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Case report

Muir- Torre syndrome (MTS): A case report

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SUMMARY

MTS is defined by at least one sebaceous gland adenoma and one internal malignancy. Malignancies are often multiple with predominance of colorectal and urogenital carcinomas. Half of the patients with colorectal cancer have at least one synchronous or metachronous lesion. The skin lesions may be the first sign of this syndrome, although more often its cutaneous signs follow the diagnosis of at least the first visceral malignancy. Identifying such patients will affect their management. Regular follow-up and search for new malignancy is mandatory. Because this syndrome is inherited in an autosomal dominant manner, identifying one patient means delineating an entire family, which should then be investigated. This syndrome may be caused by a defective mismatch DNA repair gene.

The Muir-Torre syndrome (MTS) is a rare autosomal-dominant disease involving sebaceous neoplasms as markers for multiple internal malignancies. Described first by Muir et al. in 1967[1] and Torre in 1968[2] it is defined by the presence of (a) at least one sebaceous gland tumour (adenoma, epithelioma or carcinoma) and (b) at least one internal malignancy. Since then, over 205 cases meeting met the criteria for the syndrome have been reported in world literature. Gastrointestinal, urogenital, and breast malignancies accounted for 90 per cent of the cancers found in those patients. Furthermore, nearly 50 per cent of MTS patients have had two or more internal malignancies, frequently low-grade visceral cacers with high potential for favourable long-term survival. This syndrome is now considered a subtype of the more common hereditary non-polyposis colorectal cancer syndrome (HNPCC).[3] In a subset of MTS families, the disease is due to an underlying DNA mismatch repair defect, usually located at hMSH2 gene. We report a case of a 40-year old man displaying the MTS phenotype.

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CASE REPORT

A 40-year-old man was referred to the surgery clinic in 1988 with an Astler-Coller C2 adenocarcinoma of the ascending colon. The patient was treated by right hemicolectomy followed by adjuvant chemotherapy.

In January 1989, two sebaceous lesions, one at the back of the trunk and the second on the buttock were excised in this patient. Histology proved these to be a sebaceous adenoma and a nevous respectively. In September of the same year another sebaceous adenoma from his face and a highly differentiated acanthoma from his back were excised. In September 1993 he had a basal cell carcinoma excised from his nose, and two years later another sebaceous adenoma was removed from his face.

The patient was put on surveillance after the resection of his colonic neoplasm (physical examination, upper GI series, colonoscopy, ct-scan, CEA serum-levels etc.), but he failed to attend the follow up clinic for 6 years. He reappeared in November 1999 with an adenocarcinoma of the rectosigmoid junction (Astler-Coller C2) which was treated by anterior resection and postoperative chemotherapy.

In June 2001 he was presented with a palpable mass in the lower end of the abdominal incision, with marked elevation of PSA serum levels (> 14,000 ng/dl). The FNA of the prostate confirmed the diagnosis of a prostate cancer. CT scan showed secondary deposits in the L1 and L2 vertebrae. Hormonal treatment was introduced

and the patient was referred for palliative external radiotherapy for the metastatic vertebral lesions.

A detailed family history for three generations was obtained from the patient and his wife. The father of our patient had died at age 51 from colonic cancer with liver, brain and bone metastases. His mother had died at age 63 with a history of ovarian cancer.

He has one brother and two sisters. His brother is 51 and is currently healthy. His elder sister is 55 years old. She was operated on for ovarian carcinoma at the age of 40 and dysplastic polyps were removed from her colon at the age of 50. The other sister, 57 years old, was operated on for cancer of the uterus at the age of 53 and of colon cancer at the age of 56, and is now suffering from breast cancer.

The patient has three children, a son aged 18 years and two daughters, 19 and 23 years old. These all are on a surveillance programme. (figure 1)

DISCUSSION

Since the independent reports by Muir et al. (1) and Torre (2) in 1967 of the association of sebaceous neoplasms with visceral cancers, 205 cases of MTS have been documented in the world literature. Age of diagnosis ranged from 27 to 90 years with a median of 53, and the male: female ratio was 2:1. The visceral malignancies most often seen in these patients are colorectal cancers (CRCs) and genitourinary tract neoplasms, predominantly originating from the bladder, uterus, renal pelvis, or ovaries, which, together, account for 75% of the observed internal malignancies in MTS. The discovery of a CRC in MTS patients occurs about one decade earlier than in the general population. The location of colorectal tumours is also different from that seen in the general population, with the majority (58-60%) located in the proximal colon (cecum to splenic flexure). Furthermore, breast, hematological, head and neck, and small intestinal malignancies have been described in combination with sebaceous gland tumours. Skin lesions frequently observed in MTS patients in addition to at least one of the defining lesions (sebaceous adenoma, epithelioma, and crcinoma) include: sebaceous hyperplasia, keratoacanthoma, basal cell carcinoma and squamous cell carcinoma.[4,5]

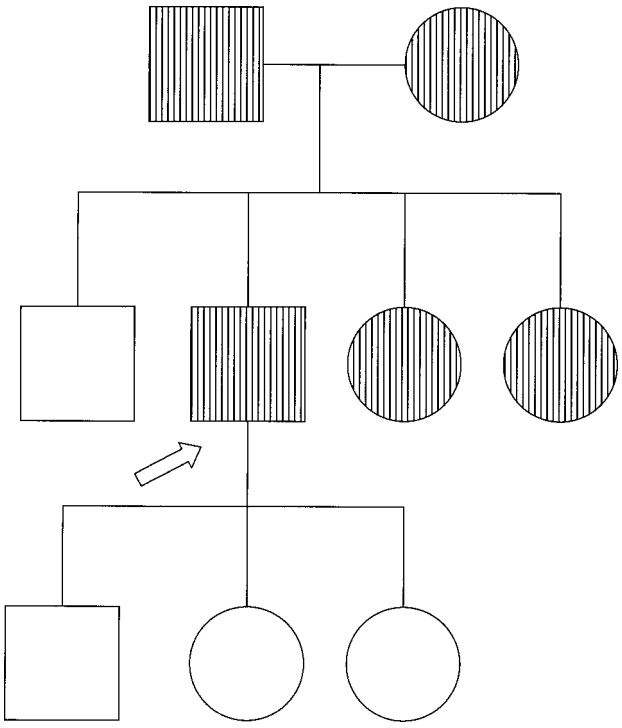

Figure 1. MTS family pedigree. Squares, males; circles, females: arrow, our patient. Shading indicates family members with malignancy.

Because a subset of patients fulfilling these criteria appeared to have HNPCC, a relation between HNPCC and MTS was first suggested by Lynch in 1981.[3] HNPCC (Lynch syndrome) is characterized by an autosomal dominantly inherited predisposition to the development of CRC or specific extracolonic cancers, such as endometrial or gastric carcinomas. CRCs in HNPCC patients present at a young age (44 years) and have a favorable prognosis compared to sporadic malignancies. HNPCC can be diagnosed on clinical grounds if all three Amsterdam criteria are fulfilled: (a) three or more relatives with histologically verified CRC, one of whom is a first degree relative of the other two; (b) CRC involving at least two generations; and (c) one or more CRC cases diagnosed before age 50.[6]

HNPCC is caused by an inherited germ-line mutation in one allele of MMR genes. When a somatic loss-of-function alteration of the remaining wild-type allele occurs, MMR deficiency develops. The MMR system repairs small errors in repeat sequences of the DNA (microsatellites), which occur during replication. Consequently, MMR deficiency results in accumulating mutations of these microsatellites, which is termed MSI. Carcinomas of HNPCC patients show microsatellite instability (MSI). To date, defects in six genes have been described leading to the HNPCC phenotype: hMLH1, hMSH2, hPMS1, hPMS2, hMSH6, and the transforming

growth factor ⇓ type II receptor gene. Molecular genetic studies in MTS patients have shown MSI in both sebaceous gland tumours and CRC. Also, MSI in keratoacanthomas and actinic keratoses from MTS patients has been described. In contrast, the degree of MSI in sporadic keratoacanthomas and other skin tumours, such as basal cell carcinomas, squamous cell carcinomas, melanomas, actinic keratoses, and Bowen's disease, is very low, although no data for sporadic sebaceous gland tumours are available. In addition, germ-line mutations in the MMR genes hMSH-2 and hMLH-1 have been described in MTS patients, further indicating that MTS might be an expression variant of HNPCC.[7-10]

In patients with both CRC and SGC available, a 100% concordance in MSI status was noted. Thus, the sensitivity of MSI as a marker for MTS in SGC patients was 69%, and the specificity was 100%. Of note, absence of MSI was found in 31% of MTS patients, indicating that another molecular genetic mechanism might lead to the MTS phenotype. This could either be a MMR-related pathway, which does not exhibit MSI, as was recently described in tumours of patients with a germ-line hMSH-6 mutation, or a MMR-independent pathway. Because SGCs are very rare (0.2% of all skin malignancies are SGCs), a coincidental occurrence with CRC in all MSI-negative MTS cases appears unlikely, although this possibility cannot be completely excluded. Recently it has been proposed that MSI plus immunohistochemical loss of expression of hMLH-1 or hMSH-2 have the same value as the marker for MTS; with 100% specificity. MSI and loss of expression of MMR genes can be used as markers for MTS in patients with SGC. Consequently, MSI and loss of MMR gene expression in a patient presenting with SGC as the initial malignancy have important consequences for the patient and family. There are at least two variants of MTS with different molecular genetic mechanisms because 31% of the patients with the MTS phenotype had no MSI.[11-16] MTS is phenotypically distinguished from HNPCC by the presence of sebaceous gland tumours and/or keratoacanthomas in patients with MTS. In MTS, 30% of the sebaceous gland tumours are sebaceous glands carcinomas (SGCs). SGCs account for a minority of skin cancers in the general population and are rarely diagnosed. In most cases, SGCs are seen in the eyelid, but they can develop in any sebaceous gland in the body; the head and neck region is the most frequently affected part of the skin . SGCs usually occur in patients aged 60–80 years. In about 41% of MTS patients, a sebaceous gland tumour presented as the first malignancy before or concurrent with an internal malignancy. Because MTS patients are often prone to multiple internal malignancies, as many as 63% of the MTS patients with a sebaceous gland tumour have a concurrent internal cancer or will develop an additional (internal) neoplasm. These data emphasize the importance of complete evaluation and close follow-up for gastrointestinal and genitourinary cancer in a patient with a sebaceous gland tumour when the diagnosis MTS is considered. The initial evaluation and ongoing surveillance for internal malignancies in patients with or suspected to have MTS include history and complete physical examination, laboratory studies, chest X-ray, and mammography in women. Evaluation of the entire colon should be done initially and every 3 to 5 years, as should endometrial biopsy in women. Cystoscopy, intravenous pyelography and abdominal/pelvis CT scan are considered optional, although in light of the fact that intra-abdominal malignancies other than CRC comprise nearly 35% of those found, a case could be made for a more central role for CT scans.[17-19]

Evaluation of asymptomatic relatives of MTS patients is indicated, especially because at least 50% of patients ultimately diagnosed with MTS present with an internal malignancy before development of associated sebaceous lesions. Initial evaluation should be started at any age, but the yield is probably small in an asymptomatic patient under 30 years of age.[20-22]

The diagnosis and management of MTS patients and their families involves a multidisciplinary approach, including the primary care physician, dermatologist, gastroenterologist, surgeon and oncologist. The surgeon, however, usually assumes a central role in the definitive management. Treatment can be longitudinal with frequent admissions, extensive preoperative workup and planning and sometimes multiple and complex surgical procedures. MTS portends the greater possibility of a favourable prognosis than might be anticipated otherwise, because the visceral cancers are usually low-grade malignancies. Because these indolent visceral malignancies tend to permit prolonged survival, even metastatic disease may respond well to aggressive surgical treatment.[23]

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