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Judicious *DICER1* Testing and Surveillance Imaging Facilitates Early Diagnosis and Cure of Pleuropulmonary blastoma

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Abstract

Pleuropulmonary blastoma (PPB) and Sertoli-Leydig cell tumor (SLCT) are both associated with germline mutations in *DICER1*. In this brief report, a maternal history of SLCT led to identification of a deleterious *DICER1* mutation in the patient and her asymptomatic infant. Radiographic screening revealed a large Type I PPB which was completely resected. Identification of *DICER1* mutation carriers and imaging of children at risk for PPB may allow detection of PPB in its earliest and most curable form, leading to increased likelihood of surgical cure and decreased risks of treatment-related late effects.

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Keywords

Pleuropulmonary blastoma; *DICER1*; Sertoli-Leydig cell tumor; lung cysts; genetic testing

Introduction

PPB is a rare but potentially aggressive tumor of the lung. More than 90% of PPB cases are diagnosed in children under 72 months of age. PPB is believed to progress along a continuum from Type I, a purely cystic lesion diagnosed at a median age of 9 months, to Type II PPB, a mixed cystic and solid lesion diagnosed at a median age of 36 months, to Type III PPB, a solid, aggressive sarcoma diagnosed at a median age of 43 months. [1,2] Survival rate decreases along the continuum with overall survival (OS) of >90% for Type I PPB, [3] 75% for Type II PPB and 58% for Type III PPB. [4] For Type I PPB, treatment includes complete surgical excision followed by observation alone or complete surgical excision followed by intermediate intensity chemotherapy. For Types II and III PPB, surgical resection followed by intensive, anthracycline-based chemotherapy with or without radiation therapy are required for cure. [5] Based on this data, patients diagnosed at the Type I stage will have improved survival and decreased toxicity from chemotherapy.

Case Report

A 33-year-old woman with a history of ovarian Sertoli-Leydig cell tumor (SLCT) enrolled in the International Ovarian and Testicular Stromal Tumor (OTST) Registry. She presented at 17 years of age with amenorrhea. Imaging revealed a pelvic mass measuring 11 cm in largest diameter. She underwent a left oophorectomy. Pathologic examination showed SLCT with intermediate differentiation. No adjuvant therapy was administered and she remains well 15 years following diagnosis. Family history is remarkable for multiple relatives with thyroid nodules and thyroid cancer. Germline *DICER1* testing showed a heterozygous loss of function mutation.

Umbilical cord blood from her third child, sampled at the time of delivery, showed inheritance of the same deleterious germline *DICER1* mutation. A chest radiograph at birth was normal. The child was clinically well without respiratory symptoms. Following the recommendation of the International Pleuropulmonary Blastoma Registry (IPPBR) physicians, the infant underwent computed tomography (CT) at 3 months of age. CT images revealed an 8.8 × 6.2 × 3.1 cm multi-septated cyst in the right lower lobe (RLL) without mediastinal shift (Figure 1). Preoperative planning involved the oncology, surgery and pathology teams. A thorascopic RLL lobectomy was performed taking care not to disrupt the cyst upon removal from the chest cavity. Pathologic examination showed a lung cyst and long interconnecting septa with variable cellularity. No well-developed cambium layers were noted, but there were scattered subepithelial collections of primitive, mitotically active cells (Figure 2). The cyst did not extend to the surgical resection margin. The final pathologic diagnosis was Type I PPB.

DICER1 testing also showed an identical mutation in the 5-year-old brother. His initial screening chest CT was normal. To screen for cystic nephroma, abdominal ultrasounds were performed in both children and were normal.

Discussion

PPB is the hallmark of the familial cancer predisposition syndrome recently attributed to germline mutations in *DICER1* [6] (OMIM # 606200, 606241). Other conditions seen in the syndrome include ovarian SLCT, cystic nephroma (CN), ciliary body medulloepithelioma (CBME), embryonal rhabdomyosarcoma of the uterine cervix (ERMS), nasal chondromesenchymal hamartoma (NCMH), thyroid nodular hyperplasia and thyroid carcinoma and rarely, Wilms tumor and central nervous system tumors. [7-9] Testing has shown germline *DICER1* mutations in 65.5% of patients with PPB. When germline and tumor DNA from patients with PPB and CN are both analyzed, the incidence of *DICER1* mutations is nearly 100%. [10,11,12] In PPB and CN, *DICER1* incurs two hits, one, a loss of function mutation and the second, a missense mutation in one of six amino acids in the RNase IIIb domain. The combination of mutations result in defective cleavage of the mature miRNA from the 5p end of precursor miRNAs and may promote cell proliferation and immaturity. [7,10] The International OTST Registry has found germline *DICER1* mutations in 56% of SLCT as well as in a small number of juvenile granulosa cell tumor and gynandroblastoma cases (unpublished data, accepted for presentation at American Society of Clinical Oncology meeting in June 2014).[13-15] The incidence of tumor *DICER1* mutations in ERMS is 3.8%, [7] but expected to be much higher in the subset occurring in the uterine cervix. *DICER1* mutations appear rare in Wilms tumors. [10,16-18] The incidence of *DICER1* mutations in other tumors seen within the familial syndrome is not as well studied. [10,16-18]

Treating physicians may consider who should be tested for *DICER1* mutation. The OTST Registry and IPPBR recommend that individuals of any age with one of the typical *DICER1*-related conditions be tested for germline *DICER1* mutation with parents, siblings and children tested as indicated by the result. [19] A normal germline *DICER1* sequence result from an affected individual may indicate they do not have a germline *DICER1* mutation or that they have a mutation not detected by standard sequencing as in the case of a deletion or intronic mutation. [20] Further, tumors may arise from somatic alterations of each the *DICER1* alleles in patients who do not have germline mutations. [9]

Although children with germline *DICER1* mutations are at risk for PPB, the optimal timing and number of radiographic studies which should be performed for early detection in children with germline *DICER1* mutations has not been established. Based on the epidemiology of PPB, with > 90% of PPB cases diagnosed before 72 months of age, screening should focus on young children. Chest radiograph may miss small cysts which may progress rapidly to aggressive forms of PPB. CT offers higher sensitivity especially for small lesions but is accompanied by radiation exposure and potential need for sedation. Formal recommendations for surveillance have not yet been defined. However, based on available information, the IPPBR suggests treating physicians consider an initial chest CT (using pediatric doses) at 3 months of age. If a cyst is identified, as in this case, then surgical management should be considered. If no concerning findings are seen on initial chest CT,

then one additional CT is recommended (between 1 and 2 years). This child, with resected Type I PPB, will undergo follow-up imaging 3 months after surgery with further plans determined by the results of that study.

In addition to chest imaging, the IPPBR recommends abdominal ultrasound to screen for CN during childhood. Age of diagnosis of CN in the PPB Registry ranged from 1-179 months. [10] Germline *DICER1* mutations also predispose to thyroid nodular hyperplasia. Mutation carriers should undergo annual thyroid palpation during their regular health care visits. Ultrasound should be obtained if suspicious findings are noted. Patients, parents and physicians should also be educated about signs and symptoms of ovarian tumors, eye tumors, and nasal polyps in older children and adults with germline mutations in *DICER1*.

This case demonstrates the potential for early identification of PPB to prevent progression to the more aggressive and potentially fatal Type II or III PPB. Preemptive testing for *DICER1* in an appropriate clinical setting followed by judicious screening of others in the family most at risk for *DICER1*-related cancers may increase the likelihood of early identification of PPB with opportunities for surgical cure and decreased long term morbidities related to the administration of chemotherapy and/or radiation in early childhood.

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Figure 1.

A) Chest radiograph performed at 3 months of age showing cystic lesion in right lower lobe.

B) Computed tomography of the chest performed at 3 months of age showing an $8.8 \times 6.2 \times 3.1$ multi-septated cyst in the right lower lobe.

Figure 2.

Pathologic examination showed characteristic features of Type I PPB. A) The lung cyst shows long interconnecting septa with variable cellularity. B) Small cartilage nodules were seen focally. C,D) No well-developed cambium layers were noted, but there were scattered subepithelial collections of primitive, mitotically active cells. (Hematoxylin and eosin: original magnification $\times 100$ (A); $\times 200$ (B); $\times 400$ (C,D)).