Diagnosis and Treatment of Pleuropulmonary Blastoma—Single Center Experience

Iskra Christosova, DMedSc,[1] Boryana Avramova, PhD,[1]* Rosen Drebov, PhD,[2] Hristo Shivachev, PhD,[2] Marya Kamenova, DMedSc,[3] Dragan Bobev, DMedSc,[1] and Ognyan Brankov, DMedSc[2]

Summary. Pleuropulmonary blastoma (PPB) is a rare and potentially aggressive intrathoracic disembryonic neoplasm typically occurring in children less than 6 years of age. We assessed the relative incidence, clinical characteristics, treatment outcome, and the prognostic factors for long- term survival in patients with PPB treated at our institution over a 25-year period, and compared these data with reports in the literature. From 1985 to 2010, 11 children (4 males and 7 females), with a median age of 5.4 years (range, 1-12 years) were treated at our hospital. Here we described the main characteristics of these patients, the diagnostic methods, and treatment modalities used.

During a median follow—up period of 80, 9 months, the overall survival (OS) and disease-free survival (DFS) rates were 54, 6% and 45, 5%, respectively Two patients survived for more than 20 years. The main prognostic factors for long-term survival were the diseases type I and II and treatment with radical surgery Our results showthat in order to improvethe prognosis of patients with PPB a timely in our opinion and accurate diagnosis needs to be established and treatment should be offered according to the disease type and extend of dissemination. **Pediatr Pulmonol. 2014; 9999:1-6.** © 2014Wiley Periodicals, Inc.

Key words: pleuropulmonary blastoma; dysembryonic neoplasm; combined modality treatment; myeloablative chemotherapy.

INTRODUCTION

Primary pulmonary tumors are uncommon in children with a broad spectrum of histopathologycal diagnoses ranging from benign to malignant conditions. This distribution is quite different from the distribution of histological diagnoses in adults.[1] The ratio of primary pulmonary neoplasms to secondary metastases to non- neoplastic lesions is 1:5:60.[2] Approximately, 75% of primary lung tumors in children are malignant. The most frequent of those that involve the parenchyma is pleuro- pulmonary blastoma (PPB) and of those that involve the airways is neuroendocrine carcinoma (carcinoid tumor).[3]

PPB is a rare and aggressive intrathoracic disem- bryonic neoplasm of the pleuropulmonary mesenchym and accounts for 0.5% of all pediatric malignancies and predominantly affects small children. More than 90% of cases PPB arise in children less than 6 years of age.

PPB was first described by Manivel et al. in 1988 and was later subdivided into three types on the basis of the morphological pattern as type I (cystic), type II (solid/ cystic), and type III (solid), in order of increasing malignancy.[4] Type I PPB is different the rest because of its subtle malignant changes and good prognosis.[5] The tumor consists of an immature interstitial mesenchymal and epithelial component, resembling that of the fetal lung. Male children are approximately equally affected as female children, according to the data from the International Pleuropulmonary Blastoma Registry (IPPBR).

The prognosis of PPB, especially type II and III is poor because of frequent relapses and distant metastases, which are often seen in the brain and bone.[6,7] Because of the rarity of these malignancy and its often nonspecific

[1]Specialized Hospital for Pediatric Oncohematology, Sofia, Sofia, Bulgaria.

[2]University Hospital for Emergency Medicine "Pirogov," Sofia, Clinic of Pediatric Surgery, Sofia, Bulgaria.

[3]Section of Pathology, University Hospital for Emergency Medicine "Pirogov," Sofia, Sofia, Bulgaria.

*Correspondence to: Boryana Avramova, PhD, Specialized Hospital for Pediatric Oncohematology, 8, Bjalo More Street, Sofia 1527, Bulgaria. E-mail: b.avramova@sbaldohz.com

clinical symptoms, it is usually not considered in the differential diagnosis of children who present with persistent pneumonitis, coughing, or atelectasis. This often results in a delay in definitive treatment and a poor prognosis.[3]

At present, the treatment of PPB is multimodal and includes surgery, chemotherapy, and/or radiation therapy. The combination depends on the type and aggressiveness of the disease.

A small number of published cases have described the use of myeloablative chemotherapy followed by rescue treatment with transplantation of autologous bone marrow or peripheral blood stem cells, which overcomes dose-limiting toxicity and facilitates chemotherapy dose escalation. However, the role of this treatment remains controversial.[8]

The purpose of this retrospective analysis was to review the morbidity clinical characteristics, treatment results, clinical outcomes, and prognostic factors affecting the long-term survival of these pediatric patients treated in a single center over 25-year period and to compare these data with those reported in the medical literature.

MATERIALS AND METHODS

We retrospectively reviewed the medical records, pathology results, and imaging findings of 11 patients with PPB treated at the Specialized Hospital for Pediatric Oncohematology in Sofia over a period of 25 years (19852010). This retrospective study was approved and registered by the Ethical Committee of Specialized Hospital for Pediatric Oncohematology (SHPOH). Eligi- ble patients were identified from the SHPOH Data Registry.

Pathologic diagnosis was established on the basis of histology and immunohistochemistry results, without the use of molecular diagnostic techniques, by experienced pathologists in the University Hospital for Emergency Medicine "Pirogov"—Sofia, Section of Pathology. Re- currence or metastases were confirmed on the basis of biopsy findings. In all cases diagnosed after 1990 (nine patients) the presence or absence of microscopic residual disease was also documented.

Statistical Analysis

survival (DFS) was performed using the Kaplan-Meier method. In each case, survival intervals were calculated from the date of diagnosis to the date of an event (recurrence or death) or to the last follow-up date. The survival curves were compared using the log-rank test.

In order to identify the prognostic factors affecting the survival of the patients, we performed multivariate analysis by using the Cox regression model. Variables considered included age at diagnosis, gender, histological type, tumor localization, volume of the surgical resection, residual disease, and radiotherapy. P values less than 0.05 were considered statistically significant.

RESULTS

With regard to the frequency of PPB in children, 11 patients in our hospital were treated over a 25-year period (between 1985 and 2010; Table 1). Most of the patients were female (7:4). The agerange was 1-12 years (median, 5, 4 years). The tumor was located in the right lung in seven patients in and in the left lung in four patients.

Of the 11 patients, one was diagnosed with histological type I, four with type II, and six with type III (including one with rhabdomyosarcomatous differentiation) PPB. Microscopic residual disease was detected in four patients after surgery: two had stage II and two had stage III disease.

Presenting complaints included respiratory distress in all children, with additional cough and fever in eight patients. Three patients were initially diagnosed as having echinococcal cyst.

The radiological findings were those of solid lesions with lung atelectasis and contralateral mediastinal shift in

TABLE 1—The Main Characteristics of the Patients

N	Age	Gender Tumor type	Stage/resection margin status	Treatment	Radio therapy	Outcome	Recurrence
1	5	Female II	Unknown margin status	Pneumon ectomy/chemotherapy	No	Alive	No
2	6	Female III	Unknown margin status	Pneumon ectomy/chemotherapy	No	Alive	No
3	12	Female II	Positive margin status	Lobectomy/chemotherapy	Yes	Death	Yes
4	3	Male III	Negative margin status	Lobectomy/chemotherapy	No	Death	Yes
5	5	Female II	Negative margin status	Lobectomy/chemotherapy	No	Alive	No
6	4	Female II	Positive margin status	Lobectomy/chemotherapy	Yes	Alive	Yes
7	12	Male III	Distant metastases	Lobectomy/chemotherapy	No	Death	Yes
8	2	Female III	Negative margin status	Complete resection/chemotherapy	No	Alive	No
9	1	Male I	Negative margin status	Complete resection/chemotherapy	No	Alive	No
10	2	Female III	Positive margin status	Incomplete resection/chemotherapy	Yes	Death	Yes
11	5	Male III	Positive margin status	Incomplete resection/chemotherapy	Yes	Death	Yes

Univariate analysis of overall survival (OS) and disease-free

six patients and cystic masses or pneumonic infiltrate in the remaining patients. The tumor was localized in the upper pulmonary lobe in four cases, in the middle lobe in two, and in the inferior lobe in the other patients. On computer tomography (CT), the tumors were visualized as heterogeneous infiltrates, with solid and/or cystic components and lung compression.

None of our patients had a history of familial disease.

All patients were initially treated with surgical resection: two patients with complete tumor resection (one with type I and 1 with type II), two with incomplete resection, five with lobectomy, and two with pneumonectomy.

Four children received postoperative irradiation with a total dose of 45 Gy to the involved lobe because of residual disease, two of them after incomplete resection and two after lobectomy.

Preoperative chemotherapy was not administered. All patients received adjuvant chemotherapy with vincristine (1.5 mg/m^2, day 1), cyclophosphamide (1,200 mg/m^2, days 1-5), and dactinomycin (0,5 mg/m^2, days 1-3) for six cycles every 28 days for type I cases and for 12 cycles every 21 days for types II and III cases.

Six patients developed local recurrence after the treatment. These occurred in two patients after an incomplete tumor resection and in four patients after previous lobectomy of the adjacent lobe despite the receipt of radiotherapy in four of them. One patient presented with distant metastasis in the bone at the time of diagnosis. All patients with positive margins after surgery developed local recurrence.

All relapsed patients were treated with salvage chemotherapy of ifosfamide (1,800 mg/m^2, Days 1-5), carboplatin (400 mg/m^2, Days 1-2), and etoposide (100 mg/m^2, Days 1-5) for six to eight cycles at 21-day interval.

One patient with type I PPB was treated with complete surgical resection of the cystic mass and six cycles of vincristin, cyclophosphamide, and doxorubicin at an interval of 28 days, according to the institutional protocol.

One patient received myeloablative therapy with autologous hemopoietic stem cell transplantation (HSCT) as salvage chemotherapy using a conditioning regimen of ifosfamide, carboplatin, and etoposide.
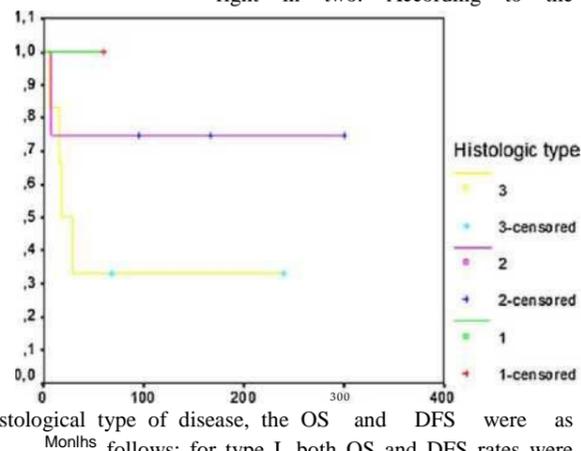
During a median follow-up time of 80.9 months, the OS rate for this cohort was 54.6% and the DFS rate was 45.5% (Figs. 1 and 2). The 6-month, 1-year, and 5-year OS rates were 90.9%, 81.8%, and 54.6%, respectively. Two patients survived for more than 20 years. The patient who received autologous transplantation is currently alive and in remission 14 years after the completion of treatment.

Among the surviving patients (five girls and one boy, all under 6 years of age), the histological type was I in one patient, II in three patients, and III in two patients. The

Fig. 1. Kaplan-Meier estimates of overall survival for patients with different histological types of PPB—type 1 (green): 100%; type 2 (purple): 75%, and type 3 (yellow): 33.3%. Different groups were compared using log-rank test. Censored are the alive patients with different long survival at the time point of study.

tumor was localized on the left side in four patients and on the

right in two. According to the histological type of disease, the OS and DFS were as follows: for type I, both OS and DFS rates were 100%, for type II, the OS rate was 75% and the DFS rate was 50%, and for type III both OS and DFS rates were 33% (Figs. 1 and 2). Survival differences on this basis did not reach statistical significance between type II and III cases ($P = 0.24$). In
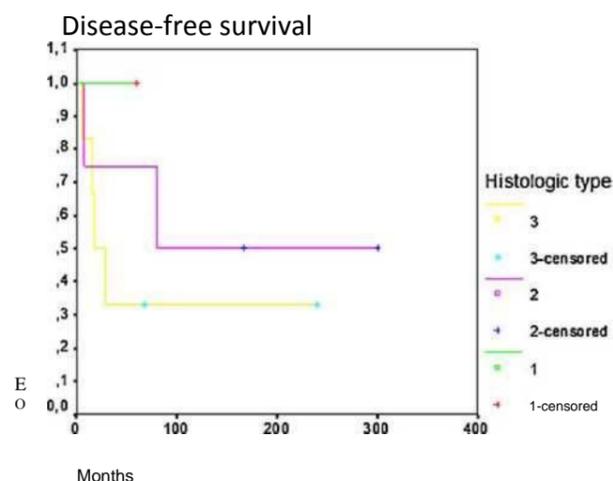

Fig. 2. Kaplan-Meier estimates of disease—free survival for patients with different histological types of PPB—type 1 (green): 100%; type 2 (purple): 50%, and type 3 (yellow): 33.3%. Different groups were compared using log-rank test. Censored are the alive patients with different long survival without relapse at the time point of study.

contrast, the difference was statistically significant between patients with type I or type II disease and those with type III disease (P = 0.02). One patient with type I disease is still alive, but this information is not sufficient for statistical analysis and interpretation.

All patients who underwent radical surgery survived, whereas two with residual disease and one with distant metastases died.

The statistical analysis of the prognostic factors for long-time survival showed that patients with type I or II disease (P = 0.023) and patients with absence of residual disease after surgery (P < 0.005) had a better prognosis.

DISCUSSION

Given the rarity of PPB, most studies in the literature report results with small sample sizes, which prevent the development of an accurate diagnostic algorithm and an evidence-based approach to treatment.[9] In the Bulgarian pediatric population, PPB is also rare, with an incidence similar to the reported for the rest of Europe. We diagnose and treat approximately one patient every 2 years (among a total population of one, 5 million pediatric patients). The proportion of PPB among childhood lung tumors in Bulgaria for this period is also similar to that described in the literature, between 15% and 30%.[2,3] Over a 25-year period, we diagnosed and treated 64 children with lung tumors, of which 11 were PPB (20, 7%).

In our cohort, we only had one patient with type I PPB (9%). In the medical literature the described frequency of patients with type I is between 10% and 14% and the survival is high (80-85%).[10] This underrepresentation of patients with type I disease in our cohort could be attributed to misdiagnosis in the years before 1990 when the resources for diagnosis and treatment were limited or the possibility that these patients were not referred to our pediatric oncology unit.

The small number of patients does not allow statisti- cally significant conclusions to be drawn, but will contribute to towards the overall European statistics, which might help improve the diagnosis and treatment of the disease in the future. The 11 patients with PPB included in this analysis were not registered with the IPPBR and their data were not included in the online database.

In 1988, Manivel et al.[11] first described 11 cases of children with primary pulmonary tumors and suggested that these intrathoracic neoplasms in childhood should be classified as PPB on the basis of their histopathology and anatomic characteristics. The prognosis of these patients was poor, with seven patients dying of their disease within 5 months to 2 years after diagnosis and only two patients surviving for 10-12 years.

Cohen et al.[2] confirmed the rarity of this disease in 1992 in a review of the English language literature. They also reported the clinical and pathological features of eight tumors arising in the lungs of preadolescent children, in a retrospective analysis of cases diagnosed between 1960 and 1991 in their pathology department in South Africa. Of these tumors, only two were PPB, characterized by aggressive behavior and association with cystic

lesions.

In 1997, Priest et al.[10] studied a large series of 50 patients diagnosed with PPB, who presented with pulmonary and/or pleural-based mass and respiratory difficulty with or without fever. Local recurrences developed in 19 patients and distant metastases were noted in 13, mainly in the brain/spinal cord or bone. The 5-year overall survival rate was 42-83% and was dependent on the pathologic subtype. The authors concluded firstly that PPB should be regarded as the pulmonary analogue of Wilms tumors in the kidney, neuroblastoma in the adrenal gland, hepatoblastoma in the liver, medulloblastoma in the brain and embryonic rhabdomyosarcoma in the connective tissue. For patients with type II and III tumors, they suggested a more aggressive.

More reports on PPB have been published since 2000, but these represent earlier studies with a small sample size or case reports. Most authors concluded that these are rare tumors, typically occurring in children, exhibiting an aggressive behavior and poor outcome, and differing from similar adult cases. Long-term survival in most studies varied between 50% and 60%.[12,13,14]

In 2007, Indolfi et al.[15] reported the clinical and pathological findings, treatment regimes, and outcomes of patients in a larger series of 22 PPB cases observed in 13 Italian pediatric hematology and oncology centers. During a median follow-up time of 22 months, nine patients had recurrences, and the 15-year OS and eventfree survival rates were 49% and 44%, respectively. They concluded that total resection of PPB performed at any time during treatment appears to provide a better outcome, whereas extra-pulmonary involvement at diagnosis worsens the prognosis.

The longest period of experience with PPB (90 years) was reported by Yu et al.[9] in 2010. They described 40 patients with primary lung tumors diagnosed and treated in the Department of Pediatric Surgery, Harvard Medical School, between 1918 and 2008. Of these patients, only six had PPB. They concluded that complete resection and adjuvant chemotherapy should be the appropriate standard treatment for these patients.

Despite its rarity, PPB should be considered in the evaluation of cystic and solid masses in children with respiratory distress. CT represents the most common used diagnostic technique, although magnetic resonance imaging (MRI) can reveal more accurately the features of solid enhancing nodules inside fluid-filled cavities, a mass causing lung compression, mediastinal shift, frequent pleural effusion, and no chest wall invasion.

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. Radiologist play an important role by using modern imaging techniques to facilitate early diagnosis and staging, thus enabling adequate treatment and follow-up.[3,4]

In order to define potential therapeutic targets in PPB, in recent years, many authors have analyzed the molecular genetic alterations underlying the pathogenesis of this tumor entity. According to the IPPBR data, PPB is genetically determined in 25% of the patients, which introduce the diagnosis PPB Family Tumor. In 30-35% of cases, PPB is associated with Dysplasia

syndrome, which also includes pulmonary cysts with pathologic features of involutes or regressed PPBs, cystic nephroma, other soft tissue sarcomas, nasal chondromesenchymal hamartoma, nodular hyperplasia, carcinoma of the thyroid gland, ciliary body medulloepithelioma, and embryonic rhab- domyosarcoma of the uterine cervix.[161718] Familial PPB is associated with germ-line mutations in Dcr-1 homo- logue *(DICER1),* which encodes an enzyme required for the production of mature micro RNAs.[19] These mutations were first described in 2009 and have been observed in many of these diseases that accompany PPB.[20]

Treatment for PPB is multimodal and includes surgery, chemotherapy, and/or radiation therapy. Surgical treatment is essential because it provides patients with the best chance for long-term survival. The role of radiotherapy is limited and is applicable most often for the treatment of relapses or residual disease. The applied standard chemotherapy regimens in most cases include vincristine, actinomycin-D, doxorubicin, cisplatin, and cyclophos- phamide/ifosfamide.[51014] In recent years, the use of novel chemotherapeutic drugs such as irinotecan has been reported for the treatment of PPBs with promising results.[21]

The role of myeloablative chemotherapy with autolo- gous HSCT in the treatment of PPBs is controversial. Only a few cases have been reported in the literature. The use of high-dose chemotherapy followed by HSCT overcomes the hematological toxicity of cytostatic regimens. For PPBs, this treatment has been used in cases of relapses or minor response to standard therapy. The conditioning regimens often include melphalan, etoposide, carboplatin, and cyclophosphamide. In some cases, similar to our experience, patients achieved long- term remission.[68]

Our results demonstrate that PPB is a rare malignant disease that affects children, with a frequency of 0.05 per 100,000 children in the Bulgarian population and female predominance (in contrast to published data). The age distribution of our patients is also different from the data of most of other centers. According to the literature, PPB affects children ranging in age ranges from 1 month to 12 years. Most cases are diagnosed before the age of 4 years, but PPB can be found prenatally or in older children and young adults. Taken together, the data from the IPPBR and the unpublished registry series (N = 128) regarding the age of presentation, provide the following age range (in months): overall: 0-431; type I: 0-32; type II: 6-431, and type III: 15-147. There was only one 36- year-old patient with documented PPB in the registry series.[22] Two (18%) of our patients were diagnosed at more than 6-year of age (both patients were 12 years old). This is very uncommon, but similar cases have been

00 OA.

described in the literature.[22,23,24] According to clinical characteristics, most of our patients had type II and III disease (91%), with right pulmonary localization (63.6%), in the middle and inferior lobes (63.6%). First presentation of the disease was severe respiratory illness in more than 90% of cases. It is very interesting that 3 of our patients presented and were diagnosed clinically and radiologically with an echinococcal cyst. The reason of this confusion is the relative high frequency of echinoc- cocal cyst in the Bulgarian pediatric population, especially in the rural areas. These patients are treated mainly in pediatric surgical department. In all these three patients, the PPB had a cystic component and was diagnosed as type I or II.

Seven (64%) of our patients relapsed or had distant metastases at various time intervals from the original diagnosis, which severely worsened the prognosis. This unfavorable disease course was attributed to the delay in diagnosis in three cases and the histological type or stage of the disease in the others.

Regarding treatment modalities and results, all of our patients received surgical tumor resection and adjuvant chemotherapy, but despite this some of the patients relapsed. We treated all cases of relapse and disease progression with salvage chemotherapy, including mye- loablative treatment in one case, but achieved a different degree of success in each case. These findings indicate that the prognosis of the disease depends predominantly on differences with regard to the type of chemotherapy received and the presence of residual disease.

The number of patients in our study is small and therefore insufficient for statistically significant conclu- sions, but our results show an OS and a DFS rate that correspond with results published in the literature (5070% and 40-50% for type II and III PPB, respectively, and 80-85% for type I PPB).[1015] According to the published data the difference in survival outcomes of patients with type I PPB and patients with type II and III is substantial.[1115] In comparison Priest et al.[11] reported a 5-year OS rate of 83% for type I and 42% for type II and III PPB; hey concluded that these observations support the premise that type I and III PPB are bridged morphologi- cally by type II PPB with its combined cystic and solid features. Indolfi et al.[15] reported a 2-year event—free survival rate of 45% for all patients, but the outcome was worse for patients with type II PPB and/or pleural than in patients without these features.

In our hospital, survival is better in cases of female patients, those less than 6 years of age, cystic or intermediate type disease, local disease, early diagnosis, and patients in who of complete surgical resection is achieved.

To achieve the best results in the diagnosis and treatment of PPB, the most important factors are the establishment of an international cooperation, inclusion of all cases in the IPPBR, and support of studies that will include larger patient sample sizes. For this reason, in 1988 the IPPBR was created (www.ppbregistry.org). This website provides information from families and physi- cians/caregivers on PPB. This tumor has come under intensive medical scrutiny only since the mid-1980. With the cooperation of families and physicians all over the world, the register has been collecting cases of PPB for more than 20 years. Through this accumulation of information, better understanding of the biological and treatment issues of the disease has been achieved along with the publication of several articles.

From this retrospective analysis, we concluded that our results are similar to those reported from other centers and can confirm that, for improving the prognosis of PPB, it is important to continue our international collaboration in order to develop an accurate diagnostic algorithm, including molecular diagnosis and

risk-adapted treatment.

REFERENCES

1. Subhalakshmi S, Uttara C, Raniana B, et al. Primary[Q2] pulmonary neoplasms in children: a report of five cases. Indian J Med Pediatr Oncol 2011;32:223-226.
2. Cohen M, Kaschula R. Primary pulmonary tumors in childhood: a review of 31 years' experience and the literature. Pediatr Pulmonol 1992;14:222-232.
3. Dishop MK, Kuruvilla S. Primary and metastatic lung tumors in the pediatric population: a review and 25-year experience at a large children's hospital. Arch Patthol Lab Med 2008;132:1079-1103.
4. Orazi C, Inserra A, Schingo PM, De Sio L, Cutrera R, Boldrini R, Malena S. Pleuropulmonary blastoma, a distinctive neoplasm of childhood: report of three cases. Pediatr Radiol 2007;37:337-344.
5. Priest JR, Hill DA, Williams GM, et al. Type I pleuropulmonary blastoma: a report from the International Pleuropulmonary Blastoma Registry. J Clin Oncol 2006;24:4492-4498.
6. Kaneko H, Isogai K, Kondo M, Hosoi K, Asana T, Funato M, Kondo N. Autologous peripheral blood stem cell transplantation in a patient with relapsed pleuropulmonary blastoma. J Pediatr Hematol Oncol 2006;28:383-385.
7. Demir H, Yalcin B, Ciftci AO, Orhan D, Varan A, Akyuz C, Kutlik T, Buyukpamukcu M. Primary pleuropulmonary neoplasms in childhood: fourteen cases form a single center. Asian Pac J Cancer Prev 2011;12:543-547.
8. de Castro CG, Jr., de Almeida SG, Gregianin LJ, Loss JF, Rivero LF, Schwartsman G, Brunetto AL. High-dose chemotherapy and autologous peripheral blood stem cell rescue in a patient with pleuropulmonary blastoma. J Pediatr Hematol Oncol 2003;25:78- 81.
9. Yu D, Grabowski M, Kozakewich H, Perez-Atayde AR, Voss SD, Shamberger RC, Weldon CB. Primary lung tumors in children and adolescents: a 90-year experience. J Pediatr Surg 2010;45:1090- 1095.
10. Priest J, McDermottM, BhatiaS, Watterson J, Manivel JC, Dehner LP. Pleuropulmonary blastoma: a clinicopathologic study of 50 cases. Cancer 1997;80:147-161.
11. Manivel J, Priest J, Watterson J, Steiner M, Woods WG, Wick MR, Dehner LP. Pleuropulmonary blastoma. The so-called pulmonary blastoma of chilhood. Cancer 1988;62:1516-1526.
12. Kantar M, Cetinguel N, Veral A, Kansoy S, Ozcan C, Alper H. Rare tumors of the lung in children. Pediatr Hematol Oncol 2002;19:421-428.
13. Walker R, Suvarna K, Matthews S. Case report: pulmonary blastoma: presentation of two atypical cases and review of the literature. Br J Radiol 2005;78:437-440.
14. Boldrini R, Devito R, Diomedi-Camassei F, Francalanci P, Inserra A, Boqlino C, Donfrancesco A, Jenkner A, Callea F. Pulmonary blastomas of childhood: histologic, immunohistochemical, ultra- structural aspects and therapeutic considerations. Ultrastruct Pathol 2005;29:493-501.
15. Indolfi P, Bisogno G, Casale F, Ceccheto G, De Salvo G, Ferrari A, Donfrancesco A, Donofrio V, Martone A, Di Martino M, Di Tullio MT. Prognostic factors in pleuro-pulmonary blastoma. Pediatr Blood Cancer 2007;48:318-323.
16. Priest J, Williams G, Hill D, Dehner LP, Jaffe A. Pulmonary cysts in early childhood and the risk of malignancy. Pediatr Pulmonol 2009;44:14-30.
17. Boman F, Hill D, Williams G, Chauvenet A, Fournet JC, Soglio DB, Messinger Y, Priest JR. Familial association of pleuro- pulmonary blastoma with cystic nephroma and other renal tumors: a report from the International Pleuropulmonary Blastma Registry. J Pediatr 2006;149:850-854.
18. Priest J, Williams G, Mize W, Dehner LP, Mc Dermott MB. Nasal chondromesenchymal hamartoma in children with pleuropulmo- nary blastoma - A report from the International Pleuropulmonary Blastoma Registry. Int J Pediatr Otorhinolaryngol 2010;74:1240- 1244.
19. Ann K, Pacheco C, Yang J, et al. Ovarian sex cord-stromal tumors, pleuropulmonary blastoma and DICER1 mutations: a report from the International Pleuropulmonary blastoma Registry. Gynecol Oncol 2011;122:246-250.
20. Bahubeshi A, Bal N, Rio Frio T, Hamel N, Pouchet C, Yilmaz A, Bouron-Dal Soglio D, Williams GM, Tischkowitz M, Priest JR, Foulkes WD. Germline DICER1mutations and familial cystic nephroma. J Med Genet 2010;47:863-866.
21. Ohta Y, Fujishima M, Hasegawa H, Kosumi T, Yonekura T. High therapeutic effectiveness of postoperative irinotecan chemothera- py in a typical case of radiographically and pathologically diagnosed pleuropulmonary blastma. J Pediatr Hematol Oncol 2009;31:355-357.
22. Hill D, Sadeghi S, Schuldz M, Burr JS, Dehner LP. Pleuro- pulmonary blastoma in an adult: an initial case report. Cancer 1999;85:2368-2374.
23. Lee C, Kim K, Kim Y, Lee MK, Kim JY, Park DY, Sol MY, Suh KS. Pleuropulmonary blastoma in a young adult presenting as a ruptured cystic teratoma in radiology. J Korean Med Sci 2003;18:595-598.
24. Numanami H, Tanaka M, Hashizume M, Hara K, Yokoi T, Haniuda M. Pleuropulmonary blastoma in a 12-year-old boy presenting with pneumothorax. Jpn J Thorac Cardiovasc Surg 2006;54:504-506