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Diagnosis and treatment of pleuropulmonary blastoma in children: A single-center report of 41 cases

Na Zhang [a], Qi Zeng [a,*], Xiaoli Ma [b,**], Chenghao Chen [a], Jie Yu [a], Xu Zhang [a], Dong Yan [a], Changqi Xu [a], Dingyi Liu [a], Qian Zhang [a]

[a] Department of Thoracic Surgery, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, China
[b] Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, China

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ABSTRACT

Objective: This study was performed to investigate the age at onset, clinical manifestations, pathological types and features, treatment, and prognosis of pleuropulmonary blastoma (PPB) in children in an attempt to reduce the misdiagnosis rate and achieve early detection and timely intervention.
Methods: We retrospectively studied the clinical data of 41 pediatric patients with PPB who were treated in our center from March 2002 to November 2018. The data comprised the age at onset, clinical manifestations, characteristics of familial diseases, pathological types, surgical procedures, and prognosis.
Results: Twenty male and 21 female patients were included, with a 0.95:1.00 male:female ratio. In total, 51.2% of the patients were misdiagnosed as having nonneoplastic lesions at the first presentation. The interval from symptom onset to surgery/chemotherapy ranged from 5 to 210 days. The pathological types were type I (cystic) PPB ($n = 5$, 11.9%), for which the median age at diagnosis was 21 months (range, 8–24 months); (solid/cystic) II PPB ($n = 12$, 28.6%), for which the median age at diagnosis was 37 months (range, 22–112 months); and type III (solid) PPB ($n = 23$, 54.8%), for which the median age at diagnosis was 39 months (range, 19–156 months). The pathologic type was undefined in one patient (2.4%). The patients were mainly treated by surgery and chemotherapy. The 5-year disease-free survival rate was 69.2%.
Conclusion: The clinical manifestations of PPB are nonspecific, its misdiagnosis rate is high, and it has a poor prognosis. Pediatricians should be aware of the seriousness of PPB. The possibility of PPB should be considered in children with pneumothorax, multiple pulmonary cystic lesions, a family history of pulmonary cysts, a family history of PPB, or space-occupying lesions associated with DICER1 syndromes. The lesion should be closely monitored and surgically removed if necessary. The nature of the lesion should be identified early to minimize the risk of progression of the PPB to worse types because of misdiagnosis and missed diagnosis. Multidisciplinary treatment including surgery, chemotherapy, and/or radiotherapy can be applied to patients with PPB.
Type of study: Treatment study.
Level of evidence: Level III.

Pleuropulmonary blastoma (PPB) is a rare and aggressive primary malignant intrathoracic tumor in children and is classified similarly to neuroblastoma and other organ-based solid dysembryonic malignant tumors of early childhood. It can arise from the lung, pleura, or both. [1]

PPB has a poor prognosis because of its low prevalence and high rate of misdiagnosis. Early diagnosis and complete resection are essential to achieve a good outcome of this potentially fatal disease by offering long-term survival opportunities for children. Few reports have described PPB based on large samples and follow-up visits. We retrospectively analyzed the onset age, clinical manifestations, pathological types and features, risk factors, treatment methods, and prognosis of PPB in children who had been treated in our center in an effort to reduce the rates of misdiagnosis and missed diagnosis and realize early detection and timely intervention of this disease.

1. Patients and methods

1.1. General data

In total, 41 children with PPB were treated in our center from March 2002 to November 2018. The children comprised 20 male and 21 female patients (male/female ratio of 0.95). The age at diagnosis ranged from 8 to 156 months (median, 36 months).

* Corresponding author at: Q. Zeng, Department of Thoracic Surgery, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, 56# Nanlishi Road, Xicheng District, Beijing, China, 100045. Tel.:+86 10 59616413.
** Correspondence to: X. Ma, Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, 56# Nanlishi Road, Xicheng District, Beijing, China, 100045. Tel.:+86 10 59617612.
E-mail addresses: zengqi-1@163.com (Q. Zeng), mxl1123@vip.sina.com (X. Ma).

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1.2. Statistical analysis

The statistical analysis was performed using the SPSS 20.0 software package (IBM Corp., Armonk, NY, USA). Count data are expressed as frequency and proportion, and measurement data are expressed as median.

2. Results

2.1. Clinical manifestations

The children exhibited diverse clinical manifestations including cough, fever, dyspnea, detection by chance, chest pain, superficial tissue masses, vomiting, abdominal pain, backache, and choking on water (Fig. 1).

Of the 41 patients in our current series, PPB was initially misdiagnosed as pulmonary cystic disease in 6 patients (14.6%), tuberculosis in 1 (2.4%), pulmonary bullae in 1 (2.4%), a pulmonary abscess in 1 (2.4%), respiratory tract infection in 7 (17.1%), pleural effusion in 3 (7.3%), pneumothorax in 1 (2.4%), pneumothorax with pleural effusion in 1 (2.4%), mediastinal tumors in 10 (24.4%, including neuroblastoma in 2 and lymphoma in 1), pulmonary space-occupying lesions in 3 (7.3%), and thoracic space-occupying lesions in 7 (17.1%, including sarcoma in 1) (Fig. 2). According to these data, up to 51.2% of the patients were misdiagnosed as having nonneoplastic lesions at the first presentation, among which the misdiagnosis rate for type I, II, and III PPB at the first presentation was 100%, 58.3%, and 39.1%, respectively (Table 1).The interval from symptom onset to surgery/chemotherapy ranged from 5 to 210 days (median, 17.5 days). Because type I is the most atypical type, it has the longest interval from symptom onset to surgery/chemotherapy (60–210 days; median, 90 days).

2.2. Pathological types

PPB can be divided into three pathological types: type I (cystic), type II (solid/cystic), and type III (solid). Our current series included 5 patients with type I PPB, among whom the median age at diagnosis was 21 months (range, 8–24 months); 12 patients with type II PPB, among whom the median age at diagnosis was 37 months (range, 22–-112 months); and 23 patients with type III PPB, among whom the median age at diagnosis was 39 months (range, 19–156 months). 1 patient's pathological type was unknown.

2.3. Complications

The complications included pleural effusion ($n = 11$; closed thoracic drainage was required in 4 patients to relieve the symptom), pneumothorax ($n = 1$; closed thoracic drainage was required), pneumothorax with pleural effusion ($n = 2$; closed thoracic drainage was required), and pericardial effusion ($n = 1$).

2.4. Medical and family histories

Radiographic examination showed multiple cystic lesions in both lungs in one patient. One patient had undergone resection of an ipsilateral cystic adenomatoid malformation (segmentectomy) 3 years previously, and one patient had undergone resection of a contralateral congenital pulmonary airway malformation (CPAM) (type II, segmentectomy) 2 years previously. Both patients had a history of pneumothorax before the previous surgery, and one patient had undergone surgical treatment of ipsilateral pyothorax. The mother of one patient had thyroid nodules, the mothers of two patients had goiter, and the grandfather of one patient had pleural effusion.

2.5. Treatment

Twenty-five patients received postoperative chemotherapy and seven patients received preoperative chemotherapy (in two patients, surgery was performed after neuroblastoma chemotherapy, and the tumors shrank in both patients). Three patients underwent surgery alone (one patient discontinued chemotherapy after surgery and died 6 months later). Surgery combined with traditional Chinese medicine therapy was applied in one patient. Three patients were discharged to

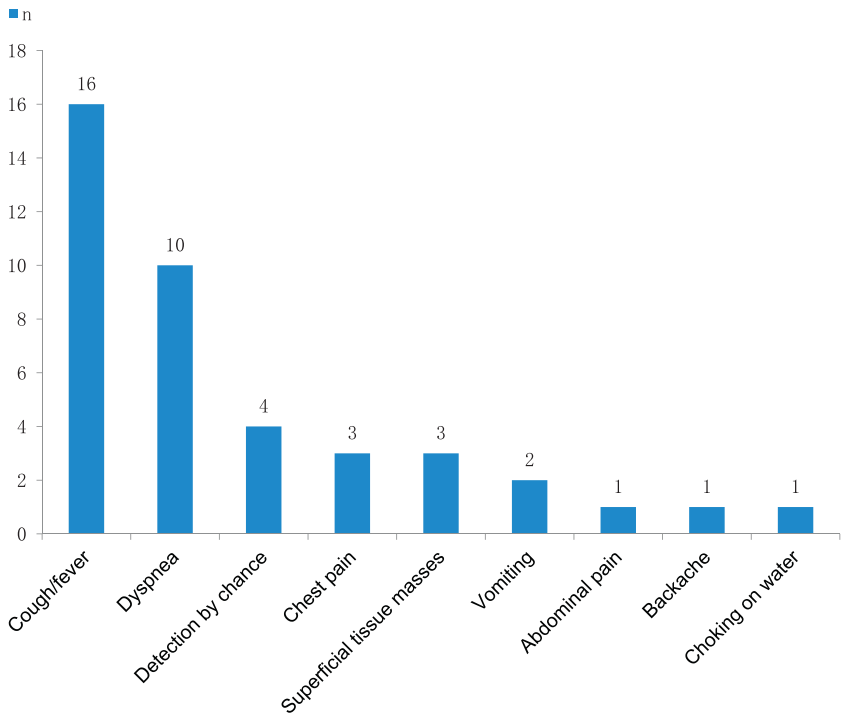

Fig. 1. Distribution of clinical manifestations.

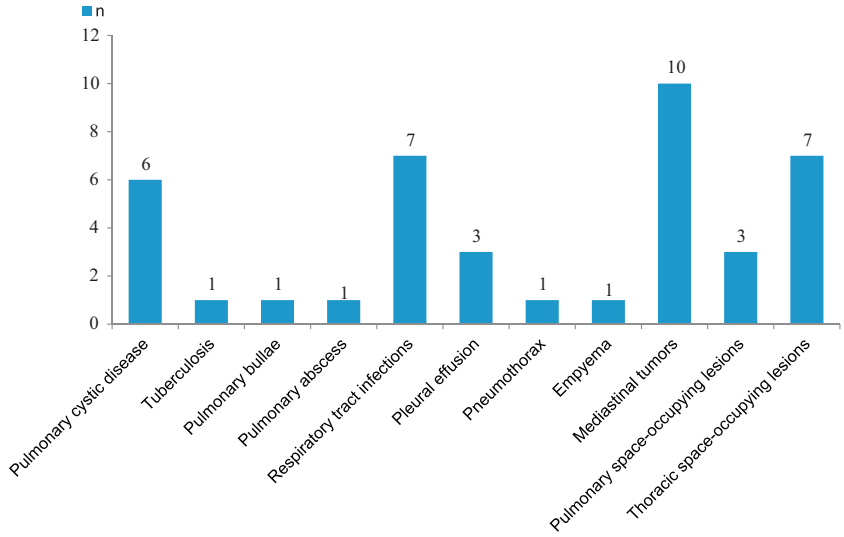

Fig. 2. Diagnoses at first presentation.

their own care (after biopsy), and two patients died early after the operation (after biopsy).

Surgical treatment was offered to 26 patients in our center, including 22 who underwent thoracotomy and 3 who underwent video-assisted thoracoscopic surgery. Conversion from video-assisted thoracoscopic surgery to open thoracotomy occurred in one patient because a substance resembling rotten meat was found after thoracoscopic resection of the mass; thus, thoracotomy was performed to resect the lung lobes. Among the patients who underwent thoracotomy, two underwent a second surgery for residual lesions after the operation in other hospitals. The tumors were 2 to 20 cm in size (median, 10 cm). The operation lasted 20 to 210 min (median, 95 min). The intraoperative blood loss volume was 2 to 500 ml (median, 45 ml). The intraoperative bleeding volume was 500 ml in one patient, in whom pleural decortication was performed.

The chemotherapy protocols were varied.

2.6. Sites of origination

PPB is a primary malignant intrathoracic neoplasm. It can arise from the lung, pleura, or both. In our series, 26 patients underwent surgical treatment, during which the tumors were found to arise from the lung lobes in 14 patients, from the pleura in 8, and from an unknown origin in 4.

2.7. Prognosis

Among the 41 patients in our series, 3 were discharged to their own care, 6 were lost to follow-up, and 32 were followed up. The follow-up duration ranged from 1 to 215 months (median, 57 months). By the end of follow-up, 28 patients had survived and 4 had died. The 5-year disease-free survival rate was 69.2%.

Table 1
Comparison of PPB case data of three pathological types.

Pathological type	Type I	Type II	Type III
Number of cases	5(12%)	12(29%)	23(56%)
Median age at diagnosis (m)	21 (8–24)	37 (22–112)	39 (19–156)
Misdiagnosis rate	100%	58%	35%
Interval from symptom onset to surgery/chemotherapy (d)	60–210	5–40	5–180
5-year survival rate	100%	67%	67%
5-year disease-free survival rate	100%	67%	56%
Follow-up duration	3–120	6–215	0.5–203
Lost to follow-up rate	0	25%	26%

3. Discussion

The prevalence of pulmonary tumors is low in children. The approximate ratio of primary pulmonary tumors to metastatic neoplasms and nonneoplastic lesions of the lung is 1:5:60, and 75% of primary lung tumors are malignant. [13] PPB is a relatively common pulmonary tumor in childhood. As a rare and aggressive primary malignant intrathoracic tumor in children, PPB can arise from the lung, pleura, or both. It accounts for 0.5% of all malignant tumors in children. [14] PPB was first reported in a study by Manivel et al. [1] in 1988. It is classified into three pathological types according to its morphological features: type I (cystic), type II (solid/cystic), and type III (solid).

The clinical manifestations of PPB are nonspecific. The main symptoms include fever, cough, and other symptoms of upper respiratory tract infection, which may also be accompanied by pleural effusion, pneumothorax, chest pain, and upper abdominal pain. Only when the tumor progresses to a certain extent will space-occupying manifestations develop, at which time patients can also exhibit symptoms such as anorexia, fatigue, and emaciation. The imaging findings of PPB are also atypical. As a result, the rates of missed diagnosis and misdiagnosis of PPB are high. The timing of surgery and standardized treatment is often delayed. In addition, the misdiagnosis rate differs among different pathological types of PPB. According to the literature, PPB may progress from type I to types II and III, the prognosis of which is worse [5–7]. Thus, early diagnosis and intervention are helpful to improve the prognosis of PPB.

PPB was classified into three pathological types by Dehner et al. [15] in 1995: cystic (type I), cystic/solid (type II), and solid (type III). Type Ir is a special type I PPB that presents as a regressed or abortive type I tumor without aggregation of subepithelial malignant cells. The age at onset and prognosis differ among these three pathological types. The pure cystic types (types I and Ir) have a better prognosis than do types II and III. [3–6] Types I and Ir have a higher 5-year survival rate (91%) and disease-free survival rate (82%), but they may progress to type II or III. Both types II and III are invasive malignant tumors with a low 5-year survival rate and disease-free survival rate (71% and 59% for type II and 53% and 37% for type III). [7] In our current series, five patients (11.9%) had type I PPB, among whom the median age at diagnosis was 21 months (range, 8–24 months) and the 5-year survival rate and disease-free survival rate were 100% and 100%, respectively; 12 patients (28.6%) had type II PPB, among whom the median age at

diagnosis was 37 months (range, 22–112 months) and the 5-year survival rate and disease-free survival rate were 66.7% and 66.7%, respectively; and 23 patients (56.1%) had type III PPB, among whom the median age at diagnosis was 39 months (range, 19–156 months) and the 5-year survival rate and disease-free survival rate were 66.7% and 55.6%, respectively. The increased age at diagnosis and number of cases and the decreased survival rate are consistent with the literature. The higher number of patients with type III PPB may be because of its insidious onset, atypical clinical symptoms, high rates of misdiagnosis and missed diagnosis, and long disease course (it is often found only after the failure of repeated medical treatment or the occurrence of compression symptoms from a space-occupying lesion). PPB may reportedly progress from type I to types II and III. [5–7] However, there was no evidence of disease progression in our series; this may be explained by the lower number of patients with type I PPB, the longer disease course, and the preexisting diagnosis of type II or III when the disease was confirmed.

Of all 41 patients, 3 discontinued treatment, 2 died early, and the remaining 36 were treated surgically. Of these 36 patients, 32 were treated by a combination of surgery and chemotherapy; at the time of this writing, 25 had survived, 1 had died, and 6 had been lost to follow-up. Only three patents were treated by surgery alone, among whom two survived and one died. One patient underwent surgery plus traditional Chinese medicine therapy and survived. Complete surgical resection played an important role in the prognosis of PPB. Therefore, if conditions permit, complete surgical resection of the lesion should be performed as soon as possible.

PPB in childhood is a highly invasive malignant tumor. Once diagnosed, it should be completely resected in the early stage. For children with huge unresectable tumors, puncture biopsy or surgical biopsy can be performed first. After the lesion has been pathologically confirmed, the size of the tumor can be reduced by four to eight courses of chemotherapy followed by radical surgery. The most effective surgical procedure remains controversial. Commonly used surgical procedures include cystectomy, segmentectomy, lobectomy, and total pneumonectomy. No study to date has investigated the correlation between the surgical procedure performed and the prognosis of PPB. Type I PPB can be easily confused with congenital pulmonary cystic diseases such as CPAM, cystic adenomatoid malformation, pulmonary sequestration, and pulmonary cyst. Thus, some cases of PPB are easily misdiagnosed before surgery. Enlarging the resection scope during surgery is not typically recommended. However, no report has described a second radical surgery after pathological confirmation of PPB that had been misdiagnosed before surgery. According to the literature, a negative surgical margin may be sufficient for type I PPB, but chemotherapy can reduce the risk of recurrence and improve the prognosis of children with type I lesions. Therefore, surgery combined with chemotherapy is recommended for all children with PPB. [12] In our series, all five patients with type I PPB were misdiagnosed as having pulmonary cystic disease before surgery. Four patients underwent segmentectomy during the surgery, and based on the postoperative pathology, they further received regular chemotherapy; no extended resection was performed. All of these patients survived with survival periods of 1, 11, 32, and 34 months. In contrast, complete lobectomy should be performed if possible for patients with suspected PPB before or during the operation.

Various chemotherapy protocols are available for PPB. We choose the protocols according to the clinical stage and pathological type of PPB. Treatment of type I PPB is dominated by surgery, and the recommended chemotherapy regimen is: vincristine, dactinomycin, and cyclophosphamide (VAC). Types II and III PPB require postoperative chemotherapy, and we use the protocol recommended by the International PPB Registry: ifosfamide, vincristine, actinomycin D and doxorubicin (IVADo). Two or three surgical probes are sometimes required, and local radiotherapy is required if residual lesions are identified postoperatively. Surgery combined with chemotherapy was the main treatment in our series, and the overall 5-year disease-free survival rate of patients with PPB was 69.2%.

In a large-sample study of 350 patients with PPB reported by the International PPB Registry in 2014, the 5-year survival rate and disease-free survival rate of patients with type I, II, and III PPB were 91% and 82%, 71% and 59%, and 53% and 37%, respectively. In our current series, the 5-year survival rate (100%, 66.7%, and 66.7%) and 5-year disease-free survival rate (100%, 66.7%, and 55.6%) of type I, II, and III PPB were higher than those of the international data, which may be explained by the small sample size in our study. In addition, some patients with PPB in our center (not those included in our current series) have achieved long survival after early treatment; the longest trackable survival was 240 months. Therefore, the posttreatment prognosis of PPB has been improved, and early active treatment should be performed after a diagnosis of PPB is confirmed.

The correlation between PPB and CPAM remains controversial. While some pathologists argue that there is no pathological similarity between PPB and CPAM, some clinicians have found a correlation between these two conditions in their clinical practice; however, there is no evidence of transformation between PPB and CPAM. In our current series, one patient had a history of surgery for ipsilateral cystic adenomatoid malformation of the lung, and another patient had undergone surgery for contralateral CPAM (type II). Imaging techniques do not readily distinguish type I PPB from type 4 CPAM, and some doctors believe that type 4 CPAM is actually type Ir PPB. However, this issue needs to be further investigated.

PPB is reportedly correlated with *DICER1* gene mutation and is often associated with other tumors. PPB is also a marker for familial syndromes. In 2009, Hill et al. [8] investigated the *DICER1* gene, which plays a role in lung development. They found that the PPB gene was located on chromosome 14q and that the loss of *DICER1* in the developing lung of mice resulted in cystic dilatation of the airways, damage of branching morphologies, and interstitial expansion similar to that in the early stage of PPB. In 2016, Faure et al. [9] proposed that PPB was a marker for *DICER1* PPB familial tumor susceptibility syndrome and that it was often associated with other tumors; knockout of *DICER1* caused fatal developmental stagnation, indicating that *DICER1* plays a key role in the development of vertebrates. The contributions of *DICER1* mutation to different tumors are variable. Up to 80% of patients with PBP carry a *DICER1* mutation. [11] *DICER1* gene mutation is evenly distributed among the three pathological types of PPB, and the *DICER1* gene status has no effect on the prognosis. Screening of *DICER1* mutant vectors for cystic PPB in children may lead to early detection of type I PPB, and subsequent surgical removal of this lesion may prevent its progression to types II and III, which are associated with higher morbidity and mortality rates. [12] However, the carcinogenetic mechanism of *DICER1* is not a complete loss of function, and some patients have no *DICER1* gene mutation. In our hospital, *DICER1* gene studies were performed in 12 children with PPB, and their parents and first-degree relatives were also tested for *DICER1* gene mutation. Among them, *DICER1* gene mutation was found in seven children, two of whom had pulmonary cysts before the diagnosis of PPB was confirmed. [10]

According to the literature [2], the risk factors for PPB include pneumothorax, bilateral or multiple pulmonary cystic lesions, and *DICER1* gene mutations; PPB can also be accompanied by pulmonary cystic lesions. In our current series, 14 patients also had pneumothorax and/or pleural effusion before surgery, 7 patients required closed thoracic drainage before surgery to relieve symptoms, 1 patient had multiple cystic lesions in both lungs on imaging examination, and 2 patients had a history of surgery for pulmonary cystic disease (ipsilateral in one patient and contralateral in the other); in addition, the mothers of 3 patients had thyroid disease. These findings are consistent with the risk factors for PPB in the literature. Whether surgical resection is required for asymptomatic pulmonary cystic lesions remains controversial. However, type I PPB is difficult to distinguish from pulmonary cystic lesions. In our series, all five patients with type I PPB

were misdiagnosed as having pulmonary cystic disease before surgery. Therefore, surgical resection is recommended for pulmonary cystic lesions.

In summary, PPB is a rare malignant tumor in children. The clinical manifestations of PPB are nonspecific, its misdiagnosis rate is high, and it has a poor prognosis. PPB may progress from type I to types II and III, the prognosis of which is worse. Risk factors for PPB include pneumothorax, multiple pulmonary cystic lesions, a family history of pulmonary cysts, a family history of PPB, and space-occupying lesions associated with DICER1 syndromes. Surgery combined with chemotherapy is recommended for all children with PPB. Early active treatment is recommended after a diagnosis of PPB is confirmed.

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