CASE REPORT

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Type II pleuropulmonary blastoma in a 2-year-old girl: a case report

TEODORA SMARANDA ARGHIRESCU[1)], ADA MARIA CÂRSTEA[1)], LICINIA ANDRADA OPRIŞONI[1)], ELENA RODICA HEREDEA[2)], OVIDIU NICOLAE BURLACU[3)], IOANA DELIA HORHAT[4)], CĂLIN MARIUS POPOIU[1)]

[1)]*Department of Pediatrics, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*
[2)]*Department of Pathology, "Louis Ţurcanu" Emergency Children Hospital, Timişoara, Romania*
[3)]*Department of Surgery I, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*
[4)]*Department of ENT, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*

Abstract

Pleuropulmonary blastoma (PPB) is a very rare, malignant aggressive primary lung tumor, which occurs mainly in children less than 5 years old. Due to its poor prognosis, it is aggressively treated with multimodal therapy including surgery and chemotherapy. We present a case of PPB in a 2-year-old girl who was brought to the pediatric clinic for fever, cough and respiratory distress. Imaging studies showed a heterogeneous solid-cystic mass (12/9/11 cm) in the upper right pulmonary lobe. Through right thoracotomy, a specimen was obtained, the histopathological and immunohistochemical features of the specimen being suggestive for type II PPB. Aggressive chemotherapy and right pneumonectomy resulted in control of disease, the patient being currently in complete remission four years after the diagnosis.

Keywords: pleuropulmonary blastoma, respiratory failure, primary lung tumor, biphasic tumors.

Introduction

Pulmonary blastomas are a group of rare neoplasms consisting of biphasic pulmonary blastoma, fetal adenocarcinoma, and pleuropulmonary blastoma (PPB) [1, 2]. However, recently, *World Health Organization* (WHO) classified separately well-differentiated fetal adenocarcinomas and PPB from the biphasic tumors [3].

PPB is most frequently diagnosed during infancy and early childhood, being first described as a distinct clinicopathological entity in 1988, by Manivel *et al.*, in a small study of 11 patients [4, 5]. PPB accounts for only 15% of all primary pediatric pulmonary tumors and for only 0.5% of all pediatric malignancies [4].

PPB arises from the intrathoracic (pulmonary, pleural or both) mesenchyme, histologically being described three types: type I – predominantly cystic, type II – mixed (cystic and solid), and type III – predominantly solid [6]. In 2006, *International PPB Registry* recognized a fourth type – type I-regressed PPB –, which is either a type I PPB, which has regressed to a cystic lesion or, alternatively, a genetically-determined lung cyst which did not evolve to become malignant [7]. Overtime, type I PPB, which is radiologically very similar to a lung cyst, can progress to aggressive type II or type III tumor. Therefore, it is very important that PPB to be differentiated from benign lung cysts and congenital airway malformations. Progression of PPB to types II or III significantly impacts the prognosis, the 5-year overall survival decreasing from 85–90% (in type I PBB) to 71% (in type II PBB) and 53% (in type III PBB), respectively [8].

Clinical presentation of patients with PBB can vary according to the tumor type, usually type I PBB being discovered incidentally on chest X-ray. Types II or III PBB present with respiratory distress or symptoms resembling a pneumonia, being easily misdiagnosed in the early clinical course, which can further lead to the specific treatment delay [9]. Additionally, types II and III PBB have an aggressive behavior and tendency to spread to the brain and bone [8, 10–12].

Currently, treatment of PBB is multimodal. In type I PBB, current treatment recommendations are limited to surgical resection without association of chemotherapy. In types II and III PBB, due to increased risk of metastasis, treatment plan includes aggressive chemotherapy in addition to radical surgery. Radiotherapy may be used in selected patients with unresectable tumors [7, 8].

Aim

Aiming to increase awareness in recognizing rare pediatric primary lung tumors, we describe the case of a type II PPB arising from the right upper pulmonary lobe diagnosed in a 2-year-old girl admitted in the pediatric clinic mainly due to signs of respiratory failure.

Case presentation

We describe the case of 2-year-old patient, D.A., with unremarkable personal and family medical history, who was admitted to the Pediatric Clinic in January 2014 ("Louis Ţurcanu" Emergency Children Hospital, Timişoara, Romania) for fever, cough and breathing difficulty, symptoms with sudden onset 48 hours before presentation. Clinical exam revealed pallor, tachypnea (46 breaths/min), intercostal retractions, equally-transmitted breath sounds, heart rate 130 beats/min, blood pressure 90/45 mmHg, oxygen saturation 90% and a body temperature of 38.7ºC. No other clinical pathological findings were noted.

Full blood counts showed anemia (hemoglobin level of 9.5 g/dL), leukocytosis 13 360/μL (neutrophils 50%, lymphocytes 36%) and thrombocytosis 704 000/μL. Her erythrocyte sedimentation rate was 100 mm/h, whereas her C-reactive protein was 14 mg/dL (normal range less than 5 mg/dL).

A chest radiograph was performed, revealing opacification of the right upper pulmonary lobe (12/9/11 cm) (Figure 1, a and b), with a solid-cystic structure on chest ultrasound (Figure 2, a and b). The patient underwent a chest computed tomography (CT) scan, which confirmed the presence of a mixed solid-cystic mass in the right upper pulmonary lobe, with adherence to the anterior-lateral pleura (Figure 3, a and b).

A surgical biopsy of the mass through right thoracotomy was performed. Macroscopic examination of the specimens revealed four gray tissue fragments presenting elastic consistencies. The smallest fragment measured 0.5/0.2/0.3 cm, followed by two medium size fragments that measured 0.6/0.3/0.2 cm and 0.9/0.6/0.2 cm, and a large fragment that measured 1/0.4/0.3 cm.

Specimens were processed for histopathological (HP) diagnosis using Hematoxylin–Eosin (HE) staining method. Routine microscopic examination showed small tissue fragments exhibiting a tumor proliferation that was constituted of small, disjointed cells, with a poorly represented cytoplasm, large, rounded, intensely stained nuclei. We also noticed mitotic activity and glandular structures that were lined by a focally Periodic Acid–Schiff (PAS)-positive cubic or columnar epithelium (Figure 4). Some of the examined fragments presented a fibrous stroma and extensive areas of tumor necrosis. We concluded that the HP features of the lesion were suggestive for a tumor proliferation closely resembling a PPB. In order to certify the diagnosis, additional immunohistochemical (IHC) analysis was applied using the following panel of antibodies (ready-to-use markers, Novocastra): anti-vimentin (Vim), anti-cytokeratin (CK) AE1/AE3, anti-chromogranin A (ChrA), anti-epithelial membrane antigen (EMA), anti-thyroid transcription factor 1 (TTF1), anti-cluster of differentiation (CD) 99, anti-CD117, anti-Ki67 protein, anti-Wilms tumor 1 (WT1) protein, anti-S100 proteins, and anti-CD34.

In our study, only Vim, CD117 and TTF1 exhibited an intense positive reaction in the tumor cells, while WT1 was positive in the stromal compartment. Also, a 40% proliferation index was noted in the tumor cells. CK AE1/AE3, ChrA and EMA were negative in the tumor compartment, while CD99 and S100 were negative overall. CD34 presented an intense reactivity in the endothelial cells of the blood vessels and was used as an internal control marker. The IHC features confirmed our presumptive diagnosis of PPB (Figure 5, a–f).

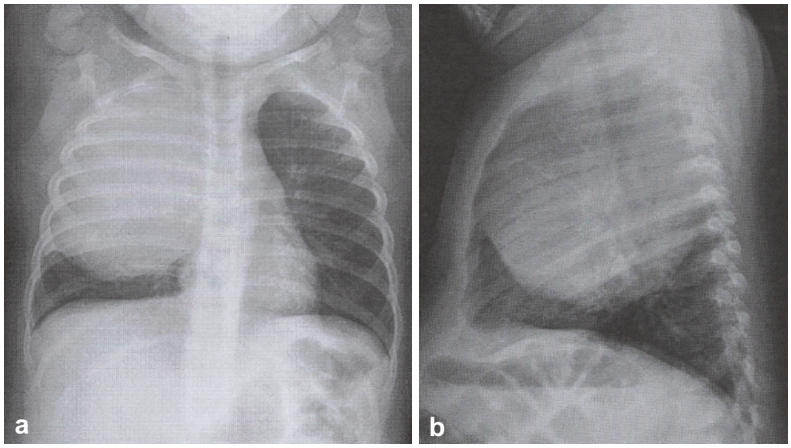

Figure 1 – ***Chest radiography at the hospital revealed the presence of a large, relatively homogeneous opacity, located in the right upper lobe: (a) Anteroposterior view; (b) Profile view.***

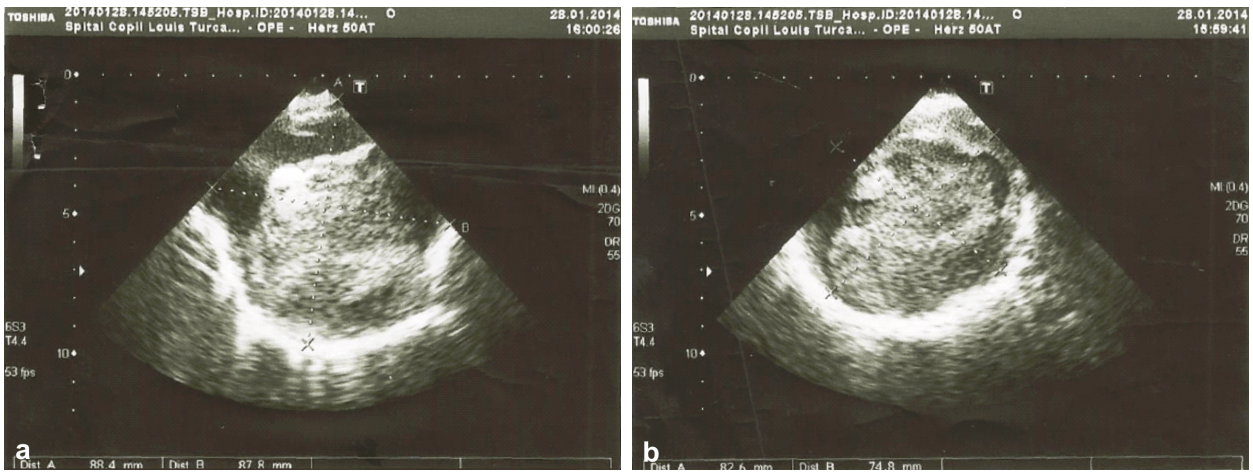

Figure 2 – ***(a and b) Chest ultrasound showing a solid-cystic structure in the right superior lobe.***

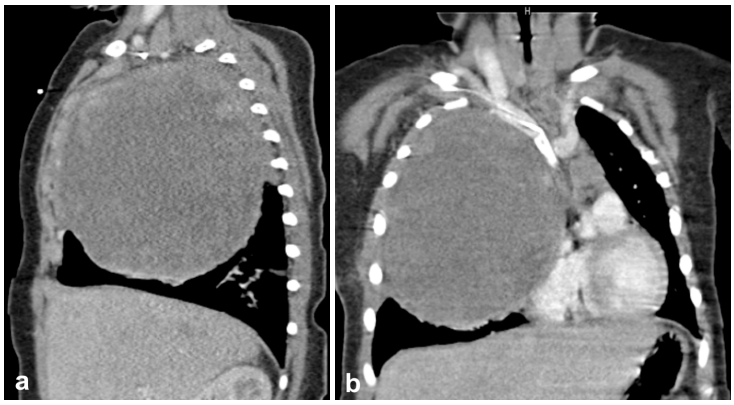

Figure 3 – ***Chest CT scan showing the presence of a mixed mass in the right superior lobe whit adherence on the anterior-lateral pleura. CT: Computed tomography.***

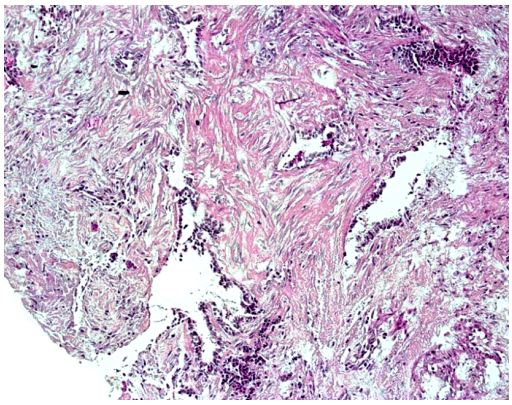

Figure 4 – ***Glandular structures that were lined by a focally PAS positive (PAS staining, ×200). PAS: Periodic Acid–Schiff.***

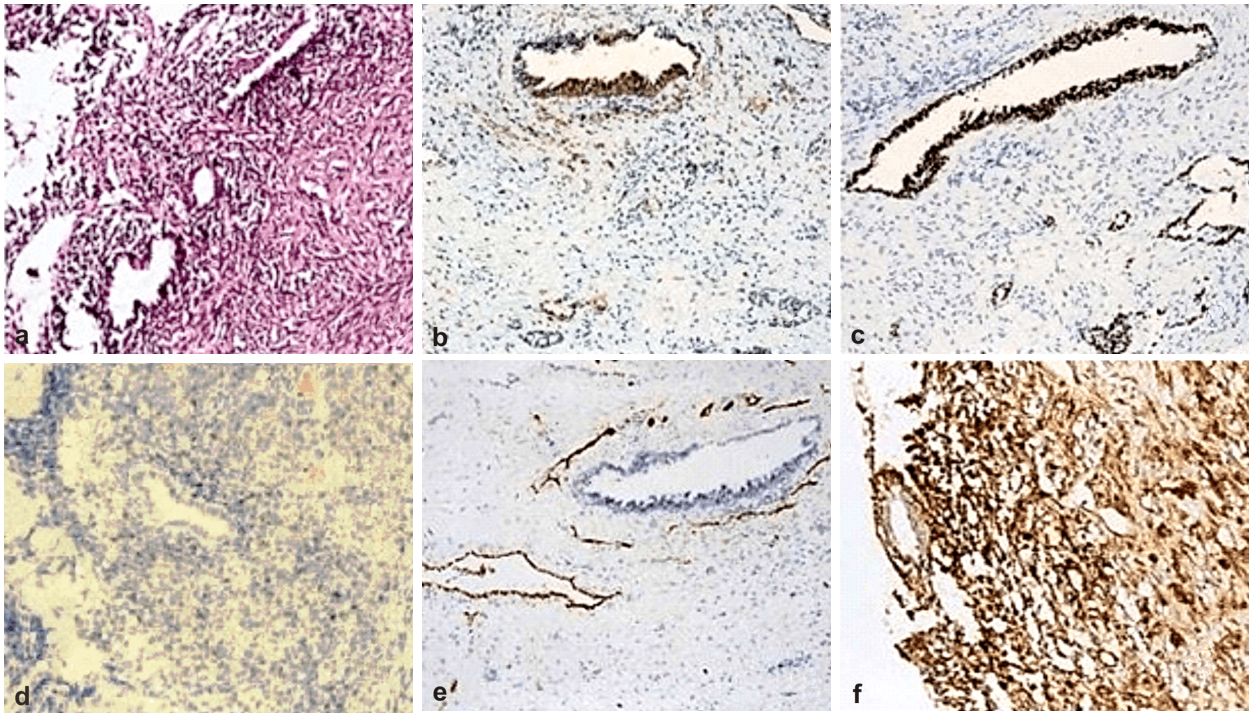

Figure 5 – ***(a) Tumor proliferation constituted of small cells and glandular structures lined by a cubic/columnar epithelium (HE staining, ×200); (b) Positive CD117 expression in the tumor cells (Immunomarking with anti-CD117 antibody, ×200); (c) Intense TTF1 expression in the tumor compartment (Immunomarking with anti-TTF1 antibody, ×200); (d) Immunohistochemical reaction for CK AE1/AE3 (Immunomarking with anti-CK AE1/AE3 antibody, ×200); (e) CD34 expression in endothelial cells (Immunomarking with anti-CD34 antibody, ×200) – note the differential diagnosis between the positive blood vessels and the glandular structures that appear negative for CD34; (f) Vim was intensely expressed in the tumor cells (Immunomarking with anti-Vim antibody, ×200). HE: Hematoxylin–Eosin; CD117: Cluster of differentiation 117; TTF1: Thyroid transcription factor 1; CK AE1/AE3: Cytokeratin AE1/AE3; CD34: Cluster of differentiation 34; Vim: Vimentin.***

Evaluation of the disease extension – CT scans of the abdomen, pelvis and brain – showed no signs of secondary tumor involvement. Therefore, chemotherapy was started according to the *International PPB Registry* protocol for type II PPB. After the third Ifosfamide–Vincristine–Actinomycin D–Doxorubicin (IVADO) cycle, the tumor has significantly reduced its volume (6/5/4 cm) (Figure 6, a and b). Due to the increased surgical risk, it was decided to continue chemotherapy – one IVADO cycle and two IVA cycles. Complications encountered throughout chemotherapy included: multiple episodes of febrile neutropenia, bilateral blepharoconjunctivitis, right orbital cellulites and thrombosis of central venous catheter at the junction between superior vena cava and brachiocephalic venous trunk.

Six months after diagnosis, a right pneumonectomy was performed, with complete excision of the tumor and without surgical complications. Due to the lack of an age-appropriate prosthesis, the chest drain tube was suppressed 24 hours after surgery.

Macroscopic analysis of the resected lung revealed the presence of three pulmonary lobes and the dimensions of the specimen were measured at 14/8.8/5.5 cm. A 5.5/4.3/4 cm tumor formation, with relatively well-lined borders, was identified. The lesion exhibited a brown color, with yellow areas located at the periphery and was characterized by a

friable consistency. Routine microscopic analysis revealed the presence of a focally proliferative tumor in the pulmonary parenchyma. The tumor lesion was constituted of glandular structures lined by a focally PAS-positive cubic/columnar epithelium. Here and there, we identified nests of small, disjointed cells containing low amounts of cytoplasm and large nuclei. We also found extensive areas of tumor necrosis and we noted the presence of hemorrhagic necrosis in the resting pulmonary parenchyma. The HP features found on routine-stained slides revealed the existence of resting areas of PPB (Figure 7).

Postoperative chest CT scan showed no signs of residual tumor, secondary hyperinflation of the left lung and movement of the heart and mediastinal structures to the right thorax (Figure 8, a and b).

Chemotherapy was continued with four more IVA cycles, with no major complications and/or toxicities. Unfortunately, before the last two IVA cycles, the parents decided not to accept further chemotherapy and the patient was discharged with indication of further oncological evaluations every three months.

Six months after discontinuation of chemotherapy, routine transthoracic cardiac ultrasound showed the presence of a hyperechogenic mass (0.5/2.73 cm) on the posterior wall of the right atrium, near the junction with the inferior vena cava (Figure 9, a and b). Although initially considered as thrombus in the right atrium, particularly due to the history of central venous catheter thrombosis and genetic risk for thrombophilia [heterozygous mutation for Factor XIII V34L, heterozygous mutation for plasminogen activator inhibitor-1 (PAI-1) 4G/5G, presence of endothelial protein C receptor (EPCR) A2/A2 alleles], this was further infirmed through chest CT angiography, which showed that the suspected mass in the right atrium was in fact *crista terminalis*.

Currently, four years after the diagnosis, the patient is alive, with no signs of disease recurrence and/or respiratory distress.

Discussions

Primary intrathoracic malignant tumors are very rarely described at pediatric age. The majority of intrathoracic malignant childhood masses result from the spread of extrathoracic solid tumors, the ratio of primary pulmonary neoplasms to intrathoracic metastases being 1:50. Although a rare tumor, PPB is the most frequent malignant tumor of the lung parenchyma in infants and children [8, 13].

In 25% of the patients with PPB, there is positive family history for malignant tumors and/or benign conditions including but not limited to PPB, thyroid carcinoma/thyroid nodules, neurofibromatosis, synovial sarcoma, rhabdomyosarcoma, cystic nephroma, germ cell and sex-cord tumors [4, 7, 14]. In our patient, the available family history was negative for both benign and malignant tumors described in association with PPB.

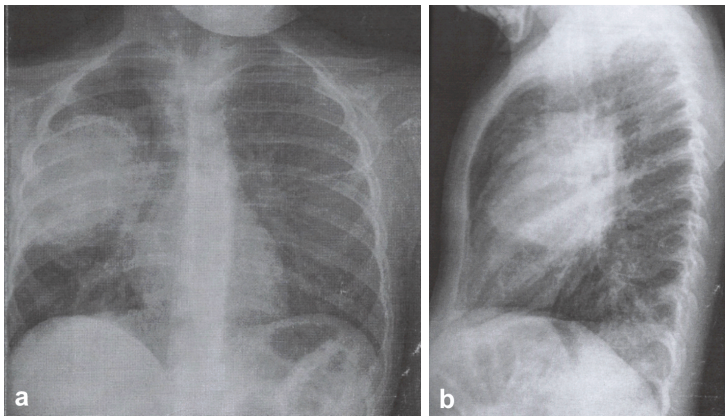

Figure 6 – ***Chest X-ray revealing reduction of the tumor volume after chemotherapy.***

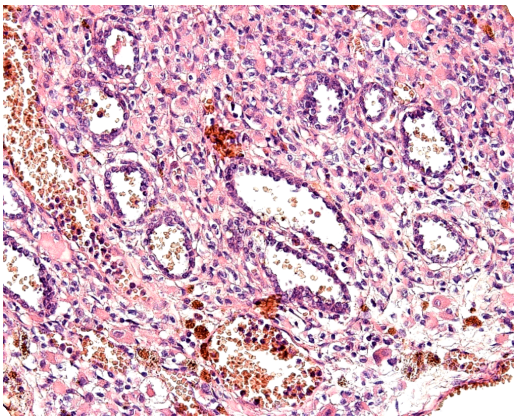

Figure 7 – ***Resting areas of pulmonary blastoma (HE staining, ×20).***

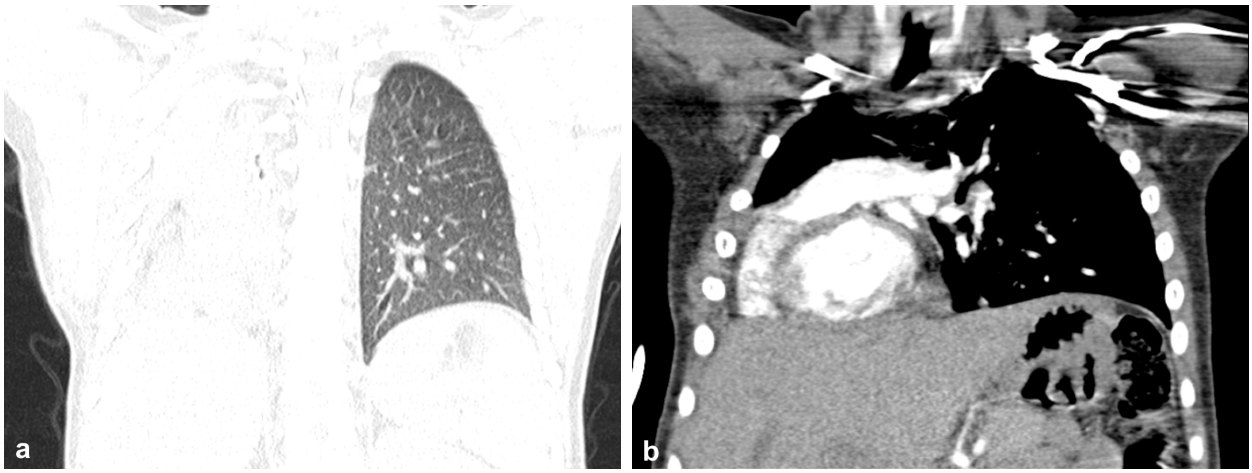

Figure 8 – ***(a and b) Postoperative chest CT scan showed no signs of residual tumor with secondary hyperinflation of the left lung. CT: Computed tomography.***

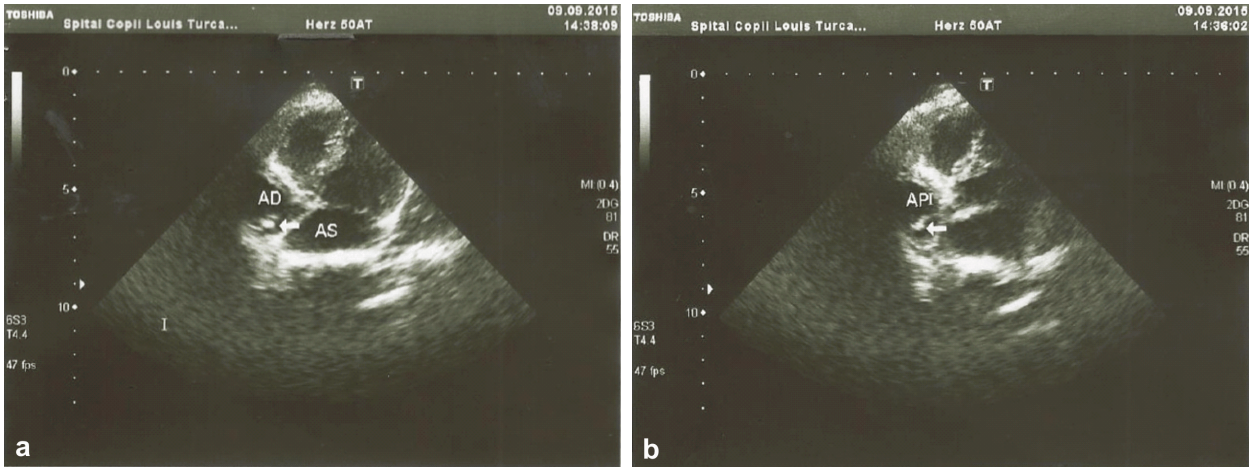

Figure 9 – ***(a and b) Transthoracic cardiac ultrasound showed the presence of a hyperechogenic mass (0.5/2.73 cm) on the posterior wall of the right atrium, near the junction with the inferior vena cava (*****crista terminalis*****).***

Morphologically, PPB contains primitive mesenchymal cells with fibroblastic, cartilaginous or rhabdomyoblastic differentiation. Histologically, PPB is classified in types I–III based on the proportion of solid/cystic components. This classification is strongly correlated with the prognosis, being reserved in types III (solid) and II (cystic and solid) and favorable in type I (cystic) [8].

Zhang *et al.* have examined four cases of PPB and have presented the difficulties encountered by pathologists when coming across such rare diseases. However, Zhang *et al.* found that the tumor cells were positive only for CK and TTF1, while Vim, EMA and S100 protein were negative in the tumor tissue. Moreover, some tumor cells exhibited a positive reaction for ChrA. We first applied a histochemical staining method, namely PAS reaction, in order to determine the secreting features of the tumor cells lining the glandular structures. The existence of PAS-positive tumor cells suggested the possibility of a PPB [15]. In order to fully evaluate the examined specimens, we made use of a totally different panel of markers. The positive expression for TTF1 found in the tumor area suggested its embryonic origin along with the positive expression for CD117. Even though CD117 is not commonly used in order to confirm the diagnosis of PPB, we considered it as a useful tool for our diagnostic orientation. CD117 is known as a stem cell receptor factor. Strong cytoplasmic expression of CD117 was found predominant in the epithelium. Expression of CD117 in tumor cells (both mesenchymal and epithelial cells) suggests that PPB can develop from a pluripotent cell [16]. Surprisingly, Vim presented a positive reaction in the tumor cells, which may suggest the fact that occasionally, PPB may exhibit IHC features of aggressive tumors, such as sarcomas. However, this hypothesis needs further investigation. WT1 positivity in the stromal compartment and not in the tumor cells excluded the possibility of a carcinoma, an aspect that was supported by the value of the Ki67 index (40%), in literature being quoted higher values of Ki67 [17]. The negative reaction for CK AE1/AE3 and EMA eliminated the diagnosis of an adenocarcinoma, while the negative expression for ChrA excluded a possible neuroendocrine tumor. Considering the age of the patient, we applied CD99 in order to exclude a T-cell lymphoma. S100 was used in order to certify the differential diagnosis with a malignant melanoma. Along with its role for the internal control of the specimen, CD34 positivity revealed the existence of a large number of blood vessels located either in the immediate vicinity of the tumor glandular structures or at a certain distance. It is quite possible for these vessels to represent the result of an active angiogenic process that characterizes PPB. Moreover, CD34-positive vessels situated in the immediate vicinity of the tumor glands was used as a differential diagnosis between the two structures due to the fact that they could easily be mistaken for one another on routine-stained slides.

Currently, the recommended approach of PBB implies multimodal treatment – surgery, chemotherapy and radiotherapy. At time of diagnosis, surgical resection of the entire tumor is essential. In patients with unresectable tumors due to involvement of vital structures, neoadjuvant chemotherapy is recommended, aiming to reduce the tumor until it becomes resectable [18]. At diagnosis, our patient had an unresectable tumor, therefore chemotherapy was administered which allowed complete excision of the tumor after six cycles of neoadjuvant chemotherapy.

Radiotherapy is to date considered controversial due to its late effects and no significant differences in overall survival and disease-free survival rates between children who received and did not received radiotherapy [19].

Generally arising from pre-existing pulmonary cystic lesions, recurrence of PPB can also be favored by insertion of chest tubes [20]. In our case, due to the lack of an age-appropriate pulmonary prosthesis, a chest tube was inserted which was suppressed one day after complete excision of the tumor. Further CT scans showed no signs of recurrence at the tube insertion site.

Conclusions

The current case report indicates that, in addition to other frequent pediatric tumors, such as neuroblastoma and Ewing's sarcoma tumors, PPB should be included in the differential diagnosis of large thoracic masses in children. Although local recurrence and central nervous system secondary determinations still hamper the prognosis, complete surgical excision and chemotherapy can lead to a long-term remission, our patient being free of disease at four years after the diagnosis.

Conflict of interests

The authors declare that they have no conflict of interests.

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Corresponding authors

Teodora Smaranda Arghirescu, Associate Professor, MD, PhD, Department of Pediatrics, "Victor Babeş" University of Medicine and Pharmacy; IIIrd Clinic of Pediatrics, "Louis Ţurcanu" Emergency Hospital for Children, 2 Iosif Nemoianu Street, 300011 Timişoara, Romania; Phone +40256–295 978, e-mail: sarghirescu@yahoo.com

Ioana Delia Horhat, MD, PhD, Department of ENT, "Victor Babeş" University of Medicine and Pharmacy, 2 Eftimie Murgu Square, 300041 Timişoara, Romania; Phone +40722–281 483, e-mail: deliahorhat@yahoo.com

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