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## BRCA1 mutation presenting with primary breast, ovarian and colon cancer

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### Summary

#### Background:

The BRCA 1 and BRCA 2 mutation carriers are well known to predispose for breast and ovarian cancer, but there are mixed reports for colon cancer. Some studies have suggested an increased risk of colorectal cancer among mutation carriers, whereas other studies have found no such association (1). We are presenting an interesting case of a woman with a strong family history of ovarian cancer. She initially presented with left breast cancer and was later found to have right primary ovarian and adenocarcinoma of colon. We are not aware that this type of case has ever been reported.

#### Case Report:

The 48 year old Caucasian woman with strong family history of ovarian cancer diagnosed of infiltrating ductal breast carcinoma of left breast following discovery of left breast lump. She underwent lumpectomy, radiation, and chemotherapy for breast cancer. The breast tumor was estrogen receptor and progesterone receptor negative. The patient was tested BRCA 1 positive. Although patient was planned for risk reducing surgery following breast cancer treatment in the form of bilateral mastectomy, right salpingo-oophrectomy and hysterectomy, she unfortunately was found to have primary right ovarian malignancy and adenocarcinoma of sigmoid colon.

#### Conclusions:

There are mixed reports of association of BRCA mutation with Colon cancer. More studies are needed to settle this issue. Till clear guidelines become available, surveillance remains the paramount way of management for patients with known BRCA mutations.

#### key words:

BRCA • PET/CT scan • colon cancer

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## BACKGROUND

The BRCA 1 and BRCA 2 mutation carriers are well known to predispose for breast and ovarian cancer, but there are mixed reports for colon cancer. Some studies have suggested an increased risk of colorectal cancer among mutation carriers, whereas other studies have found no such association [1]. We are presenting an interesting case of a woman with strong family history of ovarian cancer. She initially presented with left breast cancer and was later found to have primary right ovarian and primary adenocarcinoma of colon. We are not aware that this type of case has ever been reported.

## CASE REPORT

The 48 year old Caucasian woman presented with infiltrating ductal breast carcinoma of a left breast following a discovery of left Breast lump in 2006. The patient underwent lumpectomy with sentinel lymph node biopsy followed by radiation and chemotherapy. The pathology specimen was of the size of 10×5.5×5 cms. Microscopically the specimen revealed adenocarcinoma and the size of invasion was 3.5×2.5×2 cms. The tumor was grade III on Nottingham score (Table 1) and on TNM classification tumor was Stage IIA(T2N0M0). The tumor was also estrogen receptor and progesterone receptor negative. The patient has past history of left oophorectomy for a simple ovarian cyst. The patient admitted that she has a strong family history of ovarian cancer in her mother and sister; diagnosed at age 48 and 56 years respectively. There were no other known cancers in her family. She was tested for possible BRCA mutation and was found positive for BRCA 1 mutation. The patient was counseled for the risk of developing other malignancies and need for risk reduction surgery in the form of bilateral mastectomy, right salpingo-oophorectomy and hysterectomy. However, it was thought prudent to first treat her breast cancer and closely observe her for other possible malignancies. She received multiple cycles of Chemotherapy and radiation therapy for a year for Breast cancer. After treatment for Breast cancer in 2007, she was planned risk reducing surgery, in the form of bilateral Mastectomy, Right salpingo-oophorectomy and hysterectomy. Before prophylactic surgery could have been done, unfortunately follow up PET/CT scan showed abnormal activity in pelvis (Figure1). Tumor markers were elevated (CEA of 10.7 and CA 27.29 of 44.1).The sonogram of pelvis showed complex right ovarian Cyst. She underwent exploratory laparotomy with total abdominal hysterectomy (TAH), right salpingo-oophorectomy, debulking of ovarian peritoneal malignancy and indicated appendectomy. She was also found to have thickening around sigmoid colon and was advised for Colonoscopy.

The pathology of surgical specimen reported as histological grade 3 (Serous carcinoma, papillary, micro papillary and invasive) and stage IIIA (Tissues microscopically involved right ovary, fallopian tube, omentum, peritoneum of appendix) tumor. Colonoscopy showed mass protruding in the lumen of sigmoid colon and biopsy confirmed adenocarcinoma of sigmoid colon. The follow up PET/CT Scan after 4 weeks of surgery showed hyper metabolic area in liver suggestive of liver Metastasis. The patient underwent again for surgical exploration with open liver biopsy, omentectomy, splenectomy, recto-sigmoid resection. The pathology of surgical specimen reported a papillary serous carcinoma on the pelvis and the liver nodule showed metastatic colonic adenocarcinoma. The omen-

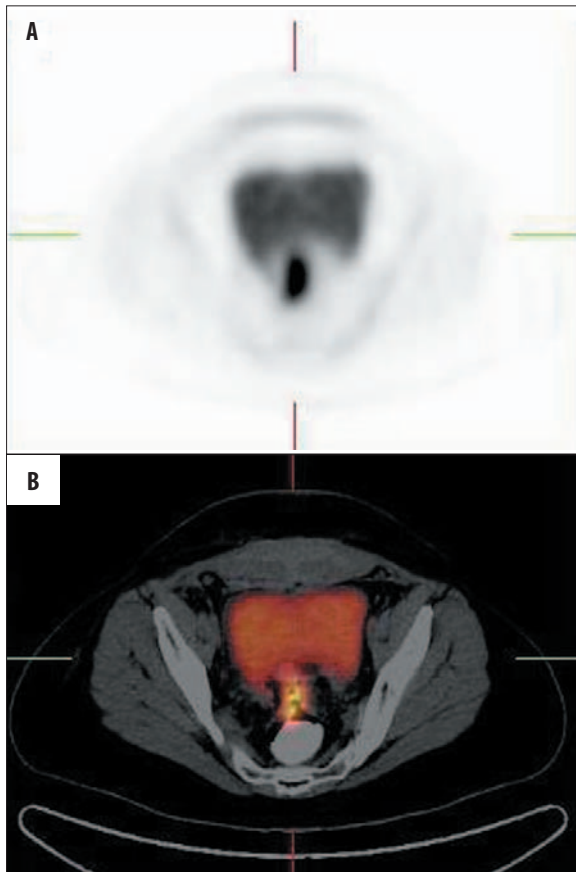
**Table 1.** Nottingham score.

Histologic type
Tubule formation: 2
Nuclear polymorphism: 3
Mitotic count: 3
Total Nottingham count: 8
Grade: III

tum showed serous carcinoma. The sigmoid colon resection reported a primary adenocarcinoma, which was 4.5 cms grade III invaded into pericolic fat, 7 out of 11 lymph nodes were involved. The tumor markers after 3 weeks of surgery showed some decrease (CEA=2.9 and CA 27.29=79.1). The PET/CT scan following surgery showed complete resolution of hyper-metabolic activity (Figure 2). The patient is currently under regular follow up and receiving chemotherapy.

## DISCUSSION

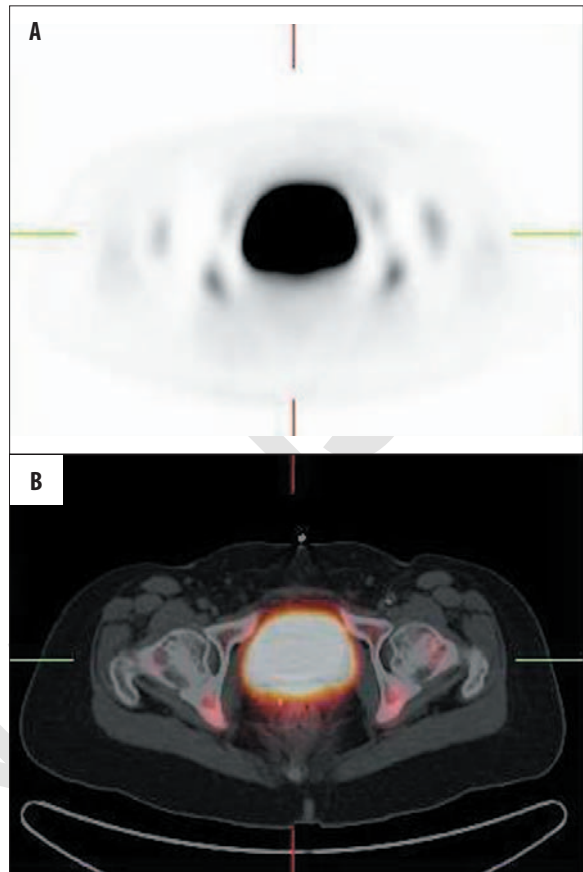
BRCA1 and BRCA2 genes are tumor suppressor genes and mutation of these genes lead to increased risk of many types of tumors [2]. Mutations in *BRCA1* gene (and *BRCA2*) are associated with inherited breast and ovarian cancer, although the exact nature of this tissue specificity is incompletely understood. The prevalence of mutations of *BRCA1* gene in the general population is between 0.07% and 0.24% and between 0.14% and 0.22% for *BRCA2* although this is higher in Ashkenazi Jews [3,4]. The study conducted by Foulkes wd, et al. showed BRCA1 mutation carriers were more likely to have Estrogen Receptor-negative breast cancers than were women in other groups, after adjustment for age, grade, and histological subtype (P<0.001). Only 3.9% of BRCA1-related breast cancers were Estrogen Receptor positive cancers in a occurring in women in their postmenopausal [5]. Breast and ovarian cancer risk in BRCA1 and BRCA2 carriers is a complex trait, affected by genetic modifiers and non-genetic factors. Germ-line mutations of the gene confer a lifetime risk of 85 percent for breast cancer and about 45 percent for ovarian cancer in families with multiple cases of such cancers [6]. The Bose et al. identified an increased risk of cancer of the colon (twofold), pancreas (threefold), stomach (fourfold), and fallopian tube (120-fold) in BRCA1 mutation carriers as compared with Surveillance, Epidemiology, and End Results (SEER) Program population-based estimates [6]. Drucker et al., Screened 136 Consecutive Israeli Jewish patients with colorectal cancer for 3 founder mutations. Preliminary study carrier of 87 tested for suggested mutation carriers were at increased risk for Colon cancer [7]. Thiffault et al. reported one family with ten cases of breast or colon cancer among twenty six first-, second- or third-degree relatives [8]. The family had a noticeable dual mutation in both BRCA2 and MSH2 [8]. However, They concluded from the study there appears to be no increase in susceptibility to the development of colorectal tumours in BRCA2 mutation carriers or to the development of breast tumours in MSH2 mutation carriers [8]. Two Studies of Kirchhoff et al. and Neill et al. did not eliminate a small augment in risk for colon cancer. The two studies actually involved small number of mutation carriers.



**Figure 1.** (A) PET and (B) PET/CT scan showing abnormal activity in pelvis.

Eight mutation carriers in Kirchkoff et al. study and twenty four mutation carriers in Neill et al. study [9,10]. The Neill et al. study showed that the elevation in colon cancer risk did not increase to statistical significance [10]. A study by Kadouri et al. on Ashkenazi Jewish women showed the four fold risk of colon cancer in BRCA1 carriers [11]. Another study by Sivarajasingham et. al by using an intragenic marker at 13q12.3 for BRCA2 (D13S171) in twenty-three duke stage C, replication error–negative carcinomas patients, an Allelic imbalance frequency of 33% was observed, and this supported the possible involvement of BRCA2 in colon cancer [12]. Allelic imbalance in the BRCA1 gene was claimed to be an independent prognostic factor in patients with stage I and stage II colorectal cancers by a study of Garcia et al. [13].

The pathogenesis of Colon cancer in BRCA mutation is not clear but one study by Romagnolo provided interesting explanation [14]. Deoxycholate promotes colon cancer in BRCA mutation. Deoxycholate also causes DNA damage. They showed, when cultured cells of colonic origin are exposed to deoxycholate at different concentrations, BRCA-1 expression is induced at a low noncytotoxic concentration (10  $\mu$ M) but is strongly inhibited at higher cytotoxic concentrations (>100  $\mu$ M). They show that BRCA-1 is substantially lower in colon adenocarcinomas from five patients compared with associated non-neoplastic colon tissue from the same patients, suggesting that the loss of BRCA-1 expression contributes to the malignant phenotype. These results imply that reduced expression of BRCA-1 may be associated with carcinoma of the colon.



**Figure 2.** (A) PET and (B) PET/CT scan showing complete resolution of abnormal activity in pelvis.

In our case, we initially thought the colon thickening at lapratomy was due to ovarian metastasis but colonoscopy and histopathology confirmed primary adenocarcinoma. The diagnosis was reached following extensive investigation and surgical resection.

## CONCLUSIONS

This is the first case reported in our knowledge. We conclude that there are mixed reports from studies on BRCA mutations leading to Colon cancer but we should still be vigilant not to miss colon cancer. In our opinion till clear guidelines become available, close Surveillance should be the paramount approach of management for patients with known BRCA mutations.

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