DOMESTIC COLLABORATION IN TREATMENT SUCCESSFULLY A PATIENT WITH PLEUROPULMONARY BLASTOMA TYPE II IN VIETNAM

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Abbreviation

PPB	Pleuropulmonary blastoma
CCAM	Congenital Cystic Adenomatid Malformation
CT	Computerized tomography
IVADo	Ifosfamid, Vincristin, Actinomycin, Doxorubicin
IVA	Ifosfamid, Vincristin, Actinomycin

ABSTRACT

Pleuropulmonary blastoma (PPB) is a rare malignant tumor in childhood cancer. This type of tumor is difficult to identify and can easily be misdiagnosed. The International PPB protocol is a complicated and aggressive protocol. It is not easily applicable to developing countries where hospitals do not have enough resources. We are presenting the first case successfully treated in Vietnam, using limited medical resources. The patient (22 month old, male) was diagnosed with congenital cystic adenomatoid malformation in his 1st hospital admission. After 6 months of onset, the patient was diagnosed with PPB type II in 4th hospitalization following analysis of a lung CT scan and a pathology report. After the aggressive chemotherapy regimen, patient had two episode of severe neutropenia and infection but luckily recovered. The patient received chemotherapy and surgery treatment at our hospital, but received radiation under general anesthesia and rehabilitation therapy to improve respiration at another hospital over 600 km away. It has been 1.5 years after entering remission, and he is starting kindergarten.

***Conclusion:** Lungs CT scan and pathology should been analyzed carefully to avert misdiagnosis PPB in patients with cyst or mixed cyst and solid part in lungs. All cases of suspected PPB send*

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to the free central pathology review. Two factors important to the successful application of the protocol are good supportive care and the multidisciplinary collaboration between medical facilities to provide proper resources during treatment. We hope to recreate more successful outcomes not only in Vietnam but also in all developing countries.

1. INTRODUCTION

Pleuropulmonary blastoma (PPB) is a very rare malignant disease in childhood cancer. The tumor is derived from the pleura or lungs. This primary tumor occurs mainly in children under 6 years old [1]. Diagnosis of this tumor is difficult both by the image and by pathology because of its similarity to other diseases. PPB is classified into three groups. Type I (cystic form) is similar to congenital cystic adenomatoid malformation (CCAM) [2]. This type is commonly seen in infants and has a more favorable prognosis than type II and III. Type I can be treated successfully with surgical resection, however it can relapse and require neoadjuvant chemotherapy. In contrast, type II (mixed form) or type III (solid form) are aggressive diseases with poor prognosis. Type II and III PPB have metastatic potential to the brain, the bone, and in some cases, to the liver. Both these types need multidisciplinary therapy including surgical resection, intensive chemotherapy and radiation if it is available [3]. Effective treatment plans are aggressive and require hospitals with all the capability to perform all the above. The International PPB protocol is only easily applicable in developed countries, as hospitals in developing countries often lack all the facilities required.

2. CASE REPORT

TDA, a 22 month-old male child was admitted to our hospital, Vietnam National Children's Hospital, in June 2017 with dyspnea. His previous medical history was unremarkable, and his family medical history shows that there were no diagnoses of cancerous or tumor-like symptoms for at least three generations. On examination, patient's breath sounds were diminished in the right lung zone. Chest X-ray showed pneumothorax. Chest CT scan showed air in the right chest wall, pneumothorax and a large lobular cystic mass in right lung (Figure 1). He was diagnosed with CCAM. In October 2017, he underwent a right thoracotomy to resect the cysts in the lower right lobe and to drain the air. During the surgery, our surgeon described the right pleural cavity as clean, non-sticky. The lesion was a large cystic mass (4x6 cm) including many small cysts of 1x2 cm in the right lower lobe.

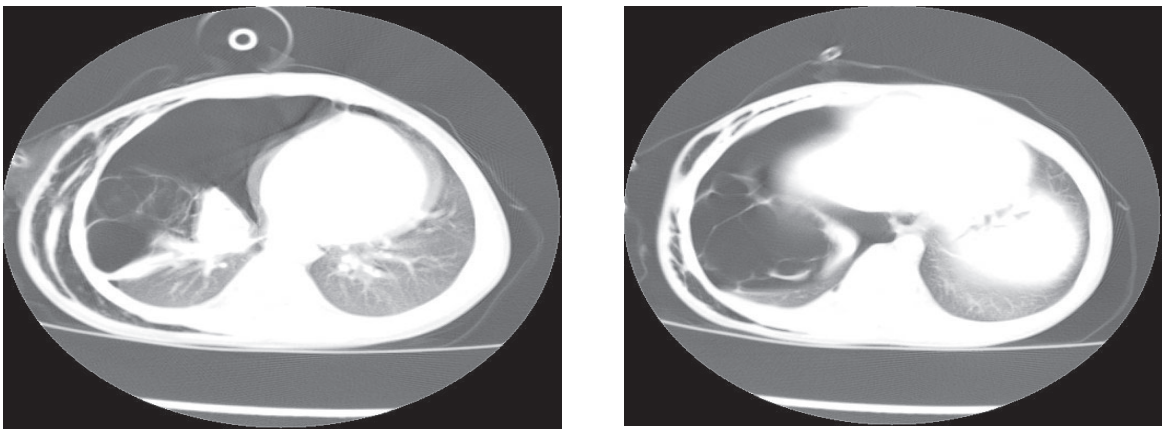

Figure 1 (A-B). Chest CT on admission (June 2017)
(1A) Air in the right pleural space (black arrow), in the subcutaneous tissue (white arrow);
(1B) Lobular cystic mass in the right lung (black arrow)

In November 2017, the patient was admitted to the respiratory department of our hospital (his 3rd hospitalization) for recurrent dyspnea. Lung CT scan showed fluid and small nodule in the right pleural space (Figure 2). He underwent a 2nd thoracotomy to solve the thick sticks of sludge in the right pleura. Our surgeon detected that the right pleural cavity was sticky with many bloody fluid and blood clots, the right pleura had some bleeding points, and the right lower lobe's surface had abscesses - assumed to be lesions ruptured into the right pleural cavity. The result of pathology had been omitted. He recovered and was discharged.

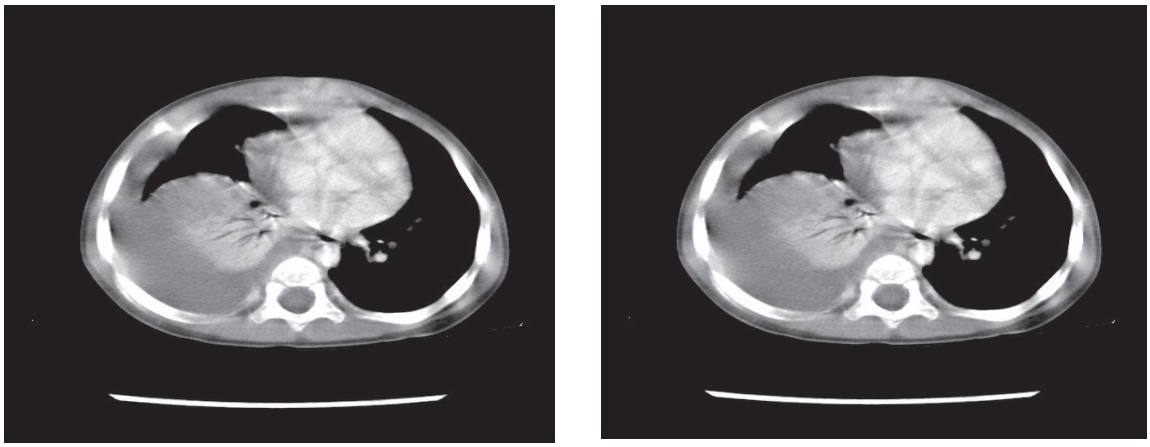

Figure 2 (A-B). Chest CT of the 1st recurrent episode (November 2017)
(2A) Fluid in the right pleural space (black arow); (2B) Small nodule in the right pleural space (black arrow)

In December 2017, his right hemithorax gradually distended. He had difficulty breathing again. He was readmitted to the Intensive Care Unit (fourth hospitalization) due to bleeding pleural effusion. The chest CT revealed a large solid mildly enhancing mass in the mediastinum and the right hemithorax, which shows the pleural thickening (Figure 3).

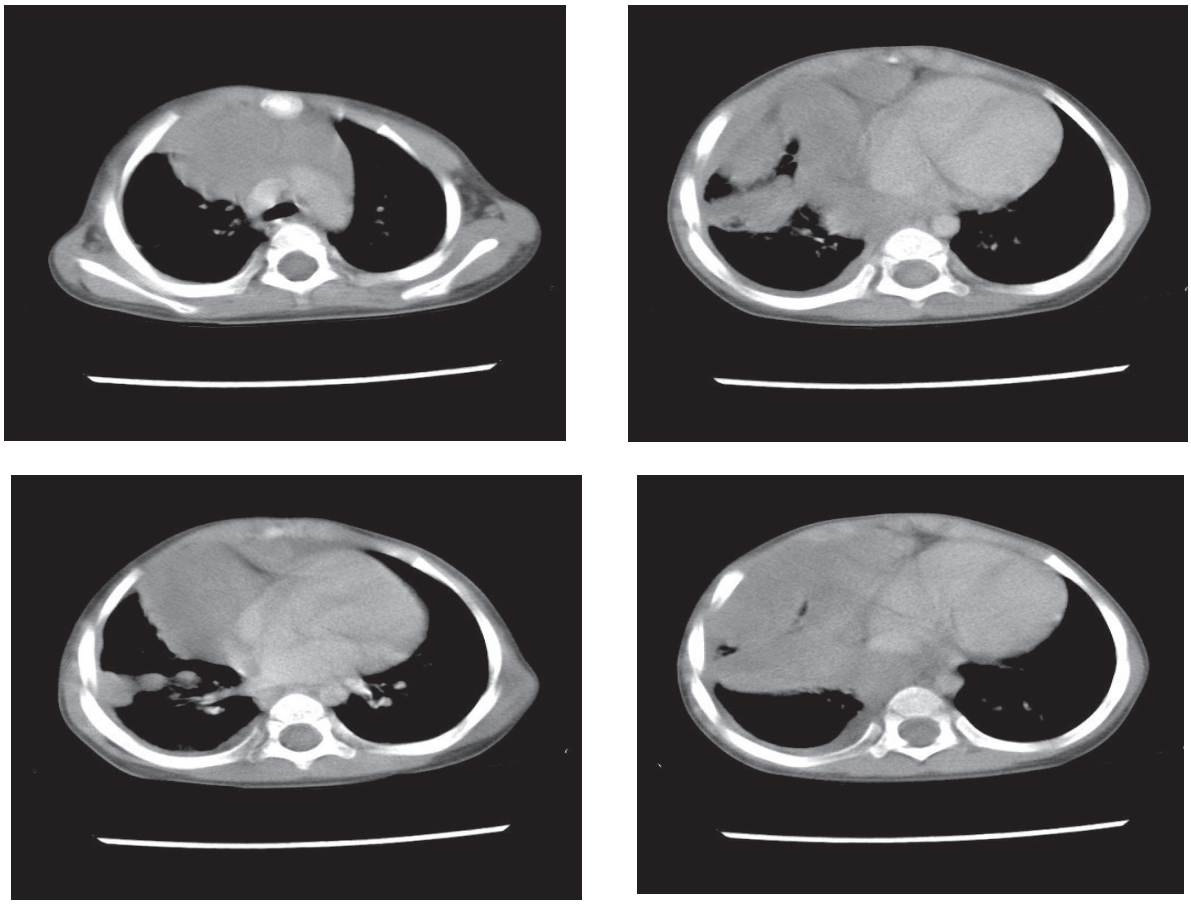

Figure 3 (A-D). Chest CT of the 2nd recurrent episode (December 2017)
(3A) Mediastinal mass (black arrow); (3B) Pleural mass in right hemithorax (black arrow); (3C) small nodule in the interlobar fissure (curve arrow); (3D) Right pleural thickening (black arrow)

The result of pathology in previous month revealed suspected PPB and needed more immunohistochemistry. The core needle biopsy under the ultrasonography was performed at this time. Microscopy showed the solid and cystic areas that contained blastema and spindle cell sarcoma features (Figure 4). Immunohistochemistry staining, the tumor cells were positive for Myogenin (10%), Desmin (focal), Vimentin, Ki67 (10%), SMA (focal) and negative for LCA, EMA. The tumor was diagnosed pleuropulmonary blastoma, type II and had been reviewed by experienced pathologists in Vietnam.

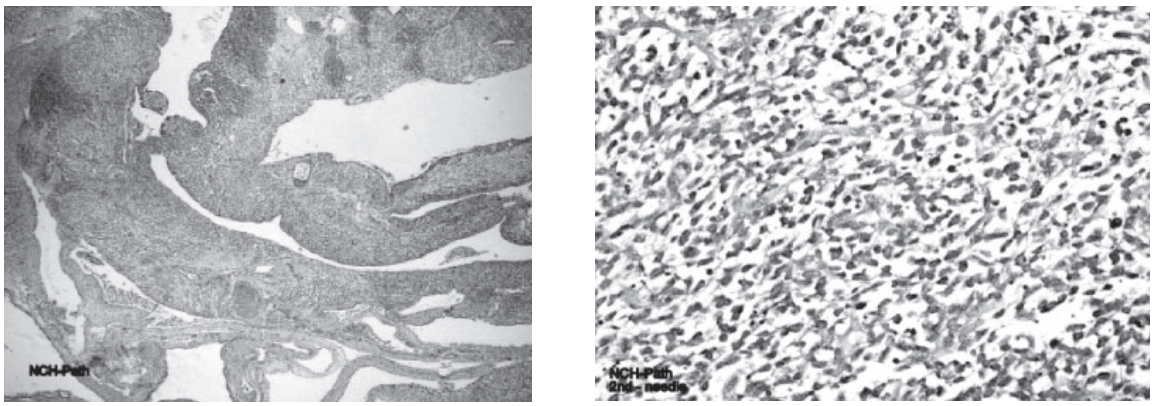

Figure 4 (A-B). A boy 27 months old, PPB type II, Hematoxylin and Eosin (HE) staining
(4A) The cyst (stars), cystic wall (arrow) contained clusters of tumor cells, and bleeding area;
(4B) Solid component shown high cellularity of tumor cells

There was no evidence of metastasis. Brain CT scan, bone scintigraphy, abdominal ultrasonography and CT scan revealed no abnormalities. Complete blood count, liver, and kidney function were normal. Our genetic lab does not have the primer to detect the DICER1 mutation.

He was diagnosed with PPB type II, stage III and prescribed with a multidisciplinary treatment based on the International PPB protocol from 5 January 2018 to 4 November 2018. Chemotherapy included first four courses of I^2VADo and subsequent eight courses IVA regimen. Cumulative dose of Doxorubicine was 240 mg/m^2, and of Ifosphamide was 48 g/m^2. The I^2VADo regimen included Ifosfamide 3 g/m^2/day and Doxorubicine 30 mg/m^2/day for two consecutive days, Actinomycin D 1.5 mg/m^2/day for day 1, and Vincristine 1.5 mg/m^2/day for day 1. Vincristine weekly was used for the 7 initial doses. The IVA regimen does not have Doxorubicin. All of courses started when his absolute neutrophil count (ANC) ≥ 1, platelet ≥ 100 and infectious disease recovered. The interval of first four courses of IVADo, after IVA 8, 10, 11 were 4 weeks, and longer than planned. Duration from IVA9 to IVA10 was 6 weeks because he was referred to other hospital for radiation treatment. He had two episodes of severe infectious conditions. The first after the completion of the first course of chemotherapy, dyspnea resolved completely but he still had a high fever, severe neutropenia, influenze virus B, and suspected septicemia. He was then transferred to the isolation room and given combined antibiotics (Meronem, Tobramycin), antifungi (Amphotericin B), antivirus (Tamiflu) and Granulocyte colony-stimulating factor (G-CSF). He recovered after 14 days. After the second course, his mass size reduced remarkably.

Surgical resection of residual tumor was performed after the third IVADo courses in March 2018. The surgical report showed pleural thickening, stickiness, and lesions multifocal yellow, solid masses. The tumors concentrated on some large cluster, even in the fissure. The surgeon was not able to totally resect the tumor to achieve negative margin. The patient had the second severe infection after the tumor resection surgery. He was on antibiotics combine for 10 days and ultimately recovered.

In 2018, there was one hospital in Vietnam,

Hue Central Hospital, which had the capacity to provide radiation treatment for small children under 5 years old. Therefore, at week 28 of regimen, in August 2018, the patient underwent thoracic irradiation under general anesthesia at Hue Central Hospital (Figure 5). The total dose was 45Gy in 30 fractions. Radiation plan included 15Gy (1.5Gy/ fraction) at whole right lung and chest wall by 3D technique and boost up to 45Gy (1.5Gy/fraction) at residual tumor by intensity-modulated radiation therapy (IMRT). During radiation, the patient was simultaneously receiving chemotherapy (Ifosfamid and Vincristine) with our instruction detailed.

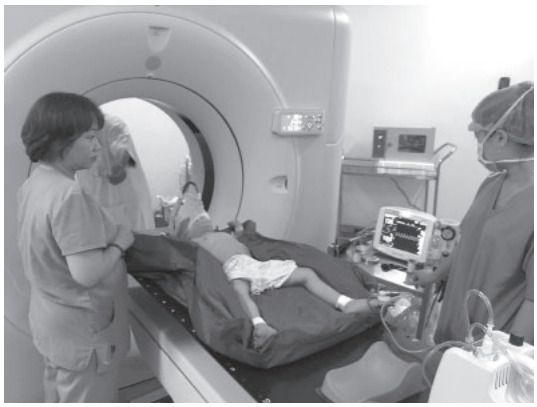

Figure 5. CT simulation under general anesthesia at Hue Central Hospital

After radiation, he went back to our hospital and continued IVA (Ifosfamid, Vincristin and Actinomycin D) until this regimen was completed. He ceased treatment on 4 November 2018. However, on this day, the patient had tachypnea, while his SpO2 was normal there was poor right lung sounds (no crackles), and the right chest was thinner than left. Cardiac ultrasound was normal. There was a patchy opacification of right lung and the cardio mediastinal silhouette was shifted to the right in the lung X ray. CT scan revealed a consolidation of the right lung, decrease of the right lung volume, trachea and bronchial tree were clear, and the left lung was well inflated and clear. No mediastinal lymph node or mass. The patient had suspected lung lesions due to radiation. The patient received IV Methylprednison 4mg/kg/day for a week and later 1 mg/kg/day for 10 days. After treatment by Corticosteroid, his clinical condition improved, breathing rate was normal and his lungs CT scan revealed reduction in lesion consolidation. Patient possibly suffered from right pulmonary fibrosis after thoracic irradiation. The patient attended physical therapy but our hospital didn't have the proper chest protection equipment. He went to Hue Central Hospital for the second time to wear this equipment in their Rehabilitation department (Figure 6). The patient followed this rehabilitation treatment in our care every month for the first year following the termination of his cancer treatment and is now on a bimonthly schedule for the second year.

Figure 6. Patient wearing chest protecting equipmen

Brain MRI for controlling metastasis had been performed after ceasing treatment 1 year and the result was normal. Although the patient has atelectasis of the right lung after radiation (Figure 7 and Figure 8) and sometime had mild pneumotitis, he still has complete remission. He is now going into kindergarten, and is proving to be an excellent student (Figure 9).

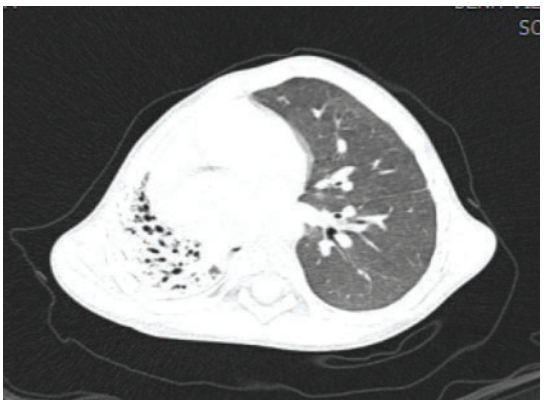

Figure 7. Chest CT scan in 24 October 2019 (atelectasis of the right lung: black arrow)

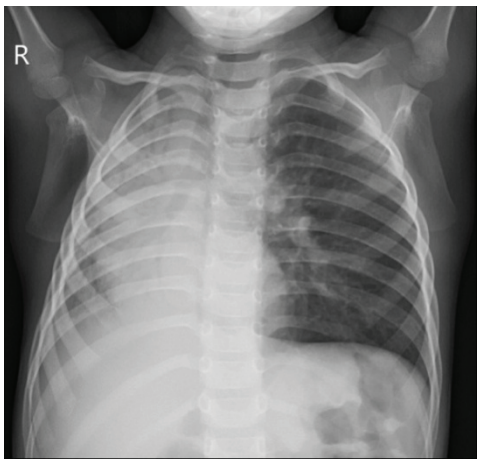

Figure 8. Chest X- ray in 6 January 2020 (opacification of the right lung after radiation: black arrow)

Figure 9. He studies very good

3. DISCUSSION

Pleuropulmonary blastoma is a malignant primary intrathoracic tumor rarely seen in children, accounting for under 1% of primary tumors in the lungs in children less than 6 years old [3]. Every year, our department has over 300 new cases, but for the last 10 years, we have only registered 5 patients with PPB: 1 patient (TDA) is alive, 2 patients (B and C) died due to toxicity, 1 patient (D) died due to progressive disease, and 1 patient (E) refused treatment. We sent the samples of the first case we encountered (patient B) to Washington University in St Louis, Missouri, USA. At that time (June 2011), Dr Louis P. Dehner reviewed pathology and Dr Yoav Messinger, the director of International PPB Registry, consulted to help us treat patient B with PPB type III. Patient B ultimately died due to toxicity. We have failed in 4 cases and this is the first case of successful treatment in our hospital, as well as in the country of Vietnam.

PPB is a dysembryonic neoplasm of thoraco - pulmonary mesenchyme, which arises from either lungs or pleural surface, or even both. Histopathology of pleuropulmonary blastoma tumors are divided into 3 types: type I cystic form (14%) observed in infants and young children less than 10 months old, type II mixed (cystic/ solid) form (48%) observed in children older than 2-3 years old, type III, completely solid (38%) observed older children older than 4 years old [2]. Prognosis deteriorates from type I (cystic form) to type III (solid form) [3]. A germline mutation in DICER1 is the genetic cause in the majority of PPB cases [5]. During the initial admission, the patient's chest CT scan revealed a tumor dominantly cystic. The lesion was similar to CCAM. At 2 years old, this age is consistent with the study of Messinger YH et al., which shows

that more than 97% of tumors in children under 3 years old are type I and in children under 4 years old are type II [2]. This was the cause of the initial misdiagnosis.

At the 2nd and 3rd hospitalization, clinical manifestation of this case was not specific: dysnea and distention of one hemithorax. He was admitted to the respiratory department with diagnosis of benign disease. He had complications of a cystic tumor rupture into the pleural cavity causing pneumothorax. According to Messinger YH et al., up to 30% of cases of PPB type I have complications of pneumothorax [2]. Moreover, the clinician in the respiratory department had omitted pathology results and patient had been late diagnosed.

At the fourth time of admission, when the disease recurred he has pleural hemorrhage and chest distention. The tumor represented the common forms of PPB with mixed form, large size 8x9cm. According to Messinger YH, up to 55% of these tumors are larger than 5 cm [2]. This tumor had dominantly cystic but a little solid component. Cystic part was lobulated with thin walls which were similar to CCAM. This solid part was hypodense with a very subtle enhancement and located in periphery of the cysts. This solid part helped to differentiate from CCAM which was purely cystic. However, this solid part was occasionally missed or misdiagnosed to consolidation of nearby lung. After 6 months, the disease recurred and the tumor progressed causing chest distention. This time the chest CT scan revealed the recurrent lesions were was completely solid, which was differed from the original primary tumor [1,2]. All authors mentioned the transition of type I to form II/III when relapse [3,4].

As reports published before, patients only usually seek treatment after tumors were already large and cause complications. Core needle biopsy should have been performed sooner. Due to various pathology characteristics of PPB, it is required that the samples were taken from different locations on the tumor which can be performed only by core needle biopsy [3]. We reviewed the previous pathology and the new pathology to give definite diagnosis for this case. There are two indicators that clinicians should evaluate to ensure that there is not a misdiagnosis in the future. First, patients with recurrent pneumothorax should be referred to experienced radiologists to carefully analyze characteristic of lesions, location, size in lung CT scan. Second, clinicians have to check pathology results when patient are discharged even if they were diagnosing benign disease and to consult experienced pathologists to find any malignant lesions. We now are in contact with some free central pathology review as the KK Children and Woman Hospital in Singapore, and St Jude Children's Research Hospital in the USA. Moreover, the International PPB/DICER1 Registry provides free central pathology review for any suspected case of PPB or other DICER1-related cancer. We, clinicians and pathologists in our hospital, will send samples of any cases of suspected PPB which include some cases of CCAM, congenital pulmonary airway malformation (CPAM) to review. This resource will hopefully avert early misdiagnosis and reduce risk for progression of disease.

Our patients with PPB had been treated by International PPB regimen with IVADo, IVA, resection tumor and radiation lungs under general anesthesia. Recent findings suggest that 5-year progression free survival (PFS) is significantly improved ($p < 0.01$) by doxorubicin containing

regimens such as IVADo [5]. This regimen is complicated and aggressive chemotherapy therefore patients always risk developing with severe toxicity. Hospitals which diagnose and treat children with cancer in Vietnam as well as in other low-income developing countries do not have enough resources or adequate facilities, such as the pediatric intensive care unit, pediatric radiation unit, specialist oncologist surgeon, and supportive care. Although we have some experience in treating children with rhabdomyosarcoma, IVA regimens are less toxic than IVADo regimen.

The first case with PPB type III (Patient B) in our hospital was treated with two courses of IVADo, resected tumor and more two course of IVADo. She had a good response after 4 months of therapy, but ultimately died after the fourth course of IVADo from a brain hemorrhage due to severe thrombopenia. The case with PPB type III (Patient D) and was treated with two courses of IVADo but her disease was progressive and died. One patient (Patient E) refused treatment due to poor prognosis. The last case with PPB type II (mixed tumor) (Patient C) was also treated with two courses of IVADo before dying due to Pneumocytis carrinia pneumonitis. After IVADo 2, this patient had a high fever at home but she did not go to the hospital immediately. One day after admission our department, she had dyspnea and had to be referred to the Intensive Care Unit. Chest X-ray revealed severe pneumonia and had required the mechanic ventilation. Her endotracheal intubation fluid was found Pneumocytis carrinia by PCR. She deteriorated with multiple organ failure.

This case (Patient TDA) who is alive also had severe neutropenia, affected influenza virus B, and suspected septicemia after IVADo. We saved the child by transferring patient to a total isolation room and gave prescribed antibiotics, antifungi, and antivirus as protocol for fever and neutropenia immediately. Luckily, he recovered after 2 weeks. This feat is not be overlooked, considering all hospitals in Vietnam (including ours) have an overload of patients, a scarcity of available rooms, and sometimes also a lack of Amphotericin B available. There are always an average of 2 to 4 patients sharing a room in the oncology department of our hospital therefore our patients who received aggressive chemotherapy always face high risk of severe infection and high mortality. The patient was also able to receive his tumor resection in our hospital because we are a specialized children's hospital, whereas most hospitals would have had to refer patients to another specialty hospital that performs surgeries. Our surgeon was able to cut off total residual tumors visible but was not able to achieve negative margin.

We had to however refer the patient to Hue Central Hospital for radiation, although the role of radiation in management of PPB remains unclear. This hospital resided 600 km away from our hospital, however it was the only hospital with the capacity to treat children under 5 with radiation. As regimen, dose 54.8 Gy had been delivered with aims to target the residual tumor. However, he was a small child and this could cause long-term cardiac damage and pulmonary fibrosis. To perform radiation under general anesthesia treatment while protecting the cardiac and left lung for small child for extended periods of time is not easy, especially in developing countries as Vietnam where we lack advanced specialty equipment. The dose was eventually reduced by 45 Gy. By all effort, he is alive and still goes to the kindergarten with atelectasis after radiation.

4. CONCLUSION

Lungs CT scan and pathology should been analyzed carefully to avert misdiagnosis PPB in patients with cyst or mixed cyst and solid part in lungs. All cases of suspected PPB should send to the free central pathology review. Two factors important to the successful application of the International PPB protocol are first, good supportive care, and second, the multidisciplinary collaboration between medical facilities to provide proper resources during treatment. We hope to recreate more successful outcomes not only in Vietnam but also in all developing countries.

Conflict of Interest

The authors have no conflict of interest in this study.

Acknowledgment

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