A case report with type II pleuropulmonary blastoma: successful treatment with surgery and chemotherapy

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Pleuropulmonary blastoma (PPB) is a very rare intrathoracic malignancy in childhood. It is an aggressive embryonal or blastemic neoplasm usually occurring in children younger than five years of age. PPB is treated with aggressive multimodal therapies consisting of surgery and chemotherapy. We present a case with PPB type II successfully treated with complete surgical resection following neoadjuvant chemotherapy. She has been free of disease for 33 months of follow-up. Complete surgical resection of the tumor at the time of diagnosis is the cornerstone of PPB management, but in the majority of patients, initial surgery is incomplete because a large tumor may involve vital structures. For this reason, patients with initially unresectable tumors should be treated with neoadjuvant chemotherapy to reduce the lesion to the point that it becomes resectable.

Key words: pleuropulmonary blastoma, children, chemotherapy, ICE/VAC.

Pleuropulmonary blastoma (PPB) is a very rare and aggressive intrathoracic malignancy that usually affects children under five years of age[1-6]. It is composed of primitive blastema and a malignant mesenchymal stroma that can be differentiated into rhabdomyosarcoma, chondrosarcoma and liposarcoma[7,8]. It may originate from the lung itself, pleura and the mediastinum[9]. PPB may arise from pre-existing cystic pulmonary lesions, which some authors recommend be removed prophylactically[1,10]. Complete surgical resection of the tumor at the time of diagnosis is essential in the management of PPB, but unfortunately, most patients have a large tumor invading vital structures that results in incomplete surgery[8]. Therefore, patients with initially unresectable tumors should be treated with neoadjuvant chemotherapy to reduce the tumor size until it becomes resectable[6,8]. On the other hand, local radiotherapy is controversial in young children because of its late effects. In several studies, the survival rates do not differ significantly between patients who receive radiotherapy and those who do not[2,6,7,9,11-13]. Here, we present a case with poor prognostic factors for PPB whose management was carried out successfully with surgical resection following neoadjuvant chemotherapy.

Case Report

A 2.5-year-old girl was admitted to the hospital with the complaints of cough, dyspnea and wheezing. Her previous medical and family history were unremarkable. Breath sounds were diminished in the right lung zones. Percussion of the lungs revealed dullness in the same regions. Chest X-ray showed an opacity filling the right hemithorax and leading to mediastinal shift to the opposite side. Thoracic ultrasonography (USG) evaluation demonstrated pleural effusion. Thorax computerized tomography (CT) and magnetic resonance imaging (MRI) revealed a mass in the right hemithorax 10x9x7 cm in size containing both solid and cystic components without invasion to adjacent structures (Fig. 1). Cloudy serous fluid was aspirated by thoracentesis and biochemical analyses of the aspirate

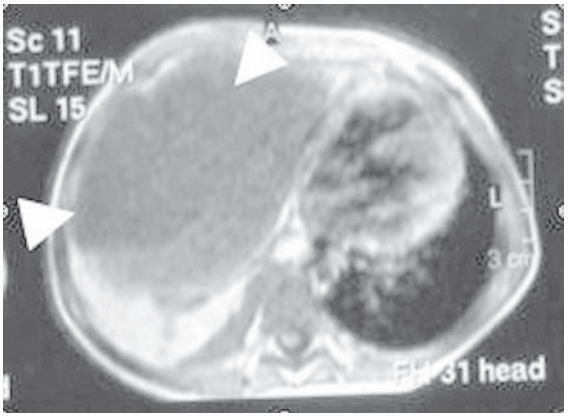

Fig. 1. MRI of tumor with cystic and solid parts which occupying entire right lung.

showed exudative pleural effusion with no malignant cells. Pleural fluid and serum levels of alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (b-HCG) were within normal limits, as were other hematological and biochemical measures. The patient underwent right thoracotomy, which demonstrated an encapsulated cystic mass (10x8x6 cm), and a biopsy specimen was taken. Histological diagnosis of the tumor was PPB type II because it contained both solid and cystic components. Bone scintigraphy and abdominal USG revealed no abnormality. We scheduled six courses of ICE (ifosfamide 2 g/m^2 on days 1 to 3, carboplatin 600 mg/m^2 on day 3, and etoposide 150 mg/m^2 on days 1 to 3) alternated with VAC (vincristine 1.5 mg/m^2 on day 1, actinomycin-D 15 gamma/kg on day 1, and cyclophosphamide 1.2 g/m^2 on day 1). The ICE and VAC courses were alternated every three weeks for a total of 12 chemotherapy courses[14]. During the first course of chemotherapy, respiratory distress worsened and thoracostomy tube was inserted in to the right hemithorax. After the completion of the first course of chemotherapy, pleural effusion resolved completely. Reevaluation of the patient after the fourth course of neoadjuvant chemotherapy revealed a 90% reduction in mass size. She then underwent tumor excision with posterolateral thoracotomy for local control of disease. The mass had intrathoracic and extraparenchymal location and originated from the subpleural space of the medial segment of the middle lobe. There was no invasion or adhesion to the adjacent structures. However, there was no definite border between tumor and the middle lobe. The mass was excised via wedge resection of the medial segment of the middle lobe. Postoperative MRI examination demonstrated no residual mass. She was given an additional eight courses of adjuvant chemotherapy (ICE/VAC). After the completion of 12 courses of chemotherapy, there was no residual mass. It was decided to follow the patient without administration of radiotherapy, as it may cause very severe morbidity in this age and especially in this case given the presence of pleural effusion along with massive presenting mass, necessitating radiotherapy over a large area. Two months after the completion of the chemotherapy courses, follow-up thoracic CT revealed a subpleural air cyst in the superior segment of the left lower lobe. She underwent a second operation for cystic lesion of the opposite lung, due to the possibility of PPB arising from a pre-existing lung cyst. There was no neoplastic finding in the pathological examination. Follow-up CT and MRI revealed no relapse or new cystic development and no tumor recurrence at the thoracostomy tube insertion site. Our patient has been free of disease for 33 months of follow-up.

Discussion

Primary pulmonary and pleural malignancies are very rare in childhood. Intrathoracic masses mostly result from the metastatic spread of extrathoracic solid tumors[6,8]. PPB, which is one of the rarest intrathoracic tumors, has an aggressive nature and very poor prognosis[1-4,12]. The tumor usually occurs in children before the age of five years[6]. In 1988, Manivel et al.[15] described PPB in children as a distinctive neoplasm, the blastematous and sarcomatous features of which have differentiated it from the biphasic epithelial-stromal morphology of the classic adult type pulmonary blastoma, which has predilection for individuals between 30 and 50 years. PPB is a blastemal tumor and may be regarded as the pulmonary dysontogenic analogue to Wilms' tumor in the kidney. It is characterized by primitive mesenchymal elements that may show cartilaginous, rhabdomyoblastic or fibroblastic differentiation[6-9]. The differential diagnosis of PPB includes primary sarcomas of childhood such as rhabdomyosarcoma (RMS), non-rhabdoid soft tissue sarcomas such as Askin tumor, leiomyosarcoma and

malignant mesenchymoma. RMS, Askin tumor and leiomyosarcoma have monodirectional myogenous differentiation, but malignant mesenchymoma is a multidirectional tumor that closely mimics PPB. Domizio et al.[10] suggested that these two malignancies probably represent the same entity.

Pleuropulmonary blastoma is classified as type I (purely cystic), type II (cystic and solid), and type III (purely solid). The prognosis is poorer in type II and III tumors that contain a solid component. Our patient's tumor had both solid and cystic components and was diagnosed as type II PPB.

Local control of PPB is very important in the prognosis. Total resection of the tumor at the time of diagnosis appears to be the preferred mode of treatment. However, in the majority of patients, initial surgery cannot be complete because of involvement of vital structures by a large tumor[13]. In contrast, the patients who undergo partial resection or biopsy at the time of diagnosis usually suffer local recurrences or metastases. Indolfi et al.[13] investigated 22 patients with PPB by means of prognostic factors. In that report, it was demonstrated that the 13 patients whose tumors were totally resected (7 patients at the time of diagnosis, 6 patients after delayed surgery following neoadjuvant chemotherapy) had significantly better prognosis. In the study conducted by Priest et al.[6], only 19 of 50 patients with PBB had totally resectable tumors at the time of diagnosis. Rate of survival in this group was significantly high in contrast to those with incomplete resectable tumors. The role of complete resection via successfully performed surgery in the long-term disease-free survival in our patient is unquestionable. Partial resection or biopsy at the time of diagnosis does not appear to prevent local recurrences or metastases. Complete surgical excision of the tumor offers the best local control. For this reason, patients with initially unresectable tumors should be treated with neoadjuvant chemotherapy to reduce the lesion to the point that it becomes resectable[8]. Our patient had an unresectable tumor at the time of diagnosis and neoadjuvant chemotherapy was administered to reduce the lesion and facilitate its removal.

Several antineoplastic agents have been used to treat PPB. The majority of these agents are also included in the therapy protocols for sarcomas and Wilms' tumor[2,6,9, 8,11,13]. In our case, we used alternating ICE/VAC regimens as the neoadjuvant setting, which is quite effective in refractory or recurrent solid tumors[14]. The common opinion about the role of adjuvant chemotherapy dictates that chemotherapy should be considered for these children based on the aggressiveness of PPB, especially in poor prognostic patients. The issue remains of how long chemotherapy should continue after surgery[2,9,13,16]. In our patient, chemotherapy was performed as eight courses in the adjuvant setting (totally 12 courses) based on the aggressive nature of the tumor and literature data[2,11]. There is a disagreement on usage of radiotherapy in PPB. Although there are reports regarding radiotherapy in patients who had unresectable, recurrent or microscopically residual tumors and poor response to chemotherapy, only 3 of 22 patients were given radiotherapy in the study of Indolfi et al.[2,8,9,13,17]. Priest et al.[6] administered radiotherapy to 16 patients with poor prognostic factors in their study including 50 cases. The authors reported that radiotherapy did not provide an advantage in survival. Similarly, Güler et al.[16] reported long-term disease-free survival by administering only adjuvant chemotherapy without radiotherapy in a 2.5-year-old boy who had residual tumor after surgery. In our patient, there was no residual disease radiologically, but we could not exclude microscopically residual disease because of inability to evaluate the surgical margins. Thus, radiotherapy might have been one of the treatment choices. However, because of the possible severe morbidity of radiotherapy in patients of this age group, we decided against radiotherapy in this case.

Development of PPB from a pre-existing cystic lesion is controversial. Some authors reported patients with pulmonary cystic lesions that progressed to PPB in the same region[18,19]. However, other reports suggested that the prophylactic resection of lung cysts will not prevent the further development of PPB[20]. In this complexity, we decided to resect the cystic lesion in the other lung of our patient. Its histological examination revealed basic lung cyst. Besides originating from the pre-existing cystic lesions, PPB may also arise from chest tube insertion sites. Tumor recurrence at thoracic sites has been reported[21]. This report

showed us the importance of avoiding spillage of tumors at the time of resection. The interval between the completion of chemotherapy and tumor recurrence was less than one year in this report. In our case, a chest tube was inserted and she was followed up for three years without any recurrence including at chest tube site.

Pleuropulmonary blastoma is highly indicative for other dysplastic and neoplastic diseases, meaning that if the patient has PPB, there is a risk of development of other malignancies in both the patient and in the patient's family. Messinger et al.[22] reported that 25% of PPB patients have constitutional or familial association with other neoplasias or dysplasias. Both the patient and their family members should be followed closely. In our case, neither our patient nor any of her family members had another malignancy as of the time of this report.

In conclusion, PPB is an aggressive tumor having poor outcome and it usually occurs in young children. It needs a multimodal therapy regimen including aggressive surgery and chemotherapy. Though radiotherapy is an alternative treatment modality, especially in cases with high risk of recurrence, it causes severe morbidity especially in younger children. We concluded that despite the presence of poor prognostic factors such as presence of solid tumor or of factors that increase the probability of local recurrence such as chest tube insertion and microscopical residual disease after surgery, chemotherapy and aggressive surgery may provide remission and a long-term disease-free period. Complete surgical resection of the tumor at the time of diagnosis is the cornerstone of PPB management, but in the majority of patients, initial surgery is incomplete because a large tumor may involve vital structures. Thus, chemo-reduction followed by complete excision may be the satisfactory treatment of this highly aggressive tumor in the childhood period.

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