Case of BRCA1 Gene Germline Mutation in Patient with Neuroendocrine tumor

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Introduction and Aim

Neuroendocrine tumors are a rare type of cancer, which arise from the endocrine and central nervous systems. It is estimated that they make up 0.5 % of all cancers and have a prevalence of 35 cases out of 100 000 per year. Because of the diffuse endocrine system they may arise from multiple sites like the digestive tract (stomach, small intestines, etc.), endocrine glands, skin, etc. Research shows that about 10 percent of gastrointestinal tumors have a germline mutation in hereditary cancer genes, mostly *in MEN1, RET, VHL, NF1*. In rare cases there might be other causative variants in cancer predisposition genes.

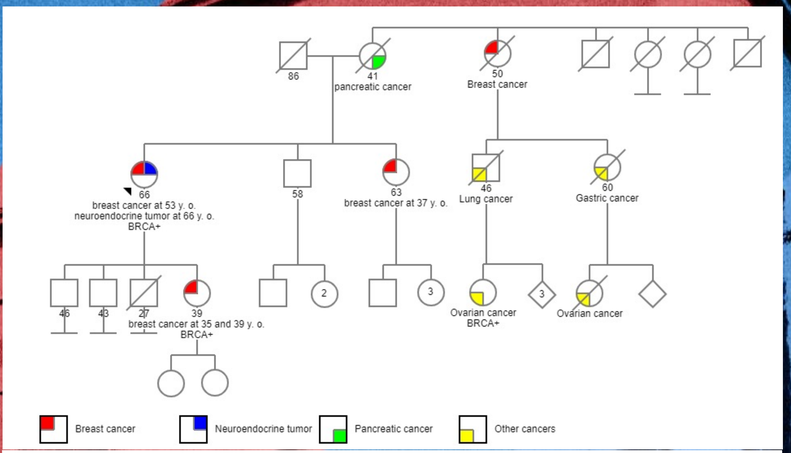
Here we report a case of neuroendocrine tumor which might be associated with a *BRCA1* gene pathogenic variant.

Case Report

66 years of age female patient was referred to a clinical geneticist due to a family history of cancer: the patient has a daughter with the BRCA1 mutation and 2 primary breast cancers at 35 and 39 years of age, also the patients sister had breast cancer at 37, mother had pancreatic cancer at 38, mother's sister had breast cancer at 50 and her pedigrees also *BRCA1/2* spectrum cancers (ovarian, gastric, lung cancers).

Patient herself was diagnosed with invasive ductal breast cancer at 52 years of age. She was treated with chemotherapy and mastectomy. At 66 years of age she was diagnosed with a gastrointestinal intermediate grade neuroendocrine tumour as there were several nodes detected during the patients liver ultrasound and computer tomography which were later confirmed by performing a biopsy.

A targeted genetic test for familial *BRCA1* gene variant NM_007294.4:c.5173_5176delGAAA was performed which was positive. This variant causes a frameshift and is expected to cause loss of protein function by nonsense mediated decay or by truncating the protein. This variant has multiple entries in ClinVar database as pathogenic and is also reported in various affected patient cases.



Pedigree scheme of the patient
Black arrow marks the patient. Affected family member are marked with colored squares according to the legend.

Discussion

BRCA1 gene pathogenic variants are well known to increase the risk of various cancers such as breast, ovarian, prostate, pancreatic, skin and others. In our patient's family the *BRCA1* variant discussed earlier is highly penetrant as multiple family members are affected. Our patient's case is unique as not only breast cancer but also a neuroendocrine tumor has developed. *Larouche V. et al. (2019*) study found 26 cases of such co-occurrence of breast cancer and neuroendocrine tumors, of which 9 were genetically studied but no *BRCA1/2* genes mutations were found. However, *PALB2, APC*, and *NTHL1* genes pathogenic variants were detected. *Scarpa E. et al. (2017*) studied pancreatic neuroendocrine tumors and on rare cases found *BRCA2* germline pathogenic variants and pathogenic variants in other DNA repair genes such as *MUTYH and CHEK2*. In two published cases (*Erdrich J. et al. 2018; Zhu M. et al 2020*) there were *BRCA1* germline frameshift variants. This shows an increasing amount of evidence that pathogenic variants in DNA repair mechanism genes are important in neuroendocrine tumors development. *BRCA1* pathogenic variants are very rare in neuroendocrine tumor patients and there is a possibility that these variants occurrence is not increased in neuroendocrine tumor patients.

DNA repair genes

- Base excision repair
  MUTYH, NTHL1
- Fanconi anemia genes
  PALB2
- Homologous recombinational repair
  BRCA1, BRCA2
- Conserved DNA damage response genes
  CHEK2

Adapted from Delesign Graphics on Iconscout

Different genes are reported from various mechanisms of DNA repair in neuroendocrine tumor cases. As each group of mechanism involves numerous genes, it is possible that in near future we can find more associated gene's mutations

Conclusions

Expanding neuroendocrine tumor patient genetic testing to also test for pathogenic variants in DNA repair mechanism genes may be needed

Key words

BRCA1, neuroendocrine tumors, breast cancer