Open Journal of
Clinical & Medical
Case Reports

Volume 8 (2022)
Issue 18

Case Report ISSN: 2379-1039

A rare type of fetal histiocytosis as a challenging prenatal ultrasound presentation: A case report

Nicastri E; Fabietti I*; Valfrè L; Zarfati A; Romiti A; Viggiano M; Vicario R; Vassallo C; Savelli S; Onelli B; Conforti A; Bonito M; Caforio L

***Corresponding Author: Isabella Fabietti**

Department of Medical and Surgical Neonatology, Fetal Medicine and Surgery Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Italy.

Tel: +39-340-408-6760; Email: Isabella.fabietti@opbg.net

Abstract

Background: Congenital lung cysts are rare condition with an incidence between 1 in 20,000 and 1 in 35,000 live, presenting a spectrum of anomalies mostly detected antenatally. Non-Langerhans cell histiocytosis type Juvenile Xantho granuloma (JXG) is the most common type of non-Langerhans cell histiocytosis. Its prenatal diagnosis has not been previously reported. We report the first case of JXG with prenatal ultrasound evidence of multiple lung cysts in the third trimester. **Case presentation:** A primigravida presented multiple bilateral hypoechoic fetal pulmonary cysts (with the biggest one that measured 19 x 17 x 17 mm) at 37 weeks of gestation. No other anomalies were associated. Magnetic resonance images confirmed the lesions characterized by hyperintense signal on T2-weighted images and mildly hyperintense on T1-weighted images, with evidence of a hyperintense central core on T1-weighted images in larger lesions. Spontaneous labor occurred at 38 weeks of GA (gestational age) without complications and clinical state of the newborn has always been excellent. A percutaneous needle biopsy of one of the peripheral lung lesions has been performed and the histological analisys gave the suspect of non-Langerhans cell histiocytosis, confirmed by Video-Assisted Thoracoscopic Surgery biopsy on day 26 of life. The patient was referred to the oncology unit and started chemotherapy with Vinblastine. **Conclusions:** This is the first case in literature of JXG, postnatally diagnosed, with prenatal evidence of multiple bilateral lung cysts. Prenatal assessment of lung lesions is based on a series of criteria such as the gestational age at diagnosis, the laterality of the lesions, the presence of vascularization, the coexistence of other anomalies or the evidence of signs of haemodynamic failure. One of the most challenging features of this case was the late timing of appearance of the cysts compared to the most common congenital lung lesions. In conclusion, although congenital histiocytoses is a very rare condition, it should be considered as part of the differential diagnoses of fetal lung cysts, especially if identified in late gestation. Multi-disciplinary team play a crucial role in ensuring that the mother and fetus are managed perinatally with utmost care, especially in challenging cases.

Keywords

Fetal; Histiocytosis; Ultrasound; Prenatal diagnosis; Lungs cysts.

Abbreviations

JXG: Juvenile Xanthogranuloma; GA: Gestational Age; BPS: Bronchopulmonary Sequestrations; CPAM: Congenital Pulmonary Airway Malformations; CLE: Congenital Lobar Emphysema; LCH: Langerhans Cell Histiocytosis; non-LCH: non-Langerhans Cell Histiocytosis; US: Ultrasound; NIPT: Non-Invasive Prenatal Test; MRI: Magnetic Resonance Imaging; DWI / ADC images: diffusion weighted imaging/apparent diffusion coefficient; CT: Computed tomography; VATS: Video-Assisted Thoracoscopic Surgery; SGS: Shared Genomic Segments; PPB: Pleuropulmonary Blastoma.

Introduction

Congenital lung lesions represent distinct anomalies [1] with an incidence between 1 in 20,000 and 1 in 35,000 live [2,3]. They include Congenital Pulmonary Airway Malformations (CPAM), Bronchopulmonary Sequestrations (BPS), bronchogenic cyst, Congenital Lobar Emphysema (CLE) and congenital lung tumors. The histiocytosis are a group of disorders of the monophagocytic system with different clinical and pathological findings characterized by the infiltration and accumulation of histiocytes primarily within the blood and tissues [4,5]. The pathogenesis is not known even if immune dysregulation phenomena have been hypothesized [3]. The classification, based on immunophenotypic criteria identifies three groups: Langerhans cell histiocytosis (LCH), non-Langerhans cell histiocytosis (non-LCH) and malignant histiocytosis [6]. Non-LCH are benign proliferative disorders that include all histiocyte pathologies that don't hold phenotypic criteria of LCH. Juvenile Xanthogranuloma (JXG) is the most common form of non-LCH that occurs most frequently in infants and children and the onset is in the first year of life in 40-70% of patients [7]. The most common presentation is a solitary skin lesion but may rarely present as a soft tissue lesion with or without organ involvement. Main visceral locations are lung, bone, liver, central nervous system, testis, gastrointestinal tract, heart, eye, and oral cavity [8]. The systemic involvement has been reported in the 27-34% of patients with perinatal JXG [9]. Cutaneous JXG is generally a self-limited condition, however the systemic form can be associated with significant morbidity and therefore aggressive medical care is required. This report presents a rare case of JXG characterized by multiple lung cysts evidenced in the prenatal period, with a diagnosis performed in the first one month of life.

Case Report

A 26-year-old primigravida, at 37,0 weeks of gestation age was referred to our fetal medicine and surgery unit because the third trimester ultrasound (US) revealed multiple bilateral pulmonary cysts. The patient didn't report any complications during pregnancy. Fetal US screening in the second trimester and TORCH complex were negative. Non-Invasive Prenatal Test (NIPT) was at low risk of aneuploidies. Our US evaluation (GE Voluson E10 scanner - GE Healthcare) showed multiple bilateral pulmonary hypoechoic cysts. Two cysts (17 x 17 x 19 mm and 19 x 17 x 17 mm, respectively) were identified in the right lung and three in the left one (the biggest 19 x 17 x 17 mm) (Figure 1A). Two cysts were characterized by central hyperechoic spots of unclear interpretation, with a negative Colour Doppler. Fetal growth, anatomy and

Dopplers were normal. The woman underwent foetal MRI (magnetic resonance imaging) (1.5 T Magnet Siemens Magnetom Aera) at 38 weeks of GA. The lungs had a normal volume with inhomogeneous structure due to the presence of multiple focal rounded lesions and clear margins (3 in the right and 4 in the left with a range's dimensions between 9 and 23 mm). Lung lesions were characterized by hyperintense signal on T2-weighted images and mildly hyperintense on T1-weighted images, with evidence of a hyperintense central core on T1-weighted images in larger lesions. In DWI / ADC images (diffusion weighted imaging/apparent diffusion coefficient) the lesions described showed a restriction of diffusivity (Figure 1B). No other organ was macroscopically affected by the disease. Diagnostic hypotheses included different congenital lung malformation such as CPAM, BPS, CPAM/BPS hybrid lesions, bronchogenic cyst, congenital lobar emphysema and congenital lung tumors. The case was discussed by a multidisciplinary team of obstetricians, pediatricians and pediatric surgeons. Both prenatal MRI and US couldn't define a certain diagnosis. Parents were informed of the prenatal ambiguous interpretation of the lesions and of the need for postnatal examinations to establish the diagnosis. Spontaneous labor occurred at 38 weeks of GA without complications. A male of 3290 gr was born and showed good adaptation (Apgar 9-10). Clinical state of the newborn has always been excellent. At birth, a chest X-ray confirmed multiple, bilateral, rounded opacifications, localized in the upper lung fields and bases. The baby underwent abdominal US which revealed no other lesions. Metabolic screening was normal. Computed tomography (CT) of the chest with intravenous contrast confirmed the multifocal and bilateral solid, nodular, inhomogeneous hypodense (76-100 HU), round lesions in the lung parenchyma, mainly in the periphery (Figures 1c). Blood tests and tumor markers were negatives. A US percutaneous needle biopsy of one of the peripheral lung lesions has been performed without complications. The first pathological exam raised the suspect of non-LCH. The newborn underwent Video-Assisted Thoracoscopic Surgery (VATS) biopsy on day 26 of life. Thoracic exploration confirmed the presence of multifocal, whitish, solid, round, hypovascularized, hard on the outside and cerebroid on the inside, not colliquative lesions. The patient had a normal postoperative period and surgical follow-up has been uneventful to date. The final pathological diagnosis was non-LCH type JXG. The Shared Genomic Segments (SGS) analisys method revealed a chromosomal rearrangement (TPM3-NTRK fusion). The patient was referred to the oncology unit where he underwent all staging exams to exclude further localizations. Considering the final diagnosis, the patient started systemic chemotherapy with vinblastine.

Multiple lung lesions detected by: **(a)** prenatal ultrasound, **(b)** prenatal MRI, **(c)** postnatal CT.

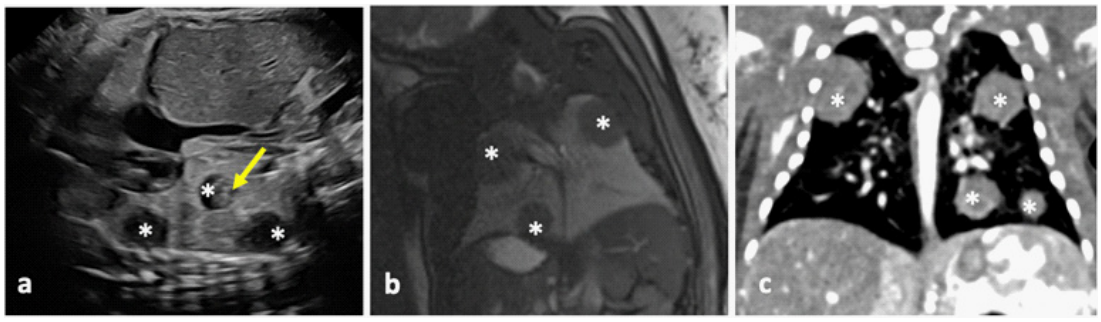

Figure 1: The lung lesions are indicated by the white *. The yellow arrow shows the hyperechoic spot inside the lesion in the US image.

Discussion & Conclusions

This is the first case in literature of JXG, postnatally diagnosed, with prenatal evidence of multiple bilateral lung cysts. Most of congenital lung cysts are detected antenatally in the second trimester. A thorough understanding of the specific defining characteristics of each diagnosis is crucial [1]. CPAMs are the most common lung lesion, with multicystic areas of over-proliferation and dilatation of terminal respiratory bronchioles with lack of normal alveoli and a normal blood supply. Usually there is a unilobar and unilateral lesion, mostly detected at 20 weeks of GA. BPS is a mass of non-functioning lung tissue with no connection with the bronchial tree and with an abnormal arterial blood supply from the aorta. BPS appears as homogeneous, solid, well-defined, hyperintense masses on T2-weighted MRI and solid hyperechoic lesions on US [1,10]. Doppler identifies the feeding vessel. CLE is a developmental abnormality resulting from bronchial obstruction of the lower respiratory tract, characterized by fluid trapping in the lungs resulting in hyperinflation of one or more lung lobes. On US CLE shows an echogenic homogeneous lung mass, usually without cysts. The increased echogenicity is secondary to an abnormal accumulation of fluid in the involved lung. Vascular flow is in the periphery of the lesion. MRI shows a homogeneously hyperintense lesion on T2-W images [10]. Bronchogenic cysts are fluid and mucin-filled, caused by abnormal budding of the primary esophagus and tracheobronchial tree.These cysts are typically anechoic on US and on T2 hyperintense MRI. Internal signal on T1-weighted imaging depends on the proteinaceous content of the cyst [11,12]. Cysts are usually unilocular but can also be multiple, located on the right close the midline and the tracheobronchial tree.Congenital lung tumors are very rare condition, characterized by well-circumscribed masses, suspected when a rapidly enlarging mass is detected at late GA. They can lead to hydrops in the late trimesters. The most important tumor with cysts is the Pleuropulmonary Blastoma(PPB) which is a malignant embryonal tumor which can appear as a single cyst or small nodule or as a large cystic or solid mass. It's difficult to differentiate PPB from other lung lesions on prenatal imaging and diagnosis is definitely postnatal. JXG is a rare condition usually diagnosed in the postnatal period, with possible lung localization. In most patients, the systemic disease undergoes a spontaneous regression. In case of perinatal diagnosis, an overall mortality of 11% has been reported, 42% in patients with systemic disease. Organ dysfunction related to the JXG has been reported in 33% of these cases [12]. The newborns with multisystem or extensive visceral involvement may need invasive treatment such as excision, radiotherapy or systemic chemotherapy. Several patients, including our case, required chemotherapy and the most efficacious chemotherapy for systemic JXG remains undetermined but corticosteroids and vinca alkaloids have largely been used successfully [13]. Our patient received chemotherapy based on the treatment protocol including vinblastine. The expected prognosis of our patient appears to be good, but the long-term sequelae are uncertain.

Prenatal assessment of lung lesions is based on a series of criteria such as the GA of onset of the disease, the unilateral or bilateral site of the lesions, the presence or absence of vascularization, the coexistence of other anomalies or the evidence of signs of haemodynamic failure. One of the most challenging features of this case was the late timing of appearance of the cysts compared to the most common congenital lung lesions. Postnatal imaging investigations, such as MRI, CT, angio CT can improve diagnostic accuracy. Nevertheless, lung lesions are definitely characterized after pathological and histological analysis. In our case the atypical characteristics of the lung lesions allowed us to perform an accurate counseling to

parents, exposing a wide range of hypotheses, including the rare condition of a lung tumor. In addition, prenatal evaluation of multiple bilateral cysts was a strong indication for delivery in a hospital with neonatal intensive care unit.

Conclusion

In conclusion, although congenital histiocytoses is a very rare condition, it should be considered as part of the differential diagnoses of fetal lung cysts, especially if identified in late gestation. Multi-disciplinary team play a crucial role in ensuring that the mother and fetus are managed perinatally with utmost care, especially in challenging cases.

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Manuscript Information: Received: August 24, 2022; Accepted: October 12, 2022; Published: October 20, 2022

Authors Information: Nicastri E[1]; Fabietti I[2]*; Valfrè L[3]; Zarfati A[3]; Romiti A[2]; Viggiano M[2]; Vicario R[2]; Vassallo C[2]; Savelli S[4]; Onelli B[1]; Conforti A[3]; Bonito M[1,5]; Caforio L[2]

[1]Department of Surgical Sciences, University of Rome Tor Vergata, Rome, Italy.

[2]Department of Medical and Surgical Neonatology, Fetal Medicine and Surgery Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Italy.

[3]Department of Medical and Surgical Neonatology, Neonatal Surgery Unit, Bambino Gesù Children's Hospital IRCCS, Rome, Italy.

[4]Department of Diagnostic Imaging, Pediatric Radiology, Bambino Gesù Children's Hospital IRCCS, Rome, Italy.

[5]Division of Obstetrics and Gynecology, San Pietro Hospital, Rome, Italy.

Citation: Nicastri E, Fabietti I, Valfrè L, Zarfati A, Romiti A, Viggiano M, Vicario R, et al. A rare type of fetal histiocytosis as a challenging prenatal ultrasound presentation: A case report. Open J Clin Med Case Rep. 2022; 1921.

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