RESEARCH COMMUNICATION

Primary Pleuropulmonary Neoplasms in Childhood: Fourteen Cases from a Single Center

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Abstract

Background: We aimed to review clinical characteristics, treatment results and outcome of pediatric patients with primary pleuropulmonary neoplasms. Methods: Medical records of 14 cases diagnosed between 1972-2009 were reviewed retrospectively. Results: The male/female ratio was 5/9 and the mean age at diagnosis was 9.1 years (2-16). All but one were symptomatic, presenting with fever, coughing, dyspnea, or weight loss. One patient presented with hemoptysis, and another with digital clubbing. One mesothelioma was diagnosed incidentally. Some 8/14 patients were initially diagnosed as having pneumonia (median delay in diagnosis of 2.5 months). Diagnoses included pleuropulmonary blastoma (PPB, n=5), inflammatory pseudotumor (n=3), mesothelioma (n=2), mucoepidermoid carcinoma (MEC, n=2), and carcinoid tumor (n=2). Patients with PPB underwent surgery and received chemotherapy ± radiotherapy. Two carcinoid tumor cases underwent surgery, one further received chemotherapy. Patients with mesothelioma were treated with chemotherapy. Inflammatory pseudotumors were all resected. Two cases with MEC received chemotherapy, one after surgery. 2/5 PPB patients survived without recurrence, 3 died; all carcinoid tumors and inflammatory pseudotumors were alive; 1/2 MEC patients was alive after 252 months, the other one was lost without disease; 1/2 mesothelioma patients was alive without disease, the other was died. For all cases, median follow-up was 30.5 months (0.6-252). Conclusions: Primary pleuropulmonary tumors are rare but clinical presentation can be varied and delay in diagnosis is common. Children with persistent coughs, recurrent pneumonia or hemoptysis should be considered as indicators for early diagnosis, very important because the prognosis of these tumors varies with histology and stage.

Keywords: Primary pulmonary tumor - mesothelioma - bronchogenic carcinoma - children

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Introduction

Primary pleuropulmonary tumors (PPT) are rare in children and most common mass lesions are due to metastatic disease (McCahon, 2006). In spite of rarity of these tumors, most of them are malignant (McCahon, 2006). In the 2004 World Health Organization (WHO) classification (Travis et al., 2004), lung tumors, which include a wide range of diseases, have been addressed under the subtitles of malignant epithelial and mesenchymal tumors. While the majority of these tumors are encountered in adult age group, these tumors are less frequently observed in childhood (Travis et al., 2004). Carcinoid tumors, mucoepidermoid carcinoma, adenoid cystic carcinoma, and pleuropulmonary blastoma are the most common malignant tumors, whereas inflammatory myofibroblastic tumors, leiomyomas, papillomas, and hamartomas are the most common benign counterparts in the pleuropulmonary system (Al-Qahtani et al., 2003). However, in the recent 2004 WHO classification, the exact classification of the inflammatory myofibroblastic tumor as benign or malignant has not been established, but the tumor has been suggested to be malignant according to its clinical and certain genetic features (translocations involving ALK gene).

Pleuropulmonary blastoma which has been addressed among the mesenchymal tumors in the 2004 WHO classification differs from the adult-type pulmonary blastoma in terms of clinical and histopathological features (Priest et al., 1997; Perdikogianni et al., 2001; Travis et al., 2004). According to the 2004 WHO classification, mesothelioma is the most common primary pleural tumor and is rarely encountered among children. The diagnosis of PPTs is difficult, because clinical and radiological findings are non-specific and most of children with PPTs have symptoms related to bronchial obstruction or pulmonary consolidation such as cough, atelectasis, hemoptysis, fever, and pneumonia. Due to rarity of these tumors, delay in diagnosis and treatment is common. We aimed to review the presentation, treatment and outcome of fourteen patients with PPTs treated who were treated at our institution.

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Materials and Methods

The medical records of 14 patients aged ≤18 years with primary pleuropulmonary tumors diagnosed at our department between 1972 and 2009 were reviewed retrospectively. Data regarding their presentation, diagnosis, treatment, pathology, and clinical course were documented.

The PPTs, which are rarely encountered in childhood, were evaluated based on the 2004 WHO classification of lung and pleural tumors. We analyzed the different histopathological diagnoses together in order to provide an overview of PPTs that are rarely encountered in childhood and due to the fact that these tumors show similarity in terms of clinical and radiological characteristics.

The demographic characteristics of the patients, as well as the diagnostic methods, treatments and the final status of the patients were examined in detail. The length of survival of the patients was calculated. The final outcome, length of survival and other characteristics are presented in Table.

Results

Over the past 37 years, 14 of 6800 (0,2%) children diagnosed with various cancers at our center were found to have primary pleuropulmonary neoplasms (9 girls and 5 boys). The mean age at presentation was 9.1 years (range, 2-16). All but one patients were symptomatic, presenting with cough (78.6%), fever (57.2%), dyspnea (50%), weight loss (21.5%), fatigue (14.3%), or chest pain (7.2%). One patient presented with hemoptysis (carcinoid tumor), and another with digital clubbing (inflammatory pseudotumor). One patient with mesothelioma was diagnosed with a chest X-ray, which was done for screening of tuberculosis. Eight patients (57.2%) were initially diagnosed as having pneumonia which contributed to a median delay in diagnosis of 2.5 months (range, 0-48).

Histopathological diagnoses included pleuropulmonary blastoma (PPB, n=5, 35.7%), inflammatory pseudotumor (n=3,21.4%),mesothelioma (n=2,14.3%),mucoepidermoid carcinoma (MEC, n=2, 14.3%), and carcinoid tumor (n=2, 14.3%). Bronchoscopy with biopsies established the diagnosis of all MECs and carcinoid tumors, while seven cases (5 PPB, 2 mesothelioma) required tru-cut biopsy and three cases (inflammatory pseudotumor) required primary surgical resection.

All patients with PPB were treated with primary surgical resection and chemotherapy with or without radiotherapy. One of carcinoid tumors was treated with surgical resection and chemotherapy. The other treated with only surgical resection. Patients with mesothelioma were treated only with chemotherapy. Three patients with inflammatory pseudotumors underwent surgical resection only. One patient with MEC was treated with primary surgical resection and chemotherapy and the other with chemotherapy only. Clinical characteristics, treatments, and outcomes of all patients with PPTs were presented in Table. At a median follow-up of 30.5 months (0.6-252), two patients with PPB survived without recurrence for 84 and 24 months, 3 died with progressive disease; all carcinoid tumors and inflammatory pseudotumors were alive with no evidence of disease; one of the patients with MEC survived without recurrence for 252 months, the other patient was lost without disease; and one of the patients with mesothelioma was alive without disease for 98 months, the other was died with progressive disease.

Discussion

Pleuropulmonary tumors are very rare in childhood. While hamartomas, hemangiomas, inflammatory pseudotumors, papillomas, and leiomyomas are seen among benign tumors, bronchial adenomas, carcinoid tumors, mucoepidermoid carcinomas, and adenoid cystic carcinomas are seen among malignant tumors (Al-Qahtani et al., 2003; Dishop and Kuruvilla, 2008). Other tumors rarely seen in children are malignant mesothelioma and pleuropulmonary blastoma (Kaufman et al., 1964; Romeo et al., 1999; Dishop and Kuruvilla, 2008).

We discussed these tumors all together since these tumors originating from pleura, lung parenchyma and bronchial structures are rarely seen in children. Only fourteen cases in a period of 37 years indicate the rarity of these tumors in children. At our center as a reference hospital, they constitute 0.2% of the total 6800 childhood cancer cases.

In contrast to the literature, one third of the cases had PPBs in our series. The patients had neither family history of cancer nor personal history of cystic pulmonary disease and/or dysplastic/neoplastic disease that could explain this frequency. According to the current data, it is accepted that PPB is a dysontogenic mesenchymal tumor, like hepatoblastoma, neuroblastoma, and Wilms' tumor that are seen particularly in children under 15 years of age (Perdikogianni et al., 2001).

Pleuropulmonary blastoma (PPB) is extremely rare in children, 50 cases have been reported in International PPB registry (Priest et al., 1997). Ages of the children in this registry vary from neonatal period to 147 months of age; and while the median age in type I PBB cases is 10 months, it is reported to be 34 and 44 months in types II and III, respectively. PPBs are divided into three histopathological subtypes including type I which has a purely cystic appearence, type II has cystic and solid components, and type III has a purely solid pathology. It is reported that PPB occurs exclusively in children younger than 5 years (Priest et al., 2006). All the patients except one were under 5 years of age, and histopathology of all patients was type III in our series.

There are different hypotheses regarding the histogenesis of PPB. While Spencer, (1961), suggested that PPB originated from pulmonary blastemas like in Wilms' tumor, Stackhause et al., (1969), suggested that PPB was a subtype of carcinosarcoma, similar to fetal lung. However, this tumor is classified within the mesenchymal neoplasms in the WHO Classification of Lung Tumors (Travis et al., 2004; Priest et al., 1997).

Priest et al., (1997), reported overall 2-year survival rate as 63% and 45%, respectively. While 2-year survival

Table. Clinical Characteristics, Treatments and Outcomes of Pleuropulmonary Tumors

Patient	Age (yrs)	Gender	Symptoms	Lag time (Months)	Method of Diagnosis	Location	Diagnosis	Treatment	Outcome/Follow-Up (Months)
1	3	F	Fever, Cough, Dyspnea	1.5	CT/Bx	RMB	PPB	VAC, RT (2000 cGy)	DOD/5
2	2.5	M	Fever, Cough	2	CT/Bx	RLL	PPB	Primary Resection/ Cisplatin+Etoposide/ RT (4400 cGy)	NED/84
3	9	M	Fever, Cough, Dyspnea	3	CT/Bx	Pleura	PPB	Primary Resection /VAC	NED/24
4	2	F	Fever, Cough, Dyspnea	1	PlainX-ray/Bx	RML	PPB	Primary Resection/ VACADR/RT (3500 cGy)	DOD/17
5	4	F	Fever, Cough, Dyspnea	2	CT/Bx	LLL	PPB	Primary Resection/ VACADR	DOD/0.6
6	10	F	Fever, Cough, Dyspnea, Weight Loss	1	Primary Resection	RUL	Inflammatory Pseudotumor	Primary Resection	NED/37
7	10	F	Cough	1	Primary resection	RUL	Inflammatory Pseudotumor	Primary Resection	NED/13
8	10	F	Clubbing	12	Primary resection	RLL	Inflammatory Pseudotumor	Primary Resection	NED/82
9	16	F	Fatigue, Dyspnea	48	Plain X-ray/ Bronchoscopy	RML	MEC	Bleomycine	Lost/8 (Without Disease)
10	8	F	Fever, Cough, Chest Pain	24	Bronchoscopy/ CT	RMB	MEC (Differentiated)	Primary Resection /VAC	NED/252
11	12	F	Cough, Hemoptysis	4	Bronchoscopy/ CT	LMB	Carcinoid Tumor	Primary Resection	NED/72
12	15	M	Fever, Cough, Dyspnea, Weight loss	24	Bronchoscopy/ CT	RMB	Carcinoid Tumor	Primary Resection / Cisplatin+Etoposide	NED/60
13	14	M	Incidental	0	CT/Bx	LUL	Mesothelioma	PIAV	NED/98
14	13	M	Fatigue, Cough, Weight Loss	5	PlainX-ray/Bx	Pleura	Mesothelioma	VACADR	DOD/3

NED, No evidence of disease; DOD,Died of disease; M, Male; F, female; MEC, Mucoepidermoid carcinoma; LUL, Left upper lobe; RMB, Right main bronchus; LMB, Left main bronchus; RML, Right middle lobe; RLL, Right lower lobe; RUL, Right upper lobe; LLL, Left lower lobe; RT, Radiotherapy; VAC, Vincristine, Actinomycine; D, Cyclophosphamide; VACADR, VAC + Adriamycine; PIAV, Cisplatin Ifosfamide Adriamycine Vincristine; Bx: Biopsy; Tbc,Tuberculosis; CT, Computed tomography

rates were 37.5% and 47% for patient with mediastinal or pleural involvement, respectively, the same rate has been reported as 80% for patients with lung involvement only. One case (case 2) only with lung involvement, and one case (case 3) with pleural invasion in our series were alive for 84 and 24 months respectively. Three cases died because of the disease.

Treatment of PPB is radical surgical excision with lobectomy or pneumonectomy, if required (Indolfi et al., 2000; Güler et al., 2001). However, since majority of the patients present with widespread disease, total surgical removal is mostly not possible. Long-term survival was ensured with surgical resection, chemotherapy (cisplatin, etoposide; vincristine, actinomycine D and cyclophosphamide) with and without radiotherapy in two patients in our series who are under follow-up currently. Since PPBs are rare, there is no chemotherapy protocol that a consensus has been reached. However, establishment of an effective chemotherapy is required in these aggressive tumors, particularly for type II and type III (Romeo et al., 1999; Büyükavcı et al., 2006; Miniati et al., 2006). Recent studies have shown that chemotherapy reduces the risk of recurrence in these tumors and improves the OS rates of the patients (Priest et al., 1997; Miniati et al., 2006).

Although results about the effectivenesss of local radiotherapy (RT) vary, there are studies recommending RT in cases with incomplete resection (Priest et al., 1997; Indolfi et al., 2000). The reason for finding RT inefficient in local control might be the poor prognostic characteristics of those patients (Indolfi et al., 2000). One of the 3 patients that RT was applied is alive for a long period, and at our center, there is the tendency to apply RT to patients with a residue.

Carcinoid tumors have been reported to account for 80% to 85% of primary malignant lung tumors in childhood (McCahon, 2006; Dishop and Kuruvilla, 2008). Approximately 75% of bronchial carcinoid tumors originate from lobar bronchi, and 15% from the periphery

of the lungs (Al-Qahtani et al., 2003; Guisti et al., 2004). In our series, both cases have originated from main bronchi. MECs are very rare in children, and reported to account for 10% of malignant lung tumors in children (McCahon, 2006; Dishop and Kuruvilla, 2008). MECs arise most commonly from the mainstem bronchus or a lobar bronchus. Presence of only 4 cases (2 carcinoid tumor, 2 MEC) in our series within a period of 37 years accounts for rarity.

Carcinoid tumor and MEC cases are mostly seen in adolescent age group, and present mostly with recurrent pneumonia, cough, fever, and hemoptysis (Curtis et al., 1998; Al-Qahtani et al., 2003; Kut et al., 2005). Paralleling the literature, 3 cases in this series applied with pneumonia not responding to nonspecific antibiotic therapy, and one case applied with hemoptysis. All the four cases with these complaints were diagnosed with bronchoscopy. Delay in diagnosis was a problem varying between 4 to 48 months because of the nonspecific symptoms. Therefore, in patients that pneumonia or other symptoms who do not improve in spite of antibiotics, diagnosis must be confirmed with computerized tomography and/or fiberoptic bronchoscopy (Curtis et al., 1998; Guisti et al., 2004; Kut et al., 2005). While the histopathology (typical vs atypical) in carcinoid tumors are important as regards to metastasis (Moreas et al., 2003; Lal et al., 2005), being low-grade or high-grade according to the mitotic activity and cellular differentiation are important in MEC for the prognosis (Torres et al., 1988; Lal et al., 2005). MECs generally arise from bronchial mucous glands in the proximal portion of lobar bronchi as an endobronchial polypoid growth that is covered by normal respiratory epithelium. Therefore, forceps biopsy is mandatory for diagnostic studies (Granata et al., 1997; Al-Qahtani et al., 2003). Diagnosis was made with biopsy using fiberoptic bronchoscopy in both of our patients because of pneumonia not recovering.

Treatment of bronchial carcinoid tumors is surgical resection, RT and/or chemotherapy are recommended as adjuvant therapies in some cases (Moreas et al., 2003; McCahon, 2006). Lung parenchyma must be preserved as much as possible while performing the resection of the tumor. While resection for the primary mass lesion was performed for both of our patients, chemotherapy was given additionally in one case (Case 12). Chemotherapy was given because of recurrence 3 months later than the primary resection in the upper lobe of the right lung, by considering the positive surgical margins. With the reasons that rich vascularization of carcinoid tumors and the phenomena of "iceberg", endoscopic resection can be risky as well as failing to ensure the removal of the mass with safe surgical margins (Curtis et al., 1998; Al-Qahtani et al., 2003; Moreas et al., 2003; Guisti et al., 2004; Fauroux et al., 2005).

Although only surgical resection could suffice in MEC treatment (Lal et al., 2005), chemotherapy and/or radiotherapy may also be applied according to the grade of the tumor and the status of the surgical margins. While one of the cases (case 10) was treated with resection of the primary mass lesion and chemotherapy, the other (case 9) was considered inoperable because of invasion in the chest wall and treated only with chemotherapy. One case was alive for 252 months, the other was lost to follow-up in 8th month (without disease).

Malignant pleural mesothelioma (MPM) is a tumor with poor prognosis rarely seen in childhood (Kelsey, 1994). Only two to five percent of MPM cases are seen in the first two decades of life (Kelsey, 1994). These cases mostly originate from pleura (85%), and also from peritoneum, pericardium, or scrotum less frequently (Dische et al., 1988; Fraire et al., 1988; Goyal et al., 2000). Majority of MPMs are seen in males, and it has not been shown that exposure to asbestos plays a role in the etiology in childhood (Grundy et al., 1972; Fraire et al., 1988). Both cases in our series were boys, and the possible risk factors could not be shown.

While the clinical status of the cases with MPM were well before presentation, they can also present with complaints like chest pain, respiratory distress, fever, or weight loss (Kauffmann and Stout, 1964; Dische et al., 1988; Kelsey, 1994). While one of our cases (Varan et al., 1999) was diagnosed by chance with the lung x-ray taken in a routine examination, the other presented with cough and weight loss. This can account for the insidious onset and rapidly progressive nature of MPM.

While surgery is applied in selected cases in the treatment of MPM, the main therapy consists of chemotherapy and radiotherapy (Goyal et al., 2000). Both cases were treated with chemotherapy, and while one patient was still under follow up for 98 months with no disease, the other case was died with progressive disease. Diffuse localization of MPMs for total surgical resection and presence of pleural effusion in most cases indicate that chemotherapy and/or radiotherapy would be more efficient rather than surgery. However, scarcity of the cases proven to be mesothelioma in the literature fails to show which chemotherapeutic agents are more effective. Complete remission was obtained with cisplatin, ifosfamide, adriamycine and vincristine in one patient in our series, and is still under follow up with no recurrence. New surgical techniques including extrapleural pneumonectomy and pleurectomy/decortication have been evolved for macroscopic complete resection (Sugarbaker and Wolf, 2010).

Pulmonary inflammatory pseudotumor (PIP) is an entity in the benign extreme of the spectrum of pulmonary fibrohistiocytic lesions (Patankar et al., 2000). Although PIPs mainly effect young adults, they occur in all age groups (Patankar et al., 2000). About 42% of patients are under 18 years of age (Agrons et al., 1998). While most of the patients present with fever, chest pain, and recurring pneumonia (Messineo et al., 1998), cases presenting with digital clubbing (Gorospe et al., 2000; Pichler et al., 2004) have also been reported. One case in our series had presented with clubbing present for 12 months. PIP must be considered in the differential diagnosis of patients presenting with calcified and well limited mass in lungs with digital clubbing (Berman et al., 2003). Clubbing improves usually following the excision of the mass lesion, like in our case (Berman et al., 2003).

Although there are different approaches for the treatment of PIP, the classical approach is surgical excision

(Verbeke et al., 1999). However, success of corticosteroid therapy or chemotherapy has also been reported in invasive or recurrent cases (Verbeke et al., 1999). Messineo et al., (1998), have reported in 3 patients out of 5 in their series that they applied mass excision by reserving the lung tissue as much as possible, and no recurrence developed throughout the follow-up period that lasted for 4-8 years. In our study, primary resection was applied to all three patients, and no recurrence was seen during a follow-up period of 13-82 months. Total resection of mass must be considered in these patients if possible, and must be under close follow-up for recurrence.

In conclusion, primary pleuropulmonary tumors are rare and clinical presentation can be varied and delays in diagnosis are common. Primary pleuropulmonary malignancy should be considered in children with persistent cough, recurrent pneumonia, or hemoptysis. Early diagnosis is very important, because the prognosis of these tumors varies with histology and stage of the disease.

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