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BRIEF REPORT

Rationale for evaluating breast cancers of Lynch syndrome patients for mismatch repair gene expression

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Abstract

Background Lynch Syndrome (LS) patients harbor germline mutations in one of several mismatch repair (MMR) genes and are predisposed to the development of colon and endometrial cancers and multiple other cancers types as well. Tumors related to LS are characterized by deficient protein expression of one or more MMR genes (dMMR) and/or demonstrate high microsatellite instability (MSI-H) (Win et al. in Breast Cancer Res 15(2):R27, 2013). The National Comprehensive Cancer Network (NCCN) Guideline states that there have been "suggestions" of increased risk of breast cancer in diagnosed LS patients, but does not endorse "increased screening above-average-risk breast cancer screening recommendations" for patients with LS (Provenzale et al. in J Natl Compr Cancer Netw 14(8):1010–1030, 2019).

Results This report describes a molecularly diagnosed LS patient who developed a dMMR breast cancer.

Conclusions Sporadic dMMR breast cancers are extremely rare (Davies et al. in Cancer Res 77:4755–4762, 2017). It seems reasonable to conclude that identifying a dMMR breast cancer in a patient with known LS strongly suggests that her LS is breast cancer-predisposing. LS patients with dMMR breast cancers might therefore be considered for above-average breast cancer screening for the development of additional breast cancers. Also, the FDA recently granted approval of checkpoint inhibitor therapy for all metastatic dMMR solid malignancies (Lemery et al. in N Engl J Med 377:1409–1412, 2017). MMR expression assays in metastatic breast cancers of LS patients would represent a more focused approach to identifying patients with breast cancers who are potentially eligible for checkpoint inhibitor therapy than would be universal MMR testing of all metastatic breast cancers.

Keywords Lynch syndrome · Breast cancer · Mismatch repair

Case report

A 58-year-old woman underwent a left modified radical mastectomy for stage II-A invasive ductal breast cancer (T2cN1miM0) in 2010. She received adjuvant chemotherapy and hormonal therapy. In 2015, she underwent a right hemicolectomy for stage II colon adenocarcinoma (T3N0M0) and hysterectomy and bilateral salpingo-oophorectomy (no malignancy identified). She received no adjuvant chemotherapy. To date, she has had no recurrence of either cancer. The patient has three brothers, two of whom had colon cancer, and there was no family history of breast cancer.

Germline testing demonstrated a MLH1 deleterious mutation (IVS7-2A > G) and an ATM variant, "likely benign" (ATMpN1230S) (Myriad Genetic Laboratories, Salt Lake City, UT 84108). Immunohistochemistry (IHC) of the 2010 breast cancer demonstrated intact nuclear expressions of MSH2 and MSH6, but loss of nuclear expressions MLH1 and PMS2 (dMMR). (Pathology Division, Wake Forest University Medical Center, Winston-Salem, NC 27157).

Discussion

Lynch syndrome patients carry pathogenic germline mutations in one of several MMR genes including MLH1, MSH2, MSH6, and PMS2. These patients are at increased risk for the development of cancers of the colon, rectum, endometrium, stomach, ovary, ureter, renal pelvis, brain, small bowel, and hepatobiliary tract. Cancers in these patients

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demonstrate DNA microsatellite instability and/or loss of MMR protein expression. Sporadic breast cancers are rarely dMMR [1, 2].

It remains largely unclear whether LS predisposes to breast cancer risk. Therefore, for LS patients, the NCCN guideline currently states that "there is not enough evidence to support increased screening above-average-risk breast cancer screening recommendations or those based on personal/family history of breast cancer" [3]. As a result, it remains uncertain whether carriers of mutated MMR genes in particular families are at increased risk of breast cancer development and might be offered above-average breast cancer screening.

Win et al. reviewed 21 risk studies and found that 13 did not observe statistical evidence for an association of breast cancer with LS, while 8 studies found an increased risk ranging from 2- to 18-fold among LS families. However, in the molecular studies they reviewed, they found 62/122 (51%) of "breast cancers in MMR gene mutation carriers were MMR-deficient" [1].

The patient described carries a germline mutation in MLH1 and her breast cancer lacked expression of MLH1. Per the NCCN guideline, currently it would not be recommended that she or her family members undergo above-average screening for breast cancer solely as a result of her being a LS patient. However, since lack of expression of MLH1 is extremely rare in sporadic breast cancer [1, 2] and she is both a LS patient and her breast cancer was dMMR, it seems reasonable to consider her to be at higher risk for future breast cancers and might be considered for above-average screening for breast cancer.

Typically, once an inherited germline alteration has been identified as cancer-predisposing in a particular family member carrying that gene, other family members who carry the same germline alteration would be considered for above-average screening. However, for the patient described, who has no breast cancer family history, it is possible that either the penetrance associated with carrying this germline MLH1 alteration is quite small or this particular patient carries other germline polymorphisms or alterations or was subject to environmental exposures that in part explain her developing a dMMR breast cancer.

Also, there are therapeutic implications resulting from identifying dMMR breast cancers. The FDA recently approved checkpoint inhibitor therapy for any patient with a metastatic dMMR solid tumor. In the pivotal study that resulted in the FDA approval, there were two patients with dMMR breast cancers, both of whom responded to the checkpoint inhibitor [4]. Since then, Kok et al. reported a dramatic response to checkpoint inhibitor therapy in a patient with a dMMR breast cancer [5]. However, the FDA agnostic approval has led to challenges in considering which patients should have their tumors studied for MMR expression due to the infrequency of dMMR tumors for nearly all solid cancer types, including breast cancer. For example, Prasad et al. predicted an enormous cost associated with MMR expression testing of all metastatic solid tumors [6]. Although it may be cost prohibitive to test all breast cancers for MMR expression, testing the tumors of LS patients would appear to be reasonable, particularly given that roughly half of these tumors will be dMMR [1].

Conclusions

Currently it remains unclear whether the average LS patient is at higher risk for breast cancer development. However, if dMMR breast cancer is identified in a LS patient, it seems reasonable to consider above-average screening for future breast cancers in such patients. Finally, LS patients with metastatic breast cancer represent a subgroup of breast cancer patients whose tumors might be considered more strongly for dMMR testing of their tumors, as roughly half of these patients will be eligible for checkpoint inhibitor therapy, based on the recent FDA agnostic approval of checkpoint inhibitor therapy for any dMMR metastatic solid tumor.

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Compliance with ethical standards

Conflict of interest Dr. Sorscher has received no research grants. Dr. Sorscher has received speaker honoraria from Celgene Corporation, Pfizer Pharmaceuticals, and Puma Biotechnology. Dr. Sorscher owns no stock that would constitute a potential conflict of interest.

Informed consent Written informed consent was obtained from the single individual referred to in the study, and all procedures involved with the single individual were in accordance with the ethical standards of the institution where the patient received her care.

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