ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.ijmio.com

International Journal of Molecular and Immuno Oncology

Case Report

A FANCA mutation carrier with enhanced toxicity to cancer directed treatment - A case report and review of literature

Dilip Harindran Vallathol[1], K. S. Vijayagopal[2], K. V. Sajeevan[1]

Departments of [1]Medical Oncology, and [2]Radiation Oncology, MVR Cancer Centre and Research Institute, Kozhikode, Kerala, India.

***Corresponding author:**
K. V. Sajeevan,
Department of Medical Oncology, MVR Cancer Centre and Research Institute, Kozhikode, Kerala, India.

drsajeevan@mvrccri.co

Received: 07 January 2023
Accepted: 19 January 2023
Published: 03 June 2023

DOI
10.25259/IJMIO_1_2023

Quick Response Code:

ABSTRACT

Chemotherapy and radiotherapy are backbones of cancer treatment. Genome instability syndromes are rare but an essential factor to be identified early in the treatment of malignancies. It can lead to the occurrence of multiple malignancies and impede treatment due to undue hypersensitivity, leading to extreme and often fatal toxicities. We, hereby, report a case of a middle-aged lady who was diagnosed with a carcinoma of the head and neck and planned for treatment with neoadjuvant chemotherapy followed by surgery or chemoradiation. However, she developed severe toxicity to all forms of treatment for cancer. Her gene-based panel screening test revealed a Fanconi anaemia, complementation group A (FANCA) gene abnormality which is associated with an autosomal recessive mode of inheritance. This case outlines the importance of considering the possibility and a high index of suspicion of a hereditary basis in cases of relatively early-onset malignancy before defining an oncological treatment strategy. The paucity of data except for case reports limits evidence-based management in such cases and requires a collective effort for treatment.

Keywords: FANCA, Toxicity, Chemotherapy, Radiotherapy, Malignancy

INTRODUCTION

Genome instability syndromes are a group of hereditary diseases caused by mutations in germline genes encoding the deoxyribonucleic acid (DNA) damage response pathways, which leads to defects in genome maintenance, sensitivity toward various therapeutic agents, and enhanced susceptibility to malignancy.[1] Fanconi anemia (FA) is a rare autosomal recessive disorder, included under the above-mentioned sect, which leads to defects in the DNA repair pathway that precipitates oncogenesis and is a source of excessive radiotherapy and chemotherapy sensitivity. FA patients usually develop solid tumors, such as squamous cell carcinoma (SCC) of the upper gastrointestinal, gynecological, and head and neck cancers. However, their demise is more often than not from hematologic malignancies, such as leukemia or bone marrow failure syndromes.[2] Moreover, FA is a cause of excessive toxicity to major cancer treatment modalities such as radiotherapy and cytotoxic agents, with reported cases varying from fulminant and fatal toxicities in the lowest doses to excellent treatment toleration at even high doses.[3,4] Although not a rare occurrence, we report a case of a young FANCA mutation carrier woman with head and neck malignancy who was treated with chemotherapy and radiotherapy, where unexpected multiple acute toxicities occurred to treatment which prompted treatment de-escalation.

CASE REPORT

A 37-year-old lady with comorbidity of diabetes mellitus presented to our outpatient department in March 2022 with a history of hard palate growth. She had a positive family history of carcinoma colon in her brother and endometrial cancer in her mother. She was evaluated at our center and diagnosed to have a locally advanced SCC of hard palate extending to other parts of the oral cavity which was not amenable for surgery. Her case was discussed in a multidisciplinary tumor board and planned for neoadjuvant chemotherapy followed by reassessment for concurrent chemoradiation. She was started on induction chemotherapy with Docetaxel-Cisplatin-5-Fluorouracil (TPF) regimen. She had prolonged pancytopenia post the first cycle of chemotherapy of more than 1 month which was complicated by mucositis and long-term hospitalization was required. Pus culture from the oral cavity showed Coagulase negative staphylococcus and *Escherichia coli*. She was given antibiotics as per sensitivity. Because of the toxicity and incomplete recovery of cytopenias, she was planned for hypofractionated radiotherapy with biological agents. She completed 15 fractions of radiotherapy with two doses of nimotuzumab. She developed a severe infection, pancytopenia, and mucositis after the above treatment and required admission. This time around the hospitalization was complicated by acute suppurative otitis media, the culture of which grew *E. coli*. Culture specific antibiotics were instituted, and she was discharged once a bit stable. On discharge, she still had mucositis and otitis media which were recovering. She was followed up in the outpatient department and had a partial recovery, but the tumor was still persistent. Because of undue toxicity to chemotherapy, she was evaluated for the possibility of abnormalities in DNA repair defects. She was planned for oral metronomic therapy alone for further treatment. The DNA repair defect test revealed a frameshift variant in Fanconi's Anemia (FANCA[p.Val107PhefsTer31-pathogenic] and FANCC[VUS]) genes leading to a loss of function, probably a FANCA abnormality carrier [Figure 1]. The possibility of this variant being homozygous could not be ruled out since the allelic burden was borderline to 90%. However, the opposite gene/allele did not show any large deletions on next-generation sequencing (NGS) post processing. Further, testing with Multiplex-Ligation Dependent Probe Amplification was suggested. This could not be done due to logistic reasons. However, there was a classic genotype-phenotype correlation of FA in this case.

DISCUSSION

As mentioned previously, FA is a complex genetic abnormality characterized by hematological issues, congenital defects, and inability to repair DNA interstrand cross-links thereby resulting in cancer predisposition. It was first described by Swiss pediatrician Guido Fanconi in 1927.[5] The major function of the FA pathway is to maintain genomic stability during DNA replication and assist in the DNA damage repair process. Promoter hypermethylation and germline monoallelic mutations of FA genes confer an enhanced risk for the development of multiple cancers including hematological and various solid tumors.[6,7] Hypersensitivity to DNA crosslinking chemotherapeutic agents, such as mitomycin C, platinum agents, and diepoxybutane (DEB) is another major feature of FA. Excessive toxicity following chemotherapeutic agents is not solely attributable to FA. It has been observed in a broad range of genome instability syndromes, such as Xeroderma pigmentosum, Bloom syndrome, Werner syndrome, and Ataxia-telangiectasia.[1] Moreover, in the analysis of the genome of nine common cancer types done by the Cancer Genome Atlas, FA genes were altered in 40% of the tumors.[5]

A frameshift variant that leads to termination and loss of function in *FANCA* gene has been detected

Note: The gene *FANCA* is associated with autosomal recessive mode of inheritance, the possibility of this variant being a homozygous cannot be ruled out, since the allelic burden is borderline to 90%. Kindly correlate with other clinical and pathological findings. The identified variant in the proband indicates possible predisposition. Additional family member screening is suggested to rule out predisposition and further risk assessment. This variant couldn't be classified using the available evidence; however, it can be classified based on segregation analysis.

VARIANT DETAILS

Gene	Genomic alteration	Protein, Mutant allelic burden (%)	Mode of inheritance	Reference
FANCA	chr16:g.89877444delC c.319delG [ENST00000389301.3]	p.Val107PhefsTer31 (87%)	Autosomal recessive	rs1411237340 VCV000860635
FANCC	chr9:g.97873745C>T c.1329G>A [ENST00000289081.3]	p.Met443Ile (37%)	Autosomal recessive	rs772133680 VCV001420331

Figure 1: Genetic analysis report.

For an oncologist, it is impossible to recognize FA carriers during outpatient visits unless a positive FA history is present, which is indeed a rare situation. Rapid methods for quickly screening patients before chemotherapy or radiotherapy have not yet been validated for clinical use. Colony survival assays can yield definitive results in 12 weeks and predict advanced warning indications of hypersensitivity to chemotherapy and radiotherapy in such patients.[8] More sensitive and reliable assays are needed to identify a larger portion of heterozygous patients, which probably includes around 5% of the population.[9] Auerbach *et al*. identified that it was possible to distinguish between FA controls and heterozygotes using the DEB test.[10] However, now, it has been recognized that the DEB test can yield false-negative results in patients with somatic mosaicism and cannot be utilized reliably to distinguish between FA carriers and normal individuals.[11] Modern genetic analyses, for example, whole-genome sequencing and NGS technologies, which investigate the complete genome of an individual, can be deployed in making a successful differential diagnosis of a genetic disorder but results in a delay of treatment initiation in cancer patients.[12] Moreover, these tests also identify variants of unknown significance, whose pathogenicity cannot be deduced without further follow-up analyses. Hence, in resource constrained settings, such expensive investigations are rarely feasible. Thus, the need of the hour is to develop methods to detect such variants in a more resourceful way at the same time in a more discernible manner.

Several case reports of FANCA gene mutations leading to chemotoxicity and radiotoxicity have been described. As indicated earlier, patients with FA who survive until adolescence typically develop SCCs of the head and neck, female genital tract, etc.[6] These malignancies are frequently associated with Human Papilloma Virus (HPV) infection and often have multifocal distribution. There are several reports on young FA patients with multiple HPV associated SCC, indicating a possible relationship between HPV-associated malignancies and FA mutations.[13] However, in our case, p16 testing (a surrogate for HPV) in biopsy showed a negative result. Further, HPV polymerase chain reaction genotyping was not contemplated.

CONCLUSION

There are no standard guidelines for the management of FA patients with malignancies except based on sporadic case reports. Patients with FA heterozygosity have a high rate of complications from chemotherapy and radiotherapy. The use of precision medicine in oncology treatment is further highlighted by this case report with a relatively early-onset cancer to identify any predisposing syndromes. A multidisciplinary team management is essential to perform an in-depth patient evaluation, followed by rapid and appropriate genetic analyses, to pinpoint a possible underlying hereditary genome instability syndrome. There is an urgent need for new rapid and predictive *in vitro* assays to assess chemotherapy and radiotherapy responses. Until then, the treatment should be individualized.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Terabayashi T, Hanada K. Genome instability syndromes caused by impaired DNA repair and aberrant DNA damage responses. Cell Biol Toxicol 2018;34:337-50.
2. Budrukkar A, Shahid T, Murthy V, Hussain T, Mulherkar R, Vundinti BR, *et al*. Squamous cell carcinoma of base of tongue in a patient with Fanconi's anemia treated with radiation therapy: Case report and review of literature. Head Neck 2010;32:1422-7.
3. Bremer M, Schinder D, Gross M, Dörk T, Morlot S, Karstens JH. Fanconi's anemia and clinical radiosensitivity report on two adult patients with locally advanced solid tumors treated by radiotherapy. Strahlenter Onkol 2003;179:748-53.
4. Spanier G, Pohl F, Giese T, Meier JK, Koelbl O, Reichert TE. Fatal course of tonsillar squamous cell carcinoma associated with Fanconi anemia: A mini review. J Craniomaxillofac Surg 2012;40:510-5.
5. Niraj J, Färkkilä A, D'Andrea AD. The Fanconi anemia pathway in cancer. Annu Rev Cancer Biol 2019;3:457-78.
6. Alter BP. Cancer in Fanconi anemia, 1927-2001. Cancer 2003;97:425-40.
7. Huang JP, Lin J, Tzen CY, Huang WY, Tsai CC, Chen CJ, *et al*. FANCA D1359Y mutation in a patient with gastric polyposis and cancer susceptibility: A case report and review of literature. World J Gastroenterol 2018;24:4412-8.
8. Engel NW, Schliffke S, Schüller U, Frenzel C, Bokemeyer C, Kubisch C, *et al*. Fatal myelotoxicity following palliative chemotherapy with cisplatin and gemcitabine in a patient with stage IV Cholangiocarcinoma linked to post mortem diagnosis of Fanconi anemia. Front Oncol 2019;9:420.
9. Leong T, Chamo M, Bassal S, McKay M. Radiation-hypersensitive cancer patients do not manifest protein expression abnormalities in components of the nonhomologous end-joining (NHEJ) pathway. Br J Cancer 2003;88:1251-5.
10. Auerbach AD, Warburton D, Bloom AD, Chaganti RS. Preliminary communication: Prenatal detection of the Fanconi anemia gene by cytogenetic methods. Am J Hum Genet

1979;31:77-81.
11. Dokal I, Chase A, Morgan NV, Coulthard S, Hall G, Mathew CG, *et al.* Positive diepoxybutane test in only one of two brothers found to be compound heterozygotes for Fanconi's anemia complementation group C mutations. Br J Haematol 1996;3:813-6.
12. Saunders CJ, Miller NA, Soden SE, Dinwiddie DL, Noll A, Alnadi NA, *et al*. Rapid whole-genome sequencing for genetic disease diagnosis in neonatal intensive care units. Sci Transl Med 2012;4:154ra135.
13. Spardy N, Duensing A, Charles D, Haines N, Nakahara T, Lambert PF, *et al.* The human papillomavirus type 16 E7 oncoprotein activates the Fanconi anemia (FA) pathway and causes accelerated chromosomal instability in FA cells. J Virol 2007;81:13265-70.

How to cite this article: Vallathol DH, Vijayagopal KS, Sajeevan KV. A FANCA mutation carrier with enhanced toxicity to cancer directed treatment - A case report and review of literature. Int J Mol Immuno Oncol 2023;8:72-5.