PEER REVIEWED LETTER

Glioblastoma in a Patient with a Hereditary Cancer Syndrome

JL Steckley, CJ Watling, W. Ng

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A 68-year-old Caucasian male presented to emergency with a spontaneous sudden onset headache localized behind the left eye. Pain was severe and associated with vomiting, agitation, anxiety, memory loss, and word-finding difficulty. There was no preceding trauma and no meningeal symptoms. Further history was significant for mitral valve repair, atrial fibrillation treated with coumadin, colorectal cancer treated with right-sided hemicolectomy 17 years prior, and multiple skin tumors, which included squamous cell and basal cell carcinomas of his face and ears. Family history was significant for colon cancer in his father (at age 50), a sister (at age 40), and a niece (at age 38), as well as primary brain cancer in his paternal aunt.

Examination showed normal vital signs, no meningismus and an unremarkable general examination. He was alert and oriented, but had difficulty finding words. However, repetition and comprehension were normal. He had a right superior quadrantanopsia, with otherwise unremarkable cranial nerve examination. Motor, sensory, and coordination examination was normal.

A CT scan of the head demonstrated a large left anterior temporal lobe hemorrhage, with mild mass effect and a possible associated mass lesion. The international normalized ratio (INR) was slightly elevated at 1.8 due to coumadin therapy. Further MRI imaging demonstrated a large mass lesion underlying the intracranial hemorrhage – see Figure 1. There was gadolinium enhancement of the mass consistent with an aggressive tumor. The patient underwent gross total resection and pathology showed glioblastoma.

The patient was treated with cranial radiation (60 Gy in 30 fractions) with concurrent oral temozolomide at a dose of 75mg/m^2/day. Following radiation treatment, 12 cycles of adjuvant temozolomide were given at a dose of 200mg/m^2/day for the first five days of each 28-day cycle. During the treatment period, he developed an unusually rapidly growing 2 cm keratoacanthoma (pathology confirmed) on his left mandible. The lesion was curetted out, but recurred rapidly within two months. At that point, the lesion was treated with local radiation using 6mV electrons (50Gy in 15 fractions), and responded well. His neurological symptoms were stable for 14 months, then he developed headaches, severe fatigue, and MRI demonstrated tumor recurrence. At this point, he declined further anti-neoplastic treatment and palliative care was initiated.

Because of the strong family history of early-onset colorectal cancer, a diagnosis of hereditary nonpolyposis colon cancer (HNPCC) was considered. This cancer syndrome is due to mutations in DNA mismatch repair (MMR) genes, commonly the *MLH1* and *MSH2* genes.[1] Direct sequencing analysis demonstrated a deletion at position 1705 (exon 11) in the *MSH2* gene, resulting in an early stop codon at position 1710_1712 and a truncated protein. The identical mutation was also identified in multiple other family members with colon cancer and in asymptomatic younger family members – see Figure 2.

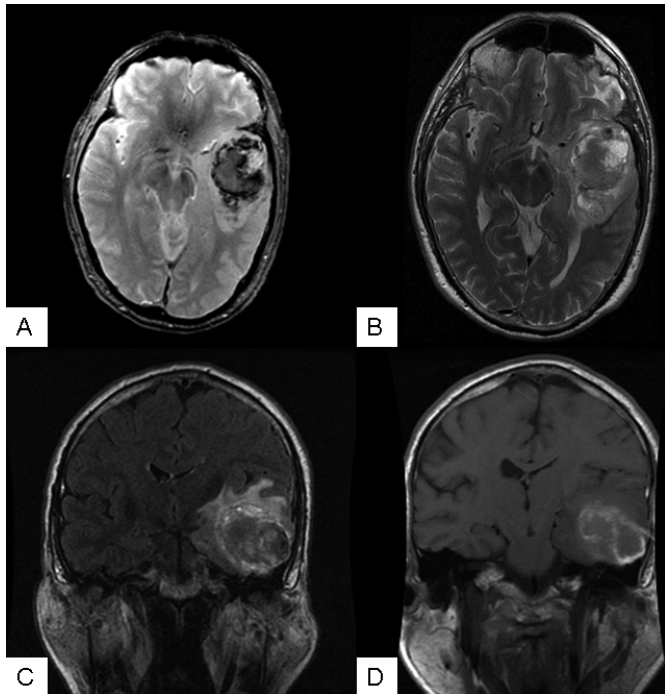

Figure 1. *MRI imaging demonstrating a left temporal lobe intracranial hemorrhage with an underlying gadolinium-enhancing mass lesion. A. gradient echo; B. T2; C. FLAIR; D. T1 with gadolinium.*

From the Department of Clinical Neurological Sciences, London Health Sciences Center, University Hospital, London, Ontario, Canada.

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Reprint requests to: JL Steckley, Department of Clinical Neurological Sciences, London Health Sciences Center, University Hospital, 339 Windermere Road, London, Ontario, N6A 5A5, Canada.

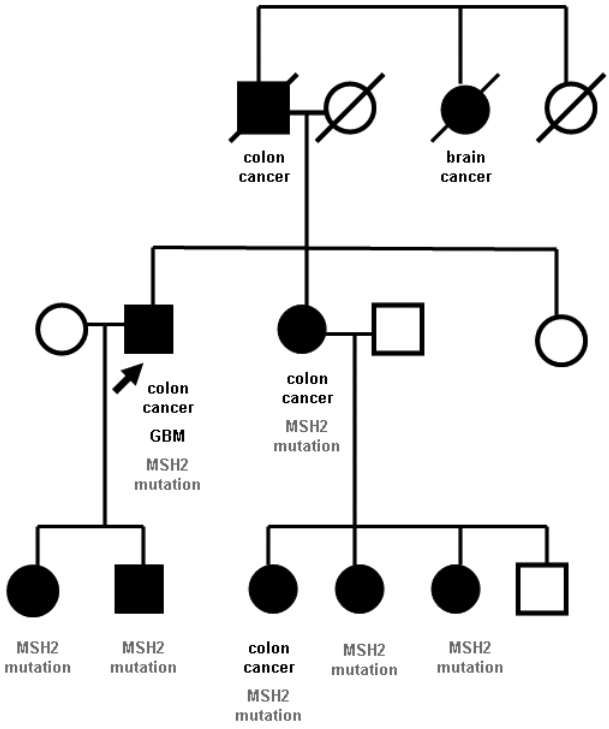

Figure 2. *Canadian family with autosomal dominant inheritance of colorectal cancer and primary brain cancer. Individuals who have tested positive for the MSH2 gene mutation are shown. GBM = glioblastoma. The proband is identified with an arrow.*

Discussion

Our patient was clinically diagnosed with Turcot syndrome due to his prior history of colorectal cancer and the subsequent presentation of a primary brain malignancy, glioblastoma. In his family, there was an autosomal dominant predisposition to malignancy, including colorectal cancer and primary brain tumour. Turcot syndrome is a rare inherited primary brain cancer syndrome, with only approximately 120 cases reported in the literature.[2] In addition to Turcot syndrome, there are numerous other hereditary causes of primary nervous system malignancy which include the neurocutaneous syndromes and other rare inherited syndromes (Table).

The association of primary central nervous system (CNS) tumors with familial polyposis or colorectal cancer was first described in 1959 by a Canadian, Jacques Turcot.[3] The primary CNS tumors that occur most frequently in individuals with Turcot syndrome are glioblastoma, astrocytoma, or medulloblastoma, but ependymoma and oligodendroglioma have also been reported.[4] In a landmark study, mutations in both the *APC* (adenomatous polyposis coli) gene and in DNA mismatch repair genes were found to be responsible for Turcot syndrome.[5] Turcot syndrome has since been divided into two syndromes based on the type of inherited colorectal cancer syndrome.[6] Turcot Syndrome type 1 occurs in patients with HNPCC. Turcot Syndrome type 2 occurs in patients with familial adenomatous polyposis due to *APC* gene mutations and is characterized by hundreds to thousands of polyps and a tendency toward left-sided colorectal cancer.

Both HNPCC and Turcot syndrome type 1 are characterized by fewer polyps and a trend toward right-sided colon cancer. Tumors demonstrate instability in microsatellite DNA with expansions and contractions. HNPCC is caused by mutations in one of the five known genes which code for the DNA MMR system, a complex of individual proteins which functions to remove DNA polymerase errors such as base-base mismatches or insertion-deletion loops. The mismatch repair system is thought to improve the fidelity of DNA replication by a factor of 1000. The genes for these proteins have been given the term "care-taker" genes because of their vital role in maintaining the genetic stability of the cell. The MMR complex includes the *MSH2*, *MLH1*, *MSH6*, *PMS1*, and *PMS2* genes; Turcot syndrome I may be caused by mutations the *MSH2*[2], *MLH1*[5], *PMS2*[5], and *MSH6*[7]. Homozygous or compound heterozygous MMR gene mutations may cause features of neurofibromatosis, malignant brain tumours (see Table) and hematological malignancies within the first decade of life;[8] the so-called Lynch Syndrome III.[9]

Tumors are not restricted to the colorectal system in HNPCC, nor to the brain and colorectal system in Turcot Syndrome type 1. HNPCC is also associated with predisposition to stomach, endometrial, ovarian, genitourinary, biliary system and skin tumours.[10] The co-occurrence of colorectal cancer and multiple skin tumors was independently described by two authors and subsequently came to be known as Muir-Torre syndrome.[11,12] This syndrome is considered a variant of HNPCC and is commonly due to MSH2 mutations and rarely due to *MLH1* mutations.[13]

Our patient was clinically diagnosed with Turcot syndrome based on his history of colorectal cancer and glioblastoma. He had an *MSH2* gene mutation, one of the known causes of Turcot syndrome type 1. His prior history of multiple squamous and basal cell skin tumors and his subsequent development of an aggressive keratoacanthoma also fulfilled the criteria for Muir-Torre syndrome. This association of Turcot syndrome with Muir-Torre syndrome is not surprising, given that both syndromes are considered variants of HNPCC and both are characterized by DNA instability due to MMR gene mutations. The *MSH2* gene has previously been implicated in both syndromes independently. Clinical association of these two syndromes has been reported twice previously,[14,15] but in these cases no MMR gene mutations were identified despite the presence of microsatellite instability. Our case is the first identification of the genetic error, an *MSH2* mutation, in a single patient fulfilling the criteria for both Turcot syndrome and Muir-Torre syndrome.

In summary, there are numerous inherited syndromes which can result in primary brain cancer. Our patient illustrates the importance of a complete family history in identifying familial cancer predisposition syndromes. Identification of the genetic abnormality in a family allows pre-symptomatic diagnosis and appropriate surveillance for the development of tumors, for example with early annual colonoscopy. Our patient with Turcot syndrome type 1 and the skin tumors typical of Muir-Torre syndrome was found to have an *MSH2* gene mutation, leading to

Table: Inherited syndromes with known primary nervous system tumors. The mode of inheritance, chromosome, gene, and protein are also identified

Syndrome	Nervous system tumor	Inheritance	Gene, locus, and protein	References
Neurofibromatosis 1	neurofibromas, neurofibrosarcoma, optic gliomas, astrocytoma, meningioma	AD	*NF1*, 17q11, neurofibromin	16, 17
Neurofibromatosis 2	neurofibroma, meningioma, schwannoma, ependymoma	AD	*NF2*, 22q12, merlin	16
Tuberous sclerosis complex	ependymoma, subependymal giant cell astrocytoma	AD	*TSC1*, 9q34, hamartin *TSC2*, 16p13.3, tuberin	16
von Hippel-Lindau syndrome	cerebellar and spinal cord hemangioblastoma	AD	*VHL*, 3p26-p25, VHL protein	16
Li-Fraumeni syndrome	astrocytoma, glioblastoma	AD	*tp53*, 17p13, p53 protein	16
Turcot syndrome type 1	glioblastoma, astrocytoma, ependymoma	AD/AR	*MLH1*, 3p21.3; *PMS2*, 7p22; *MSH6*, 2p16; *MSH2*, 2p22; all proteins are part of the DNA MMR complex	2, 5, 7
Turcot syndrome type 2	medulloblastoma, glioma	AD/AR	*APC*, 5q21, APC protein	5
Lynch III syndrome	neurofibroma, astrocytoma, oligodendroglioma, PNET, medulloblastoma,	AR	Homozygous or compound heterozygous MMR gene mutations (*MLH1, MSH2, MSH6, PMS2*)	8, 9
Basal cell nevus (Gorlin) syndrome	cerebellar hemangioblastoma	AD	*PTCH*, 9q22.3, patched1	16
Melanoma-astrocytoma syndrome	astrocytoma	AD	*CDKN2A*, 9p21, $p16^{INK4A}$	18
Carney Complex	schwannoma	AD	*PRKAR1A*, 17q23-q24, protein kinase subunit	19
Familial meningioma	meningioma	AD	22q12.3-qter, unknown gene	20
Familial schwannomatosis	schwannoma	AD	*INI1/SMARCB1*, 22q11.2, tumor suppressor gene	21
Familial glioma	astrocytoma, glioblastoma	unknown	15q23-q26.3, unknown gene	22

PNET - Primitive neuroectodermal tumour; AD - autosomal dominant; AR - autosomal recessive

defective DNA MMR function. This is the first identification of the molecular abnormality in a patient who clinically meets the diagnosis of both Turcot syndrome and Muir-Torre syndrome. This patient with multiple malignancies represents a severe phenotype of the DNA instability seen in patients with DNA MMR mutations.

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