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CASE REPORT

A case of Muir-Torre syndrome associated with mucinous hepatic cholangiocarcinoma and a novel germline mutation of the *MSH2* gene

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Abstract Muir-Torre syndrome (MTS) is a rare cancer-predisposing syndrome that is autosomal dominantly inherited and characterized by the development of sebaceous skin lesions (adenomas, epitheliomas, basaliomas and carcinomas). These lesions are typically associated with tumors that belong to the spectrum of hereditary nonpolyposis colorectal cancer (HNPCC) (i.e. tumors of the colorectum, endometrium, stomach or ovary). Biliary malignancy in association with MTS has only rarely been reported. We report a case of Muir-Torre syndrome associated with intrahepatic cholangiocarcinoma, a location not previously described, and associated with a novel missense mutation of the MSH2 gene (c.2026T > C), predicted to disrupt the function of the gene.

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Abbreviations

CEA	carcino embryonic antigen
HNPCC	hereditary non polyposis colon cancer
MTS	Muir-Torre syndrome
MRI	magnetic resonance imaging
MSI	microsatellite instability

Introduction

Muir-Torre syndrome (MTS) is a rare autosomal-dominant cancer-predisposing syndrome, first described in the 1960s [1, 2]. MTS is characterized by the association of sebaceous skin lesions (adenomas, epitheliomas, basaliomas and carcinomas) or keratoacanthomas and one or more visceral tumors that belong to the spectrum of HNPCC (i.e tumors of the colon and rectum, endometrium, stomach, ovary, biliary tree) [3, 4]. Molecular studies have documented microsatellite instability in both skin and visceral tumors [5], linked to inactivation of a mismatch repair protein, as a result of a germline defect in either the *MLH1* or the *MSH2* gene [6, 7].

Biliary malignancy in association with MTS has only rarely been reported [8] and our observation of MTS associated with primary cholangiocarcinoma of the liver is, to our knowledge, the first to be described as a consequence of a missense mutation of the *MSH2* gene. The clinical manifestations, rapid evolution to metastatic disease and the localization of the metastases are shown to be atypical for HNPCC.

Case report

A 41-year-old Caucasian female presented to our surgery department with a firm and asymptomatic mass of the upper right quadrant, noticed about 3 weeks before. No other complaint was mentioned except multiple nodules of the skin. Two of these nodules located in the right and left retro-auricular area have recently emerged. One nodule was dark and located in the right temporal scalp and the other nodules were yellow and were located on the face. The patient had two polyps of the colon resected 4 years and 1 year before, respectively. The polyps were located in the transverse colon and were surgically removed by segmental transverse colectomy. Pathological diagnoses were tubulovillous adenoma with foci of high grade dysplasia and villous adenoma with high grade dysplasia, respectively. No invasive features were observed in these two adenomas. Besides, at the age of 39 an endometrial polyp had been discovered at a gynecologic control. Radiological investigations were carried out with a thoraco-abdominal CT-SCAN and a hepatic MRI. Both showed a very large tumor, occupying almost all the right liver. Laboratory investigations revealed a carcinoembryonic antigen (CEA) increased to 983 ng/ml (normal value 0–6 ng/ml).

Pre-operative endoscopy of the gastrointestinal tract and pelvic CT-SCAN was undertaken to rule out a primary carcinoma. A right liver lobectomy (segments IV–VIII) was performed. Surgical specimen weighted 4,250 kg. The tumor measured 22 cm of maximal diameter and presented with a whitish and fleshy aspect and in some parts with a gelatinous consistence (Fig. 1). There was no other nodule in the remaining hepatic lobe. Microscopic examination showed a mucinous adenocarcinoma. In the absence of any primary extrahepatic tumor, the final pathological diagnosis was a primary mucinous cholangiocarcinoma of the liver. Biopsies of the cutaneous nodules of the face indicated that the right and left retro-auricular nodules corresponded to metastasis of a mucinous adenocarcinoma whereas the nodule of the scalp corresponded to a sebaceous epithelioma. The other nodules of the face were not biopsied but were clinically suggestive of sebaceous hyperplasia or sebaceous adenomas. Family history indicated that the patient's mother had three metachronous colon cancers at the age of 44, 62 and 63 years, a cancer of the uterus at 62 years, and a cancer of the ureter at 70 years (Fig. 2). She had no lesions of the skin.

Considering family history and the fact that tumors of the colon, the scalp, the uterine corpus and the biliary tract in a young patient, are suggestive of the

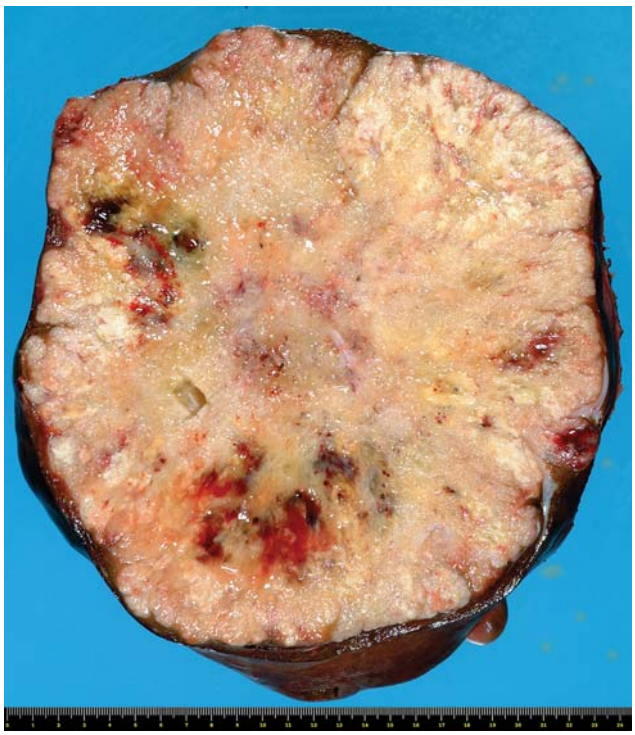

Fig. 1 Macroscopic feature of a hepatic cholangiocarcinoma

HNPCC tumor spectrum, we searched for microsatellite instability in the tumors of the colon and in the cholangiocarcinoma. The reference panel of five microsatellites (BAT25, BAT26, D5S346, D2S123 and D17S250) was used, based on recommendations of the National Cancer Institute workshop on microsatellite instability (MSI) [9]. The results indicated a MSI-high status for each tumor. The immunohistochemical staining revealed a loss of nuclear expression, in both hepatic tumor and colonic adenomas, of MSH2 *and* MSH6 proteins, whereas the expression of MLH1 *and* PMS2 proteins was preserved (Fig. 3). Final pathological diagnosis of the hepatic tumor was primary mucinous cholangiocarcinoma and a Muir-Torre syndrome was suggested.

After obtaining the patient's written informed consent, a peripheral blood sample was taken to perform analysis of the *MSH2* gene from genomic DNA. Bidirectional sequencing of exons and introns/exons junctions of the *MSH2* gene (Genebank UO4045) was performed after PCR amplification of genomic DNA. This showed a c.2026T > C transition which is predicted to result in replacement of a serine amino acid by a proline at position 676 (p.S676P) of the MSH2 protein. A serine has been particularly conserved during evolution at this position, from bacterial to human species. Furthermore, this amino-acid is located in the ATP-binding domain and its replacement by a

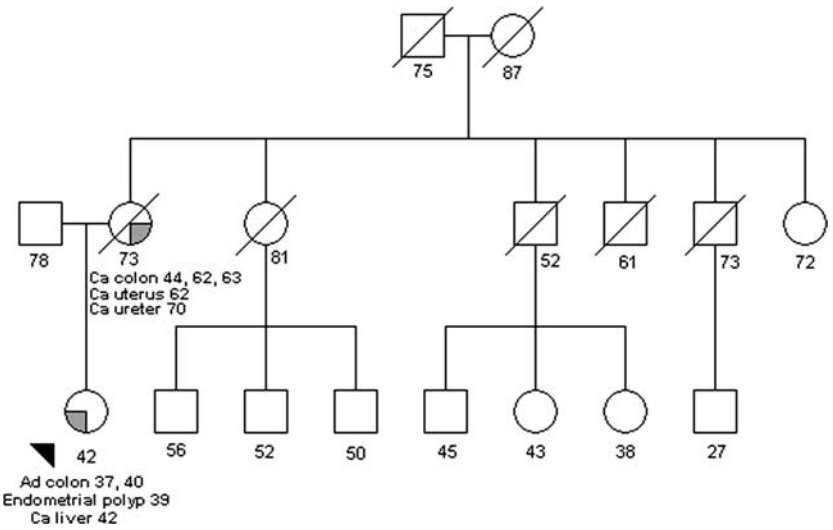

Fig. 2 Pedigree of the probant's family: Ca: carcinoma; Ad: adenoma

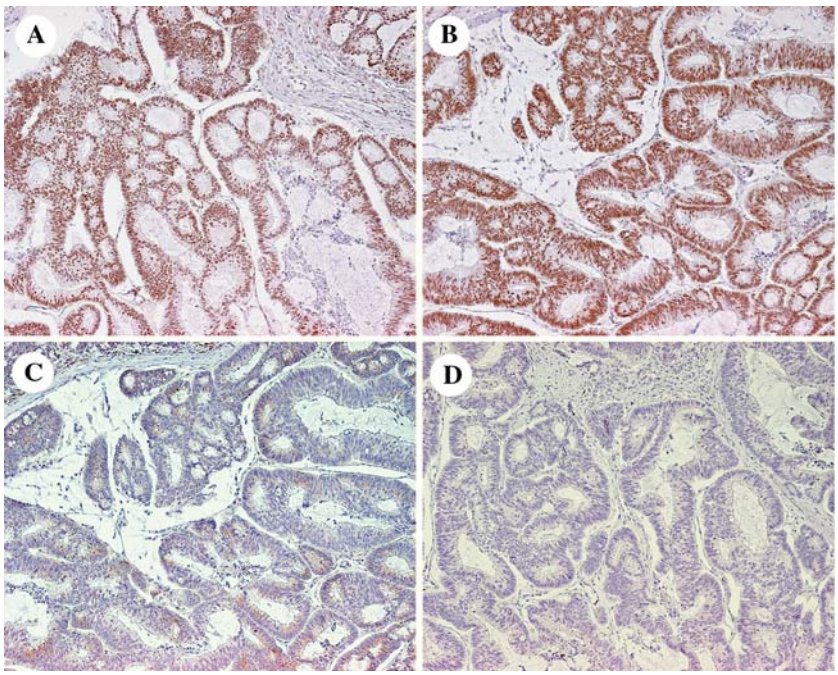

Fig. 3 Immunostaining of a hepatic cholangiocarcinoma showing normal expression of the MLH1 and PMS2 protein genes (**a**, **b**) and loss of expression of MSH2 and MSH6 protein genes (**c**, **d**)

proline is incompatible with an alpha-helix structure. Besides, the replacement of the lysine in the adjacent position 675 is clearly pathogenic [10]. Thus, the modification of the structure of the MSH2 protein containing the S676P alteration is predicted to impair the function of the gene. Nevertheless, formal confirmation of the pathogenicity can only be brought by functional studies. Analysis by Multiplex Ligation-dependent Probe Amplification (MLPA) did not show any *MSH2* anomaly. Besides, the *MSH2* gene has now been entirely screened for mutations in 157 patients suspected of HNPCC, residing in Switzerland. As the *MSH2* c.2026T > C change was not found among 314 chromosomes from these individuals, it is unlikely to be a variant present in the Swiss population. The absence of the MSH2 protein in the hepatic cholangiocarcinoma strongly supports its causative role in the development of this tumor.

Ten months after her initial admission, the patient was re-hospitalized because of persistent headache. CT-SCAN and MRI of the head reveals two brain metastases which were surgically resected and histologically assessed as metastasis of mucinous adenocarcinoma.

Discussion

MTS, a clinical variant of HNPCC syndrome, has rarely been associated with tumors of the biliary tree. Except the primary carcinoma of the ampulla of Vater originally described by Torre [2], to our knowledge no other case of biliary tumors has been reported in MTS [3, 8]. Considering the spectrum of tumors seen in the HNPCC syndrome, biliary tract is still a rare location, accounting for far less than 10% of all locations [11]. Mecklin et al. [12] reported 11 cases of tumors of the biliary tract or the papilla of Vater representing 4% of all tumors distribution among 315 patients in families with HNPCC. The sex distribution was 5 men and 6 women and the mean age was nearly the same for both sexes: 59 years. The location of the tumor was as follows: 1 intrahepatic, 6 common bile duct and 4 ampulla of Vater.

Sporadic cholangiocarcinomas account for 3% of all gastrointestinal cancers and 60–70% arise at the bifurcation of the hepatic ducts (Klatskin tumors) and 20–30% in the distal common bile duct. About 5–10% of cholangiocarcinomas are peripheral, arising within intrahepatic ducts of the liver parenchyma itself, and correspond to the second commonest hepatic tumor. Known risk factors account for only a few cases of cholangiocarcinomas and seem to be associated with chronic inflammation of the biliary epithelium (primary sclerosing cholangitis, parasitic infection, fibropolycystic liver disease, intrahepatic biliary stones, chemical carcinogen exposure and viral hepatitis) [13]. None of those conditions were found out in our reported case. More than 90% of cholangiocarcinomas are usual adenocarcinomas whereas the important mucinous production within the tumor is an uncommon finding in intrahepatic cholangiocarcinomas [14].

Here we report a case of mucinous cholangiocarcinoma in a background of MTS characterised by adenomas of the right colon, polyp of the endometrium, and sebaceous tumors. The possibility that the liver tumor was a metastasis has been considered. However, careful re-examination and re-sectioning of the two colonic adenomas did not show any sign of invasiveness. Moreover, a pre-operative endoscopy of the gastrointestinal tract did not reveal any additional tumor, exploration of the urogenital system, including a pelvic echography and breast examination were also negative. Thus, we consider that the lesion observed in the liver was a primary tumor. The case reported here is of particular interest because the tumors of the genital and digestive tracts were still benign, whilst the hepatic cholangiocarcinoma was very aggressive with development of cutaneous and cerebral metastases.

While the proportions of *MLH1* and *MSH2* mutations in HNPCC are almost equal, in MTS the vast majority of germline mutations were identified in *MSH2* [7]. Most of the pathogenic mutations identified in HNPCC are protein truncating mutations, but the transition c.2026T > C, which we identified in the *MSH2* gene in our MTS patient, is a missense mutation which has not been reported so far in HNPCC patients.

Summary

In conclusion, we report an unusual case of Muir-Torre syndrome, associated with primary mucinous cholangiocarcinoma of the liver, and we present evidence that a novel germline mutation of the *MSH2* gene is the underlying cause of this severe cancer.

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