Muir–Torre syndrome: clinical features and molecular genetic analysis

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Summary

We report a 62-year-old man with rectal cancer, two keratoacanthomas and multiple sebaceous adenomas, epitheliomas and sebaceous hyperplasia. His brother and father died from colorectal cancer. A subgroup of patients with the Muir–Torre syndrome (MTS) is allelic to the cancer family syndrome. This genetic disorder is caused by an autosomal dominant inherited germline mutation in one of the DNA mismatch repair genes. It is thought that a somatic mutation of the other allele leads to a genomic instability responsible for tumorigenesis. In the patient presented here the instability was detected in two characteristic skin lesions; sebaceous adenoma and epithelioma. The search for a causal germline mutation revealed a frameshift mutation in the mismatch repair gene hMSH2 leading to a truncated protein. A presymptomatic molecular diagnosis can be offered to the children of the patient.

The Muir–Torre syndrome (MTS) is an autosomal dominant inherited predisposition to internal and cutaneous tumours.1 It has been shown that a subgroup is allelic to the cancer family syndrome (CFS), hereditary non-polyposis colorectal cancer (HNPCC).2,3 In tumour tissues of both the MTS subgroup and HNPCC a genomic replication error known as microsatellite instability (MIN) is striking.4,5 The instability is caused by alterations in at least one of four DNA mismatch repair genes.5–9 These genes play a crucial role in the correction of mismatched base pairs. Mismatches physiologically originate from replication of the DNA during the cell cycle. For the repair mechanism an interaction of proteins coded by at least five different mismatch repair genes is essential.10 In a study of 48 HNPCC patients, germline mutations in the mismatch repair genes hMLH1 or hMSH2 have been detected in 33 or 31% of the patients, respectively, and mutations in the hPMS1 or hPMS2 in 6%.5 In MTS a germline mutation in the hMLH1 gene has been described in only one family,11 while the great majority of Muir–Torre patients have germline mutations in the hMSH2 gene.8,12

The predisposition to tumours in distinctive tissues is caused by a heterozygous germline mutation in one of the DNA mismatch repair genes. It is thought that an additional somatic mutation of the other allele leads to a loss of mismatch repair and so can result in a subsequent manifestation of a tumour. Thus a defective mismatch repair gene is recessive at the cellular level. After further cell cycles, accumulated base pair mismatches can lead to a large number of somatic mutations in several loci of the whole genome. These alterations can be demonstrated by an instability of individual DNA microsatellites (MIN). If oncogenes and/or tumour-suppressor genes are also mutated then a neoplasm can develop.13 Why colonic epithelium and sebaceous glands are affected predominantly, remains unclear. While most of the internal tumours of HNPCC patients show MIN,14 the actual frequency of MIN in the different types of skin tumours associated with the MTS is still unknown.

Case report

A 62-year-old man presented with 3-year history of facial papules. These measured 2–4 mm and were yellow or skin-coloured (Fig. 1). Approximately 3 months prior to presentation the patient noted the onset of two enlarging lesions on the left nostril and below the left nipple. On examination, round tumours with a central indentation were seen. These averaged 2–2.5 cm in diameter. Histological examination showed
keratoacanthoma. The biopsies of 16 facial papules showed sebaceous adenoma, epithelioma and hyperplasia.

At the age of 57 years a rectal carcinoma Dukes’ stage B was excised. The patient’s father and brother also had colorectal cancer, but had no skin tumours. The brother died at the age of 33. The three children of the patient are healthy, and have decided against knowing their carrier status or having further investigations.

Molecular genetic analysis

Paraffin-embedded tissues from three different skin tumours (sebaceous adenoma and epithelioma, keratoacanthoma) were examined for MIN. Genomic DNA from tumours was extracted with the QIAamp tissue kit (QIAGEN). The normal DNA was isolated from peripheral blood by the salting out procedure. Subsequently, pairs of tumour and normal DNA were amplified by PCR with up to 10 microsatellite markers. The electrophoretic mobilities of the corresponding amplification products were compared on polyacrylamide gels. Microsatellite instability was observed in both the sebaceous adenoma and the sebaceous epithelioma with three and four microsatellite markers, respectively. The keratoacanthoma did not show instability with 10 markers tested (Fig. 2). Tissue from the colon carcinoma was not available.

Figure 1. A 62-year-old with 3-year history of facial papules.

Figure 2. Microsatellite instability (MIN) in skin tumours of the patient. DNA from peripheral blood (N) and tumour tissues (SA, sebaceous adenoma; SE, sebaceous epithelioma; KA, keratoacanthoma) were examined with the microsatellite marker D2S136. Additional alleles in the sebaceous tumours are marked by arrowheads.
To screen for germline mutations in the mismatch repair genes we applied non-radioactive heteroduplex analysis and single strand conformational analysis (SSCA) as described. A variant SSCA and heteroduplex pattern was observed in exon 2 of the hMSH2 gene (Fig. 3). Sequencing revealed an insertion of 22 base pairs at codon 97 (Fig. 4). This frameshift mutation (289ins22) leads to a stop codon after nine further codons and thus to a truncated hMSH2 protein.

Discussion

In April 1958 Smith presented a 33-year-old man with multiple keratoacanthomas and sebaceous hyperplasia of the face during a meeting of the Dermatological Section of the Royal Society of Medicine. In March 1967 Muir et al. reported the same patient, who in the meantime had developed four carcinomas of the colon.
two of the duodenum and one of the larynx. In October 1967 Torre et al. presented a 57-year-old man with more than 100 sebaceous adenomas or carcinoma, respectively, on the face, scalp and trunk to the New York Dermatological Society. The case history revealed carcinoma of colon and papilla vateri. In 1971, Bakker et al. reported a third case and considered that the three patients represented a rare syndrome. In 1974 the designation ‘Torre’s syndrome’ was proposed. Since then the name ‘Muir–Torre syndrome’ has been accepted.

Criteria for diagnosis as reviewed by Schwartz et al. are at least one visceral cancer and one sebaceous gland tumour; either adenoma, epithelioma or carcinoma (in decreasing order of frequency). Sebaceous hyperplasia and nevi sebacei of Jadassohn are not diagnostic. The same applies to keratoacanthoma, which occurs in 20% of MTS cases. Fifty-one per cent of the patients develop at least one colorectal carcinoma, which occurs on the average 10 years earlier than in the general population. Twenty-four per cent of the patients develop genitourinary cancer. Sixty per cent of the cases of MTS occur in men and in 60% the internal neoplasia is the first sign.

The differential diagnosis includes Gardner’s syndrome (epidermal cysts, fibromas, colon adenomatosis, osteomas, retinal pigmentation), Cowden’s syndrome (facial trichilemmomas, oral papules, acral fibromas, carcinoma of breast, thyroid gland, stomach and bowels), Goltz–Gorlin syndrome (multiple basaliomas, jaw cysts with tendency to malignant transformation, broad bridge of the nose, ovary fibromas, hypertelorism), multiple self-healing keratoacanthoma (Ferguson–Smith type), generalized eruptive keratoacanthoma (Grzybowski type), multiple trichoepitheliomata and Bourneville–Pringle disease (adenoma sebaceum, epilepsyform attacks, mental defects).

Treating the cause of the MTS is not currently possible. Any skin tumour should be excised. Prevention can be tried with oral isotretinoin up to 0.8 mg/kg per day. Although the cancers in this syndrome are less aggressive, a periodic search for visceral cancer is recommended for patients and relatives from the age of 25.

The family history of the patient presented here reveals two first-degree relatives with colorectal cancer. One of them died at 33 years of age. Thus the family structure fitted previous criteria (Amsterdam criteria) for HNPCC. Our patient was diagnosed as having MTS since he had characteristic sebaceous tumours in addition to rectal carcinoma.

Using periodic acid Schiff (PCR) techniques microsatellite instability in the two typical sebaceous skin lesions was found in this patient. This suggested the existence of a DNA mismatch repair defect. The keratoacanthoma did not show genomic instability. This observation is in agreement with data of Halling et al. who found MIN only in part of the keratoacanthoma both in randomly selected patients and in patients with additional visceral tumours, including MTS. A mutation analysis revealed an insertion of 22 base pairs in exon 2 of the DNA mismatch repair gene hMSH2. The resulting frameshift is predicted to lead to the synthesis of a considerably truncated mismatch repair protein.

The identification of a germline mutation in the DNA mismatch repair gene hMSH2, in addition to the clinical feature and the microsatellite instability in tumour tissues, confirms the diagnosis of MTS in the family presented here. For the three adult children of the patient, who have an a priori risk of 50% to inherit the cancer predisposition, a presymptomatic molecular diagnosis can be offered. For those children who have not inherited the germline mutation in the hMSH2 gene specific cancer surveillance is not necessary, while those who have inherited the mutation must undergo regular examinations especially of the skin, the colon and the genitourinary tract as recommended by Cohen et al.

However, it has to be kept in mind that the predictive diagnosis of a tumour predisposition may have deep psychological implications. The identification of a germline mutation implies that this still healthy person is at high risk to develop a disease-associated tumour; but it is not known, if, when or in which tissue a tumour will arise. Therefore, each predictive diagnosis should be preceded by a careful genetic counselling that includes full information on the possibilities and limits, as well as on the consequences of a predictive test.

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References


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