Case Report
A Paternally Inherited BRCA1 Mutation Associated with an Unusual Aggressive Clinical Phenotype

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This report highlights the necessity of genetic testing, at least for BRCA1 mutations, of young females diagnosed with triple negative breast cancer, even in the absence of or limited family history. A 34-year-old female with a locally advanced, triple negative tumour, which perforated the skin, is described. At the time of diagnosis, the patient had already multiple lung metastases and although chemotherapy was started immediately, she died with rapid systemic disease progression. The patient was found to carry the BRCA1 p.E1060X mutation, which is located on exon 11 of the gene. The high penetrance of BRCA1 gene is not represented in the patient’s family, since the mutation was paternally inherited. It is evident that females belonging to small families, along with paternal inheritance of pathogenic BRCA mutations that predispose for breast cancer, in most cases will probably be genetically tested only after being diagnosed with cancer.

1. Introduction

BRCA1 and BRCA2 genetic testing has been available in the clinic at least for the past decade, allowing the characterization of people that face an increased breast and ovarian cancer risk. Although the selection criteria for genetic testing are quite established, many times the small size of the family or the paternal inheritance of the pathogenic BRCA mutation can be misleading when referring patients. Therefore, loss-of-function mutations can be genetically transmitted from male BRCA mutation carriers, who can be in many cases cancer-free, to their daughters, who will have a lifetime breast cancer risk that can be as high as 84% [1–3]. Estimated lifetime breast cancer risk for male BRCA2 carriers is approximately 8% [4], while there is high relative risk for pancreatic and prostate cancer, when compared to the general population [5]. On the contrary, relative and cumulative cancer risks are much lower in male BRCA1 carriers [6]. Since our current knowledge is advanced on understanding the cancer predisposition of mutation carriers, it seems rather important to successfully identify these individuals in order to offer appropriate clinical management.

2. Case Report

A 34-year-old premenopausal female with a locally advanced tumour presented as a dirty ulcer, perforating the skin, in her right breast is described. Biopsies of the damaged tissue showed an invasive, grade III ductal carcinoma, with areas of papillary shaping, areas of necrosis, and invasion of the skin. The breast tumour was classified as triple negative, since there was a lack of estrogen and progesterone receptor expression and absence of HER2 oncoprotein after immunohistochemical staining. Staging revealed multiple lung metastases and enlargement of right axillary lymph nodes. Consequently, she was diagnosed with a stage IV infiltrating ductal cancer in her right breast which was triple negative and grade III.

The patient was started on first line chemotherapy with the regimen carboplatin 2AUC and paclitaxel 80 mg/m²...
The updated NCCN guidelines (http://www.nccn.org/) and with the distinct immunophenotype, the patient fulfilled the requirements for genetic testing. Direct Sanger sequencing revealed the nonsense mutation p.E1060X (c.3178G>A) in BRCA1, which is located on exon 11 of the BRCA1 gene. This is a rare, inheritable and inherited BRCA1 mutation that is associated with a higher probability of nodal involvement, distant metastasis, and low grade tumours [7, 8]. This observation is consistent with this case.

Due to the early age of breast cancer diagnosis, along with the distinct immunophenotype, the patient fulfilled the updated NCCN guidelines (http://www.nccn.org/) and was therefore tested for deleterious mutations in BRCA1 and BRCA2 genes. The direct relationship between BRCA1 mutations and triple negative breast cancer has been widely reported [9]. Direct Sanger sequencing revealed the nonsense mutation p.E1060X (c.3178G>A) in BRCA1. This is a rare, inheritable and inherited BRCA1 mutation that is associated with a higher probability of nodal involvement, distant metastasis, and low grade tumours [7, 8]. This observation is consistent with this case.

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3. Discussion

This case report highlights the necessity of genetic testing even when family history is not prominent, at least for BRCA1 mutations, of young females diagnosed with triple negative breast cancer. Individuals belonging in small families in combination with paternal inheritance of pathogenic mutations can remain undiagnosed. Some recent research studies indicate that females with paternally inherited mutations in BRCA gene mutations develop breast cancer at younger age when compared to women who inherit the gene mutations from their mothers. This can be partially explained by different imprinting patterns in maternal and paternal chromosomes and more specifically in the BRCA1 or BRCA2 locus [10].

We report this case as it highlights the importance of careful selection of individuals for genetic testing. The necessity for identification of mutation carriers is enlarged since there are promising, targeted therapies for BRCA1 carriers, such as PARP inhibitors.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors’ Contribution

Florentia Fostira and Nikolaos Tsoukalas equally contributed to this work.

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