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Common Neoplasms of DICER1 Syndrome in Pediatric Pathology

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Abstract

DICER1 syndrome is an autosomal dominant tumor predisposition disorder with a DICER1 germline mutation, and it frequently appears in the practice of pediatric pathology. Here the common diseases of DICER1 syndrome have been reviewed with epidemiologic and histopathologic features, such as pleuropulmonary blastoma (PPB), cystic nephroma, embryonal rhabdomyosarcoma, and Sertoli-Leydig cell tumor. During routine practice, these histopathologic findings should be paid attention for the possible DICER1-related neoplasm and potential detection of DICER1 mutation clinically.

Keywords: DICER1; Pleuropulmonary Blastoma (PPB); Cystic Nephroma, Embryonal Rhabdomyosarcoma; Sertoli-Leydig Cell Tumor

Abbreviations

PPB: Pleuropulmonary Blastoma; SLCT: Sertoli-Leydig Cell Tumor; CPDN: Cystic Partially Differentiated Nephroblastoma.

Introduction

Dicer protein is a ribonuclease (RNase) III endoribonuclease to produce microRNAs (miRNA) by the cleavage of pre-miRNA or double-stranded RNA [1-3]. Dicer protein is generated by DICER1 gene, located at chromosome 14q32.13.

By the interaction with mRNA, miRNA is important to regulate the expression of protein-coding genes [4]. Research studies indicated that DICER1 gene is crucial for organ development because there would be developmental arrest and death of the embryo when both alleles are lost [5,6]. Biologically, DICER1 gene could function as a tumor suppressor gene due to loss-of-function mutations or an oncogene due to gain-of-function mutations. Many of the neoplasms in DICER1 syndrome harbor one inherited DICER1 mutation and an acquired somatic missense DICER1 mutation [7,8]. Here several common neoplasms of DICER1 syndrome in pediatric pathology would be reviewed.

Pleuropulmonary Blastoma (PPB)

PPB is the embryonal tumor of lung and pleura with epithelial and mesenchymal components and this tumor is presented often in early childhood with majority of them in less than 6 years old. There are three types of PPB, basically based on its gross features of cystic or solid, including type I PPB (cystic), type II PPB (cystic and solid), and type III PPB (solid).

Grossly, type I PPB arises from the peripheral and presents as a multicystic well-demarcated lesion. Histologically, type I PPB is characterized with large cysts lined by benign single layer of cuboidal to flattened epithelium and subepithelial layer of small primitive round cells with or without rhabdomyoblastic differentiation. The small primitive round cells are also called as "cambium-like layer". Type 1r (regressed) PPB presented as type 1 PPB without subepithelial small primitive cells and needs to be diagnosed

after complete submission and examination of whole cyst. Type II PPB and type III PPB are grossly mass lesions. Type II PPB is differentiated from type III PPB by the presence of cystic lesion of type I PPB in addition to a mass. Solid areas in type II and III PPB are composed of higher grade sarcomatous which may be anaplastic, rhabdomyosarcomatous, or chondrosarcomatous components.

Immunohistochemical stains for desmin and myogenin could indicate rhabdomyoblastic differentiation. CD56 could be used as a primitive marker for primitive cells. p53 shows more positive in type II/III because the expression of p53 is significantly associated with recurrence-free survival and overall survival in PPB [9].

Pediatric Cystic Nephroma

Pediatric cystic nephroma usually occurs at or before 4-years of age. Grossly, it represents as a multiloculated cystic neoplasm presenting as a unilateral, well-demarcated renal mass. Histologically, the cystic structures are lined by a simple epithelium with flat, cuboidal or hobnail features and there is bland fibrous stroma with scattered entrapped benign tubular structures in septa. It is worth to mention that the differential diagnosis is Cystic Partially Differentiated Nephroblastoma (CPDN) with immature nephroblastic elements in stroma. Tumor progression from pediatric cystic nephroma to anaplastic sarcoma of kidney is extremely rare, which is histologically similar as type II or III PPB with or without anaplasia. Due to the possible rare progression to anaplastic sarcoma of kidney, an abdominal ultra sound is recommended during infancy at the time of a chest CT for PPB surveillance [10].

Embryonal Rhabdomyosarcoma of the Cervix and other Genitourinary Tract

Embryonal rhabdomyosarcoma of the cervix usually occurs in adolescents and young adults with a median age of 13–14 years. Histologically, this neoplasm typically has the features of the favorable botryoid embryonal rhabdomyosarcoma with a cambium layer and frequent foci of cartilage, which looks like a unique presentation of embryonal rhabdomyosarcoma with DICER1 mutation while there is no cartilage in the sporadic embryonal rhabdomyosarcoma. The differential diagnosis includes adenosarcoma.

Embryonal rhabdomyosarcomas with DICER1 syndrome have been reported arising elsewhere in the genitourinary tract, including three cases in the urinary bladder, one case in the fallopian tube, two cases in the ovary [11,12]. There is cambium-like layer and mature cartilage in embryonal rhabdomyosarcomas of the fallopian tube and ovaries.

Sertoli-Leydig Cell Tumor (SLCT)

SLCT is rare and represents less than 1% of primary ovarian tumors. The age ranges from infancy to later adult.

Grading is based on tubular differentiation of Sertoli cell component, including well differentiated with hollow or compressed tubules, moderately differentiated with compressed tubules, nests or sheets, and poorly differentiated with diffuse sheets with sarcomatoid features. In DICER1 syndrome, most SLCTs are moderately or poorly differentiated. Heterologous elements of cartilage and rhabdomyosarcoma is not uncommon. Compared to the sporadic SLCT, DICER1-associated SLCTs usually present at a younger age [13]. A study identified a DICER1 mutation in 60% of SLCTs, thus it is beneficial to test DICER1 mutation especially in the younger age patients with moderately to poorly differentiated SLCTs [14].

Conclusion

DICER1 syndrome is one of the common syndromes in childhood and it appears frequently in routine practice of pediatric pathology. The first report in DICER1 syndrome is the case of PPB [15] and many cases have been reported since that [16-18]. Interestingly, some of the organs affected by DICER1 mutation, such as lung and kidney, have branching morphogenesis for normal development. The mutations of DICER1 gene may interrupt the normal branching process and in turn causes cystic lesions. Some of the tumors are cystic in the early stage while progress into solid at later or progressive stage, such as PPB and pediatric cystic nephroma. TP53 mutation could participate in the progression to a DICER1-associated neoplasm acting as an additional mutation. There are other neoplasms associated with DICER1 syndrome which are not discussed in this review, and we here only focus on the common neoplasms in routine practice of pediatric pathology. DICER1 syndrome is a cancer predisposition syndrome with germline mutation, so it is essential to bring up the potential molecular test for the family when there is a positive DICER1 mutation which is important for the practice in pediatric pathology.

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