Identifying Muir-Torre syndrome in a patient with glioblastoma multiforme

Deric M. Park, Gabrielle A. Yeaney, Ronald L. Hamilton, Jennifer Mabold, Nikki Urban, Leonard Appleman, John Flickinger, Frank Lieberman, and Arlan Mintz

Department of Neurological Surgery (A.M.), University of Pittsburgh Cancer Institute (D.M.P., J.M., N.U., L.A., J.F., F.L., A.M.), Department of Pathology (G.A.Y., R.L.H.), University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Patients with Muir-Torre syndrome, an autosomal-dominant familial tumor condition caused by germline mutation of the DNA mismatch repair genes, MSH2 or MLH1, present with tumors of the sebaceous gland and visceral malignancies characterized by microsatellite instability. Here we show development of glioblastoma multiforme in a patient with Muir-Torre syndrome. Immunohistochemical analysis of the brain tumor and colon cancer revealed loss of the DNA mismatch repair gene detected by the genetic test, suggesting a pathogenic link.

Muir-Torre syndrome is a rare autosomal-dominant familial tumor condition clinically characterized by tumors of the sebaceous gland and visceral malignancies. The underlying molecular pathogenesis involves a germline mutation of the DNA mismatch repair genes, MSH2 or MLH1. Here we describe the development of glioblastoma multiforme (GBM), a grade IV glioma, in a patient with Muir-Torre syndrome. In addition we present the clinical-pathological findings from the proband. A 58-year-old man with a history of colon cancer sought medical attention in October 2007 with complaints of episodic left hemisensory disturbance. The colon cancer had been addressed with a right hemicolectomy followed by 5-FU adjuvant chemotherapy in 1999. He has been disease free since the initial treatment. The initial as well as subsequent surveillance colonoscopies failed to demonstrate presence of colonic polyps. The current physical examination revealed presence of multiple skin lesions described by a dermatologist as sebaceous adenomas (Fig. 1A) and lateralizing signs. Magnetic resonance imaging study of the brain revealed a 2.2-cm enhancing mass in the right parietal lobe without significant mass effect (Fig. 1B). Due to the eloquent location of the tumor, a biopsy was initially performed, but it was non-diagnostic. He then underwent an awake craniotomy with intraoperative mapping of the sensory cortex for resection of the tumor. Histopathological analysis revealed a GBM (Fig. 2A) with a Ki-67 proliferation index of 25%. Immunohistochemical study showed presence of glial fibrillary acidic protein, p53 (Fig. 2B), and epidermal growth factor receptor (EGFR). EGFR showed no amplification by fluorescence in situ hybridization. Loss of heterozygosity studies by polymerase chain reaction revealed partial loss of 1p and complete loss of 17p. Detection of the p16 gene by fluorescence in situ hybridization analysis revealed deletion of the gene in 25% of the tumor cells. Molecular phenotype was consistent with the histological diagnosis of GBM.

The diagnosis of Muir-Torre syndrome in this gentleman was suspected due to the colon cancer in the background of the sebaceous adenomas, as well as extensive family history for colorectal cancers (Fig. 3). In addition to the colon cancers, his sister passed away at the age of 44 from GBM. Genetic tests of our patient revealed a heterozygous deletion of AG dinucleotide at position 1226 in exon 7 of MSH2 gene located on chromosome 2.

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Address correspondence to Deric M. Park, University of Pittsburgh Cancer Institute, UPMC Cancer Pavilion, 5th floor, 5150 Centre Ave., Pittsburgh, PA 15232, USA (parkdm@upmc.edu).
Immunohistochemical staining of the colon cancer demonstrated absence of MSH2 expression (Fig. 4A). The immunohistochemical stain was performed on formalin fixed paraffin-embedded tissue cut at 6-micron thickness. Heat-induced antigen retrieval (Ventana Medical Systems, Tucson, AZ, USA) method was used followed by incubation with anti-MSH2 monoclonal antibody (BD Biosciences, San Jose, CA, USA) at 1:200 dilution. To establish a pathogenic link between the Muir-Torre–associated genetic defect and the GBM, we analyzed the brain tumor for MSH2 expression. Similar to the colon cancer, immunohistochemistry revealed absence of MSH2 expression, suggesting a potentiating role of the DNA mismatch repair dysfunction on the GBM pathogenesis. Fig. 4B shows the immunohistochemical staining of MSH2 protein in the GBM from this patient. The bulk tumor failed to stain for MSH2 while the intravascular lymphocytes and few infiltrating inflammatory cells retained the enzyme expression. In agreement with impaired DNA mismatch repair activity, this tumor showed microsatellite instability at 5 of the 10 loci tested.

Common visceral malignancies associated with Muir-Torre syndrome are largely gastrointestinal and urogenital. Unusual histopathological phenotypes include cancers of the breast, parotid gland, larynx, and hematopoietic system. Similar to other familial tumor syndromes, patients with Muir-Torre syndrome inherit a mutated copy of one gene. Somatic inactivation of the second gene leads to the complete loss of enzy-
defect of the adenomatous polyposis coli gene, DNA mismatch repair defects were also seen in patients originally described by Turcot. Therefore, Turcot syndrome can include gliomas and either familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer. Such observations have resulted in debates over whether Turcot syndrome is a distinct entity and in need of reclassification. It is also unclear whether Muir-Torre syndrome represents a variant of Lynch syndrome or is a distinct clinical entity. The observation that loss of MSH2 can occur in both Muir-Torre syndrome and HNPCC, with Muir-Torre having a distinctive skin manifestation not seen in the latter, suggests the presence of additional molecular disruptions in Muir-Torre. This may provide an important insight into the pathogenesis of GBM. The GBM from this particular individual demonstrated complete loss of the DNA mismatch repair gene, MSH2. Since most sporadic GBM retain the expression of MSH2, the loss of DNA repair activity likely contributed to the pathogenesis of the GBM in this patient.

A remaining question is whether the loss of MSH2 activity alone is sufficient for tumorigenesis. Is it necessary to incur additional genetic “hits” in the background of lost MSH2 activity to develop gliomas? For instance, impaired DNA repair activity may lead to mutation of critical genes such as p16 to assist in the formation of GBM. This also implies the presence of multiple pathways in the pathologic development of GBM and further hints at the heterogeneous nature of the disease. Disease heterogeneity is supported by predictably different clinical responses to chemotherapy in patients with gliomas based on molecular characterization. Our patient began concurrent temozolomide chemotherapy with external beam radiation therapy. Interestingly, upon treatment with temozolomide, he began to note reduction in the size of the sebaceous adenomas.

Fig. 3. Many members of this patient’s family were afflicted by development of colon cancer. Our patient had both colon cancer and glioblastoma multiforme (arrow).

Fig. 4. A) Immunohistochemical staining of the colon cancer demonstrated absence of MSH2 expression. B) Labeling of the glioblastoma multiforme tissue for MSH2 by immunohistochemistry demonstrates the presence of the DNA repair enzyme in scattered inflammatory cells while the bulk tumor fails to stain.
References