Egyptian Journal of Medical Human Genetics

CASE REPORT Open Access

Germline rad 50 mutation in a case with synchronous breast and kidney cancer: a rare case

Bhargavi Ilangovan[1,4*], Ganapathy Raman[2] and Vikas Mahajan[3]

Abstract

Background Breast cancer has been reported to occur synchronous with ovarian, endometrial and even colon cancers. A synchronous renal cancer is rare. And its association with *RAD 50* mutation is not known.

Case presentation We are reporting a 42 year old lady who was evaluated for a breast lump and was incidentally found to have a renal lesion. She underwent surgery for both and was found to have a T1c breast tumour and a renal cell carcinoma-clear cell variant. She was advised germline testing with next generation sequencing and multiplex ligation—dependent probe amplification due to synchronous tumours and age at diagnosis. It revealed a likely pathogenic variant in the *RAD 50* gene.

Conclusion The *RAD 50* gene is part of the MRN complex (Mre11, Rad50 and Nbs1 also known as nibrin), which is essential for DNA repair. The recommendations for follow-up and screening are not clear for patients with a pathogenic variant of the gene. This case is presented for its rarity.

Introduction

Breast cancer has been reported to occur synchronous with ovarian, endometrial and even colon cancers [1]. But a synchronous breast and renal cancer with a likely pathogenic variant in the *RAD 50* gene has not been reported so far. We are writing to highlight the possibility of this combination and to discuss the challenges we faced, with this case.

*Correspondence:
Bhargavi Ilangovan
bhargavi.ilangovan@gmail.com
[1] Department of Radiotherapy, Apollo Cancer Institute, 320, Cenotaph Road, Teynampet, Chennai 35, India
[2] Department of Medical Oncology, Apollo Cancer Institute, 320, Cenotaph Road, Teynampet, Chennai 35, India
[3] Department of Surgical Oncology, Apollo Cancer Institute, 320, Cenotaph Road, Teynampet, Chennai 35, India
[4] Chennai, India

Case report

A 42 year old lady presented with the complaints of lump in the right breast of 1 month duration. She was found to have a grade 2–3, Invasive carcinoma, Not otherwise specified, with Oestrogen and progesterone receptor positivity. A PET CT scan was done as a routine staging procedure when an incidental renal mass was detected.

She underwent breast conservation surgery with sentinel lymph node biopsy and a partial nephrectomy. Histopathologic examination revealed a T1c breast tumour with negative sentinel nodes and a renal cell carcinoma, clear cell variant. She received adjuvant chemotherapy with four cycles of Taxol and Cyclophosphamide and adjuvant radiotherapy to the right breast.

In view of her age at diagnosis and synchronous malignancies, she was referred to the hereditary cancer clinic. Her family history was not significant. There was one second degree relative with breast cancer and a third degree relative with ovarian cancer (Fig. 1).

She was advised to undergo germline testing to detect the genetic mutations associated with hereditary cancers.

Springer Open

© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

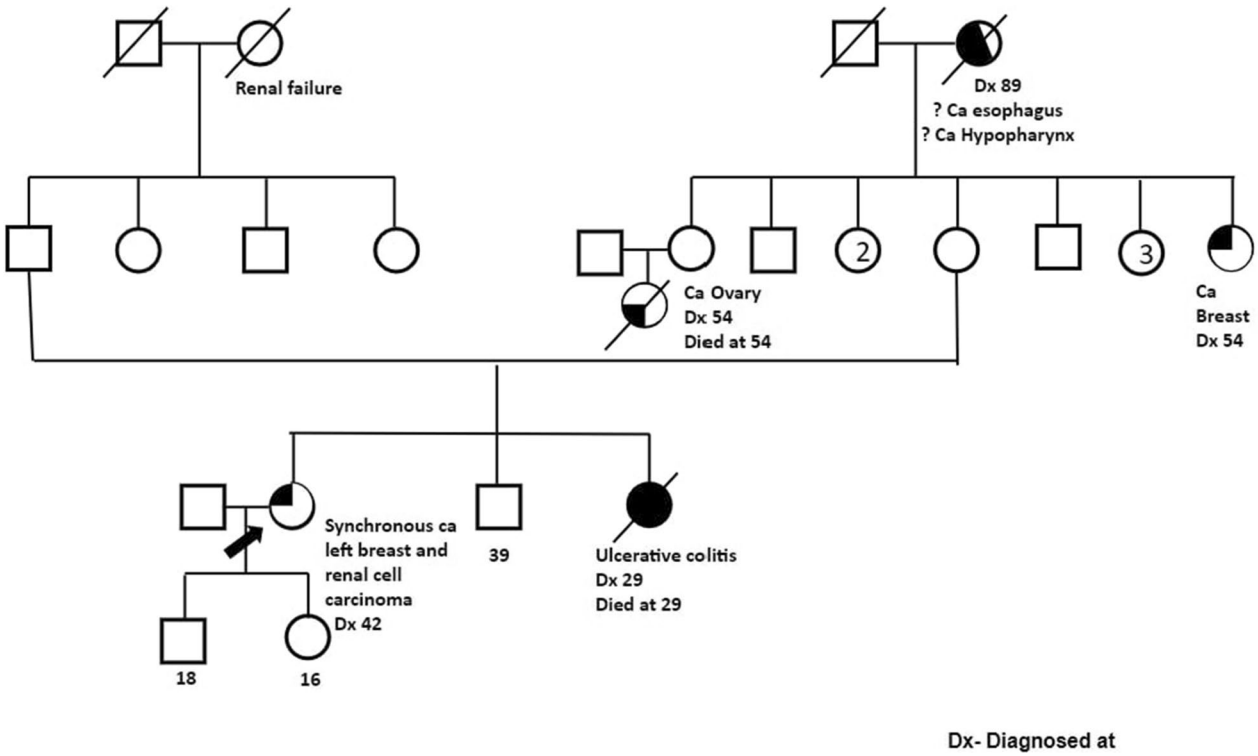

Fig. 1 Pedigree chart of the family

An NGS (Next generation sequencing) and an MLPA (multiplex ligation—dependent probe amplification) was performed on the blood sample of the patient. This included a multi gene panel testing looking for high and moderate penetrance genes associated with hereditary breast and ovarian cancers.

A heterozygous likely pathogenic variant (c.2156_2157insA; p.Asp387His) wasidentified in the exon 13 of RAD50 gene in NGS. This mutation in our patient, in the *RAD 50* gene, namely the single base pair insertion in the exon 13, has been reported to result in frameshift and premature truncation of the protein 5 amino acids, downstream to codon 723 (Fig. 2).

This has been found to be associated with breast and ovarian cancer patients. The association with renal cancers has not been reported.

She was advised high risk screening for breast and ovarian cancers. As this is reported to be a low penetrance gene, prophylactic surgeries were not advised.

Discussion

RAD 50 gene codes for a protein which forms a complex with MrE11 and Nbs1 (MRN complex). The protein complex binds to thee DNA and plays a major part in non-homologous end joining repair. Homologous loss of this gene is associated with Nijmegen breakage syndrome like disorder [2]. The MRN complex functions upstream of the ATM signalling. It senses DNA DSB (Deoxy ribo nucleic acid double strand break). The Mre 11 protein binds to thee DNA. Nbs 1 recruits activated ATM to the damaged sites. The interactions of Mre11 with *RAD 50* provide the energy source for the MRN complex [3].

RAD 50 is considered to be a low penetrance gene with a relative risk less than 1.5, in the development of hereditary breast cancers [4]. These breast cancers have reported to have poorer outcomes when compared with their normal counterparts. No clinic pathological character of these breast cancers has been reported so far [5]. The other cancers that have been reported to manifest in association with the *RAD 50* gene mutation are the ovarian, oesophageal and stomach cancers [6].

Hereditary renal cell cancers have been reported as a part of about 10 syndromes [7]. DSB repair pathways have also been implicated in them. Defects in the MRN complex has been reported to cause renal cancers [8]. The possible explanation that defects in the DSB repair pathways contribute to the development of cancers is most likely. Due to the paucity of data, we advised high risk screening for the patient and cascade testing for the first degree relatives.

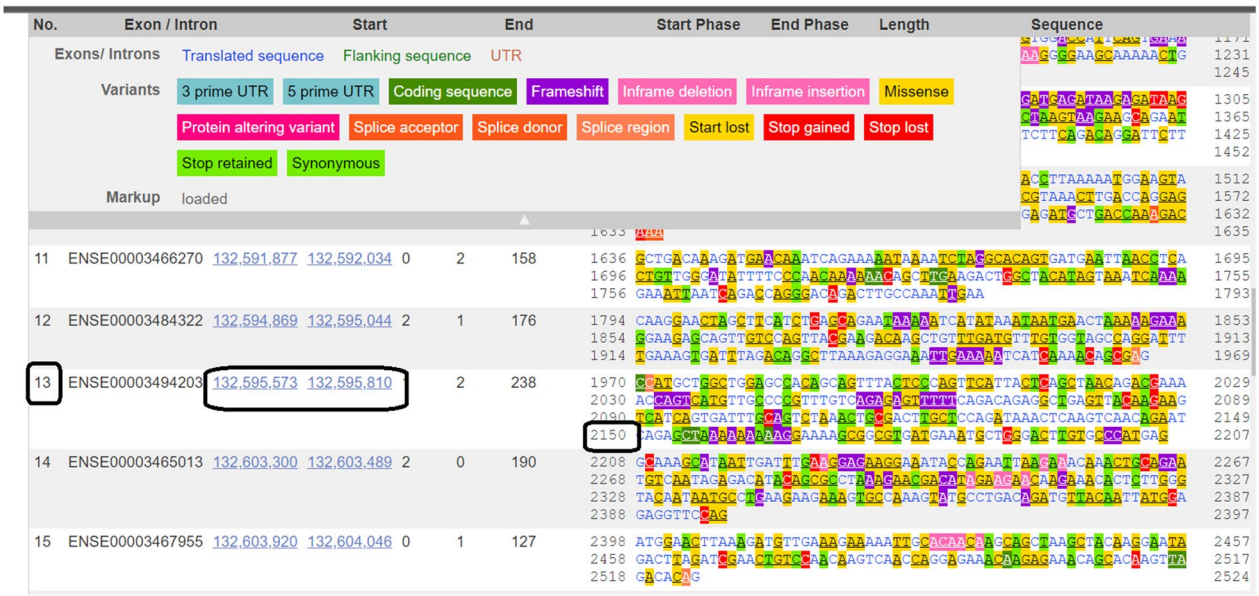

Fig. 2 Showing the exon number, chromosomal coordinates and coding position of the variant. Chromosomal position: chr5:132595759_132595760insA. Exon number: 13. CDS position: c.2156_2157insA

Conclusion

RAD 50 mutation related breast cancers are rare. More so are the synchronous renal cell carcinomas. We are writing to report the rarity and to emphasise the need for improved genetic testing and serial follow-up of these patients to better understand the patient outcome and to tailor the treatment as required.

Acknowledgements
Nil.

Author contributions
All authors have contributed to this manuscript equally. Myself, GR and VM have been involved in the conception, design and have contributed to the drafting of the work and revision. We have also approved the submitted and modified version. We have agreed to be personally accountable for the author's contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Funding
NIl.

Availability of data and materials
Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate.
Anonymised case studies do not require ethics clearance in our institution.

Consent for publication
Yes. Will be made available by mail.

Competing interests
The authors do not have any competing interests.

Received: 6 January 2023 Accepted: 5 December 2023
Published online: 13 December 2023

References

1. Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, Cerny T et al (2017) Multiple primary tumours: challenges and approaches, a review. ESMO Open 2(2):e000172
2. RAD50 RAD50 double strand break repair protein [Homo sapiens (human)]—Gene—NCBI [Internet]. [cited 2022 Mar 2]. Available from: https://www.ncbi.nlm.nih.gov/gene/10111
3. Hsu HM, Wang HC, Chen ST, Hsu GC, Shen CY, Yu JC (2007) Breast cancer risk is associated with the genes encoding the dna double-strand break repair Mre11/Rad50/Nbs1 complex. Cancer Epidemiol Biomark Prev 16(10):2024–2032
4. Heikkinen K, Rapakko K, Karppinen SM, Erkko H, Knuutila S, Lundán T et al (2006) RAD50 and NBS1 are breast cancer susceptibility genes associated with genomic instability. Carcinogenesis 27(8):1593
5. Fan C, Zhang J, Ouyang T, Li J, Wang T, Fan Z, et al. RAD50 germline mutations are associated with poor survival in BRCA1/2-negative breast cancer patients. Available from: http://www.ncbi.nlm.nih.gov/clinvar/
6. Ko JMY, Lam SY, Ning L, Chai AWY, Lei LC, Choi SSA et al (2021) RAD50 loss of function variants in the zinc hook domain associated with higher risk of familial esophageal squamous cell carcinoma. Cancers 13(18):4715
7. Haas NB, Nathanson KL. Hereditary renal cancer syndromes; 2013.
8. Margulis V, Lin J, Yang H, Wang W, Wood CG, Wu X (2008) Genetic susceptibility to renal cell carcinoma: the role of DNA double strand break repair pathway. Cancer Epidemiol Biomark Prev 17(9):2366

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.