CASE REPORT

Muir–Torre syndrome: Diagnostic and screening guidelines

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SUMMARY

A 65-year-old man presented with a history of multiple skin coloured papules on his face that were asymptomatic. He had an adenocarcinoma resected from his proximal colon 12 years prior to presentation as well as a family history of colon cancer on the maternal side. Diagnostic biopsies showed the lesions to be sebaceous adenomas and epitheliomas and the diagnosis of Muir–Torre syndrome was made. The sebaceous tumour tissue showed microsatellite instability and immunohistochemical staining indicated diminished expression in the DNA mismatch-repair protein complex MSH2/MSH6. Genetic analysis showed a germline mutation in the MSH2 gene confirming the diagnosis of Muir–Torre syndrome. The patient and his first-degree relatives have been referred for genetic counselling and screening. We review the diagnostic criteria in this syndrome and review the recommended screening guidelines.

Key words: genodermatoses, hereditary non-polyposis colorectal cancer, Lynch syndrome, microsatellite instability, mismatch-repair gene, sebaceous adenoma, sebaceous carcinoma, sebaceous epithelioma.

INTRODUCTION

Muir–Torre syndrome is one of the cancer-associated genodermatoses now considered to be a subset of the HNPCC or Lynch syndrome.1 The diagnostic criteria is one or more sebaceous neoplasm in association with at least one internal malignancy.2 The sebaceous neoplasm required for diagnosis is usually restricted to sebaceous adenomas, epitheliomas and carcinomas.2 The most frequent visceral neoplasms associated with Muir–Torre syndrome is colorectal cancer, accounting for approximately 50% of cases and genitourinary accounting for approximately 25% of cases.2 Other associated cancers include breast, lung, gastric, small intestine and haematological malignancy.3 The internal malignancy may occur several years before or after the skin lesions.4

The diagnosis has screening and genetic counselling implications for the patient and family members. Recent changes to the appropriate screening guidelines in Muir–Torre syndrome have not been well described in the dermatological literature. We present a case of Muir–Torre syndrome and review these screening recommendations.

CASE REPORT

A 65-year-old man presented with a 2-year history of multiple asymptomatic lesions on his face. Twelve years prior to this he had a Duke’s B, moderately differentiated, mucinous adenocarcinoma resected from his ascending colon. He also had a squamous cell carcinoma excised from his back 7 years previously. He subsequently remained well, had no other medical history and took no medications.

There was a family history of colon cancer with the patient’s maternal aunt and uncle dying from this condition at ages 27 years and 57 years respectively. There was no history of cancer in his parents or siblings and his three children aged 44, 41 and 24 years were healthy.

On examination there were multiple yellowish to skin coloured papules on his forehead and cheeks (Figs 1, 2). Some showed central umbilication and they were of moderate to firm consistency on palpation. Two excision biopsies reported the papules to be a sebaceous adenoma and a sebaceous epithelioma. The diagnosis of Muir–Torre syndrome was made. He has since had multiple sebaceous adenomas (Fig. 5) and one sebaceous carcinoma excised from his face.

The patient’s biopsy tissue and blood was sent to a reference laboratory (Institute of Human Genetics and Institute

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of Pathology, University of Bonn, Germany) for immunohistochemical staining, microsatellite analysis and to search for a germline mutation. The immunohistochemical staining showed a diminished expression of the DNA mismatch-repair protein complex MSH2/MSH6 and, of the five markers, three indicated microsatellite instability. Genetic analysis confirmed a germline mutation in the MSH2 gene, a common finding in Muir–Torre syndrome. The patient is now undergoing annual colonoscopies and his family members have been referred for genetic counselling, predictive testing and screening measures.

**DISCUSSION**

Advances in molecular medicine over the past 10 years have established the underlying genetic mutations responsible for Muir–Torre syndrome. These occur in the DNA mismatch-repair genes MSH2 and MLH1 which are also two of the genes identified in hereditary non-polyposis colorectal cancer.\(^5\,\)\(^6\) Whereas the proportions of mutations in these two genes are approximately equal in hereditary non-polyposis colorectal cancer the majority of mutations in the Muir–Torre syndrome subset are MSH2.\(^6\)

All tumours associated with a mismatch-repair gene defect exhibit high microsatellite instability, which is the presence of repetitive DNA sequences of varying length. As most skin tumours of Muir–Torre syndrome patients exhibit microsatellite instability, it is a useful screening test for the syndrome.\(^5\)

Separate clinical diagnostic criteria have been established for the diagnosis of hereditary non-polyposis colorectal cancer families which include the Muir–Torre syndrome subset. These were known as the Amsterdam criteria and the more sensitive Bethesda guidelines (Table 1). Meeting these criteria then warrants microsatellite instability testing and immunohistochemical analysis on the patient’s tumour followed by germline MSH2 or MLH1 testing on the patient’s blood.\(^8\)

Sebaceous neoplasms, such as adenomas, epitheliomas and carcinomas, are reported to be so rare that finding one should alert to the possibility of Muir–Torre syndrome and warrants further microsatellite instability and immunohistochemical evaluation and a search for an underlying malignancy.\(^3\,\)\(^4\)

A mismatch-repair gene mutation cannot be found in all cases of high microsatellite instability, but if it is found then it enables the family members to have formal genetic testing and counselling. Genetic counselling is an integral part of dealing with families with cancer-associated genoderma-

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**Figure 1** Forehead of patient showing multiple skin-coloured sebaceous adenomas.

**Figure 2** Sebaceous epithelioma and adenoma below the right eye and on the nasal tip respectively.

**Figure 5** Histology of a punch excision from the forehead of the patient showing a sebaceous adenoma. There are sebaceous lobules present with peripheral sheets of basaloid cells (H&E).
Table 1  Revised Amsterdam criteria and Bethesda guidelines used to diagnose hereditary non-polyposis colorectal cancer

<table>
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<tr>
<th>Revised Amsterdam criteria (Amsterdam II)</th>
<th>Revised Bethesda guidelines</th>
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<tr>
<td>• Three or more relatives with HNPCC-related tumour (CRC, endometrial, small bowel, renal) and one is a first degree relative of the other two</td>
<td>• Diagnosed with CRC before age 50 years</td>
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<td>• Two or more generations are affected</td>
<td>• Presence of synchronous or metachronous CRC or other HNPCC related tumour†</td>
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<tr>
<td>• One patient is diagnosed before age 50 years</td>
<td>• CRC with high MSI morphology and diagnosed before age of 60 years</td>
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<tr>
<td>• Tumours are verified by a pathologist and FAP is excluded</td>
<td>• CRC with at least one first-degree relative with CRC or other HNPCC-related tumour† (diagnosed before age 50 years)</td>
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<tr>
<td></td>
<td>• CRC with at least two relatives (regardless of age) with CRC or other HNPCC-related tumour†</td>
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Further microsatellite instability testing or germline mutation analysis is recommended if all of the Amsterdam criteria or one of the Bethesda guidelines is met. Mortality, urinary bladder, ureter, renal pelvis, biliary tract, brain, sebaceous gland adenomas, keratoacanthomas, small bowel. CRC, colorectal cancer; FAP, familial adenomatous polyposis; HNPCC, hereditary non-polyposis colorectal cancer; MSI, microsatellite instability.

Table 2  Screening recommendations for patients with Muir–Torre syndrome and their first-degree relatives

| Physical exam: Yearly including breast in women, testicular and prostate in men and laboratory tests including FBC, CA-125, CEA, FOB, urinalysis. | Colonooscopy: Every 1–2 years from age 25 years or 5 years before the youngest age of diagnosis of CRC in family, and annually from age 40 years. |

CA-125, carbohydrate antigen 125; CEA, carcinoembryonic antigen; CRC, colorectal cancer; FBC, full blood count; FOB, faecal occult blood; USS, ultrasound scan.

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