Original Article

Pleuropulmonary blastoma: A single-center case series of seven patients

M Masood Sidiqi, Ling Xu, Parshotam Gera, Colin Kikiros

From Department of Pediatric Surgery, Perth Children's Hospital, Australia

ABSTRACT

Introduction: Pleuropulmonary blastoma (PPB) is a rare and aggressive primary neoplasm of pleuropulmonary mesenchyme occurring in children. The International PPB Registry was established in 1988 to collect and assess data on PPB worldwide. **Objectives:** The objectives of the study were to assess the clinical characteristics, histopathology, genetic studies, management, and treatment outcomes of patients with PPB in our institution, and to compare with the published literature. **Materials and Methods:** We retrospectively reviewed the medical records of all PPB cases diagnosed at Princess Margaret Hospital for Children in West Australia over a period of 26 years (1990–2016). Their clinical characteristics, histopathology, genetic studies, management, and treatment outcomes were recorded. **Results:** Seven children (four boys and three girls) were treated for PPB at a mean age of 11.5 months (ranges 1 month–3.55 years). Histopathology showed type I PPB in five, type II in one, and type III in one. All seven patients underwent thoracotomy/lobectomy of the corresponding site. One patient required additional bladder resection for coexisting rhabdomyosarcoma. One patient was found to be positive for DICER1 gene mutation. Six patients received adjuvant chemotherapy with vincristine, Adriamycin, and cyclophosphamide regime, with the mean duration of treatment for five patients being 9.4 months excluding one patient who deceased without completion of chemotherapy. During a mean follow-up time of 9 years, the overall survival rate for this cohort was 85.7% (6/7). **Conclusion:** Our results are comparable to those reported in the literature. It is crucial for clinicians to consider PPB in the evaluation of patients presenting with a cystic lung abnormality, especially in cases with DICER1 mutation or a strong family history of unusual cancers.

Key words: Bladder botryoid rhabdomyosarcoma, Pleuropulmonary blastoma, DICER1

Pleuropulmonary blastoma (PPB) is an exceedingly rare intrathoracic neoplasm that arises from pleuropulmonary germ cells. Although PPB accounts for approximately 0.5% of all pediatric malignancies, it is the most common primary malignancy of the lungs in childhood [1,2]. It was first described as a distinct entity by Manivel *et al*. in 1988 as a tumor with a blastematous and sarcomatous pattern arising from cystic lung lesions [3]. Based on the histological and morphological appearance, it has been subdivided into three types. Type I lesions only have a cystic component, type II has both cystic and solid components, and type III is predominantly solid representing its most advanced stage [4]. Since 2006, a fourth type of PPB has been recognized known as "Type Ir PPB" or "Type 1-regressed PPB." These include cystic lesions similar to Type I PPB but without malignant cells and have been reported in individuals from infancy to adulthood.

Type I PPB is present in infants, as a multilocular lung cyst, and can easily be misdiagnosed with congenital cystic adenomatoid malformation (CCAM). It is diagnosed by histology of the resected specimen showing immature interstitial mesenchymal and epithelial components, resembling fetal lungs [5]. Type I lesions have a better prognosis and may either spontaneously regress (type Ir PPB) or advance to types II or III PPB if untreated. These advanced types carry an increasingly worse prognosis and patients may present at diagnosis with distant metastases, most commonly in the brain, bone, and liver [1,6].

PPB can present in a wide variety of ways depending on the pathological stage. Type I PPB can be found incidentally on chest X-ray (CXR) or in children with mild respiratory distress. Patients with more advanced PPB may exhibit fever, cough, chest pain, malaise, or even present with a pleural effusion [7]. Due to the rarity and its non-specific symptoms, PPB is usually not considered in the differential diagnosis, often leading to a delay in definitive treatment and a poor prognosis.

PPB is now being recognized as a component of a familial tumor predisposition syndrome and it has been reported that up to 25% of all PPB patients were associated with a constitutional or familial basis in their occurrence [4,8]. In particular, germline mutations in the DICER1 gene were demonstrated to be associated

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Correspondence to: Dr. M Masood Sidiqi, Royal Perth Hospital, Perth, Australia. E-mail: masood.sidiqi@health.wa.gov.au

with an increased risk of neoplastic lesions, including PPB, botryoid embryonal rhabdomyosarcoma, cystic nephroma, thyroid carcinoma, ovarian Sertoli-Leydig cell tumors, and others [9,10].

Management of PPB is multimodal and includes surgery, chemotherapy ± radiation therapy. After complete surgical resection, subsequent treatment depends on pathological determination of type. Recent studies have suggested a role of adjuvant chemotherapy post-surgical excision to improve overall survival and reduce recurrence [1]. The prognosis of patients with PPB is improving due to increased awareness of the disease and development of standardized chemotherapeutic protocols through the International PPB Registry (IPPBR). Despite great advancements in medical imaging resulting in PPB being diagnosed at an earlier stage, it is still a rare condition with a limited number of studies assessing survival outcome of current treatment. The purpose of this study is to discuss our institution's experience with the diagnosis, treatment, and management of PPB and compare this data with those reported in the medical literature.

MATERIALS AND METHODS

After obtaining Institutional Ethics Approval, we retrospectively reviewed the medical records and pathology results of all PPB cases diagnosed at Princess Margaret Hospital for Children in Western Australia over a period of 26 years (1990–2016). Clinical presentation, antenatal history, family history, perioperative imaging, pathologic summaries, genetic studies, treatment protocols, and outcomes were reviewed and are presented here.

RESULTS

During the 26-year period, a total of seven children (four boys and three girls) were treated for PPB at our institute, all were diagnosed after birth. Their mean age of diagnosis was 12±14.15 months (range – 1 month–3.55 years), and the median age was 6 months.

All seven patients were found to have persistent respiratory symptoms including increased respiratory effort/distress, and three patients also had recurrent upper respiratory tract infection unresponsive to antibiotics. One patient had a previous diagnosis of asthma 3 months before the diagnosis of PPB with multiple presentations for persistent tachypnea and wheeze complicated by apneic episodes from the neonatal period. One patient was found to have spontaneous pneumothorax on CXR. Overall, all patients were diagnosed initially by abnormal CXR, four of the seven patients had pre-operative computed tomography (CT) chest, and one patient also had pre-operative magnetic resonance imaging (MRI).

Three patients had lesions found on the left lung (two upper and one lower lobes) and on the right for the remaining four patients (two upper, one middle, and one lower lobe). Local invasion was seen in three patients (two pleura and one sub-pleural space). All seven patients underwent thoracotomy/lobectomy of the corresponding site. Surgical margins varied between 1 and 26 mm (five patients with unclear surgical margins as per histopathology).

Patient 4 in the study was found to have type III PPB. CT showed right upper lobe consolidation with calcification, extending past mediastinum with concern regarding middle lobe involvement and almost total collapse of the right lower lobe. Initially, planned for the right upper lobectomy, the tumor appeared to be encircling the carina around the right upper lobe bronchus intraoperatively. This was subsequently changed to total right pneumonectomy by dividing the right main pulmonary artery and veins (flush with atrium and inside pericardium) and then stapling the atrium. There were no perioperative complications with a good recovery. The patient then received vincristine, Adriamycin, and cyclophosphamide (VAC) adjuvant chemotherapy with multiple admissions for febrile neutropenia and deceased 6 months post-diagnosis from multiorgan failure secondary to sepsis.

Patient 2 presented with frank hematuria and respiratory symptoms and he was found to have an irregular soft-tissue mass on ultrasound scan of the pelvis. Further, CT investigation showed polypoid bladder tumor and right upper lobe lung cyst with moderate mass effect (Fig. 1). Biopsy of the bladder lesion showed botryoid appearance and was later confirmed as Stage 2 Group 2 embryonal rhabdomyosarcoma of bladder. The patient underwent right upper lobectomy and bladder tumor resection, receiving VAC adjuvant chemotherapy for 12 months and radiotherapy for bladder rhabdomyosarcoma. He was followed up in clinic for annual review and assessment for total of 12 years with no evidence of recurrence.

The remaining five patients presented with types I and II PPB with no evidence of extrapulmonary involvement. One patient was found to be positive for DICER 1 gene mutation. All seven patients underwent subsequent resection, as indicated in Table 1, with post-operative intercostal catheter and routine intensive care unit admissions for ventilation support. No surgical complication was recorded in any of these patients.

Six out of the seven patients received adjuvant chemotherapy with VAC regime, the duration varying depending on subtype, with no cases of recurrence (Table 2). The mean duration

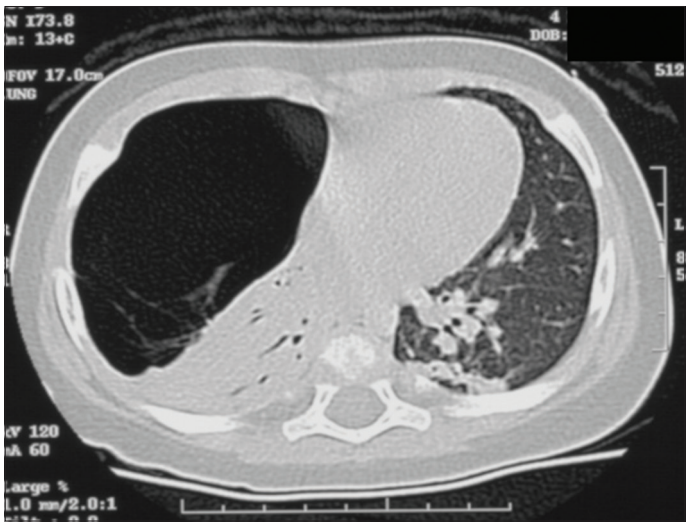

Figure 1: Right upper lobe lung cyst with moderate mass effect

Table 1: Details of operative procedures

No.	Age	Gender	Operation	Metastasis	Type	DICER 1
1	16 months	M	Left lower lobectomy	Nil	I	NA
2	6 months	M	Right upper lobectomy	Nil	I	+
3	5 months	M	Transbronchial decompression then right lower lobectomy	Nil	II	NA
4	42 months	F	Right upper lobectomy → Right total pneumonectomy	Nil	III	NA
5	12 months	F	Cystectomy, left upper and partial left lower lobectomy	Nil	I	NA
6	11 weeks	F	Left upper lobectomy	Nil	I	-
7	4 weeks	M	Right cystectomy and middle lobectomy	Nil	I	-

Table 2: Pathology, adjuvant therapy, and outcome

Patient	Type	Other treatment	Duration	Outcome	Follow-up
1	I	None	N/A	No evidence of disease	6 years
2	I	VAC, radiotherapy	12 months	No evidence of disease	12 years
3	II	VAC	6 months	No evidence of disease	5 years
4	III	VAC, Mesna	N/A	Died of disease	<1 year
5	I	VAC	6 months	No evidence of disease	13 years
6	I	VAC	12 months	No evidence of disease	5* years
7	I	VAC	11 months	No evidence of disease	2* years

V: Vincristine, A: Actinomycin D, C: Cyclophosphamide. *Indicates in active follow-up at the time of the study, VAC: Vincristine, Adriamycin, and cyclophosphamide

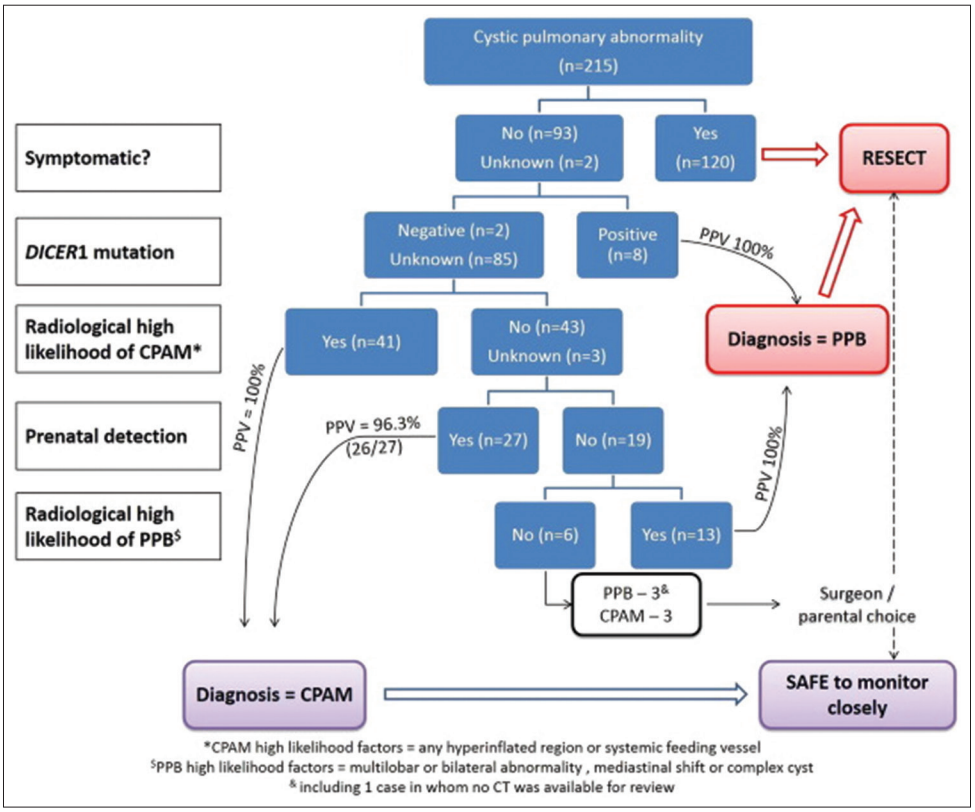

Figure 2: Diagnostic algorithm proposed by Feinberg *et al*

of chemotherapy for five of the seven patients was 9.4 months excluding one patient who did not receive adjuvant chemotherapy and one patient that deceased without completion of chemotherapy. The number of cycles ranged from 6 to 16 months. A recurrent simple cyst was found and excised in patient 5, 9 months post-initial surgical resection for PPB; however, there was no histological or radiological evidence of PPB recurrence.

During a mean follow-up time of 9 years, the overall survival rate for this cohort was 85.7% (6/7). One patient deceased 8 months post-surgery and two patients still remain in the process of active follow-up. One patient was still receiving ongoing chemotherapy at the time of the study. Among the surviving patients (four boys and two girls, all under 1 year of age), the histological type was I in five patients and II in one patient. All six

patients underwent surgical and chemotherapeutic treatment and all are alive and without recurrence 2–22 years after treatment.

DISCUSSION

The previous studies suggested that patient outcomes correlate with the age and tumor type at presentation. Current data from the PPB registry suggest that the mean age of presentation is 10, 35, and 41 months for types I, II, and III, respectively [6]. Our study showed a similar trend with mean age of presentation for type I being 7 months, type II at 5 months, and III at 42 months. According to the data obtained by Messinger *et al*., a study with 350 cases of PPB by the IPPBR, the estimated survival is 91% (type I) and 71% (type II) and 53% (type III) [1]. The number of patients in our cohort was small, and therefore, insufficient for statistically significant conclusions, the survival rates were similar to the aforementioned literature.

During the past decade, more focus has been made on exploring the familial/genetic aspect of PPB. Previous large series suggests that approximately 20% of children with PPB have a family history of neoplasia; especially, those who present with cystic nephroma of the kidney and rhabdomyosarcoma [4,8]. Hill *et al*. identified the role DICER1 gene mutations in familial PPB by mapping locus to chromosome 14q in a family-based linkage study [11]. Up to 65% of children diagnosed with PPB express a germline mutation of this gene [1,7,12]. Therefore, the current data suggest a strong role of genetic testing for DICER1 gene mutation in those diagnosed with PPB. It is important to note that a small percentage (~10%) of patients may exhibit a mosaic pattern of mutation or have the mutation solely in the tumor tissue, and hence, workup should not be limited to germline sequencing [7].

In our study, three patients underwent genetic testing with one patient positive for DICER1 gene mutation. Interestingly, the patient who was found to be positive for DICER1 mutation also presented with coexisting bladder rhabdomyosarcoma picked up by frank hematuria. A previous study by Boman *et al*. identified eighteen patients with PPB associated with 20 renal tumors either in patient themselves or family members. Approximately 9.2% of 152 registry-reviewed PPB cases also had coexisting cystic nephroma or related tumors [13].

Detecting germline DICER1 mutations in a child may help early identification of malignancy in young family members through screening and educating families and their treating physicians about early signs of disease (e.g., androgenic symptoms in Sertoli-Leydig cell tumor, thyroid nodules, etc.) [10] However, since the conditions associated with PPB are diverse and may emerge in the first 10–20 years of life, routine screening of family members remains controversial. Unless a strong family history exists, the IPPBR generally believes that it is too burdensome on families to embark on such screening [14]. As further data are collected on PPB patients and families, it may be possible to define further the ages at onset, frequency, and spectrum of PPB-associated conditions for which screening of family members might be appropriate [13]. There is still much to be learnt about the implications of DICER1 mutations for PPB and the associated conditions, and additional patients and families are currently under study by the PPB registry.

Despite its rarity, PPB should be kept in the differential diagnosis of all children who present with respiratory distress along with cystic or solid masses. CT represents the most common used diagnostic modality; although for patients with type II or III PPB, the IPPBR recommends a brain MRI and bone scan at diagnosis to evaluate the presence of metastases. MRI can also show the imaging features of solid enhancing nodules inside fluid-filled cavities, a mass causing lung compression, mediastinal shift, frequent pleural effusion, and chest wall invasion [15]. The CXR and CT reports in our study suggested a differential diagnosis of CCAM. One patient (patient 4) had pre-operative histopathology diagnosis of PPB based on biopsy aspiration. Given the difficulty to distinguish CCAM (types I and IV) and PPB type I, Feinberg *et al*. proposed a diagnostic algorithm for the management of congenital cystic lesions based on symptoms, germline mutation of DICER 1 gene, and radiological features (Figure 2) [16,17]: Despite its usefulness, the gold standard for diagnosis of PPB ultimately lies on pathological findings of the surgical specimen.

Early evaluation and treatment significantly impacts the prognosis of patients with PPB, as removal of tumor before histological progression correlates with significantly improved outcomes [7,9,10,14,16]. Progression of histological type before surgical resection significantly diminishes 5-year overall survival, from 85% to 90% for type I to 71% for type II and 53% for type III [1,7]. Complete surgical resection is the primary treatment goal when managing children with PPB. The role of chemotherapy in patients with type I PPB remains unresolved, however for types II and III, recent studies suggest increased survival rates and a reduction in recurrence [1]. Due to its rarity, most studies have presented data with small sample sizes, which prevented the development of accurate diagnostic algorithms and an evidence-based approach to treatment. The small number of patients in our study does not draw statistically significant conclusions, but will contribute to overall statistics in the literature which may help to improve the diagnosis and treatment of the disease in the future.

CONCLUSION

It is important for medical practitioners to consider PPB in the evaluation of patients presenting with a cystic lung abnormality, especially in cases with DICER1 mutation or a strong family history of unusual cancers. Given that it is an exceedingly rare malignancy, it requires a high index of suspicion. From this retrospective analysis, we concluded that our results seem comparable to those reported in the literature and that early diagnosis, surgical resection with clear margins, and adjuvant chemotherapy are critical to improve survival outcomes for this rare but potentially lethal disease.

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