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Glioblastoma multiforme in the Muir–Torre syndrome[☆]

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Abstract

Muir–Torre syndrome (MTS) is an autosomal dominant subtype of nonpolyposis colorectal carcinoma (HNPCC) characterized by the development of sebaceous gland tumors and visceral malignancies. The most common subtype of MTS is characterized by germline mutations in mismatch repair (MMR) genes leading to microsatellite instability (MSI). Central nervous system tumors have only rarely been associated with MTS. In this report, we describe the development of a glioblastoma multiforme (GBM) in a patient with MTS. Immunohistochemical analysis of the patient's colon carcinoma and his GBM both revealed loss of the mismatch repair proteins mutS homolog 2 (MSH2) and mutS homolog 6 (MSH6).

Keywords

Muir–Torre; Glioblastoma; Mismatch repair protein; Brain cancer; Mutation

1. Introduction

Muir–Torre syndrome (MTS) is an autosomal dominant subtype of nonpolyposis colorectal carcinoma (HNPCC) characterized by cutaneous lesions and visceral malignancies [1–3]. The cutaneous disorders observed in MTS include sebaceous adenomas, carcinomas and keratoacanthomas. The visceral malignancies include colorectal, endometrial, urological, and upper gastrointestinal tumors [2]. Skin lesions may be the initial sign of the syndrome; however, more often they follow diagnosis of visceral malignancies [4]. Approximately 65% of MTS cases are associated with a germline mutation in a mismatch repair (MMR) gene and of these, the most commonly mutated are mutS homolog 2 (MSH2) and mutL homolog

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1 (MLH1) [2]. Microsatellite instability (MSI) caused by deficiency of MMR genes is considered to be a hallmark of MTS. Approximately 35% of cases do not show MSI or mutation in the MMR genes, representing a second class of MTS [2].

Brain tumors occurring in association with MTS have only rarely been reported. In this study, we describe the development of a glioblastoma multiforme (GBM) in a patient with MTS who did not have prior chemotherapy or radiation treatment. Both his GBM and colonic tumor demonstrated a loss of expression of the MMR proteins MSH2 and MSH6. We also review the literature of brain tumors occurring in association with MTS and postulate that these tumors can be part of this genetic syndrome.

2. Case report

2.1. History and treatment

The patient is a 45-year-old Caucasian male with a past medical history significant for multiple neoplasms. In December of 2002, he had a segmental resection of his rectosigmoid colon for a moderately differentiated adenocarcinoma (Fig. 1A and B). Over the course of 21 months, from March 2004 through December 2005, the patient had sebaceous adenomas removed from four sites including his left cheek, back, left eyelid and left shoulder (Fig. 1C and D). Based on the presence of sebaceous adenomas and the colon adenocarcinoma, a diagnosis of MTS was made.

The patient's family history was also significant for multiple cancer diagnoses (Fig. 2). His father was diagnosed with colon cancer, squamous cell carcinoma, melanoma and bladder cancer between the ages of 55 and 64. His brother had colon cancer at age 29. His mother had a basal cell carcinoma and his maternal aunt was diagnosed with breast cancer at age 58. A maternal great aunt and great uncle passed away from cancer of unknown types (not shown).

The patient presented to a regional hospital in October of 2006 with headaches, personality changes and memory deficits. An initial work-up included magnetic resonance imaging (MRI) of the brain which showed a 6.3 cm × 3.6 cm × 6.2 cm mass located in the right frontal lobe and right-to-left midline shift. The patient underwent a craniotomy and subtotal resection. In November of 2006, he was admitted to our institution with increasingly severe headaches. A repeat MRI showed an irregular ring-enhancing lesion in the right frontal lobe measuring approximately 3.9 cm × 6.7 cm × 5.3 cm with increased midline shift (Fig. 3A). The patient underwent a second, more radical, resection (Fig. 3B).

2.2. Postoperative course

After the patient's second resection he received cranial irradiation with concurrent temozolomide. He passed away on July 17, 2007.

2.3. Pathologic analysis

Microscopic evaluation of the patient's colon tumor demonstrated moderately differentiated infiltrating adenocarcinoma forming cribriforming glandular structures in the submucosal stroma. The adenocarcinoma invaded into the submucosal tissue but not into the muscularis

propria (Fig. 1A and B). Eleven regional lymph nodes were resected and found negative for malignancy.

Pathologic evaluation of the skin lesions revealed circumscribed, benign proliferations of vacuolated sebaceous cells organized around multiple ducts in communication with the cutaneous surface (Fig. 1C and D). All were diagnosed as sebaceous adenomas. An additional area of sebaceous hyperplasia was removed at a later date from the patient's scapular region (not shown).

Both brain tumor specimens demonstrated features of a high grade glioma (WHO grade IV), including extensive necrosis and vascular proliferation (Fig. 3C). Some of the tumor cells were bizarre and astrocytic in morphology, with elongated and pleomorphic nuclei, while others had homogeneous small round nuclei containing delicate chromatin, in a manner typical of oligodendroglia. Tumor cells were immunopositive for glial fibrillary acidic protein (GFAP) (Fig. 3D). Molecular analysis for 1p19q co-deletion, the hallmark of oligodendroglioma, was performed on both specimens using a polymerase chain reaction (PCR) based assay for loss of heterozygosity (LOH) of several microsatellite markers on the short arm of chromosome 1 and the long arm of chromosome 19 [5]. This assay, however, was non-diagnostic due to the appearance of secondary PCR products ('stutter patterns') that obscured interpretation of LOH at several of the loci. This stutter pattern was attributed to MSI, although this assay is not validated for formal MSI testing. The final pathologic diagnosis was GBM. The surgical neuropathologist made special mention of the oligodendroglial features to highlight the possibility of a 'mixed glioma' or a GBM with an oligodendroglial component [6].

2.4. Immunohistochemical analysis

Immunohistochemical staining for four of the common MMR gene products lost in patients with MTS were performed on the GBM tissue and a sample of the patient's colon adenocarcinoma (Fig. 4) by the Johns Hopkins Medical Institutes Department of Pathology. Briefly, the primary antibodies used were anti-MLH1 (1:50, clone G168-15, BD Pharmingen, San Jose, CA), anti-MSH2 (1:100, clone FE11, Calbiochem, Gibbstown, NJ), anti-MSH6 (1:100, clone 44B, BD Transduction Labs, San Jose, CA), and anti-PMS2 (1:100, clone A16-4, BD Pharmingen, San Jose, CA). Biotin-free BOND™ polymer refine detection reagent was added after primary antibody binding and the reaction was developed using substrate 3,3'-diamino-benzidine hydrochloride (DAB).

Both the GBM and the colonic adenocarcinoma demonstrated retention of MLH1 (Fig. 4A and E) and PMS2 (Fig. 4B and F) and loss of MSH2 (Fig. 4C and G) and MSH6 (Fig. 4D and H) immunostaining. Internal control cells, including vascular endothelium, inflammatory cells, and admixed non-neoplastic oligodendroglial cells, retained immunostaining for all four of the MMR proteins.

3. Discussion

We report a case of GBM in a patient who was previously diagnosed with MTS. He initially presented with colorectal cancer and subsequently developed multiple sebaceous adenomas.

His family history was positive for multiple neoplasms including two cases of colorectal cancer. Cases of MTS with primary malignant brain tumors are rare and only a few cases have been reported [7–10]. Park et al. described a patient with MTS who presented with a GBM [8]. Immunohistochemical analysis of this patient's tumor demonstrated loss of MSH2 expression. Steckley et al. reported a case of a patient who was clinically diagnosed with Turcot syndrome [9], a syndrome classified by colon carcinomas and central nervous system (CNS) tumors, due to a history of colorectal cancer and a GBM. The patient subsequently developed a keratoacanthoma and fit the clinical diagnosis for MTS. A mutation in MSH2 was identified in this patient. A third case report involved a patient with a prior MTS diagnosis who developed a WHO Grade III astrocytoma. A mutation in the p53 gene was identified in this patient [7]. Watwe et al. described a patient who developed a GBM at age 19 and a colon carcinoma at age 21 and several years later a right parietal sebaceous adenoma [10].

MTS is characterized by multiple sebaceous neoplasms and visceral tumors including those of the breast, colon and genitourinary tract [2,3]. Because of its association with mutations of mismatch repair genes, MTS is a variant of HNPCC [11,12]. Although CNS tumors are not often found in this syndrome, there are several cases including our own describing this association. Another variant of HNPCC, Turcot syndrome, is characterized by colon cancer and neuroepithelial tumors, primarily gliomas or medulloblastomas. Turcot syndrome is associated with mutations in the adenomatous polyposis coli (APC) gene [13]. This study, along with the previously mentioned case reports, confirms overlap between Turcot syndrome and MTS, at least clinically.

The most commonly mutated MMR genes in MTS are MSH2, MLH1, MSH6 and PMS2 [11]. Immunohistochemical analysis of this patient's GBM and rectosigmoid adenocarcinoma demonstrated loss of MSH2 and MSH6. MSH2 is the most commonly mutated MMR protein observed in MTS patients [14]. Previous studies have shown that MSH2 stabilizes MSH6 by forming a heterodimer and, in the absence of MSH2, MSH6 may be undetectable [15]. Therefore, we believe that a mutation in MSH2 is responsible for the negative staining of MSH6 in our patient's tumors. In support of this, deletion of exons 8–15 of MSH2 has been identified in the patient's father [16]. The patient underwent genetic counseling but declined to be tested. Although we are unable to confirm the MSH2 sequence in our patient, the autosomal dominant inheritance pattern of MTS, the immunohistochemical findings demonstrating a loss of MSH2 in the patient's tumors, and the genetic analysis of the patient's father together strongly suggest our patient inherited the deleted MSH2 allele.

There are now several case reports of patients with MTS developing primary CNS tumors. We demonstrate loss of the mismatch repair gene MSH2 in both our patient's GBM and colon tumor. We propose that, although CNS tumors are not typically associated with MTS, there should be a low threshold to evaluate for CNS neoplasms in such patients.

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Fig. 1.

Diagnosis of MTS by hematoxylin and eosin stain of colonic carcinoma and sebaceous adenomas. (A, B) Infiltrating colonic adenocarcinoma: (A, low power) A section of colon demonstrating normal colonic epithelium on the left and a nest of infiltrating adenocarcinoma within the submucosal stroma on the right of the panel. Between are a number of thrombosed vessels (arrow). (B, high power) The moderately differentiated tumor is composed of hyperchromatic cells with high nuclear-to-cytoplasmic ratios and frequent mitoses within a cribriforming glandular architecture. (C, D) Sebaceous adenomas from nasal tip (C) and upper eyelid (D). The lobulated masses are comprised of large nests of vacuolated sebaceous cells opening onto the surface via multiple ducts, which are typical of adenoma.

Fig. 2.

Family tree of the proband. Glioblastoma multiforme (GBM), squamous cell carcinoma (SCC), basal cell carcinoma (BCC), polycystic kidney disease (PKD).

Fig. 3. (A, B) T1-weighted post-gadolinium MRI pre-surgery (A), and post-surgery (B). (C, D) Pathologic specimens from the patient's second resection demonstrate extensive necrosis with focal pseudopalisading necrosis (C). The glial nature of the tumor cells is confirmed by diffuse staining for GFAP by immunohistochemistry (D).

Fig. 4. Immunohistochemistry of colon cancer (A–D) and GBM (E–H) for DNA MMR genes MLH1 (A, E), PMS2 (B, F), MSH2 (C, G), and MSH6 (D, H). MLH1 and PMS2 stain positive in the tumor beds as well as adjacent normal tissue. MSH2 and MSH6 stain positive only in the normal tissue, whereas the tumor cells are negative.