

A Pathogenic Germline BRCA1 Variant in a Patient With Cellular Congenital Mesoblastic Nephroma: A Case Report

Review began 07/27/2023

Review ended 08/18/2023

Published 08/21/2023

© Copyright 2023

Dholakia et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Gayatri Dholakia ¹, Julia Meade ²

1. Public Health, University of Pittsburgh, Pittsburgh, USA 2. Pediatrics, University of Pittsburgh Medical Center, Pittsburgh, USA

Corresponding author: Julia Meade, julia.meade@chp.edu

Abstract

Benign cystic tumors of the kidney are well-described in infants and young children. Here we report an infant diagnosed with a cellular congenital mesoblastic nephroma (CMN) with a germline pathogenic variant in BRCA1. This finding is novel because BRCA1 is an adult-onset cancer predisposition gene causing breast, ovarian, pancreatic, and prostate cancers. However, increasing studies are indicating the presence of germline BRCA1 in both malignant and benign childhood cancers.

Categories: Genetics, Pediatrics, Oncology

Keywords: case report, genetic syndromes, pediatric hematology-oncology, brca1 germline mutation, cystic nephroma

Introduction

Congenital mesoblastic nephromas (CMN) are the most common renal tumors in infancy [1]. Though they are pathologically distinct from other benign kidney tumors by the presence of an ETV6 fusion, they have not been associated with a germline cancer predisposition syndrome [2]. By contrast, cystic nephroma is well-associated with DICER1 syndrome, and genetic testing is recommended for any child with this diagnosis [3,4]. With a lack of associated cancer predisposition syndrome and clear guidelines for germline genetic testing in infants with CMN, panels limited to renal/urinary tract cancers, Wilms tumor or DICER1 may be used if genetic testing is taken out of context of the family history. Here, we report an infant with a CMN and a germline BRCA1 pathogenic variant, discovered via a comprehensive germline panel.

Case Presentation

A five-month-old boy presented with a three-day history of hematuria and blood clots in his diaper. The physical examination revealed a palpable right-sided abdominal mass and an atrophic right testis was also incidentally noted. An ultrasound revealed an 8.3 cm solid mass in the right kidney, which leads to a CT scan revealing a large, well-defined hypodense mass measuring $9.8 \times 7.9 \times 7.8$ cm with a volume of about 302 cm^3 arising from the inferior pole of the right kidney (Figure 1). Imaging demonstrated heterogeneous enhancement with areas of necrosis, and a claw sign on the mass suggested its origin from the kidney. The child underwent a right radical nephrectomy and right orchiectomy. The pathology report returned as a stage II cellular CMN. A $t(12;15)(p13;q26)$ translocation was consistent with an ETV6 fusion, though the partner gene was not identified by Fluorescence in-situ hybridization (FISH). Following surgery, no further adjuvant therapy was required. The child did well with no evidence of tumor recurrence, now seven years out from surgery.

How to cite this article

Dholakia G, Meade J (August 21, 2023) A Pathogenic Germline BRCA1 Variant in a Patient With Cellular Congenital Mesoblastic Nephroma: A Case Report. Cureus 15(8): e43857. DOI 10.7759/cureus.43857



FIGURE 1: Right kidney cystic nephroma

The patient was referred for a cancer predisposition evaluation due to his personal diagnosis of CMN of the kidney and strong family history of cancer on his maternal side. The family history was significant with a maternal aunt diagnosed at age 25 with stage IV breast cancer and a maternal grandmother with stage IV ovarian cancer at age 49. The maternal grandmother's sister was also diagnosed with breast cancer in her 30s (Figure 2). There was no family history of renal abnormalities.

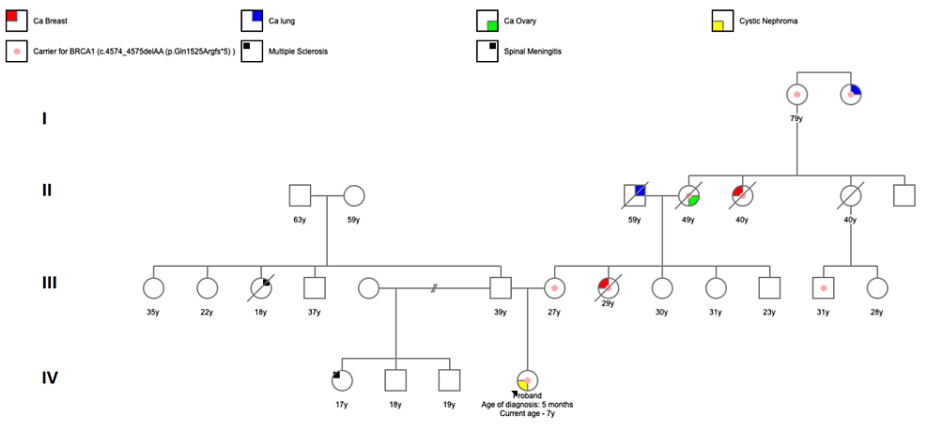


FIGURE 2: Family Pedigree

Due to the maternal aunt's early diagnosis of breast cancer, which occurred at the same time as the patient's CMN diagnosis, she had undergone germline genetic testing and was known to carry a BRCA1 pathogenic variant. Based on parental preference for comprehensive germline testing, genetic testing consisting of a panel of 43 genes with a focus on solid tumors was performed. Germline genetic testing revealed a c.4574_4575delAA (p.Gln1525Argfs*5) BRCA1 pathogenic variant in our patient, giving the child a diagnosis of hereditary breast and ovarian cancer (HBOC) syndrome. The boy's pathogenic variant was consistent with the maternal aunt's variant and the child's mother was counseled that she also has HBOC. This particular variant has a 40-87% risk for breast cancer, along with a male breast cancer risk of 1-2%. Screening guidelines for children do not exist, therefore no additional surveillance outside of monitoring for tumor recurrence was performed [5,6]. However, the patient will become eligible for screening guidelines for males with HBOC in adulthood. The patient's mother was referred for clinical management per the National Comprehensive Cancer Network (NCCN) guidelines.

Discussion

Ten percent of children with malignancy have a genetic predisposition to the development of cancer [7]. Indications of a cancer predisposition syndrome include phenotypic physical features, a family history suggestive of a cancer predisposition syndrome, specific malignancies like choroid plexus carcinoma

suggestive of Li-Fraumeni syndrome (LFS), specific somatic markers of the malignancy like low-hypodiploidy in acute lymphoblastic leukemia in LFS, bilateral, metachronous, synchronous, or multiple primary tumors, and severe toxic side-effects when exposed to chemotherapy or radiation therapy as part of the routine treatment [8]. However, the absence of any of these indications does not exclude the possibility of a cancer predisposition syndrome due to the occurrence of de novo mutations, low penetrance of certain cancer predisposition syndromes, and incidental findings [9]. This case demonstrates that incidental findings on broader panel testing still have health implications for patients and their families.

A recent study by Kratz et al. reported increasing associations between adult-onset genes like BRCA1 and the development of childhood malignancies [10]. Kratz et al. conducted a meta-analysis of 11 studies that included comprehensive germline testing for children and adolescents with cancer and have established pathogenic variants in BRCA1 and BRCA2 in children with a diagnosis of acute lymphoblastic leukemia, ependymoma, Ewing sarcoma, gliomas, Langerhans cell histiocytosis, medulloblastoma, neuroblastoma, rhabdoid tumor, and rhabdomyosarcoma [10]. The dataset, however, did not include benign tumors such as cystic nephroma, which may therefore be underrepresented in the literature.

Cancer predisposition genes have historically been classified as pediatric and adult-onset cancer predisposition genes because they confer an increased risk of developing malignancies in childhood and adulthood, respectively, and the risk of cancer in the other age group is relatively low. As HBOC confers a high risk for breast cancer, ovarian cancer, pancreatic cancer, prostate cancer, and male breast cancer in adults, many providers are reticent to perform testing for this condition in the pediatric setting. However, based on parental preference and family history this genetic testing was able to impact health decision-making for the child's family. This child is also able to receive graduated education on HBOC in annual visits to the cancer predisposition program to increase health literacy and ability to navigate cancer screening as a young adult.

Conclusions

This case highlights the importance of assessing for germline variants in genes other than pediatric kidney tumor-related genes, most commonly DICER1, which has a well-established association with pediatric renal tumors. Patients may benefit from broader panel testing, exome, and paired tumor-germline DNA analyses to further aid the discovery of both adult and pediatric-onset cancer predisposition syndromes in rare pediatric tumors.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Treece AL: Pediatric Renal Tumors: Updates in the Molecular Era. *Surg Pathol Clin*. 2020, 13:695-718. [10.1016/j.path.2020.08.003](https://doi.org/10.1016/j.path.2020.08.003). Epub 2020 Oct 9
2. Vokuhl C, Nourkami-Tutdibi N, Furtwängler R, et al.: ETV6-NTRK3 in congenital mesoblastic nephroma: A report of the SIOP/GPOH nephroblastoma study. *Pediatr Blood Cancer*. 2018, 65:4. [10.1002/pbc.26925](https://doi.org/10.1002/pbc.26925). Epub 2017 Dec 29
3. Druker H, Zelle K, McGee RB, Scollon SR, Kohlmann WK, Schneider KA, Wolfe Schneider K: Genetic Counselor Recommendations for Cancer Predisposition Evaluation and Surveillance in the Pediatric Oncology Patient. *Clin Cancer Res*. 2017, 23:e91-7. [10.1158/1078-0432.CCR-17-0834](https://doi.org/10.1158/1078-0432.CCR-17-0834)
4. Schultz KA, Williams GM, Kamihara J, et al.: DICER1 and Associated Conditions: Identification of At-risk Individuals and Recommended Surveillance Strategies. *Clin Cancer Res*. 2018, 24:2251-61. [10.1158/1078-0432.CCR-17-3089](https://doi.org/10.1158/1078-0432.CCR-17-3089)
5. Ford D, Easton DF, Stratton M, et al.: Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet*. 1998, 62:676-89. [10.1086/301749](https://doi.org/10.1086/301749)
6. Evans DG, Susnerwala I, Dawson J, Woodward E, Maher ER, Lalloo F: Risk of breast cancer in male BRCA2 carriers. *J Med Genet*. 2010, 47:710-1. [10.1136/jmg.2009.075176](https://doi.org/10.1136/jmg.2009.075176)
7. Zhang J, Walsh MF, Wu G, et al.: Germline Mutations in Predisposition Genes in Pediatric Cancer. *N Engl J Med*. 2015, 10:2336-2346. [10.1056/NEJMoa1508054](https://doi.org/10.1056/NEJMoa1508054). Epub 2015 Nov 18
8. Ripperger T, Bielack SS, Borkhardt A, et al.: Childhood cancer predisposition syndromes-A concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. *Am J Med Genet A*. 2017, 173:1017-37. [10.1002/ajmg.a.38142](https://doi.org/10.1002/ajmg.a.38142)
9. Li S, Silvestri V, Leslie G, et al.: Cancer Risks Associated With BRCA1 and BRCA2 Pathogenic Variants. *J Clin Oncol*. 2022, 40:1529-41. [10.1200/JCO.21.02112](https://doi.org/10.1200/JCO.21.02112)

10. Kratz CP, Smirnov D, Autry R, et al.: Heterozygous BRCA1 and BRCA2 and Mismatch Repair Gene Pathogenic Variants in Children and Adolescents With Cancer. *J Natl Cancer Inst.* 2022, 114:1523-32. [10.1093/jnci/djac151](https://doi.org/10.1093/jnci/djac151)