Rhabdoid Tumor Predisposition Syndrome and Pleuropulmonary Blastoma Syndrome

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Abstract

Keywords

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In recent years, hereditary cancer syndromes have developed greater interest in the scientific community. Two such syndromes, rhabdoid tumor syndrome and pleuropulmonary blastoma (DICER1) syndrome, have appeared increasingly in the literature. This review will discuss these two syndromes in terms of clinical parameters, associated tumors, and genetic associations.

Introduction

There are several hereditary cancer syndromes that can affect people in the earliest years of life and in some cases extend into adulthood. Many of these are familiar, including the neurofibromatoses, Li–Fraumeni syndrome, and retinoblastoma syndrome. These better known syndromes have been tirelessly studied and have been the subject of numerous manuscripts throughout the English and world literature.

In addition to these well-known syndromes, there are more recently described hereditary cancer syndromes that are not as widely known. Two of these are the rhabdoid tumor predisposition syndrome and the pleuropulmonary blastoma (PPB) syndrome. In each of these syndromes, affected individuals present with a constellation of different tumors which have been linked to a specific gene. This review will address each of these syndromes individually, including clinical presentation and associated tumors, genetic correlation, and prognosis.

Rhabdoid Tumor Predisposition Syndrome

The term “rhabdoid tumor predisposition syndrome” was proposed in 1999 by Sévenet et al¹ to encompass a variety of malignancies which are linked by mutations in the SMARCB1 (also known as *hSNFS* and *INI1*) gene. Rhabdoid tumors disproportionately affect the pediatric population and are some of the most lethal, aggressive malignancies encountered in medicine.^{1,2} Malignant rhabdoid tumor, the first tumor described with the SMARCB1 mutation and the tumor for which the predisposition syndrome was named, was initially described as a tumor of the kidney in pediatric patients. The term malignant rhabdoid tumor was coined by Beckwith and Palmer in 1978 as a variant of Wilms tumor.¹ As pathologists learned the appearance of the disease, malignant rhabdoid tumors were described in numerous extrarenal sites,^{1,2} although the kidney and brain continue to be the most commonly involved organs. The tumors are also named depending upon the site of origin; in the kidney, the tumor

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is referred to as malignant rhabdoid tumor, in the liver and soft tissues the tumor is referred to as malignant rhabdoid tumor of the liver and soft tissues, and in the central nervous system the tumor is referred to as atypical teratoid/rhabdoid tumor.^{3,4}

As was mentioned earlier, these tumors are most commonly seen in the pediatric population. Most of these patients are under the age of 2 years at the time of initial diagnosis.³ Many of these affected children also have affected family members when disease pedigrees are examined.³ There are also sporadic malignant rhabdoid tumors with similar genetic profiles⁴ but these are outside the scope of this article. Once these tumors are diagnosed, treatment decisions are based upon the age of the patient, the location of the tumor, and the clinical stage. Age of the patient appears to be the most critical prognostic factor, as younger patients have a much poorer prognosis.²

The SMARCB1 gene is located on chromosome 22q11.2.^{1,2,4-6} In 1999, Sévenet et al were able to establish that SMARCB1 mutations were identified not only in malignant rhabdoid tumor of the kidney, but also in extrarenal malignant rhabdoid tumors and many different central nervous system tumors including medulloblastoma, choroid plexus carcinoma, and primitive neuroectodermal tumor.¹ In 2000, Roberts et al performed an extensive mouse study; in their model, mice who were heterozygotes for SMARCB1 began to develop malignant rhabdoid-like tumors as early as 5 weeks of age.⁷ This led to the important conclusion that SMARCB1 functions as a tumor suppressor gene. In fact, acquired somatic biallelic inactivating truncating mutations are identified in rhabdoid tumors regardless of the presence of a germline mutation, further supporting SMARCB1 as a tumor suppressor gene.² The mice (and human children as well) were born phenotypically normal, but present with disease at young ages.⁶

Most of the discoveries regarding the genetics of the rhabdoid tumor predisposition syndrome occurred in the second half of the last decade of the 20th century and the first half of the first decade of the 21st century. However, in 2006, Frühwald et al proposed that there might actually be a second locus involved in predisposition to rhabdoid tumors.⁶ They reported a family of two healthy parents that gave birth to two children who developed malignant rhabdoid tumor. There were three children total.⁶ The two affected children presented at 8 and 7 months, respectively, and ended up dying of their diseases at 10 and 18 months. The authors used karyotype analysis, fluorescence in situ hybridization, polymerase chain reaction, comparative genomic hybridization, and immunohistochemistry to demonstrate that a mutation was indeed present; however, the patients were both wild type for the SMARCB1 gene.⁶ They believed that this finding indicated an involved locus somewhere other than 22q11.2. Another group demonstrated a single case with a mutation in *SMARCA4*.² However, more cases would be needed to demonstrate if this gene is also truly involved in rhabdoid tumor predisposition syndrome.

If there is clinical suspicion for rhabdoid tumor predisposition syndrome, tumor should be sampled at the time of either biopsy or resection with frozen or formalin-fixed,

paraffin-embedded tissue submitted for SMARCB1 or SMARCA4 genetic testing. As in most genetic testing, fresh-frozen tissue is preferred, but the assay can be performed on formalin-fixed, paraffin-embedded tissue.² If the testing is positive, all family members (parents and siblings) should be screened for somatic mutations in the implicated gene.

Lastly, there is a reported link between rhabdoid tumor predisposition syndrome and neurofibromatosis type 2 (NF2), as both can demonstrate mutations in the SMARCB1 gene.² SMARCB1 lies close to the NF2 locus on chromosome 22; however, multiple families with NF2 demonstrate mutations in the SMARCB1 gene.² In the latter half of the last decade, it was suggested that there is a "four-hit" model responsible for the tumors identified in some NF2 kindreds.⁸ The first "hit" is a germline mutation of SMARCB1. The second and third "hits" are a loss of the portion of chromosome 22 that contains both NF2 and the second SMARCB1 allele. The final "hit" involves a mutation in the second NF2 allele.⁸ This model may provide a plausible explanation as to why SMARCB1 mutations may be observed in NF2 patients.

In conclusion, rhabdoid tumors are extremely aggressive malignant neoplasms most commonly seen in the pediatric population. Even with prompt diagnosis and treatment, the prognosis is uniformly poor, with death occurring within months of the initial diagnosis. If a rhabdoid tumor is identified, genetic testing should be performed on all family members to rule out the possibility of rhabdoid tumor predisposition syndrome.

Pleuropulmonary Blastoma (DICER1) Syndrome

PPB was originally described in a series of 11 cases by Manivel et al in 1988.⁹ In their series, each of the 11 patients demonstrated intrathoracic (mediastinal, pleural based, or intrapulmonary) tumors which shared a distinct histologic characteristic: the presence of small round blue cells with blastema-like features separated by an undifferentiated stroma.⁹ There were foci of chondrosarcomatous, liposarcomatous, and rhabdomyosarcomatous differentiation in some of the tumors. The patients were all pediatric with age at the time of presentation ranging from 2.5 to 12 years. Of the 11 patients, 7 died of their diseases with an interval of 5 to 24 months after the initial diagnosis.⁹ This entity was originally reported in the literature as "pulmonary blastoma in children," as pulmonary blastoma is an adult entity; however, the authors felt strongly that this diagnosis was an entity distinct from adult pulmonary blastoma and time and time again they would be proven correct.

In 1993, Delahunt et al¹⁰ reported a family of three siblings, two of whom were diagnosed with cystic nephroma, and one was diagnosed with PPB. This was the first time in which any familial connection was seen with these tumors. Cystic nephroma is a rare renal neoplasm thought to be on the benign end of the spectrum with Wilms tumor.¹⁰ An intermediate lesion, cystic partially differentiated nephroma shares many of the histologic characteristics of cystic nephroma but also contains blastemal elements within the septa of

the cysts.¹¹ Cystic nephroma most commonly occurs in the first 2 years of life in the pediatric variant, which is distinct from the variant that occurs in adults.

As the clinical association between PPB and cystic nephroma grew stronger, researchers began to search for a possible genetic association between the two tumors. Bouron-Dal Soglio et al made an attempt at a genetic link, citing an association with several chromosomes and genes; however, they could not link the two tumors to a specific gene.¹¹ Sciò et al attempted to link PPB to other embryonic tumors.¹² In the patient they examined, there were abnormalities of chromosome 2q; this abnormality can also be seen in hepatoblastoma and embryonal rhabdomyosarcoma, leading them to suggest a potential link.¹² In 2003, Hong et al reported a complex karyotype of a PPB which included a trisomy of chromosome 2.¹³ This was followed by a report of several patients in which gains of chromosome 8q was shown to be a frequent finding in PPB.¹⁴

In 2009, the study that changed the way we observe familial PPB was published. Hill et al¹⁵ reported for the first time that the *DICER1* gene was mutated in these tumors. Twenty percent of children with PPB will harbor another tumor; cystic nephroma was among the most common. In their study of 15 patients, Hill and colleagues mapped the PPB locus to chromosome 14q and found mutations in *DICER1* in every patient's tumor, leading them to implicate *DICER1* mutations as a causative event in the development of these tumors.¹⁵

The *DICER1* gene product is a ribonuclease (RNAse) III endonuclease which plays a role in the production of micro-RNAs and small interfering RNAs.¹⁵ It is also important in lung development. In most patients, the mutation is a germline heterozygous mutation leading to truncation of RNAse III endonuclease, resulting in a loss of function.¹⁵

Since 2009, the number of tumors with *DICER1* mutations has expanded. The PPB, or *DICER1* syndrome now, in addition to cystic nephroma, includes ovarian sex cord-stromal tumors, ciliary body medulloepithelioma, embryonal rhabdomyosarcoma, botryoid variant, pineoblastoma, pituitary blastoma, thyroid nodular hyperplasia, and thyroid cancers.^{16–18} In one study, *DICER1* mutations were seen in the above-listed tumors, and in some cohorts, PPB was never diagnosed in the family despite having the mutation. The authors suggested that the syndrome be renamed the *DICER1* syndrome to include families that do not have PPB but demonstrate the appropriate mutation.¹⁸ Furthermore, both Hill et al and Slade et al acknowledge that the *DICER1* mutation follows a haploinsufficiency model^{15,18} which is different from other known cancer predisposition genes.

The study provided by Slade et al also demonstrates that penetrance of *DICER1* mutations is low, and most carriers of *DICER1* mutations do not go on to develop neoplasms. This obviously creates issues for treating clinicians.¹⁸ Even if one member of a family develops a *DICER1*-related tumor and the rest of the family is screened, the other family members are at low risk even if a mutation is discovered. Currently, the only screening performed in *DICER1* families is lung computed tomography; in pediatric patients, this must be done under

sedation and has the added risk of radiation exposure.¹⁵ At this time, routine screening of *DICER1* mutation-positive individuals is not recommended.

The *DICER1* syndrome represents a constellation of neoplasms, most commonly PPB, cystic nephroma, and ovarian sex cord-stromal tumors, which have familial predisposition. Of these, PPB is the most aggressive, resulting in death in most patients within 5 months to 2 years of diagnosis. The penetrance of the mutation is low, and most mutation carriers never develop neoplasms.

Conclusion

The two syndromes presented are both rare in the pediatric population. However, that is where the similarities end. The rhabdoid tumor predisposition syndrome is inherently deadly in that rhabdoid tumors are some of the most malignant known to man. The life expectancy of these individuals is on the order of months. The *DICER1* syndrome has a low penetrance, giving mutation positive carriers a chance at a normal life span. Research continues on these newer cancer predisposition syndromes and there is likely much more to discover and learn.

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