CASE REPORT

Type II pleuropulmonary blastoma in a fetus: case report of a rare mesenchymal mediastinal tumor and literature review

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ABSTRACT

Mediastinal tumors are exceedingly rare during fetal development, presenting significant diagnostic challenges and potentially leading to severe outcomes such as stillbirth or metastatic disease if not promptly identified and managed. Pleuropulmonary blastomas are primitive mesenchymal tumors often linked to mutations in the DICER1 gene, indicating a hereditary pattern associated with other common adult neoplasms with dominant inheritance. This report describes a case involving a 20-year-old Caucasian woman whose pregnancy was complicated by a stillbirth in the second trimester. Initial suspicions of a mediastinal tumor arose from blood tests and ultrasound examinations during pregnancy surveillance. However, the definitive diagnosis of a type II pleuropulmonary blastoma was established through a pathological examination at autopsy. This case underscores the complexities of diagnosing fetal mediastinal tumors and contributes to the sparse literature on neonatal pleuropulmonary blastomas. Our comprehensive review of the differential diagnoses and literature emphasizes the unique characteristics of pleuropulmonary blastoma and its similarities to other soft tissue sarcomas, enhancing understanding of their clinical and genetic profiles.

KEYWORDS: type II pleuropulmonary blastoma; mediastinal tumor; mesenchymal tumor; DICER1 gene; fetus; immunohistochemistry

INTRODUCTION

Pleuropulmonary blastoma (PPB) was defined in 1988 by Manivel et al. in a series of 11 cases describing this intrathoracic pulmonary neoplasm in young children [1]. PPB, as an entity, has been described by various terms, including pneumoblastoma, and cystic mesenchymal hamartoma. It typically affects young patients, often under 5 years old. These tumors may present at birth and develop within the lungs or in proximity, if located in the mediastinum. PPBs are multiphasic proliferations containing epithelial, sarcomatous, and blastematous components.

In this context, the tumour can exhibit heterologous components, including diverse mesodermal tissues such as bone, cartilage, or muscle, indicative of its complex cellular differentiation. However, the inclusion of interstitial Cajal cells, which are typically characteristic of the gastrointestinal tract, would be unusual. Nevertheless, in tumors with multipotent cellular diversification, such unexpected elements can occur. Stromal tumors, although an important entity in the realm of mesenchymal tumors, are not relevant to the differential diagnosis of PPB due to their distinct anatomical, demographic, and pathological characteristics.

Neoplastic diseases in pediatric patients, although rare, can pose life-threatening conditions. Solid tumors in pediatric populations account for a significant percentage of cases. The progression of these tumors can result in metastasis and local complications. This case report has been documented in accordance with the SCARE guidelines [2].

CASE PRESENTATION

A 20-year-old mother attended a routine fetal morphometry consultation in her second trimester at a private healthcare facility. She expressed concerns about a lack of fetal movement but did not report any other symptoms. The patient, mother of two children (a boy and a girl), had a history of natural deliveries without any prior surgical interventions. She mentioned a maternal lineage history of

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thyroid carcinoma, for which her mother was treated with surgery and iodine isotopes in the'90s. There were no known allergies or chronic medications in her medical history.

The patient was leading an active social and professional life, working in the food industry. She reported no smoking habits, though occasional alcohol consumption was acknowledged. She denied any use of recreational drugs.

Clinical Findings

During the general physical examination, the mother was found to be in good condition without any complaints. A comprehensive ultrasound scan of her systems and organs was conducted, followed by an obstetrical evaluation. The gynecological examination, in conjunction with the ultrasound, revealed a 22-week pregnancy without signs of fetal viability. An anterior mediastinal mass in contact with the right atrium and a collection of fluid in the pericardial sac were described. This information was communicated to the patient and her husband. After unsuccessful attempts to induce natural expulsion with intravaginal misoprostol over a 24-hour period, a cesarean section under spinal anesthesia was proposed on her second day of admission. Laboratory values fell within normal ranges, and both the electrocardiogram and pre-anesthetic assessments were unremarkable. The patient had a body mass index (BMI) of 29, fell under Mallampati Class 2, and was classified as ASA risk 2. Following the extraction of the conceptional material, the patient experienced an uneventful recovery.

Autopsy findings

The dissection performed on the specimen revealed the following gross aspects: The fetus had macerated skin with an extent of 90%. The placental disc measured 13 cm in diameter and weighed 160 grams, including an 11 cm umbilical cord stump. Histological examination of the placental disk showed a normal appearance within the expected parameters for the duration of the pregnancy, with the only abnormality being a mild to moderate edema of the cord and membranes. The fetus, weighing 360 grams and measuring 28 cm (Figure 1a). External genitalia were

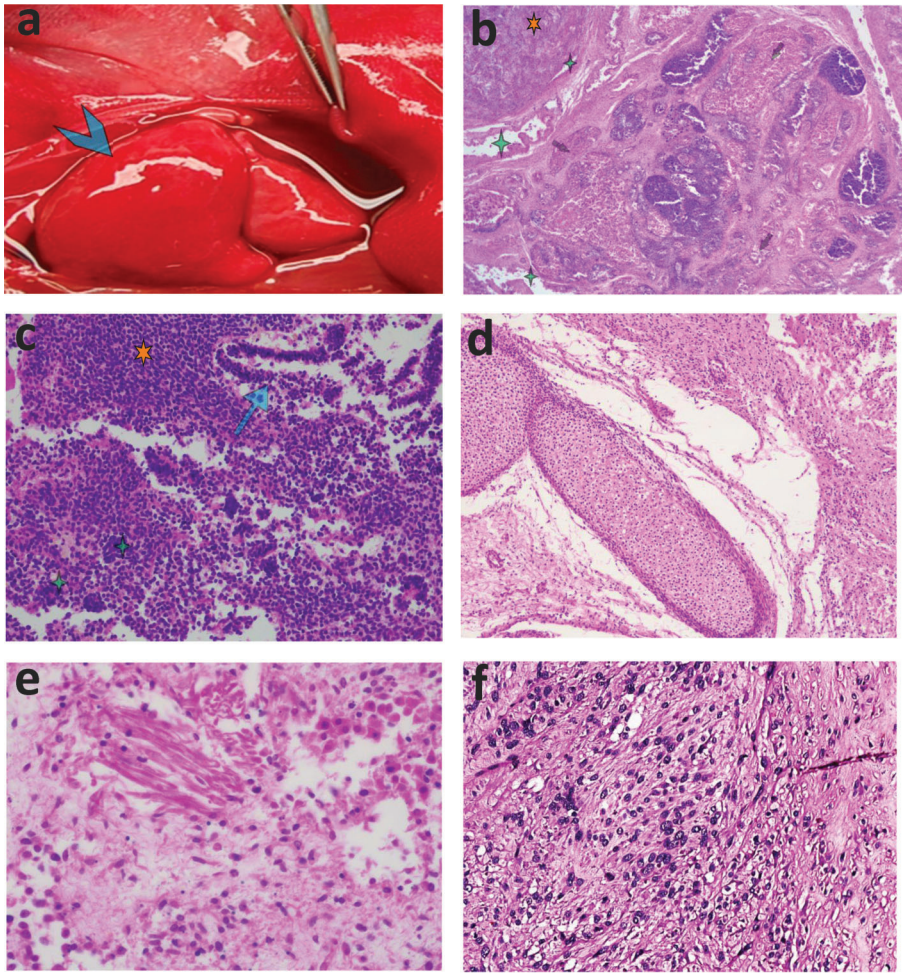

Fig. 1. Type II pleuropulmonary blastoma. Autopsy and histological findings: **a.** A mediastinal mass (blue arrowhead), compressing the heart with fluids accumulation into pericardium. **b.** Histopathological exam of the specimen - note a heterologous mass with epithelial islands (black arrows), cartilage (orange 5 points star), cysts (green points stars). (HE, x40); **c.** The mesenchymal component comprised undifferentiated primitive tissue (orange star) and blastoid structures (green star) while cyst is lined by a cuboidal epithelium with varies degrees of atypia (blue arrow) (HE, x100); **d.** Complete developed cartilaginous island inside the tumoral mass (HE, x100). **e.** Heterologous rhabdoid cells are not unusually findings in PPB (HE, x400); **f.** The presence of focally atypia, as presented here in a focus of stromal cells, mandatory for a PPB diagnosis (HE, x400).

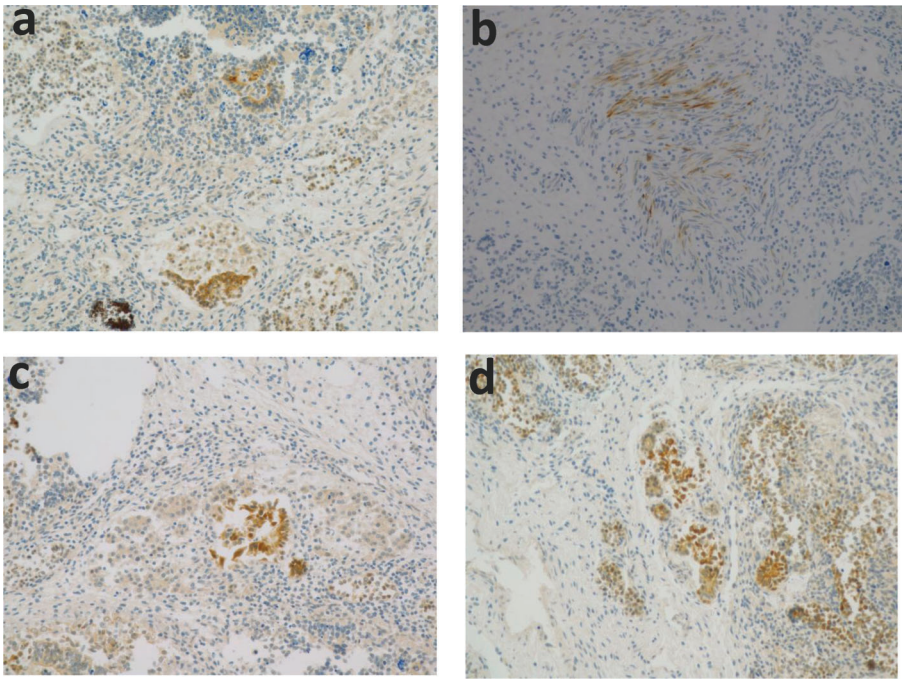

Fig. 2. Type II pleuropulmonary blastoma. Immunohistochemistry findings: **a.** CK7 positive in the remaining epithelium lining the collapsed cyst (top center) and in the conglomerate immature epithelial components (bottom center) (IHC, anti-CK7 mAb, x100); **b.** Desmin positive in rhabdoid neoplastic components (IHC, anti-Desmin mAb, x200); **c.** Intense nuclear staining with p53 antibody in majority of epithelial cells is indicative for malignant transformation (IHC, anti-p53 mAb, x100); **d.** Beta catenin nuclear positivity in cluster of cells and epithelium lining cystic component (IHC, anti-beta catenin mAb, x100)

identified as male, with normal ears and no other external features noted. The anus was patent, and the palate was closed. Upon opening the thoracic-abdominal-pelvic cavities, an anterior mass was found in the mediastinum, along with a significant sero-sanguinolent pericardial effusion exceeding 10ml in volume. The mass measured 3.5 x 2.3 x 1.6 cm and displayed an encapsulated appearance (Figure 1b). On sectioning, it appeared predominantly solid spongy, with a heterogeneous grey-brown texture. A fragment of the tumor was cryopreserved in the hospital's tumor archive. The thymus (1.3x0.9x0.4cm) did not present any abnormalities. All other organs were normal and appropriately developed for gestational. The entire heart-lung block was sent for further dissection, revealing no abnormalities in growth.

Histopathological findings

The mediastinal mass displayed an inhomogeneous composition with cystic areas and solid formations consisting of epithelial components and immature mesenchymal tissue (Figure 1b). The cystic areas were variably lined with atypical cuboidal ciliated epithelium (Figure 1c). The mesenchymal component comprised undifferentiated primitive tissue (Figure 1c orange star) and blastoid structures (Figure 1c green star). The presence of normal histological tissue such as cartilage (Figure 1d), pathological like rhabdoid structures (Figure 1e), or some bizarre multinucleate cells with nuclear atypia were observed (Figure 1f). Low mitotic activity was noted, likely attributed to prolonged ischemia.

Immunohistochemical analysis revealed positive staining for AE1/AE3, CK7 (Figure 2a), and TTF1 in the epithelial component, as well as desmin (Figure 2b) and myogenin in rhabdoid structures. Noteworthy our findings include aberrant localization of p53 (Figure 2c) and beta-catenin (Figure 2d). Negative staining was observed for CK5, CK20, MPO, CD45, ALK, and S100 Synaptophysin. The last two tests exhibited variable staining in cartilage as well in mesenchymal tissue, suggesting potential neuroendocrine structures, altered by autolysis. Both DOG1 and CD117 antibodies tests did not yield positive results.

Based on the histopathological findings, a diagnosis of pleuropulmonary blastoma type II was established. The cause of fetal arrested development was attributed to direct mechanical compression on the heart leading concurrent with exudative pericarditis.

DISCUSSION

We focus this section on two primary areas: a review of current literature, including ongoing studies and the differential diagnosis of Pleuropulmonary Blastoma (PPB).

Literature review

Relevant literature on this topic is not abundant, reflecting the rarity of this mesenchymal tumor. We conducted a literature review on focusing on English-language databases, particularly those curated by the NIH National Center for Biotechnology Information (NCBI) and its branch libraries (including Clinical Trials.gov), with a specific emphasis on neonatal and fetal studies. Inclusion criteria were articles indexed in PubMed or NHLM, involving patients aged one year or below or in the fetal stage. We aimed to identify articles that included a comprehensive differential diagnosis with slide review, frequent use of immunohistochemistry (IHC) and genotyping (in any form). Search terms included "pleuropulmonary blastoma", "pulmonary blastoma cystic",

and "mediastinal hamartoma". We aimed to exclude overlapping cases with congenital cystic malformation and cystic teratoma of the mediastinum. Our focus was on papers addressing soft tissue tumors located in the mediastinum, specifically pleuropulmonary blastoma.

One European study, initiated in France in 2017 (NCT03044834), identified a maximum of 20 cases of PPB between 2009 and 2020 [3]. The study transitioned from a prospective design auditing previous cases of PPB to an observational one, functioning as a national France registry for PPB since 2020. This collaborative study, conducted in partnership with the International Pleuropulmonary Blastoma Registry (IPPB), highlighted the significance of age at diagnosis and the prognostic implications of different histological subtypes. A consensus was reported regarding medical interventions based on histological type, including surgery and chemotherapy, with DICER1 testing and genetic counseling offered to the entire family. Another ongoing European observational study on lung malformations, initiated in 2016 (NCT03044769), aims to register new cases of lung pediatric tumors including PPB and to develop a tumoral biobank. However, no results or public papers were posted [4].

The International PPB/DICER1 Registry (ID NCT03382 158) stands as the most comprehensive database, incorporating data from French and Swiss European registries. It collects information on applied treatments, case accrual, and survivability. The registry remains in operation and actively recruits patients, offering case consultations and expert opinions. It published a series of 20 original papers from 2009 to 2021 [5]. Notably, many US studies aim to register PPB cases globally, posing challenges in determining the true incidence or number of active studies based on published literature [6].

The International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry (NCT01464606) aims to collect data on PPB treatments. While active until 2024, it has ceased recruitment for studies evaluating chemotherapy survival rates. No published data or article where publicly made [7].

Only one study directly addressed the drugs, pharmacokinetics, and other relevant parameters for Lorvotuzumab Mertansine therapy in younger patients with relapsed or refractory Wilms tumor, rhabdomyosarcoma, neuroblastoma, pleuropulmonary blastoma, malignant peripheral nerve sheath tumor, or synovial sarcoma (ID NCT02452 554). This study, although closed, published results, reporting only one PPB case [8].

A PubMed search yielded 455 publications, including original research articles and review papers. After an initial screening, 221 articles remained. Focusing on studies with documented pathological sections we further reduced the number to 95 articles. The studies documented a total of 132 histopathologically confirmed PPB cases, most being single-case reports and a few case series reporting between 2 and 20 cases [9]. The median age at diagnosis was 4 years, with the youngest patient being 2.5 months old. Only 4 cases were diagnosed in utero and one at autopsy [10]. Interestingly, 1 case lacked DICER1 mutations [11]. Only three cases involved a diagnosis outside the lungs area, with 2 concerning the pleura and 1 the mediastinum [12]. Notably, 7 cases had a significantly different initial diagnosis, including emphysema, aspergilloma, cystic congenital malformation, or hamartoma. The differential diagnosis of fetal masses did not include distinguishing low-grade type I PPB from mediastinal cystic hamartoma.

Differential diagnosis of Pleuropulmonary blastoma

In children, the differential diagnosis for pleuropulmonary blastoma (PPB) include fetal adenocarcinoma, mediastinal hamartoma, congenital pulmonary airway malformation, cystic synovial sarcoma, congenital peribronchial myofibroblastic, and fetal lung interstitial tumor.

Fetal adenocarcinoma is a rare entity, clinically presenting after birth, mainly in young adolescents. It manifests as a solid mass located in the lung. Some investigators consider it a variant of PPB without a malignant mesenchymal component. It is characterized as a proliferation of immature epithelial alveolar-like structures. Notably, it shares the same driving mutation DICER1 as PPB, which brings it closer in resemblance [13].

Mediastinal hamartomas (MH) are abnormal developments of normal tissues derived from one or all layers of the embryonic trilaminar disc, including skin and cutaneous structures like sebaceous glands, and occasionally intestinal structures and diverse types of endocrine structures, most commonly thyroid follicles. Teratomas are neoplastic lesions of pluripotent cells containing tissue from all three embryonic germ layers and are classified as mixed germ cell tumors. They often contain traces of germ line cells. Mediastinal hamartomas are more often associated with a benign clinical course. Their rapid expansion can potentially deteriorate heart mechanics and lead to premature death in rare cases. Microscopically, mediastinal hamartomas do not exhibit significant atypia or mitotic activity. Although they share some histological similarities with low-grade pleuropulmonary blastoma, they remain neoplastic in nature [14].

Congenital pulmonary airway malformation (CPAM) encompasses a spectrum of developmental anomalies characterized by abnormal cystic structures lined by mature respiratory epithelium. These malformations are classified as cystic, microcystic, or solid, primarily affecting a single lobe or a portion of the lung. Histologically, CPAMs exhibit a lining of ciliated cuboidal or columnar epithelium and lack components like smooth muscle or cartilage. The surrounding mesenchyme typically shows a connective tissue stroma with a myxoid to lose appearance and a myofibroblastic component. Notably, microcystic and solid CPAM often demonstrate the presence of heterologous structures, including mucinous glands, considered preneoplastic alterations. Furthermore, all CPAM subtypes are now recognized to harbor mutations in the KRAS gene. While typically benign, CPAM can rarely present as a precursor for PPB [15].

Cystic synovial sarcoma is a rare mesenchymal tumor that exceptionally affects neonates and fetuses. It can occur in the mediastinum or lung. In its biphasic variant, it closely mimics PPB due to the presence of epithelial components. Cystic synovial sarcoma is characterized by the absence of heterologous tissue. Microscopically and by immunohistochemistry, it exhibits a monotonous population of bland spindle cells arranged in small fascicles, interspersed with uniform bland glandular structures. Regardless of age and type, cystic synovial sarcoma exhibits pathognomonic gene fusions involving SS18 and SSX1 or 2 or 4, resulting from translocation events t(X;18). The resulting fusion gene produces a translated protein detectable by immunohistochemistry or western blot techniques when real-time sequencing (PCR) or fluorescence in situ hybridization (FISH) is unavailable [16,17].

Congenital peribronchial myofibroblastic tumor (PMF) is a rare benign mesenchymal neoplasm primarily affecting infants and newborns. It presents as an incidental finding, typically located in the peribronchial region of the lung. Grossly, PMF appears as a well-circumscribed, solid mass without cystic components. Microscopically, it is characterized by a proliferation of monotonous spindle cells with a low mitotic rate, arranged in a fascicular or storiform pattern. A prominent feature is the presence of thick-walled blood vessels within the tumor. Cells exhibit mild to moderate atypia, with a scant eosinophilic cytoplasm and elongated nuclei. Immunohistochemistry typically reveals positivity for smooth muscle actin and desmin, supporting the myofibroblastic differentiation. The proliferative activity is generally low, with a Ki-67 proliferation index typically below 5%. PMF is a benign tumor with an excellent prognosis following surgical resection. Distinguishing PMF from other spindle cell lesions, such as inflammatory myofibroblastic tumor and cellular mesenchymal neoplasms, is crucial for accurate diagnosis and management [18,19].

Fetal lung interstitial tumor (FLIT) is an exceedingly rare, benign neoplasm that can manifest as either a microcystic or solid mass. It typically arises during fetal development, often presenting as a relatively well-defined, occasionally encapsulated mass within the lung interstitium. Macroscopically, FLITs may exhibit a variegated appearance, ranging from tan-white to gray-brown. Microscopically, the tumor is characterized by a distinctive microcystic architecture, with cysts lined by a single layer of cuboidal to columnar epithelial cells. The intervening stroma is composed of large, monotonous cells with abundant clear cytoplasm, often exhibiting a myofibroblastic appearance. Immunohistochemistry typically reveals positivity for vimentin, smooth muscle actin, and desmin, supporting the pure mesenchymal origin of the tumor cells. While some FLITs may harbor activating mutations in the ALK gene, there is no evidence of overlap with genetic alterations associated with pleuropulmonary blastoma (PPB), such as DICER1 or beta-catenin mutations. The differential diagnosis of FLIT includes other congenital lung lesions, such as congenital pulmonary airway malformation (CPAM), congenital peribronchial myofibroblastic tumor (PMF), and cystic synovial sarcoma. Distinguishing FLIT from these entities is crucial for accurate diagnosis and management [20].

Distinguishing PPB from other congenital lung lesions, particularly CPAM and MH, can be challenging. The presence of cysts lined by cuboidal ciliated epithelium that is positive for TTF1 or CK7, along with immature mesenchyme, favors a diagnosis of CPAM. In contrast, PPB is characterized by the addition of primitive mesenchymal components, at least a degree of atypia, and nuclear positivity for beta-catenin. Malignant transformation of mediastinal hamartoma is typically associated with p53 and KRAS mutations. In the absence of DICER1 testing, identifying a biphasic neoplasia with primitive mesenchymal component is crucial for diagnosing PPB. A comprehensive clinical evaluation, including detailed history, physical examination, imaging exams, and pathological assessment, is essential for accurate diagnosis and appropriate management.

Comparing our case to the reviewed literature, we find it to be one of the five reported cases documenting PPB development in the fetal stage and the second with a mediastinal location. Furthermore, our case demonstrates fetal demise resulting from direct mechanical compression, with metastatic events occurring later in the development of mesenchymal components. Our study, however, lacks determination of the fetus' DICER1 status, while the mother's mutational status remains undisclosed.

CONCLUSION

Pleuropulmonary blastoma (PPB) is an exceedingly rare tumor, with even rarer occurrences in the mediastinum. Its malignant potential is undoubtedly established. Further studies are necessary to differentiate immature/malignant cystic hamartoma of the mediastinum from PPB in the fetal stage and neonates. Regarding our aim to identify interstitial cells of Cajal (ICC), given the negative results for c-Kit and DOG1 markers in our PPB tissue samples, we conclude that ICC are absent at this location. Additional immunohistochemical markers (such as Anoctamin-1b) might be considered for further investigations.

In conclusion, we emphasize our report's originality as the first to document a fetal-stage PPB in our region. While the extra-digestive proliferation of ICC remains a topic of debate, ranging from outside the digestive tract gastrointestinal tumors to hamartomatous collections, our study found no such cells in the mediastinal region.

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Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this paper. The Troyes Hospital's Ethical Committee was informed and approval was obtained for publishing an anonymized case report.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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