Article is available online at http://www.webio.hu/por/2005/11/1/0053

CASE REPORT

Familial Cystic Nephroma in Two Siblings with Pleuropulmonary Blastoma

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Cystic nephroma (CN) and pleuropulmonary blastoma (PPB) are rare tumors. In the cases presented here, a 13-month-old boy underwent right radical nephrectomy for CN. From the family history we learned that four years ago the patient's older sister underwent left radical nephrectomy for CN at a different center when she was 4 years old. A lung tumor was detected in the sister one year after nephrectomy. Biopsy from the lung tumor revealed PPB, and the sister died within one year after biopsy. To the knowledge of the authors, these cases represent the second reported familial occurrence of CN and the fourth of CN and PPB. (Pathology Oncology Research Vol 11, No 1, 53–56)

Key words: Cystic nephroma, familial tumors, pleuropulmonary blastoma

Introduction

Cystic nephroma (CN) and pleuropulmonary blastoma (PPB) are rare tumors that are usually diagnosed in childhood.[1-13] CN is a very rare, benign cystic kidney tumor of uncertain etiology.[9-13] Many different designations are used for this entity in the literature, namely, cystadenoma, cystic renal hamartoma, polycystic nephroma, and papillary cystadenoma.[10] These masses may be found in patients from the neonatal age to the age of 70-80 years, but most are diagnosed in children. Pediatric CN is most frequent in boys younger than 4 years, and girls older than 4 years.[10,12,13] The most common presenting symptoms are painless abdominal mass, abdominal or flank pain, and hematuria.[9,10,12] To the best of our knowledge only one case of familial CN has been reported in the English literature.[1]

PPB is an intrathoracic malignant neoplasm that typically occurs in children less than 5 years old.[1-8] These tumors arise from the lung and/or the pleura, and develop from blastemal elements.[1] Dysplastic or neoplastic diseases in the same patient or in close family members have been reported in 25% of the PPB cases documented to date.[2-4] More than 70% of patients with PPB exhibit right-side involvement.[1-7] Children with these tumors tend to present with signs and symptoms of respiratory distress, fever, chest pain and cough. In most cases, these problems are initially attributed to infection or spontaneous pneumothorax. Histologically, PPBs exhibit a primitive, variably mixed blastematous and sarcomatous appearance.[1-7] They are classified as type 1 (purely cystic), type 2 (cystic and solid) or type 3 (purely solid).[1-4]

Synchronous occurrence of these two neoplasms has been reported previously,[1,2] and Delahunt et al documented this in three siblings.[1] In this report, we describe two siblings with CN, one of them with PPB. As far as we know, our report is the second case of CN diagnosed in siblings and the fourth case of PPB diagnosed together with CN.

Cases

A 13-month-old boy presented with signs of right-sided abdominal pain. A tender mass was detected on physical examination, by ultrasonography and CT revealed a multicystic mass occupying the middle and upper portions of the baby's right kidney. The lesion contained thin septae and appeared to have no solid components. Intravenous pyelography showed pelvicalyceal dilatation in the right

Received: Jan 4, 2005; *accepted:* Febr 5, 2005

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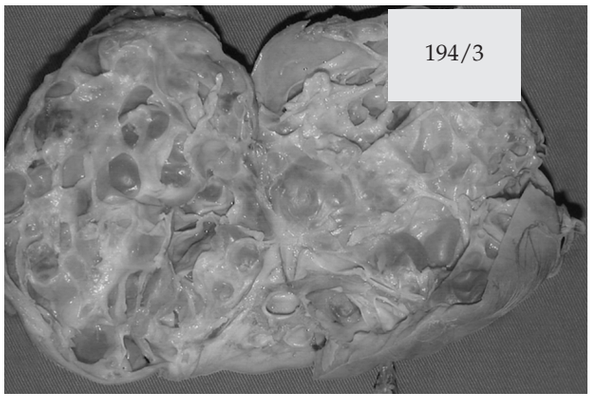

Figure 1. *13-month-old boy. Right kidney with cystic nephroma.*

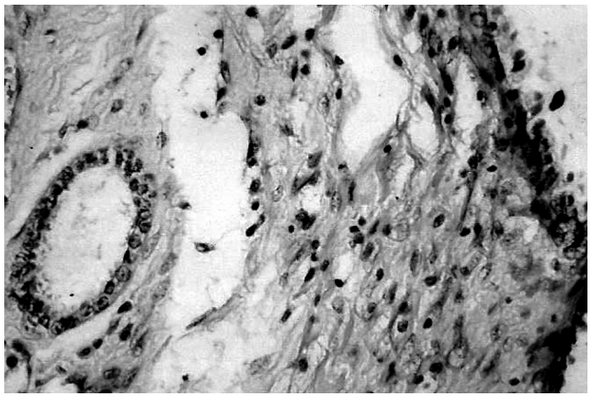

Figure 2. *Cysts lined with flattened cuboidal or hobnail epithelium (HE, x400)*

kidney. Computerized tomography of the chest was found normal.

Right radical nephrectomy was performed, and the resected specimen weighed 638 g. Gross inspection revealed a large multilocular cystic tumor originated from the middle and upper parts of the kidney. The mass was within a thin pseudocapsule, and it measured 14x10x10 cm. A cut section showed a multilocular cystic lesion composed of non-communicating fluid-filled cysts of various sizes separated by thin or relatively thicker fibrous septae. The mass was clearly demarcated from the surrounding normal renal tissue (*Figure 1*). Based on gross appearance, we tentatively diagnosed the lesion as a multicystic nephroma.

Microscopic examination revealed that the cyst walls were lined with a layer of flattened or hobnail cuboidal epithelium (*Figure 2*). The septae were mainly composed of fibrous tissue, and contained dilated vessels. In some areas, the septae were edematous and contained focal aggregates of lymphocytes and occasional tubular structures (*Figure 3*). No blastemal or poorly differentiated tissue was observed, and the histological features were compatible with CN.

On obtaining a detailed history, we learned that four years earlier the patient's older sister had undergone left nephrectomy in another hospital for a cystic mass in her left kidney. We obtained her reports and learned that she was 4 years old at that time. The surgical specimen from this patient weighed 500 g. The tumor measured 11x6x8 cm and appeared cystic. Cut section revealed a multiloculated cystic mass occupying the lower pole of the kidney, and dilatation of the pelvicalyceal structures. Based on gross appearance, the mass was diagnosed as CN.

The girl was followed closely for 1 year after nephrectomy, and a lung tumor was detected during this period. Biopsy revealed PPB, and the patient died within one year after biopsy.

Microscopically, the sister's kidney and lung lesion appeared histologically identical. The specimen deriving from the pulmonary neoplasm was very small. It contained areas of necrosis and small, atypical oval, circular cells with hyperchromatic nuclei, which resembled spindle blastemal cells (*Figure 4*). The diagnosis was PPB.

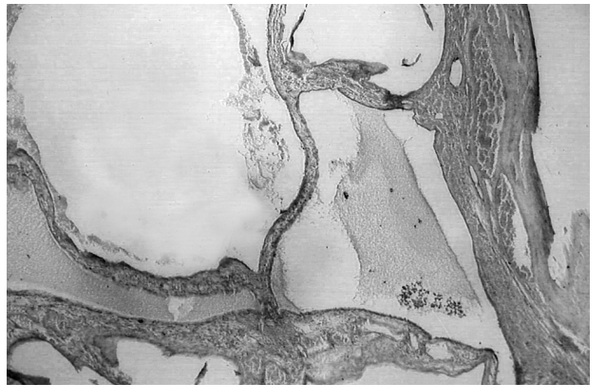

Figure 3. *Cystic nephroma of right kidney of the patient, containing large cysts with epithelial lining (HE, x100)*

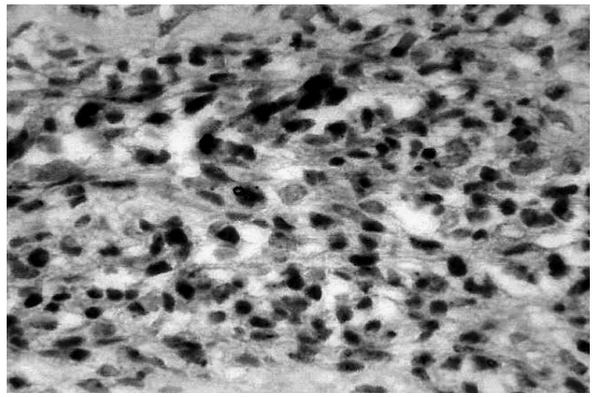

Figure 4. *Pleuropulmonary blastoma. Histology of the pulmonary mass showed small, atypical oval, circular cells with hyperchromatic nuclei, which resembled spindle blastemal cells (HE, x400)*

For cytogenetic examination, 2 ml of heparinized peripheral blood sample was obtained from the 13-month-old boy and the parents. Peripheral blood lymphocyte cultures were set up in RPMI 1640 medium containing 20% fetal calf serum, 1.5% phytohemagglutinine, 1% 200 mM L-glutamine, 100 U/ml penicillin and 100 mg/ml streptomycine.[14] Colchicine was added to the cultures at the 68th hour, and chromosome harvesting and trypsin-Giemsa banding were performed according to standard protocols.[15] At least 20 metaphases were analyzed. Peripheral blood samples obtained from all family members revealed normal karyotypes.

A periodic follow-up program was suggested to the patient, and was consigned to another oncology center. Other relatives were not screened for CN, PPB or other tumors.

Discussion

CN was first described in 1892 by Edmunds who called the lesion "Cystadenoma of the kidney".[9,13] These benign tumors are well-circumscribed encapsulated masses that contain multiple, non-communicating, fluid-filled cysts. The cysts are lined by epithelium and separated by distinct stroma, and a clear line distinguishes neoplastic tissue from normal renal parenchyma.[9,13]

Powell et al proposed eight criteria in CN diagnosis, and these were later modified by Boggs and Kimmelstiel and by Joshi and Beckwith.[9] The currently accepted criteria are as follows: 1) unilateral involvement, 2) solitary, 3) multilocular, 4) no communication among the cysts, 5) locules lined with epithelium, 6) no fully developed nephrons in the interlocular septae, 7) normal residual renal tissue, and 8) no communication with the renal pelvis.[9-12] Our two cases fulfilled all of these conditions.

The association of CN with primitive renal elements similar to those seen in Wilms' tumor (WT) led to the conclusion that CN is a differentiated form of WT. If pathological examination of a resected specimen reveals blastemal cellular elements between the cysts, then the diagnosis is cystic partially differentiated nephroblastoma, a very rare, low-grade malignant tumor.[9] This is a separate entity with characteristics that are intermediate between WT and CN. There were no primitive cellular elements in our two cases.

PPB was first described in 1952, and its morphology is similar to that of WT. Previous reports have suggested that PPB is actually mediastinal WT containing both blastemal and sarcomatous elements.[1] The biological importance of this neoplasm is its potential as a marker for predisposition to dysplastic or neoplastic disease in the patient or in close family members.[2-4] Such conditions include synovial sarcoma, acute lymphoblastic leukemia, malignant germ cell tumor of the testis, thyroid carcinoma, medulloblastoma, Langerhans' cell histiocytosis, mature cystic teratoma of the ovary, and CN.[3] The frequent association of PPB with other neoplasms in close family members suggests oncogenetic factors. Family history is very important when evaluating patients with this tumor type.[3]

It is postulated that a familial tumor can only develop if an individual inherits the germline mutation, and also that actual tumor occurrence requires a second mutation.[1] The latter mutation is thought to take place in the early stages of embryogenesis, and to cause blastemal tumors.[1,2] Trisomy 8 was detected in cases of PPB.[8] Some investigators showed Wilms' tumor suppressor gene (WT1) abnormality in one patient with both PPB and intralobar nephroblastomatosis.[4] This finding is not specific to this neoplasm; it is a feature of several other solid malignancies in children. However, in clinical practice, the finding of trisomy 8 in a child with a thoracic tumor that displays morphologic features compatible with PPB lends considerable support to the diagnosis of PPB.[4-8] We did not observe abnormal karyotypes in the parents and their son. However, this does not exclude the presence of a mutation in one of the parents, resulting in susceptibility to develop these tumors in two siblings.

As noted above, synchronous occurrence of CN and PPB in the same patient has been reported previously.[2,4] However, our cases are of particular interest because both siblings had CN, which is very rare, and one also had PPB. *Delahunt et al*. documented CN in two of three siblings.[1] They also detected PPB in the third child. In the cases described here, the older child had a mass detected in her right lung during the year after she was operated for CN. Biopsy of the lung mass revealed PPB. The detection of both tumor types in these two siblings is strong evidence that oncogenetic factors play a role in the development of these neoplasms.[3] Based on the literature to date, the incidence and distribution of CN and PPB indicates that the majority of these tumors are not inherited, but result from sporadic genetic mutations.[1] The occurrence of these tumors in our patients may have been the result of inheritance of a sporadic gene mutation.

Although CN is a benign tumor, children with a past history of CN need a close follow-up for development of this and other forms of neoplasia. Though genetic factors have not been suggested as a major etiologic factor, tumor development is a multistep process, and genetic tests, probably mutation screening of protooncogenes and tumor suppressor genes could be performed in such patients.

In conclusion, we suggest that genetic analysis, such as the presence of trisomy 8, WT1 gene abnormality, and the development of other tumors should be investigated in patients with CN and/or PPB and in their relatives.

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