CASE REPORT

BRCA 1/2 gene mutation and gastrointestinal stromal tumours: a potential association

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SUMMARY

Mutations of the *BRCA1/2* genes have been described in association with a number of malignancies including cancers of the breast, ovary, prostate and stomach, but have never been described in relation to gastrointestinal stromal tumours (GIST). We describe a patient with a *BRCA2* 8642del3insC mutation who developed prostate cancer, breast cancer and GIST. GIST has been shown to be associated with a number of malignancies, including some of the common *BRCA1/2*-related cancers, but it has never been associated with *BRCA1/2* gene mutations. This report highlights the potential association between *BRCA1/2* mutations and GIST, and aims to raise awareness for further genetic screening in GIST patients.

BACKGROUND

BRCA1/2 mutation carriers are known to have a higher risk of developing breast and ovarian cancer.^{1–2} Over the last decade, awareness of the *BRCA1* and *BRCA2* genes in the oncological community has led to more aggressive patient screening and the subsequent discovery of other *BRCA*-related malignancies. Cancer of the prostate, pancreas, gallbladder, bile duct and stomach, along with malignant melanoma, have all been described at increased incidences in *BRCA* mutation carriers.¹

Gastrointestinal stromal tumour (GIST) is a mesenchymal stromal cell tumour associated with *c-KIT* and *PDGFRA* gene mutations.^{3–4} This tumour is rare with an annual incidence estimated between 7 and 20 per million per year in the USA and Sweden.^{5–6} While GIST more commonly presents in isolation, the coexistence of synchronous or metachronous malignancies has been well described in the literature with an incidence ranging from 3% to 30%.^{7–9} These GIST-associated malignancies include other forms of gastric cancer, breast cancer and prostate cancer.^{7–10} *BRCA1* and *BRCA2* are critical proteins in the process of homologous recombination repair of double-strand DNA breaks. Homologous recombination deficiency (HRD) can occur in cells with defective copies of *BRCA1* or *BRCA2*.¹¹ The purpose of this case report is to describe a *BRCA2* mutation positive man with breast cancer, prostate cancer and GIST, and to discuss the potential association between GIST and *BRCA1/2* gene mutations.

CASE PRESENTATION

We describe a case of a 65-year-old man with a remote history of prostate cancer, who was subsequently diagnosed with *BRCA2* positive breast cancer and GIST. His prostate cancer was originally

diagnosed in 2008, at the age of 61 years, after routine prostate-specific antigen (PSA) screening. His clinical stage was T1C with a Gleason score of 3+4 and a PSA of 31. Owing to the elevated PSA, his adenocarcinoma was classified as high risk. He was treated with 79.2 Gy of whole pelvic radiation and androgen deprivation therapy (ADT) with bicalutamide (Casodex) and Goserelin (Zoladex). He completed a 2-year course of ADT in June 2011, with an appropriate clinical response and normalisation of PSA.

He had been doing well until February 2012, when he developed bloody nipple discharge and was found on examination to have a palpable breast mass. Mammogram and breast ultrasound revealed a large soft tissue mass, 2.5×2.3×2.2 cm. Ultrasound-guided biopsy confirmed invasive lobular carcinoma, grade 2 (3+2+2). The mass was oestrogen receptor 90% positive, progesterone receptor 20% positive, HER2 negative (score 0), Ki-67 30% high/unfavourable and p53 negative. Immunohistochemical stain for cytokeratin seven was positive. E-cadherin, cytokeratin 20 and thyroid transcription factor (TTF) -1 immunostains were negative. Given a family history of female breast cancer in two maternal cousins and male breast cancer in a distant maternal cousin, the patient underwent genetic testing, which was positive for a *BRCA2* 8642del3insC mutation.

Neoadjuvant chemotherapy was initiated in March 2012, with doxorubicin 60 mg/m² intravenously and cyclophosphamide 600 mg/m² intravenously every 2 weeks for four cycles, followed by paclitaxel 175 mg/m² every 2 weeks for four cycles.

The patient was re-evaluated with breast MRI in June 2012, which incidentally showed a 3 cm soft tissue mass abutting the stomach and proximal duodenum. He subsequently underwent CT scan of the chest, abdomen and pelvis, which revealed a 2.9 cm soft tissue mass abutting the stomach and proximal duodenum. The patient underwent upper endoscopy with core biopsy of the stomach mass in July 2012, which showed GIST. Immunostain for CD117 was positive with no mitoses. Tissue was sent to Myriad Genetics for detection of homologous recombination defects via the HRD assay. The assay confirmed the *BRCA2* germline mutation in one *BRCA2* copy. The second *BRCA2* copy was intact. There was no loss of heterozygosity (LOH) seen. The HRD score was eight, which represents a low score.

Further management of GIST tumour was not pursued as the patient's breast cancer posed a greater risk to his health. The patient underwent mastectomy with sentinel lymph node biopsy and

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axillary dissection followed by radiation and initiation of tamoxifen. Pathological examination of the surgical specimen status postneoadjuvant chemotherapy revealed residual grade II invasive lobular carcinoma, 0.25 cm in greatest dimension with 7/9 positive lymph nodes. He was followed routinely with CT scans for the GIST, which remained stable in size.

The patient developed metastases in the liver, lung, stomach, bladder and bone. Biopsy of the liver and lung lesions confirmed breast adenocarcinoma consistent with his previous malignancy. He was discontinued from tamoxifen and switched to fulvestrant (Faslodex), but imaging continued to show progression of disease throughout. His care was transitioned to palliative measures and he passed away in March of 2014.

DISCUSSION

While GIST has never been reported in a patient with *BRCA1/2* mutation, it has been described in association with *BRCA1/2* related malignancies such as breast, prostate and ovarian cancer.^{7 12–14} Presumably, in such studies, the patients were not worked up for *BRCA1/2* mutations due to the absence of known risk factors. Additionally, genetic databases such as COSMIC and the NCBI's genetic testing registry have not shown associations between the *BRCA* gene and GIST.

To our knowledge, this report highlights the first case of GIST in a *BRCA2* mutation-positive patient, thus raising the question of a potential association between GIST and *BRCA2*.

BRCA1/2 gene mutations are associated with multiple malignancies, the most common being breast and ovarian cancer. *BRCA1* and *BRCA2* are involved in DNA damage recognition, double-strand break repair, checkpoint control, transcription regulation and chromatin remodelling.^{15 16} These functions are essential and important for all cell types, and thus it can be speculated that *BRCA1/2* mutation carriers have increased risk of spontaneous malignancies at multiple sites.¹⁶

BRCA2 mutations, in particular, have been shown to be associated with male breast cancer, prostate cancer and pancreatic cancer, as well as gallbladder cancer, stomach cancer and melanoma.^{1 17} Lobular breast cancer, similar to that in the case-presented patient, is seen in 5–15% of *BRCA*-mutated breast cancers and is more often associated with *BRCA2* gene mutation.^{18 19} *BRCA1* mutations are associated with increased risk of colon, liver, pancreatic, uterine and cervical cancers.² The exact incidence of cancers other than breast and ovary in *BRCA1/2* patients varies widely, especially in studies of different population subgroups.¹⁶ Despite this variation, most studies demonstrate a statistically significant increased incidence of at least one other sporadic cancer besides breast and ovarian.¹⁶ The higher incidence of multiple malignancies in *BRCA1/2* mutation carriers suggests that *BRCA1/2* gene mutations may convey an overall increased risk for malignant cell transformation.

A GIST is an uncommon tumour that arises from mesenchymal stromal cells of the gastrointestinal tract. It is rare, with an incidence ranging between 7 and 20 per million people per year in the USA and Sweden, and is often found in patients over 40 years old.^{5 6 20} It most often occurs spontaneously, although it can be associated with tumour syndromes such as neurofibromatosis I or Carney's triad.^{21 22} Rare familial forms exist as well.²³ Currently, there are no consensus guidelines recommending routine GIST screening, even in suspected high-risk individuals.²⁴

GIST is nearly uniformly KIT positive (CD117) and/or *C-KIT* or *PDGFRA* mutation driven.^{25 26} Activating mutations of *KIT* and/or *PDGFRA* genes perpetuate tyrosine kinase signalling and result in increased cellular proliferation and decreased apoptosis, ultimately leading to neoplasia.^{3 25 26} Exome sequencing studies

in GIST have revealed somatic mutations in *BRAF*, *CDH1*, *EGFR*, *ERBB4*, *FLT3*, *KRAS*, *PDGFRA*, *PTEN*, *TP53* and *VHL* genes.^{27 28} It does not appear that *BRCA1/2* genes were mutated in any of these studies. In addition, it is currently thought that the mechanisms by which the *KIT*, *PDGFRA* and *BRCA1/2* mutations lead to neoplasia are unrelated.

In the case-reported patient, tissue was sent for a HRD assay. HRD testing is used to detect hereditary and somatic defects in genes that support homologous recombination, such as *BRCA1* and *BRCA2*. The HRD score is a combination of three different DNA-based measures of HRD: telomeric allelic imbalance (TAI), large-scale state transitions (LSTs) and LOH. Research has shown that high levels of TAI are inversely associated with *BRCA1* expression.²⁹ In addition, LSTs, defined as chromosomal breaks between adjacent regions, have been shown to identify basal-like breast tumours with *BRCA1/2* inactivation.³⁰ Finally, recent studies have demonstrated that the number of long subchromosomal LOH regions predicts homologous recombination repair defects.³¹ These measures of DNA repair have been combined in a single assay along with *BRCA1/2* mutation status to provide a comprehensive HRD result.³²

The HRD score has been validated as associated with HRD in all subtypes of breast cancer, ovarian cancer and pancreatic cancer.^{31 32} It has also been shown that tumours with high HRD scores are more responsive to treatment with poly-ADP ribose polymerase (PARP) inhibitors, and chemotherapy that induces double strand breaks, such as platinum salts.^{33 34}

The HRD score on the GIST in this case-presented patient was 8 (low score). There was confirmation of the *BRCA2* mutation and there was no LOH seen at the *BRCA2* locus. Given the low HRD score, it is unclear whether the *BRCA2* germline mutation played a role in the development of the GIST. However, the presence of haploinsufficiency has been described in *BRCA2* mutation carriers, and it is therefore plausible that haploinsufficiency may have led to the development of the GIST even with only one intact copy of *BRCA2*.³⁵

In recent years, the coexistence of GIST with multiple malignancies has been addressed in the literature. The synchronous or metachronous occurrence of GIST and other primary neoplasms is not uncommon, with an incidence ranging between 3% and 33%.^{7–9 14 21} The most common site of an additional malignancy is in the gastrointestinal tract, but studies have also shown occurrences of breast, prostate, uterine, lung and renal cancer.^{7 8 14 36} Of the studies reporting GIST with additional malignancies, *BRCA1/2* mutation status was either not tested or not reported.

A number of theories as to why GIST is often found with multiple malignancies have been suggested. The theory of a common gene mutation contributing to the development of malignancies at multiple sites has been proposed, but not proven.^{14 37} Other rationale is that the association of GIST and sporadic malignancies is more likely coincidence or due to a higher incidence of certain tumours among a given population.¹³

In this *BRCA2* mutation-positive patient with breast cancer, prostate cancer and GIST, it remains unclear whether these three malignancies are related. One can theorise that the *BRCA2* mutation led to a systemic predisposition to malignancy, ultimately leading to three metachronous primary malignancies. Alternatively, the malignancies may have developed simply due to chance or non-related spontaneous mutations. It is also feasible that the GIST developed as a direct or indirect result of inactivation of the *BRCA2* pathway. Although there is no reported relation between *BRCA2* mutations and GIST, the established association of GIST and *BRCA1/2* related malignancies alludes to a potential relationship.

Ultimately, further studies are needed to elucidate whether *BRCA1/2* mutations are involved in the molecular pathways of carcinogenesis leading to GIST. This may have implications for therapeutic interventions with medications such as PARP inhibitors.

Patient's perspective

The below statement was written by the patient's next of kin: (11/12/14)

In all of my years, I've never seen nor heard of anyone with the "stamina" of Claudius E Whitelaw. I sometimes wondered if his mental capabilities prevented him from expressing the depth and seriousness of what he was going through both physically and emotionally. I learned after some time that he was determined to get better, not complain and keep pushing forward because he had a goal. His goal was to get better because he had finally found someone who loved him unconditionally. He planned to marry her. Even when she, the love of his life, told him things that made our lives extremely difficult, we had to be mindful that her mental capacity matched his own. It was then I realised that when you love someone so intensely, no one could break that connection. Therefore, we endured and persevered because we truly loved him too. Claudius continuously pushed past his pain day in and day out. It was 2 days before his death that he accidentally admitted that he was in pain. Every single morning I would stop by his room and ask how he was doing. He would always say, "I'm doing fine". This particular morning, I believe that the pain was so intense that he didn't realise he had revealed to me how bad it was. Once he realised it, he tried to retract his statement. I pressured him, but he still would not admit it. I decided to call my sister who had spent some time with him in Tennessee. I knew she might be able to get it out of him. She did! Once he took his first dose of morphine and realised that it had the ability to relieve some of his discomfort, he couldn't get enough of it. Through it all, we were by his side. Our faith in God helped us hold it all together. We had no doubt that he was a fighter. The day of his passing, we saw what we thought was his last breath, but he came back fighting with all his might. We finally told him that we would take care of Josie, his love, and that it was ok. He quietly succumbed.

Learning points

- ▶ *BRCA1/2* gene mutations are well known to increase carriers' risk of cancer of the breast, prostate and ovary, but have never been described in relation to gastrointestinal stromal tumours (GIST).
- ▶ GIST has been shown to coexist in patients with *BRCA* associated malignancies, such as breast and prostate cancer, but has never been related to the *BRCA* gene mutation.
- ▶ To date, this is the first study describing a potential association between *BRCA* gene mutation and GIST.
- ▶ An association between the *BRCA* gene mutation and GIST would have implications in genetic screening of GIST patients, and would provide a role for targeted therapeutic interventions, such as poly ADP ribose polymerase inhibitors, in the treatment of GIST.

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