Glioblastoma multiforme as initial internal malignancy in Muir-Torre syndrome (MTS)

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Muir-Torre syndrome (MTS) is an autosomal-dominant variant of Lynch hereditary cancer syndrome. MTS is defined by sebaceous neoplasms occurring in association with 1 or more internal malignancies.[1] The sebaceous neoplasms that characterize MTS are rare among the general population and include sebaceous adenoma, sebaceoma, sebaceous carcinoma, keratoacanthoma with sebaceous differentiation, and basal cell carcinoma with sebaceous differentiation.[2] A recent case series described several central nervous system (CNS) malignancies associated with MTS occurring after the development of colon cancer.[3] We report a case of MTS with glioblastoma multiforme as the initial internal malignancy.

Abbreviations used:

CNS:	central nervous system
IHC:	immunohistochemistry
MMR:	mismatch repair
MTS:	Muir-Torre syndrome

CASE REPORT

A 69-year-old Caucasian man presented for evaluation of 2 separate orange-yellow papules with telangiectases of the side of the neck and upper aspect of the back (Fig 1). Shave biopsy specimen of the lesions demonstrated sebaceous carcinoma and sebaceous adenoma, respectively. He had a personal history of 3 prior sebaceous carcinomas diagnosed at age 58, 65, and 68 years and 1 sebaceous adenoma diagnosed at age 66 years. In addition he had a family history of colon, breast, and renal carcinoma in his grandfather, mother, and brother, respectively. The patient had no personal history of internal malignancy. Because of family history and multiple sebaceous neoplasms, immunohistochemistry (IHC) for *MSH-2*, *MSH-6*, *MLH-1*, and *PMS-2* was performed on tumor samples. IHC demonstrated loss of nuclear expression of *MSH-2* and *MSH-6* with retained expression of *MLH-1* and *PMS-2*. Subsequent genetic testing of the patient and his brother indicated a germline mutation in *MSH-2*. Based on these results a diagnosis of MTS was suspected, although our patient had not yet had an internal malignancy. The patient underwent screening colonoscopy, which revealed negative findings for colorectal carcinoma.

Less than 1 year later the patient began experiencing episodes of expressive aphasia, visual disturbance, and memory difficulty. Magnetic resonance imaging revealed scattered lesions in the left temporal lobe and left putamen (Fig 2). Biopsy specimen of the lesions confirmed the diagnosis of glioblastoma multiforme World Health Organization grade IV. IHC was performed on tumor specimens, which demonstrated loss of expression of *MSH-2* and *MSH-6* with maintained expression of *MLH-1*, consistent with his diagnosis of MTS (Fig 3).

DISCUSSION

MTS is a variant of Lynch syndrome with sebaceous and internal neoplasms demonstrating microsatellite instability and mutations in the mismatch repair (MMR) genes *MSH-2*, *MLH-1*, and *MSH-6*.[4,5] The internal malignancies most commonly associated with MTS include: colorectal, urogenital, breast, and upper gastrointestinal.[6] Sebaceous neoplasms

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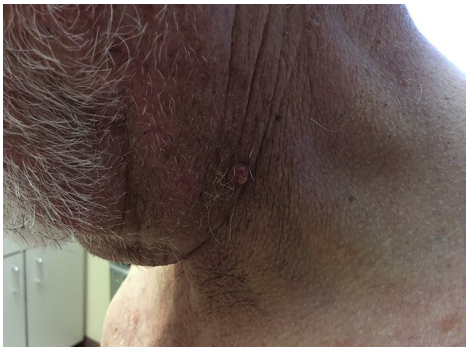

Fig 1. Orange-yellow papule with telangectasis located on left side of neck of 69-year-old Caucasian man.

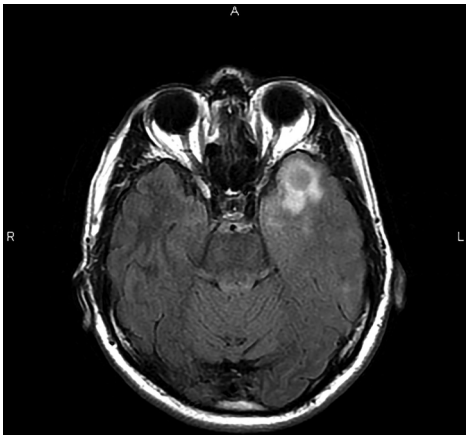

Fig 2. T2 fluid-attenuated inversion recovery magnetic resonance imaging of glioblastoma multiforme in left temporal lobe.

precede or occur simultaneously with the diagnosis of internal malignancy in 28% to 41% of patients with MTS.[2,6] Glioblastoma multiforme occurs in 1.2% to 6.3% of patients with *MSH-2* mutation dependent Lynch syndrome, but is not commonly reported in patients given a diagnosis of MTS.[7,8]

Our patient had an extensive history of sebaceous neoplasms including 4 cases of sebaceous carcinoma and 2 cases of sebaceous adenoma. The sebaceous neoplasms in our patient predated the development of CNS malignancy by 11 years. Interestingly, routine screening colonoscopies revealed negative results for both our patient and his brother. Although the patient's mother and maternal grandfather had an extensive cancer history including diagnosis in their early 40s, neither of them were aware of the Lynch syndrome diagnosis. Our patient was the only member of his family to develop sebaceous neoplasms characteristic of MTS.

A recent report by Kurtzman et al[3] described 7 cases of CNS malignancy occurring in patients given a diagnosis of MTS. In each of the previous cases a diagnosis of colorectal carcinoma (age 41-50 years) preceded the diagnosis of CNS malignancy. This was notably absent in our patient. Sebaceous adenoma was the most commonly diagnosed sebaceous neoplasm in these cases (5 of 7 patients), whereas sebaceous carcinoma was diagnosed in 3 of 7 patients. Sebaceous adenomas occurred as multiple neoplasms in all but 2 patients, whereas sebaceous carcinomas occurred as isolated lesions in all but our patient. Sebaceous neoplasms were diagnosed between the ages of 46 and 58 years. Five of the patients also reported a previous diagnosis of squamous cell carcinoma or keratoacanthoma. CNS malignancy occurred between the ages of 45 and 68 years.

A family history of CNS malignancy was positive in a majority of reported cases (6 of 7), which was also absent from our patient. Among patients given a diagnosis of Lynch syndrome there is heterogeneity of tumor development dependent on whether *MSH-2* or *MLH-1* is mutated.[8] Mutations in *MSH-2* are more commonly associated with CNS and upper urogenital carcinoma when compared with mutations in *MLH-1*, which are more commonly observed in patients with gastric and small bowel carcinoma. The predilection for upper urogenital tract carcinoma is consistent with our patient's family history. Several studies have examined MMR mutation frequencies within MTS, showing mutations in *MSH-2* predominating over *MLH-1*, although mutations in *MLH-1* are identified in a proportion of patients.[4,9,10] It is important to note that all reported cases of CNS malignancy occurring in patients with MTS who underwent IHC demonstrated loss of function of *MSH-2*.[3]

Loss of nuclear expression of *MSH-2* or *MLH-1* in sebaceous neoplasms does not in itself define MTS. A significant number of sebaceous neoplasms demonstrate sporadic mutations in MMR genes resulting in a low specificity (48%) and positive predictive value (PPV) (22%) of MMR IHC in diagnosing MTS in patients without other history suggestive of the diagnosis.[11] However, among patients with multiple sebaceous neoplasms (≥ 2), early diagnosis of sebaceous neoplasms (age <60 years), or a personal or family history of Lynch syndrome or related cancer, the specificity of MMR IHC increases significantly.[12,13] Once the diagnosis of MTS is established screening recommendations for associated malignancies are variable but generally include increased frequency and lower threshold for screening related to colon, breast, endometrial, urogenital, and small bowel carcinoma.[1] Kurtzman et al[3] also suggest neurologic screening as a component of routine cancer screening for patients with MTS. They suggest a baseline neurologic examination be performed at the time of MTS diagnosis and repeated annually. They also suggest that patients with a family history

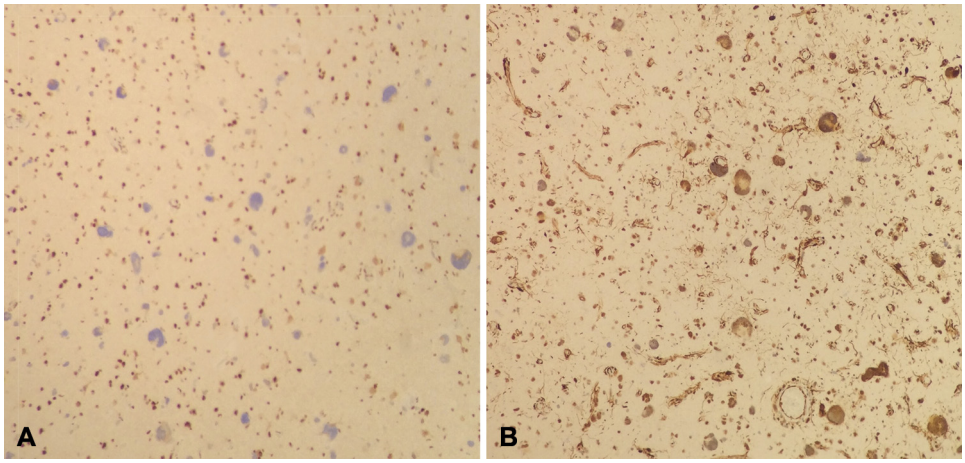

Fig 3. Immunohistochemical staining for *MSH-2* (**A**) and *MLH-1* (**B**) in glioblastoma tumor sections. Staining of sebaceous carcinoma showed similar staining pattern. Note the absence of *MSH-2* nuclear staining and the maintenance of *MLH-1* nuclear staining.

of CNS malignancy consider use of serial imaging for early detection of CNS malignancy.

Although colon cancer is the most common initial internal malignancy in MTS, we report a case of CNS malignancy occurring in absence of preceding colorectal malignancy and in the absence of family history of CNS malignancy. Furthermore we would like to note that 100% of patients who underwent MMR IHC for CNS malignancy, including our patient, demonstrated loss of expression of *MSH-2* and maintenance of *MLH-1*. Although *MSH-2* mutations are by far the most common MMR mutations among patients with MTS this association further suggests loss of expression of *MSH-2* as a risk factor for development of CNS malignancy. All patients with MTS who develop neurologic symptoms should have a low threshold for evaluation of possible CNS malignancy, especially those with family history of CNS malignancy or known *MSH-2* germline mutations.

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