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Letter to the editor

Oral squamous cell cancer in a patient with Lynch syndrome

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ABSTRACT

For patients with Lynch Syndrome (LS) (formerly known as hereditary nonpolyposis colorectal cancer or HNPCC), inheritance of one of several mutated mismatch repair genes (MMR) results in an increased risk for a variety of malignancies including colon, rectal, endometrial, urinary tract, gastric, small bowel and others [1]. Confirmation of increased risk of particular malignancies for patients harboring an MMR germline mutation has typically been the result of population studies of families tracked for the development of the possible associated cancer.

When cancer results from inheritance of a particular mutated MMR gene, the malignancy has a characteristic fingerprint referred to as microsatellite instability-high (MSI-H), which results from deficient expression of the inherited MMR gene product (dMMR). Therefore, if sporadic tumors of a particular tissue of origin are only rarely dMMR, identifying a tumor as dMMR in a known LS family member suggests that, in that particular family, inheritance of the mutated MMR gene does predispose to that malignancy.

Here we describe a patient diagnosed with a germline mutation in the MMR gene MSH6 who developed an oral pharynx cancer. Oral pharynx cancers are not known to be associated with LS. By confirming that the tumor was not dMMR and not MSI-H, it was concluded that his oral pharynx cancer was sporadic, rather than LS-related, and other family members carrying the mutated MSH6 are unlikely to be at above-average risk for the development of oral cancers, as a result of the LS. In additional, he would not be eligible for the so-called FDA agnostic approved immunotherapy which is endorsed for dMMR or MSI-H tumors [2].

Case presentation

A 72 year old man underwent a segmental mandibulectomy with bilateral radical neck dissection in 5-2017 and pathology revealed this to be a T4aN2 squamous cell cancer of the inner lower lip. The patient's mother had pancreatic, ovarian cancer and colon cancer. Two of her siblings had colon cancer.

There was no evidence of more distant spread. He received adjuvant radiation therapy with concurrent carboplatin chemotherapy. In 11-2018 recurrent disease involving the floor of his mouth, neck and regional skin was identified. Biopsies of left and right buccal ulcers - showed invasive moderately to poorly differentiated squamous cell carcinoma. Immunohistochemistry showed retained expression of MLH1, PMS2, MSH2 and MSH6.

Next generation sequencing of this biopsy showed microsatellite stability (MS-Stable), low mutational burden, BCL2L2 amplification, CASP R68 alteration, CDKN2A H83Y alteration, FGF10 amplification, MSH6 E463 alteration, RICTOR amplification, TERT promotor-124C > t, TP53 V173L alteration (FoundationMedicine, Inc., Cambridge, MA 02141).

Due to his family history germline testing was done and demonstrated a “positive result. Pathologic variant identified in MSH6″ (c.1387G > T) (Invitae Corp., San Francisco, CA 94103).

He received palliative systemic therapy with cetuximab, carboplatin, paclitaxel. In 4-2019 a CT neck showed no new soft tissue enhancing lesions and the ST floor of mouth enhancing ST area was less discrete. Systemic therapy was held with plans to rescan in a few months.

Discussion

For years, diagnosing patients with LS resulted when a patient fulfilled the Amsterdam II clinical criteria for diagnosing LS, which is based on personal and family history. Currently, it is recognized that LS is the result of inheritance of one of several mutated mismatch repair genes and a diagnosis of LS is confirmed by germline testing.

Inheritance of a mutated MMR gene (LS) predisposes to loss of expression of the MMR gene product in normal cells, microsatellite instability, an inability to repair DNA damage, abnormal miRNA processing and lack of activation of normal apoptosis pathways which are thought together to result in transformation and tumorigenesis [3]. In fact, microsatellite instability related to loss of heterozygosity a variety of genes has been associated with progression from dysplasia to head and neck malignancy [4].

Harboring a mutated germline MMR gene increases the risk of developing a variety of cancer types including colon, rectum, endometrium, stomach, ovary, urinary tract and hepatobiliary [1]. It remains unclear whether carrying a mutated germline MMR gene predisposes to primary cancer development from other tissues of origin. For example, currently there is not definitive proof that breast cancer is a LS-related malignancy and the National Comprehensive Cancer Network recommends against above-average screening for breast cancer in LS patients [5]. However, dMMR or MSI-H tumors are exceedingly rare in sporadic breast cancer. Consequently, it is felt reasonable to conclude that in a LS patient whose breast cancer is dMMR or MSI-H, that cancer developed as a result of being a LS patient [6].

Mechanisms other than those resulting from loss of normal MMR

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gene product expression have been studied for oral cavity squamous cell cancer cell lines and include PIK3CA amplification, CDKN2A deletions, TP53 and CASP8 mutations [7].

In spite of LS patients being predisposed to developing a variety of cancers, LS patients have not been shown to carry an increased risk of head and neck cancers. In a study of 504 cancers from LS patients, there were no oral cavity cancers [8]. Many years ago, Lynch et al reported a LS patient and son, both of whom developed laryngeal carcinoma, but neither MMR nor MSI testing was reported for their tumors [9]. Recently, Ziegler and Thorpe reported "the first case in the literature of oral cavity cancer in a patient with HNPCC." However, apparently neither MMR nor MSI testing was done on the patient's oral cavity tumor [10].

For the LS patient we describe, the dMMR testing and lack of MSI testing confirm that, in all likelihood, his was a sporadic cancer, not LS-related. If our LS patient's oral cancer were demonstrated to be either dMMR or MSI-H or both, it would suggest that in that particular LS family, LS patients would appear to be predisposed to developing oral cancers. Because MSI is extremely rare in head and neck squamous cell cancers (HNSCC) (roughly 1%) [8], a dMMR or MSI-H HNSCC cancer in a LS patient would almost certainly be LS-related, rather than sporadic, particularly if the same mutated germline MMR gene that defined the patient as having LS was the same gene not expressed in the dMMR tumor assay.

In conclusion, our patient was diagnosed with LS but in all likelihood developed an unrelated sporadic oropharyngeal cancer. There appear to remain no reported cases of molecularly-confirmed LS-related oropharyngeal cancers. Finally, as result of the recent so-called agnostic approval of immunotherapy for all metastatic solid tumors characterized as dMMR or MSI-H (whether LS-related or not), identifying an oral cancer as dMMR or MSH-H has important therapeutic implications [2]. For example, Tardy et al recently reported "a complete durable response" for a patient whose head and neck cancer demonstrated microsatellite instability [11]. The patient described illustrates that it is not safe to assume an oral cancer in a LS patient to be LS related (dMMR or MSI-H) and therefore likely to benefit from immunotherapy based on the MMR status as the predictive biomarker.

Declaration of Competing Interest

There are no relevant conflicts of interest for either author

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