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CASE REPORT

Familial Renal Tumor Associated with a Novel Loss-of-Function Germline Variant in DICER1

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ABSTRACT

We present a case of a 2-year-old girl with a clinically diagnosed Wilms tumor, which after surgical removal appeared to be a pediatric cystic nephroma. A heterozygous germline variant in the DICER1 gene, that has not been previously reported in literature, was detected in the patient and her relatives. Heterozygous germline pathogenic variants in DICER1 are proved to promote tumorigenesis and are associated with an increased risk of developing a variety of different tumors. The purpose of this case report is to illustrate the connection between a germline DICER1 variant and a familial renal tumor.

KEYWORDS

DICER1; Cystic nephroma; Haploinsufficiency; Familial renal tumor

INTRODUCTION

DICER1 encodes a protein that acts as a ribonuclease and is a haploin sufficient tumor suppressor gene [1,2]. Germline pathogenic variants in DICER1 gene are associated with DICER1 syndrome, inherited as an autosomal dominant condition. It is a genetic disorder leading to an increased risk of developing a variety of benign and malignant tumors. A heterozygous state of DICER1 gene is sufficient to predispose the development of neoplasms

[3,4]. Although the prevalence of this syndrome is unknown, it has been associated with pleuropulmonary blastomas (PPB), cystic nephroma (CN), Wilms tumor (WT), rhabdomyosarcoma, thyroid carcinoma, ovarian sex-cord-stromal tumors, especially Sertoli-Leydig cell tumor, and other neoplastic diseases [4-7]. CN is a benign cystic parenchymal renal tumor, usually affecting children younger than 4 years of age and is the most common renal tumor in individuals with DICER1 syndrome [4,8,9].

We describe a case of a familial renal tumor associated with a germline DICER1 loss-of-function variant that has not been reported before.

RESULTS

A 2 years and 9 months old girl was admitted to the Department of Pediatrics due to a palpable abdominal mass. A few days before her grandmother noticed an enlargement of the abdomen and found a painless derivation on the right side, no other symptoms were observed.

Family history revealed that the paternal uncle of the patient (Figure 1) at the age of 2 was clinically diagnosed with WT, which was surgically removed. In addition, he has a thyroid goiter. Proband's cousin is also diagnosed with thyroid goiter, histological examination did not reveal any abnormalities. Moreover, patient's paternal grandmother was diagnosed with *diabetes mellitus* at the age of 38. The proband was born from Vth pregnancy, during which her mother used Tybon 0.75 ng/day (Liothyronine). Birth and infancy were uncomplicated. At the age of 2 years 4 months the girl was examined by a pediatric endocrinologist and diagnosed with low degree protein-energy deficiency.

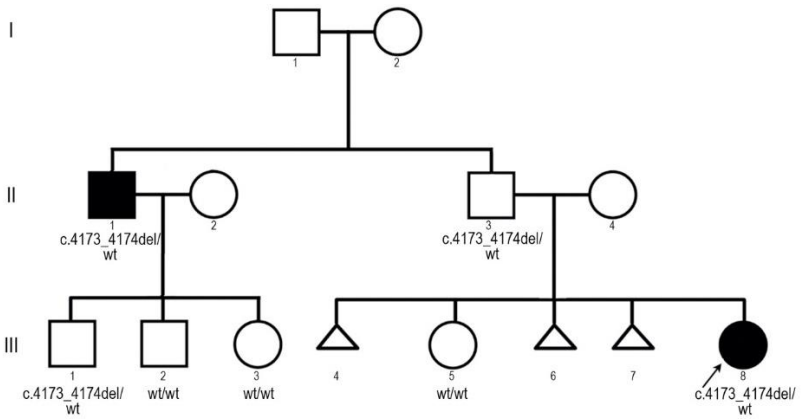

Figure 1: The genealogy of the family presenting a proband (III-8) and her affected uncle (II-1). The familial heterozygous *DICER1* variant was detected in affected individuals (black symbols), proband's father (II-3) and cousin (III-1).

During the examination at the time of admission the abdomen was soft, without any peritoneal irritation, a stiff structure of limited mobility was discovered under the right side of costal margin, about 7 cm in size. Abdominal ultrasound (US) showed a large cystic formation of about 97 mm protruding from the right kidney. The cysts inside of the formation were separated by abundant thick septa. Only a little of compressed renal parenchyma was found in the periphery.

Chest-abdominal-pelvis computed tomography (CT) was performed to evaluate tumor dissemination. No metastatic foci or infiltration were detected in the lungs. A large hypovascular tumor measuring 93 mm × 84 mm

× 81 mm with contrast enhancing septa was observed on the ventral surface of the right kidney. The rest of renal parenchyma was shifted dorsally. Laboratory tests did not display any changes.

A clinical diagnosis of right renal nephroblastoma (WT) was made. The patient underwent a 4-weeks neoadjuvant chemotherapy course that was initiated according to the UMBRELLA SIOP - RTSG 2016 protocol: vincristine and actinomycin D. After completion of chemotherapy abdomen CT was performed again in order to evaluate the effect of chemotherapy and examine tumor's contact with blood vessels before surgery. No significant changes were visualized as compared with the diagnostic imaging: no signs of local dissemination and no visible size dynamics. Chest-abdomen-pelvis magnetic resonance imaging (MRI) confirmed no change in the size of the tumor (Figure 2).

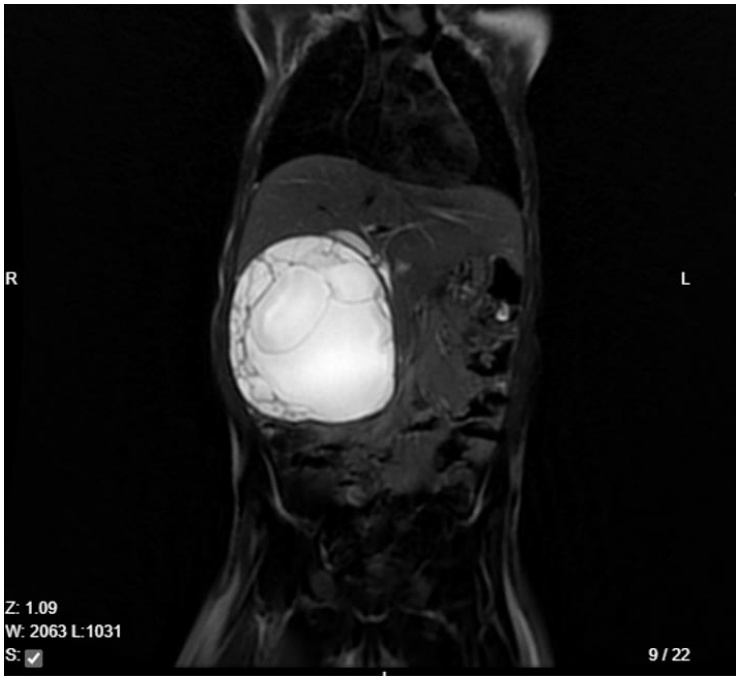

Figure 2: Chest-abdomen-pelvis MRI of the patient shows a large right kidney tumor with abundant septa. The tumor makes close contact with the liver. The gallbladder is compressed.

A right radical nephrectomy with lymph node biopsy was performed. Pathology evaluation showed kidney cystic nephroma (13.5 cm), radical tumor removal and reactive lymphadenopathy.

Due to history of renal tumors in the family, the patient was examined by a geneticist. Next generation sequencing was performed on genomic DNA of a proband using Core Exome Kit (Twist Bioscience) and genes, associated with childhood solid tumors and cancer susceptibility, were analyzed. A heterozygous variant NM_177438.2:c.4173_4174del in exon 22 of *DICER1* was detected. The variant had not been previously reported in the scientific literature or the Human Gene Mutation Database and was not found in reference population database GnomAD. In silico, this variant results in a translational frameshift of 4 amino acids and formation of premature termination codon thus resulting in a truncated 1392 amino acids protein NP_803187.1:p.Ser1392GlnfsTer4. Segregation analysis was performed and the familial variant of *DICER1* was identified in the proband's healthy father, affected uncle and healthy cousin (Figure 1). There was no possibility to analyze tumor sample for somatic *DICER1* variants.

DISCUSSION

CN is a rare, benign tumor that must be differentiated from other cystic renal tumors. Morphological similarities between CN and partially differentiated nephroblastoma can cause diagnostic errors as in our case [10]. Radical nephrectomy is the recommended choice of CN treatment in order to prevent the development of renal sarcoma [4,11].

Cancer predisposing syndromes (CPS) are of increasing importance in trying to understand the development of both benign and malignant tumors. *DICER1* syndrome is one of the most recently discovered CPS in children, first described in 2009 [1,9]. Since the recognition of this syndrome, it has been associated with a variety of different neoplasms, thus understanding of the *DICER1* role in tumorigenesis has been expanded. *DICER1* is a member of ribonuclease III family and modulates the expression of targeted genes [1]. Broad spectrum of associated neoplasms may be the result of disturbed miRNA processing in *DICER1* syndrome.

In a review by Robertson et al. [4], 88 *DICER1* germline pathogenic variants have been included, most of them predicted to be loss-of-function. Although DICER1 syndrome is characterized by a variety of renal tumors, including Wilms' tumor, renal sarcoma or nephroblastoma, cystic nephroma is the most common of renal manifestations. Bahubeshi et al. [12] first reported two families with multiple cystic nephroma and heterozygous germline *DICER1* variants, resulting in truncating proteins, which exclude ribonuclease III domain. In these two families, there were four affected individuals, one of them had bilateral CN, and one additionally had PPB. According to *Doros et al*. [11] germline truncating variants in *DICER1* have been detected *in* 13 of 18 (72%) *patients with CN. The reports of* adult patients with confirmed *DICER1* germline loss of function variants and a history of CN in childhood, followed by diagnoses of other cancers later in life, present additional evidence of variable expressivity of the disorder [13].

In our family, renal tumor manifested in two of four family members with germline pathogenic variant in *DICER1* gene. Although penetrance is not complete, genetic testing and counselling are highly recommended for individuals with a CN diagnosis and their family [2,4,10]. Along with *DICER1* germline pathogenic variant the acquired somatic in trans missense variant within *DICER1* hotspot loci occurs in most individuals with *DICER1* syndrome. Biallelic pathogenic variants in *DICER1* may increase prevalence or development of tumor, but other mechanisms may be possible patients with germline *DICER1* pathogenic variants require further surveillance. Screening recommendations have been established according to the location and type of tumor, age of onset, potential benefits of early detection and risks of screening procedures. As the overall prognosis for most individuals with *DICER1* syndrome is good, it is important to evaluate the potential risks and benefits of lifelong follow-up. To begin with, family and individual education about the disorder is strongly recommended. Specific surveillance guidelines for patients with renal tumors include abdominal US every 6 months to 12 months until at least 8 years of age. Annual US is recommended between 8 years and 12 years of age [2]. Surveillance and early detection of any suspicious changes are of great importance because the progression of CN to renal sarcoma has been reported [11,14].

In conclusion, this case demonstrates that germline *DICER1* frameshift variant c.4173_4174del can cause the development of a familial renal tumor. It is important to note that pediatric CN can be mistaken with WT and a

thorough, especially histological, examination is necessary to make a correct diagnosis. Our case also confirms the suggestion that patients with a pediatric CN diagnosis and their families should be tested for *DICER1* variants.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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