CLINICAL VIGNETTE

CHEK2 Mutation and Cancer Risk

Melissa Gee, MD and Kristin Masukawa, MD

A 58-year-old female with a 59-year-old sister with breast cancer and BRCA1 mutation. The patient was seen by genetics and found to have CHEK2 and ATM mutations.

Per genetics report, patient had CHEK2, Exon11.c.1232 G>A (p.Trp411*), which is associated with a predisposition to breast, colon, thyroid and prostate cancers. She also demonstrated ATM, Exon52.c.7816 A>G (p.lle2606Val) this variant has been observed in an individual with colon cancer; and ATM, Gain(Exons 62-63), copy number = 3, which has been observed in patients with colon and renal cancer.

Our patient's ATM mutations were reported as uncertain significance due to insufficient evidence to determine the role of this variant in disease. Patient had an unremarkable colonoscopy 2 years prior and was advised to repeat colonoscopy in 10 years. The recommendation was made prior to knowledge of patient's CHEK2 mutation.

Discussion

CHEK2 (cell cycle checkpoint kinase 2) is a gene that is a cell cycle checkpoint regulator and tumor suppressor that becomes activated upon DNA damage.[1] A mutation in CHEK 2 can increase a patient's cancer risk for breast, colon, thyroid and prostate cancers.

There is also some evidence that a CHEK2 mutation confers an increased risk of stomach cancer, sarcoma and kidney cancer.[2] As there are several variants of CHEK2 mutations, the risk is based on the individual's gene mutation and family history.[3]

Among patients with family history of breast cancer that test negative for BRCA1 and BRCA2, 12% demonstrate a large genomic deletion or duplication of one of these genes, and approximately 5% demonstrate a mutation to CHEK2 or TP53.[4] The lifetime risk for breast cancer for a woman with CHEK2 mutation and no family history is around 20%.[5] This underscores the importance of a genetics evaluation for patients with a significant family history of breast cancer to determine if they also carry a mutation that will increase their lifetime risk of breast cancer or require monitoring for additional cancer risks.

Current recommendations for breast, colon, thyroid and prostate cancer screening for patients with CHEK2 mutation are summarized below.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, recommends patients with CHEK2 mutation should undergo annual mammogram beginning at 40 years old, with consideration of annual breast MRI. There was insufficient evidence for risk-reducing mastectomy, but may be considered based on family history.[6]

Due to the increased risk of colon cancer with the CHEK2 mutation,[7,8] the NCCN Guidelines recommend those with CHEK2 mutation to be managed similarly to those with adenomatous polyposis coli (APC) I1307K mutation which involves colonoscopy screening every 5 years beginning at age 40 or 10 years prior to age of first-degree relative's age at CRC diagnosis. Recommendations will differ if the patient has polyps or colorectal cancer.[9]

There is no current high-level evidence to support thyroid cancer screening. However, patients with familial adenomatous polyposis (FAP) have a hereditary colon cancer syndrome with an increased chance of developing other cancers including thyroid cancer. Some studies evaluated the use of thyroid ultrasound to screen for early thyroid cancer in these patients.[10,11] At this time the NCCN does not recommend screening for thyroid cancer in patients with CHEK2 mutation. Similarly, USPSTF advises against screening for thyroid cancer in asymptomatic adults.

There are no specific screening guidelines for prostate cancer screening in CHEK2 mutation carriers at this time. African-American men and those with BRCA 1/2 mutation are recommended to begin shared decision making about PSA screening at age 40 years and consider annual screening.[12] Generally, the NCCN recommends patients with family or personal history of high-risk germline mutations be referred to a cancer genetics professional.

Our patient's individualized plan, includes annual screening mammography in addition to annual breast MRI since her calculated lifetime risk of breast cancer was >20%.[13] Her initial colonoscopy was negative and will be repeated in 5 years. We will continue to see the patient annually and do additional testing/screening if indicated. With regards to genetic screening recommendations for her family members, there are different

guidelines based on the expert group. This patient's sister is BRCA1 positive. The NCCN recommends genetics referral for all first and second-degree relatives of the BRCA1 mutation carrier for discussion of genetic testing and counseling.[6]

Each patient's family history and specific mutation will impact their risk uniquely, emphasizing the importance of genetics consultation to carefully evaluate the risks to the patient. The expanding body of literature on known, recently identified, and future understandings of mutations makes it important to routinely reevaluate cancer risk in patients with known mutations and consider potential modifications to their cancer screening plan, as well as the consideration of additional genetic screening for family members as new gene sequences are discovered.

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