Muir Torre Syndrome (A Variant of Lynch Syndrome) Case Report

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Abstract

Lynch Syndrome (LS), also known as hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant inherited disorder with high penetrance. Individuals are at an increased risk for early onset of colorectal cancer, usually in the proximal colon and other extracolonic cancers, which include endometrial, ovarian,stomach, pancreatic, and urinary tract cancers. LS is caused by a germline mutation in the DNA mismatch repair genes, which results in microsatellite instability. There are two known variants of Lynch Syndrome, Muir-Torre Syndrome (MTS) and Turcot Syndrome (TS). We report a 67 year old female patient who presented with abdominal pain. Initial thoughts were diverticulitis with abscess formation. However, this was proven to be carcinoma of the colon with perforation and abscess formation. A later colonoscopy would reveal another mass below the hepatic flexure in the ascending colon. She would then develop endometrial cancer and skin cancer (squamous cell and sebaceous carcinoma) . Genetic testing would reveal a MSH2 mutation, confirming the diagnosis of Lynch Syndrome. Her diagnosis of sebaceous carcinoma would classify her LS as the variant MTS. Our case demonstrates how a rare condition can present itself as a common symptom, and the importance of continuous monitoring of patients with LS, as atypical cancers for LS can be LS variants.

Introduction:

LS is an autosomal dominant inherited disorder with high penetrance that places individuals at an increased risk for colorectal cancers at an early age. 3% of colorectal cancers are attributable to LS. Individuals with LS are at a 50-70% lifetime risk of developing colorectal cancers and usually before 50 years old [1]. LS can also put individuals at an increased risk for endometrial (40-60%), ovarian, stomach, pancreatic, and urinary tract cancers. It is caused by a germline mutation in the DNA mismatch repair genes MLH1, MSH2, MSH6, PMS2. In some patients, it is also caused by a 3'end deletion of the EPCAM gene, which leads to an epigenetic silencing of MSH2 gene. MLH1 and MSH2 genes are most commonly mutated in LS patients accounting for in MSH2) [1]. It is estimated 1 in 279 individuals in the United States have a gene mutation associated with LS [2].

Screening for LS includes testing for microsatellite instability (MSI), immunohistochemistry staining (IHC), and methylation/BRAF V600E testing [2]. Screening should be offered to individuals who meet the criteria for Amsterdam II criteria or revised Bethesda guideline (Fig. 1 and Fig. 2). Within LS, there are two variants, MTS and TS. MTS is characterized by skin cancers (sebaceous or keratoacanthomas) in association to colorectal cancer [3]. TS is characterized by primary brain tumors (medulloblastomas, glioblastomas, ependymomas, and astrocytomas) in association with colorectal cancer [4]. In this study we discuss an atypical presentation of MTS.

Figure 1:

Amsterdam II criteria for Lynch Syndrome
There should be at least 3 relatives with any Lynch Syndrome-associated cancer (colorectal cancer, cancer of the endometri

Amsterdam II criteria for Lynch Syndrome
1 should be a first-degree relative of the other two
At least 2 successive generations should be affected
At least 1 should be diagnosed before age 50
Familial adenomatous polyposis should be excluded in the colorectal cancer case(s), if any
Tumors should be verified by pathological examinations

Adapted from VASEN, H, et al. "New Clinical Criteria for Hereditary Nonpolyposis Colorectal Cancer (HNPCC, Lynch Syndrome) Proposed by the International Collaborative Group on HNPCC." *Gastroenterology* , vol. 116, no. 6, June 1999, pp. 1453–1456, 10.1016/s0016-5085(99)70510-x. Accessed 19 Mar. 2020.

Figure 2:

The revised Bethesda guidelines for testing colorectal tumors for microsatellite instability (MSI)
Colorectal cancer diagnosed in a patient who is less than 50 years of age
Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors, regardless of age
Colorectal cancer with the MSI-H like histology diagnosed in a patient who is less than 60 years of age
Colorectal cancer diagnosed in a patient with 1 or more first-degree relatives with an HNPCC-related tumor, with 1 of the c
Colorectal cancer diagnosed in a patient with 2 or more first- or second-degree relatives with HNPCC-related tumors, regar

Umar, Asad, et al. "Revised Bethesda Guidelines for Hereditary Nonpolyposis

Colorectal Cancer (Lynch Syndrome) and Microsatellite Instability." *Journal of the*

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Case Presentation:

The proband is a 67 year old female, with a past medical history of Rheumatoid Arthritis (RA), who presented with abdominal pain in August of 2002 at age 48. She was suspected to have diverticulitis with abscess formation. However, this was proven to be a left sided carcinoma of the colon with perforation and abscess formation. Lymphnode was not involved and she was treated with chemotherapy. She then underwent a colonoscopy in February 2003 that revealed a 2-3cm mass below the hepatic flexure in the ascending colon, characterized as moderately differentiated adenocarcinoma. She had a resection, underwent ileostomy, and received 5-FU and Leucovorin after the resection. Following the resection she had dehiscence and had to be reoperated. In November of 2004 she had a reanastomosis of her small bowel to transverse colon. She denied a total colectomy. In 2007, she then experienced abnormal vaginal bleeding that was evaluated and diagnosed as grade 3 endometrial cancer, papillary serous type. She was treated with a total abdominal hysterectomy and bilateral salpingo-oophorectomy, lymphadenectomy, omentectomy, peritoneal biopsy, adjuvant Taxol and Carboplatin, and brachytherapy to the vaginal vault.

Further investigation into her family history revealed an older sister who was diagnosed with uterine cancer at 53 years old; an older brother with kidney cancer in his 20's; a mother with a diagnosis of uterine cancer at age 50, bladder cancer, and kidney cancer; a father with prostate cancer and possible colon cancer; maternal grandmother with breast and colon cancer; and paternal grandmother with colon cancer (Fig. 3). Her diagnosis and family history met the Amsterdam II criteria which qualified her for LS screening. In 2009, she underwent genetic testing, which showed germline MSH2 mutation R389X, resulting in premature truncation of the MSH2 protein at amino acid position 389, confirming her diagnosis of LS. In 2012, she had peritoneal cancer which was treated with 2 cycles of Taxol and Carboplatin. Recently, she was evaluated and found to have a recurrence of her colon cancer. She was surgically treated with a total proctocolectomy,

small bowel resection, and placement of a colostomy. She is currently being treated for squamous cell and sebaceous skin carcinomas, which first appeared in 2008, with Cemiplimab (Fig. 4). Her dermatologist at the time took a biopsy of a lesion on the right side of her neck measuring .6x .4x .3cm and pathology reports showed a "well circumscribed nodule composed of basaltic cells with foci of sebaceous differentiation", congruent with sebaceous carcinoma and therefore MTS. However, her most dominant skin cancer would be squamous cell carcinoma. Due to recurrent steroid treatments for RA, she remains immunosuppressed and requires IVIG infusions every 5 weeks with hematology/oncology. She continues to follow up with her GI doctors every 6 months and dermatologist every 3 months for continuous monitoring.

Figure 3:

Proband's Family Tree and Known Ages of Diagnoses

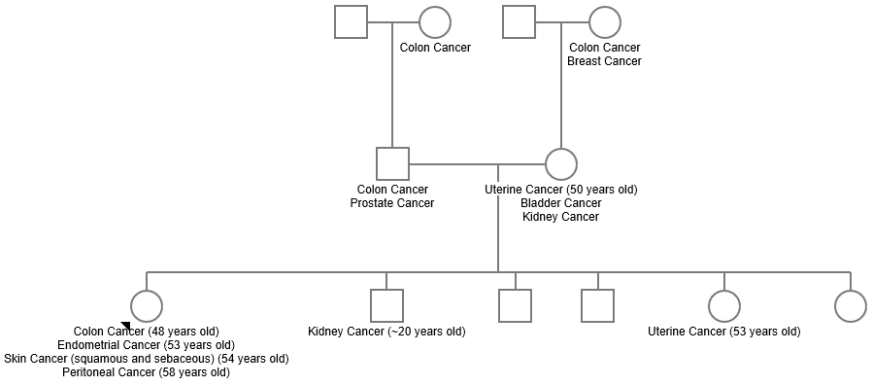

Figure 4:

Conclusion:

LS accounts for 3-5% of all colorectal cancers. Two different variants of LS have been discovered, MTS and TS. In this paper, we focus more on MTS, which is characterized by diagnosis of at least one sebaceous (adenoma, carcinoma, and epithelioma) or keratoacanthomas skin neoplasms and at least one visceral malignancy. The tumors can precede, coincide, or follow the visceral malignancy. In our proband, it followed her visceral malignancy. She also displays autosomal dominant inheritance likely inherited from her maternal grandmother. Genes commonly mutated in MTS include MLH1, MSH2, MSH6, and PMS2, the same gene mutations seen in Lynch Syndrome. MTS is seen in 9.2% of patients with Lynch Syndrome [5]. Treatment for MTS consists of surgical excision or Mohs micrographic surgery for the skin lesions. Oral isotretinoin alone or with interferon-alpha has been shown to suppress new development of sebaceous neoplasms in MTS [6]. Annual skin checks are recommended for continued monitoring for any new skin carcinomas.

Along with managing the skin carcinomas, the various cancers caused by LS must also be managed in these

patients. It is recommended that patients with LS undergo annual surveillance colonoscopy from age 25, or 2-5 years from the age of the earliest family member diagnosed before 25 years old [7]. Females diagnosed with LS are recommended to have annual pelvic exam, transvaginal ultrasounds, and in office endometrial biopsy starting at the age of 30-35, it is also recommended that females with LS undergo prophylactic hysterectomy and bilateral salpingo-oophorectomy as a prevention strategy [8]. Annual upper endoscopy with biopsy of gastric antrum is recommended starting also at age 30-35. Treatment of LS is specific to the cancer the patient develops. Treatment can consist of surgery, chemotherapy, and radiation therapy.

In this case, we presented a patient with the Muir-Torre variant of Lynch Syndrome. She originally presented with abdominal pain secondary to left sided metachronous colon cancer. She would then have endometrial cancer. Her history met the Amsterdam II criteria to be screened for LS and her genetic testing revealed mutation of the MSH2 gene. The MSH2 gene accounts for 38% of the gene mutation associated with LS [1]. She also would later be diagnosed with skin cancer (squamous cell and sebaceous), and peritoneal cancer respectively. Her diagnosis of sebaceous carcinoma that presented back in 2008 would further specify her LS diagnosis as MTS. Considering squamous cell carcinoma is her most dominant skin cancer, her case is not the typical presentation of MTS as that is characterized more by sebaceous (adenoma, carcinoma, and epithelioma) or keratoacanthomas skin neoplasm. However, she still meets qualifications required for MTS due to having at least one sebaceous carcinoma along with colon cancer. This patient is currently doing well and continues to receive treatment for her squamous cell carcinoma and IVIG infusions for her immunosuppression. At the age of 67, she demonstrates the high long term survival rate for patients with MTS or LS, as tumors can be monitored with preventative care and are responsive to treatment. Her case also demonstrates the importance of continuous monitoring of all types of cancers in this patient as an atypical cancer for LS can be typical for its variants.

Patient Consent:

Patient gave written informed consent for the release of images and other clinical information related to their case to be reported in a medical publication.

Author Contributions:

Bukky F. Tabiti : conceptualization, investigation, formal analysis, supervision, visualization, project administration, resources, writing- original draft, writing-review & editing. **Alexander W. Worix** : investigation, visualization, project administration, resources, writing- original draft, writing-review & editing. **Edem Agamah** : conceptualization, investigation, validation, formal analysis, supervision, visualization, project administration, resources, writing-review & editing.

Ethical Statement:

As this is a case report, there is no ethics committee certification.

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