caution while labeling a case of FLIT as cystic PPB on basis of the presence of trisomy 8 alone, as this cytogenetic abnormality is seen in many other pediatric tumors. Dishop *et al*. were reluctant to conclude that FLIT is a precursor of cystic PPB based on the association with trisomy 8, as the latter requires an aggressive treatment. Furthermore, their ten cases of FLIT had no instances of recurrence or sarcomatous transformation, as is seen with cystic PPB; their clinical presentation and biologic outcome set them apart.[5] In 2013, Yoshida *et al*. reported the first Japanese case of FLIT in a 13-day-old girl with beta-catenin expression in the epithelial and interstitial cells by IHC but without mutations in beta-catenin or trisomy 8. They speculated that the localized beta-catenin accumulation triggered the Wnt signaling pathway causing epithelial-mesenchymal transition, thereby progressing to FLIT, but they could not confirm the neoplastic origin of this tumor as the cytogenetic analysis was negative.[1] In 2014, a novel ALK rearrangement A2M-ALK was demonstrated by Onoda *et al*. in a case of FLIT, who proposed the possibility of FLIT being a subtype of inflammatory myofibroblastic tumor (IMT). This raised the possibility of using ALK inhibitors as potential therapeutic agents.[6] However, the molecular mechanisms by which this transcript contributed to the development of FLIT remains unexplained. Further studies are required to determine the exact pathogenesis of FLIT and to establish its relationship to other tumors if any. Wedge resection of the tumor or lobectomy appears to be the treatment of choice. Ex-utero intrapartum treatment (EXIT) procedure was performed in two cases in view of fetal hydrops and worsening condition of the fetus.[3,4] No recurrences or malignant transformation have been observed in the cases of FLIT reported till date and therefore adjuvant chemotherapy does not appear warranted.

CONCLUSION

We report a case of FLIT in a newborn with an unusual pseudo-papillary architecture, expanding the spectrum of morphological changes described previously. We present this case to familiarize practicing clinicians and pathologists with this rare and unusual entity and to help avoid misdiagnoses of FLIT as PPB, thus preventing overtreatment in what appears to be a benign condition.

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Conflicts of interest
There are no conflicts of interest.

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