Muir-Torre Syndrome Associated With Turcot Syndrome

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Citation

Abstract

Muir Torre syndrome (MTS) is a rare inherited syndrome consisting of a sebaceous gland tumor and at least one visceral malignancy. We report a case of 23-year-old Caucasian male with Turcot syndrome who subsequently developed sebaceous adenoma and met the clinical criteria for MTS. MTS is thought to be a subset of HNPCC. MTS may be related to mutations in the MMR genes viz. MSH2 and MLH1. Genetic testing for the above patient revealed high microsatellite instability. However, immunohistochemistry analysis revealed normal protein production. Since Turcot syndrome can be associated with mutations in either HNPCC associated genes or with the APC gene, this latter gene was tested; no mutations were noted. Although genetic basis of our case is yet to be clarified, we propose that clinical syndromes like HNPCC, FAP, MTS and Turcot represent different phenotypic expressions of mutations in similar genes.

INTRODUCTION

Muir Torre syndrome [MTS] is a rare autosomal dominant inherited genodermatosis with malignant potential. It consists of at least one sebaceous gland tumor such as sebaceous adenoma, epithelioma, or carcinoma, with at least one visceral malignancy. [1, 2, 3] In 1967 Muir et al and in 1968 Torre et al independently described this syndrome. Muir described a Maltese man who had multiple sebaceous adenomas and keratoacanthomas of the face and also had carcinoma of larynx, four synchronous colorectal adenocarcinomas, three colorectal polyps and two duodenal carcinomas. [1] Torre described a case of a 57 year old man with more than 10 sebaceous tumors of the face, trunk and scalp in association with ampullary and colonic cancer. [3] Of the cases reported so far, more than half were associated with gastrointestinal malignancy such as colorectal cancer. [2,4]

Genetic mutations have been identified as the cause of inherited cancer risk in some colon cancer-prone families. The most common clinical syndromes associated with these mutations include familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). The former is associated with mutations of the APC gene, and the latter with mutations of MLH1, MSH2, MSH6, and PMS2 genes. [3] These inherited syndromes are estimated to account for only 2% to 6% of colorectal cancer cases overall. [5] Turcot syndrome is a clinically defined, inherited syndrome associated with both colorectal cancer and a primary brain tumor.

The association between MTS and Turcot syndrome has not yet been described. We report a case of clinically diagnosed Turcot syndrome, who subsequently met the clinical criteria for MTS.

CASE REPORT

A 23-year-old Caucasian male with past medical history of colorectal cancer and glioblastoma multiforme presented with a lesion on the scalp. The patient presented at the age of 19 years with glioblastoma multiforme, which was treated with craniotomy and postoperative adjuvant brain radiation and chemotherapy. Two years later, at the age of 21, he developed symptoms of anemia and abdominal pain and was diagnosed with colorectal cancer. He underwent colonoscopy and was diagnosed with two tumors, carcinoma of cecum and carcinoma of rectum. He underwent total proctocolectomy. The caecal cancer was stage III moderately differentiated carcinoma, and rectal cancer was stage II moderately differentiated carcinoma. During surgery, 54 polyps were noted around the sites of the tumors in the large intestine. Postoperatively, he underwent adjuvant fluoropyrimidine chemotherapy and pelvic radiation therapy. After about nine months, the patient presented with midfacial numbness, blurred vision, right upper teeth and gum numbness. A lumbar puncture was done and he was diagnosed with leptomeningeal disease. On cytological exam, the findings were suggestive of metastatic colon

cancer. He underwent treatment with systemic and intrathecal chemotherapy and craniospinal radiation. He showed modest improvement in his symptoms.

One year later, the patient was diagnosed with liver metastasis and underwent hepatectomy and had a hepatic infusion pump placed. The histology had shown metastatic mucinous adenocarcinoma from the colon cancer primary. He was treated with systemic and intrahepatic chemotherapy. Intrahepatic 5-fluorouracil chemotherapy resulted in sclerosing cholangitis and was stopped after two months. Subsequent neurological problems included development of hydrocephalus, for which a ventriculopleural shunt was placed. New enhancing lesions in the right parietal lobe of cerebrum and right cerebellum were noted at this time, for which he underwent gamma knife radiosurgery. One month after the gamma knife radiosurgery or three years after the initial treatment of the colorectal cancer, he presented with a right parietal scalp lesion near the site of the shunt. He underwent biopsy of the scalp mass.

FAMILY HISTORY

Paternal grandmother with rectal cancer diagnosed at age 79 with brain metastasis; paternal first cousin with colon cancer diagnosed at age 36.

PAST MEDICAL HISTORY

The patient had complications at birth with meconium aspiration and PDA (patent ductus arteriosus). In adulthood, patient had a history of colorectal cancer and glioblastoma tumor of the brain.

PHYSICAL EXAMINATION

The patient is a thin, young, Caucasian male. Mucocutaneous examination revealed two, small, pinhead sized light brown spots on the outer border of lower lip. A 2 cm, well circumscribed, nontender, swelling was noted on the right scalp. Skin: several [eight] coffee colored café-au-lait spots present on arms, back and abdomen.

No other remarkable findings were noted on physical examination.

TREATMENT

A complete excision of the tumor on the scalp was successfully done.

HISTOPATHOLOGY

The lesion on the scalp showed sebaceous adenoma with foci of pleomorphism, mitotic activity, and Pagetoid

migration into the overlying epidermis.

Figure 1

Figure 1: Components of Muir-Torre Syndrome. a). Sebaceous adenoma (100X) b). Colonic mucinous adenocarcinoma (100X)
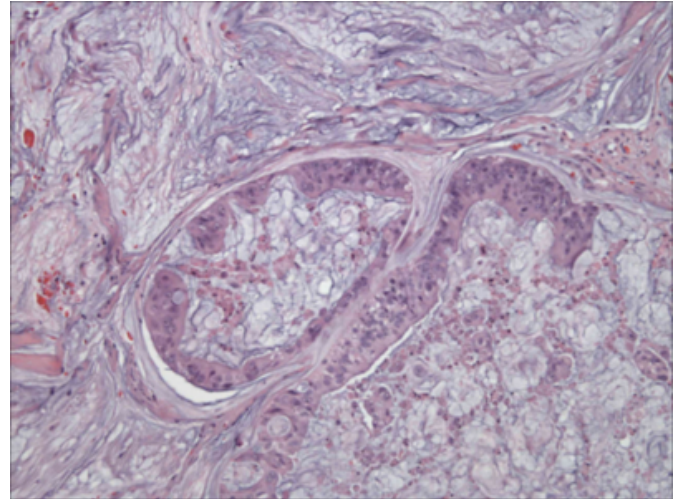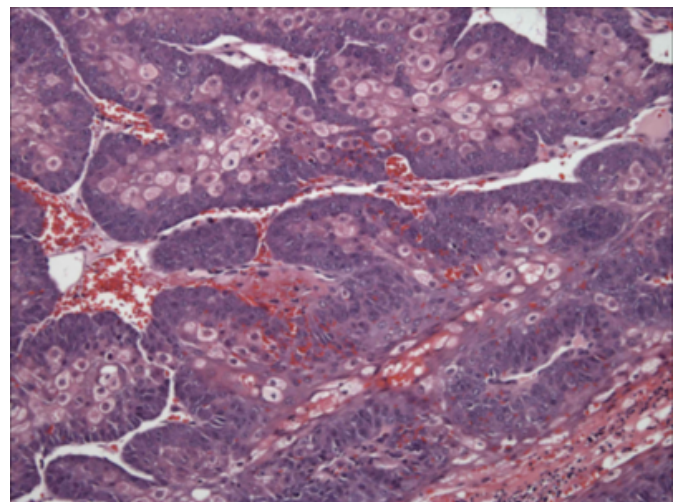

Figure 2

GENETIC TESTING

The patient was referred for genetic consultation and risk assessment. Based upon medical evaluation, including personal and family histories, as well as results of physical evaluation, we initially pursued HNPCC screen. This involved analysis of the colorectal tumor tissue, and included microsatellite instability testing (MSI) and immunohistochemistry (IHC) for mismatch repair genes. [4] MSI was noted to be high, specifically in 5 of 9 markers studied. However, immunohistochemistry analysis of expression of the 4 genes associated with HNPCC, specifically MLH1, MSH2, PMS2, and MSH6, all noted

normal protein production. Thus, actual sequencing of these genes was unlikely to identify a mutation, and was not performed consistent with current recommendations. [6] Alternatively, since mutations within the APC gene, typically associated with familial adenomatous polyposis, have also been reported in association with Turcot syndrome, and the patient's phenotypic manifestations supported this condition in the differential diagnosis, this gene was also tested. No mutation was identified upon sequencing of the APC gene. Thus, any molecular genetic basis for the diagnosis of Turcot and Muir Torre syndrome in our patient is not clarified yet.

DISCUSSION

Colorectal cancer is the third most common malignant neoplasm worldwide and second leading cause of cancer deaths in the United States. Approximately 75% of the patients have sporadic disease with no evidence of hereditary cancer. The remaining 25% of patients have a family history of colorectal cancer suggestive of genetic contribution, common exposures among family members, or a combination of both. [5]

There are at least two major pathways by which genetic events can lead to colorectal cancer. In examination of tumor tissue, about 85% of colorectal cancers are due to events that result in chromosomal instability (CIN) associated with numerical or structural chromosome abnormalities and the remaining 15% are due to events that result in microsatellite instability (MSI or MIN, also known as replication error) reflective of instability at a molecular level. [5, 18] Genetic alterations confined to the tumor tissue are somatic changes and do not pose inherited risk to relatives. In contrast, germ line mutations within genes associated with colorectal cancer syndromes, such as HNPCC, FAP, Turcot, and MTS, are present in all germ cells (eggs and sperm) and pose 50% risk of transmission to offspring. The majority of mutations are insertions, deletions, and nonsense mutations that lead to frame shifts and/or premature stop codons in the gene, thus altering the resulting protein product and its ability to function. Select commoner syndromes have been depicted in Table 1.

Figure 3

Table 1: Inherited Colorectal Cancer Syndromes.

Name	Clinical characteristics	Genetics/Type of Testing
FAP	Classic: Presence of more than 100 adenomatous colorectal polyps. Atypical/Attenuated: Fewer than 100 colorectal polyps and delayed onset of colorectal cancer compared to classic FAP.	Germ line mutations in the adenomatosis polyposis coli (APC) gene, on chromosome 5q21-q22/ DNA sequencing of APC gene
HNPCC	Early age of onset of colon cancer. Also associated with other extracolonic tumors like endometrium, ovary, stomach, ureter, hepatobiliary tree. (Please refer to modified Amsterdam and Bethesda criteria) [6]	Germ line mutations in one of five DNA mismatch repair genes. Persons meeting clinical criteria for diagnosis: DNA sequencing of MLH1 & MSH2. Persons/families suggestive of HNPCC: HNPCC screen (MSI & IHC)
Turcot Syndrome	Colorectal cancer associated with brain tumors, commonly medulloblastomas and gliomas	Mutations in APC gene and DNA mismatch repair genes/sequencing or screen for above genes, dependent upon individual & family history
MTS	Colorectal cancer associated with sebaceous tumor or keratoacanthoma	Mutations in hMSH2 and hMLH1 genes/DNA sequencing of above genes
Gardner Syndrome	Colorectal cancer associated with desmoid tumors, sebaceous or epidermoid cysts, lipomas, osteomas (especially of the mandible), supernumerary teeth, gastric polyps, and juvenile nasopharyngeal angiofibromas	Mutation in the APC gene [considered a subset of FAP]
Peutz Jeghers Syndrome	Pigmented mucocutaneous macules and multiple gastrointestinal polyps, which are usually benign but may undergo malignant transformation; risk for intussusceptions	Germ line mutations in the gene LKB1 /STK11 (on chromosome 19p13.3)
Familial Juvenile polyposis	Presence of 10 or more juvenile polyps with history of similar lesions in at least one first-degree relative. They have an increased risk of developing colorectal cancer at an early age.	Autosomal dominant disease with high penetrance. Germ-line mutations in a gene (DPC4) located on chromosome 18q21.1

Familial Adenomatous Polyposis is associated with the APC gene. HNPCC demonstrates genetic heterogeneity in that; alterations in more than one gene can result in the HNPCC phenotype. Germ line mutations have been reported in at least 5 DNA mismatch repair genes, namely hMSH2 on chromosome 2p16, hMLH1 on chromosome 3p21, hPMS1 or hPMS2 on chromosome 2q31 and 7p22 respectively, and hMSH6. [6] The function of these genes is to act as proofreaders and correct the mispairing of nucleotide bases. Genetic testing for HNPCC is a complex issue. [16] Gene sequencing is clinically available for only the first two genes, and detects mutations in only up to 60% of persons who meet criteria for testing. (See Modified Amsterdam and Bethesda criteria for diagnosing HNPCC). [6]

Diagnosis of MTS can me made based on following clinical criteria: [5]

1. Presence of at least one sebaceous tumor or keratoacanthoma with sebaceous differentiation and a visceral malignancy, in absence of any predisposing factor or

2. In the absence on any sebaceous tumor if the

patient has multiple keratoacanthomas with multiple visceral malignancies and family history of MTS. Keratoacanthomas are squamous proliferative lesions that, when fully developed have a characteristic appearance with hyperkeratosis and a central crater like lesion.

Out of the cases reported, more than half were associated with gastrointestinal malignancy. [2, 4] The next common association is with genitourinary malignancy. [2, 4] In the patients with MTS and colorectal cancer more than half were at or proximal to the splenic flexure. [10] The male to female ratio is 2:1 with mean age being 53. [10] Kruse et al. showed that 69% of the studied MTS patients exhibit mutations in hMSH2 and hMSH1 gene, significantly more in hMSH2 (88%) than hMLH1 gene (12%). [6] There have been other studies showing similar results. MTS is now thought to be a subset of HNPCC. [11] . Presence of one copy of the defective gene makes one more susceptible to develop the cancer. Micro satellite instability in tumor tissue develops after somatic inactivation of the corresponding second mismatch repair gene ('Knudson's two-hit hypothesis'). [7]

The clinical diagnosis of Turcot syndrome is made based upon an association between brain tumors (primarily medulloblastomas and gliomas) and colorectal cancer. On a molecular genetic level it has been reported in association with two distinct genetic errors, those involving the APC gene and those involving HNPCC associated genes. [8] Association with APC gene is more common [about 66%] whereas association with mismatch repair gene is less common [about 33%]. Furthermore, occurrence of medulloblastoma was associated more with APC gene mutations whereas occurrence of glioblastoma multiforme is associated more with mutations in mismatch repair genes. [9]

As discussed above, MTS and Turcot syndromes have been found to involve mutations in FAP and HNPCC associated genes in some cases and families. Thus these clinically diagnosed conditions could actually represent different phenotypic expressions of alterations in the same gene/s, dependent upon the nature and/or position of the mutation.

Our patient's paternal grandmother had colorectal cancer with brain metastasis; her records were unavailable for review. Early onset cancer/s, more than one primary cancer and positive family history of the same or a related cancer, are all consistent with an inherited susceptibility syndrome. However, genetic testing thus far did not detect any

definitive etiology. There could be following explanations for our case wherein we did not find any of the expected genetic abnormalities except for a high MSI:

1. There exists a mutation in the APC gene, which the current technology does not detect

2. There exists a mutation in another, as yet unknown, gene associated with cancer risk in this patient and/or family

3. An HNPCC gene mutation exists in one of the 4 genes stated above which is supported by the high MSI finding, yet the nature and limitations of IHC testing do not allow for measurable expression of such. 10 Immunohistochemistry testing does not involve sequencing of genes; this can be done as part of further investigations. At present time, clinical testing (sequencing) for the MLH1 and MSH2 is available but is not for the PMS1 and MSH6 genes.

4. This case represents a different cancer associated genetic syndrome, possibly warranting other genetic testing. The differential diagnoses include Peutz-Jeghers syndrome, since this condition is associated with colon cancer, multiple colonic polyps, and perioral-pigmented spots - all of which are present in our case or neurofibromatosis as our patient also has café-au-lait type patches and a reported history of neurologic problems in the neonatal period. It is important to examine the potential value, for the patient, family and physicians managing and treating the patient, of pursuing further genetic evaluation and/or testing together with its benefits and limitations.

Treatment for Turcot syndrome is resection of the brain tumor with or without adjuvant radiation therapy. Chemotherapy also has a role in treatment of medulloblastoma. The colorectal cancer should be resected with/without neoadjuvant chemoradiation therapy depending on other factors like size, stage of tumor, etc. In MTS the sebaceous adenoma, sebaceous epithelioma can be excised or treated with cryosurgery. [2, 4] Sebaceous carcinomas should be excised with wide margin of resection along with removal of involved lymph nodes. Radiotherapy may also be effective. Excision is the most suitable therapy for single keratoacanthoma although cryotherapy can be tried for multiple keratoacanthomas. Oral isoretinoin may prevent the

cutaneous neoplasms in this syndrome.

In our case, the patient had already been treated for his colorectal cancer and brain tumor. He underwent complete excision of the sebaceous adenoma without any complications. It has been shown that most of the patients with MTS have a non-aggressive course and prolonged survival after the diagnosis. [11] Visceral malignancies in MTS are mostly low grade; early surgical removal of primary tumor and even metastatic disease may be helpful and at times lead to cure. Despite the complicated course noted in our patient, he remains alive with an ECOG performance status of 2.

In almost 40% of MTS patients, the cutaneous markers appear before or at the same time as the visceral malignancy. [9, 10, 11] Hence the skin lesion might be a harbinger for an internal malignancy. Such patients with suspicious skin lesions should undergo thorough screening for any internal malignancy. It has been thought that strong association of colorectal cancer with MTS mandates annual colonoscopy in this setting. Also, all patients with typical cutaneous lesions of MTS and positive family history should be referred for genetic risk assessment and consideration of genetic testing. [2, 9, 10, 11]

CONCLUSION

In conclusion, it should be kept in mind that diagnosis of one syndrome could just be a phenotypic expression of a disease spectrum from genetics point of view and evidence of any other genetically associated conditions should be sought for. It should be kept in mind that inherited clinical syndromes such as MTS or Turcot's represent different phenotypic manifestations of mutations in similar genes. Underlying conditions such as colorectal cancer should be identified.

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