A case of a male BRCA2 mutation carrier with gastric adenocarcinoma with signet ring cells

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ABSTRACT

Introduction: BRCA1 and BRCA2 are tumor suppressor genes with an autosomal dominant inheritance. Germline mutations of BRCA2 have more impact on men than on women. An increased risk of cancer of breast, prostate, pancreas, uveal melanoma, as well as gastric and esophageal cancer is associated with BRCA2 mutations. Case Report: We present a case of a middle-aged male, who was on follow-up because of a BRCA2 mutation and a familial history of many neoplasia. During the follow-up, the patient presented nonspecific symptoms of gastric malaise. The upper endoscopy revealed an ulcerated lesion at the incisura angularis, which on pathologic report revealed an adenocarcinoma with signet ring cells. Conclusion: There is growing evidence that BRCA2 mutations increase the risk of gastric cancer, especially in men. Surveillance endoscopic programs directed to families with these mutations should be considered to diagnose early-stage gastric cancer.

Keywords: BRCA2, Carcinoma, Endoscopy, Gastrectomy, Genes, Signet ring cell, Stomach neoplasms

INTRODUCTION

Germline mutations of BRCA genes (BRCA1 and BRCA2) are major risk factors for breast and ovarian cancer in women [1]. BRCA1 and BRCA2 are tumor suppressor genes and have an autosomal dominant inheritance. Those mutations have two major expressions. Mutations of the BRCA1 type represent a concern among the women, while the BRCA2 type relates with an increased risk among men. Male BRCA mutation carriers additionally have an increased risk for breast cancer (cumulative age-adjusted risk 5.8%) [1], as well as prostate, pancreas, uveal melanoma, but also gastric and esophageal cancer [2, 3].

We present a case report, when we reviewed the demographic, surgical, postoperative, and histological data of the patient submitted to gastric surgery at our institution.
CASE REPORT

A 43-year-old male patient was on a follow-up in the outpatient oncogenetics clinic because of a BRCA2 mutation carrier. His medical history included a lumbar surgical instrumentation 23 years ago, and the diagnosis of epilepsy and depression. He was on clonazepam and fluvoxamine on a daily basis. He was a light smoker. He had a familial history of cancer (Figure 1): breast cancer in his mother and two sisters (both at 33-year-old and one of them an index case for diagnosis of BRCA2 gene mutation), a brother with nasopharynx cancer is 19 years old, two aunts and father diagnosed with gastric cancer at age 48 and breast cancer at 47-year-old, and two cousins with breast and gastric cancers.

After two years of follow-up he started with nonspecific epigastric discomfort. An upper gastrointestinal endoscopy (UGE) was performed that depicted an ulcerated lesion at the incisura angularis. Biopsy revealed an adenocarcinoma with signet ring cells and the patient was referred for treatment.

Thoraco-abdominal-pelvic computed tomography (CT) scan did not show abnormal findings or distant metastasis (Figure 2).

According to our protocol, the patient was submitted to laparoscopic total gastrectomy with D2 lymphadenectomy. He was discharged on the sixth postoperative day with no complications.

Pathologic examination of the surgical specimen revealed adenocarcinoma with signet ring cells, without involvement of the 34 resected lymph nodes. There was no histological evidence of venous, lymphatic, or perineural permeation. Pathologic staging was pT1N0 (Stage IA – pT1N0M0) [4].

The patient was scheduled for regular follow-up. Due to the age, family history of gastric cancer and the presence of adenocarcinoma with signet ring cells, we proceeded to the search for the E-cadherin mutation (CDH1) which was negative.

DISCUSSION

The BRCA1 gene was the first identified susceptibility gene for breast cancer followed by the report of BRCA2, shortly afterward [5]. The BRCA1 and BRCA2 genes are involved in pathways important for DNA damage recognition, double-strand break repair, checkpoint control, transcription regulation, and chromatin remodeling. Mutation of these genes may increase the proliferation of cancer cells, because cells lacking BRCA are highly prone to DNA damage and marked genetic instability. In other words, BRCA1 and BRCA2 are tumor suppressor genes. These genes have an autosomal dominant inheritance [1, 5, 6].

BRCA mutations in women confer a high risk for breast and ovarian cancer [1]. On the other hand, the male BRCA mutation carriers are also susceptible to breast cancer (cumulative age-adjusted risk 5.8%) [1] and have higher risk for prostate, pancreatic, gastric, melanoma, and hematologic cancers [1, 2, 7].

In contrast to women, who have a greater lifetime risk of cancer with mutations of the BRCA1 gene, BRCA2 gene is more concern for men [1] (for cancers of all sites combined, the estimated penetrance of BRCA2 mutations was greater for males than for females, 35% vs. 38%) [8]. Male carriers of BRCA1 mutation have an increased risk of prostate and breast cancer, while those with BRCA2 mutation carriers have an increased risk of breast, prostate, and pancreatic cancers, but also at risk of stomach, esophagus cancers and melanoma (of the skin and eye), and the relative risk is higher before the age of 65 years [2, 7].

In some studies, the relative risks in stomach and esophagus cancers and uveal melanoma are 2.7, 4.1, and 99.4, respectively. The risk for prostate and pancreatic cancers in BRCA2 carriers is equivalent to a four-fold risk [2].

Other studies provide strong confirmation of an increased risk of pancreatic and prostate cancer, in BRCA2 mutation carriers, as well as in stomach (sex related, as it occurs primarily in males), gallbladder and bile ducts.
symptoms, for the success of early diagnosis of gastric cancer, especially in men. This family documents the oncological aggressiveness of these mutations. It is important to perform an UGE, even with nonspecific symptoms, for the success of early diagnosis of gastric cancer, preferably inserted in surveillance programs, beginning at 40 years of age or earliest, if they have symptoms.

**CONCLUSION**

The BRCA2 mutations increase the risk of gastric cancer, especially in men. This family documents the oncological aggressiveness of these mutations. It is important to perform an UGE, even with nonspecific symptoms, for the success of early diagnosis of gastric cancer, preferably inserted in surveillance programs.

**REFERENCES**

Author Contributions
Vítor Devezas – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

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