Microsatellite Instability and Expression of hMLH-1 and hMSH-2 in Sebaceous Gland Carcinomas as Markers for Muir-Torre Syndrome

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ABSTRACT

Sebaceous gland carcinomas (SGCs) are rare malignant skin tumors occurring sporadically or as a phenotypic feature of the Muir-Torre syndrome (MTS). A subset of patients with MTS have a variant of the hereditary nonpolyposis colorectal cancer syndrome caused by mutations in mismatch repair (MMR) genes, which lead to microsatellite instability (MSI). We evaluated the value of MSI and loss of expression of the MMR genes, hMLH-1 and hMSH-2, as a marker to identify and distinguish MTS from sporadic SGC.

Using a nationwide pathology report database system, we identified patients with the MTS phenotype. SGCs from 10 MTS patients and the colorectal carcinomas from 3 additional MTS patients were collected. In addition, SGCs from eight patients without a history of visceral neoplasm were collected. MSI was detected in 9 of 13 MTS-associated tumors (69%) versus 0 of 8 sporadic SGCs (P = 0.002). Except for the age of onset of colorectal carcinoma [58 years in the MSI-positive group versus 69.8 years in the MSI-negative group (P = 0.17)], no differences were seen between the MSI-negative and the MSI-positive MTS patients. Loss of expression of hMLH-1 (n = 4) or hMSH-2 (n = 4) was found in MSI-positive patients only.

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.

INTRODUCTION

In 1967, Muir (1) and Torre (2) described independently a patient with both sebaceous gland tumors and intestinal malignancies. Since then, >150 patients have been reported with the MTS (3, 4).

MTS is defined as the presence of: (a) a sebaceous gland adenoma, epithelioma, or carcinoma; and (b) an internal malignancy. Internal malignancies that are most often seen in MTS patients are 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. Furthermore, breast, hematological, head and neck, and small intestinal malignancies have been described in combination with sebaceous gland tumors (3, 4). Also, the diagnosis MTS is appropriate for a patient with multiple KAs in combination with more than one visceral malignancy and a positive family history of the MTS (4). 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 (5).

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 MSI (7). Presently, defects in six genes have been described leading to the HNPCC phenotype: hMLH1, hMSH2, hPMS1, hPMS2, hMSH6, and the
transforming growth factor β type II receptor gene (8–10). Molecular genetic studies in MTS patients have shown MSI in both sebaceous gland tumors and CRC (11, 12). Also, MSI in KAs and actinic keratoses from MTS patients has been described (13–15). In contrast, the degree of MSI in sporadic KAs and other skin tumors, 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 tumors are available (13–16). 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 (17–19).

MTS is phenotypically distinguished from HNPCC by the presence of sebaceous gland tumors and/or KAs in patients with MTS. In MTS, 30% of the sebaceous gland tumors are SGCs. SGCs account for a minority of the 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 (20). SGCs usually occur in patients aged 60–80 years. In about 41% of MTS patients, a sebaceous gland tumor 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 tumor have a concurrent internal cancer or will develop an additional (internal) neoplasm (3). These data emphasize the importance of complete evaluation and close follow-up for gastrointestinal and genitourinary cancer in a patient with a sebaceous gland tumor when the diagnosis MTS is considered.

In 1996, a 61-year-old man with a SGC on the back (“index patient”) presented to our institution for evaluation. Investigation revealed that this patient had a history of intestinal malignancies. This index patient prompted us to address whether MSI can distinguish between patients with SGC as part of MTS and patients with sporadic SGC. In addition, IHC for the expression of proteins encoded by the MMR genes hMLH-1 and hMSH-2 was evaluated as a potential marker to distinguish between MTS and sporadic SGC.

MATERIALS AND METHODS

Index Case. The index patient was a white male who presented at age 61 with a SGC on the back. The tumor could be excised completely. The patient’s past medical history revealed a moderately differentiated adenocarcinoma of the cecum at age 36; a signet cell carcinoma in the transverse colon at age 41; a moderately differentiated adenocarcinoma in the rectum at age 59; and recently, a poorly differentiated medullary type adenocarcinoma in the remaining sigmoid. All carcinomas were surgically resected, and no lymph node metastases were detected. Two years after the diagnosis of the SGC, a poorly differentiated medullary type adenocarcinoma of the duodenum with lymph node metastases was diagnosed, and surgical resection was performed. The family history was positive for both SGC and CRC and met the Amsterdam criteria for HNPCC. All tumors were paraffin-embedded and formalin-fixed, and archival material was available.

Remaining Study Subjects. Additional cases with SGC were identified by searching the surgical pathology files from 1984 to 1997. Eight patients with SGCs were found. None of them had a history of intestinal or other visceral carcinomas. This group was considered to have sporadic SGC. Then, a nationwide search was done for patients with SGC and a history of one or more gastrointestinal carcinomas (fulfilling the criteria for MTS) using the PALGA system, a computerized database system of all pathology reports in the Netherlands. The PALGA system has nationwide coverage since 1992 and is considered complete. Pathology reports of 12 patients with a history of both intestinal tumors and SGCs, from whom tissue was available, were identified. Paraffin-embedded tissue from both SGC and CRC of three of these patients, tissue from only SGC of six of these patients, and tissue from only CRC of the three remaining patients were obtained. All tumors were reexamined by an experienced pathologist at our institution. Besides the date of birth, gender, and the date of the pathology report, no clinical data were available.

Tissue and DNA Preparation. Unstained sections of 5 μm were cut from paraffin-embedded tumor samples and microdissected. The microdissected tumorous tissue contained at least 75% neoplastic cells and was put in an Eppendorf tube containing protease K solution [100 μg/ml protease K, 50 mM Tris (pH 8.5), 0.2% Tween 20, 1 mM EDTA] to degenerate the proteins in the tissue. The samples were incubated overnight at 56°C and protease K was inactivated by heating the solution at 96°C for 10 min. This solution was used as a stock for PCR reactions.

MSI Analysis. MSI was analyzed using PCR markers as recently described by the Bethesda working group on HNPCC (21, 22). We used as primers BAT-25, BAT-26, BAT-40, D2S123, and D17S250. PCR was performed in 10-μl reactions using 25–50 ng of DNA, 1–3 mM MgCl₂, 175 μM dNTPs, and 5 pm of each primer. The forward primer was end-labeled with [γ-32P]ATP and 0.5 units of AmpliTaq Gold polymerase (Perkin-Elmer). Amplification consisted of 33 cycles (95°C for 30 s, 55°C for 60 s, 72°C for 2 min) after an initial step of 9 min at 95°C. After PCR, the samples were mixed with loading buffer (95% formamide, 20 mM EDTA, 0.05% bromophenol blue, 0.05% xylene cyanol), heat-denatured, and run on a 6% polyacrylamide, 7 M urea gel for 2–3 h at 2 kV. After the run, gels were vacuum-dried and autoradiographed overnight. Tumor samples were scored as unstable for a marker when new alleles were seen in the wild-type sample. Tumors were defined as MSI-positive if more than one marker showed shifts in length when compared with normal tissue (21, 22).

IHC for hMLH-1 and hMSH-2. Unstained 5-μm sections of the paraffin-embedded samples of the SGCs (n = 18) and CRCs (n = 3) were cut. Sections were dewaxed and rehydrated in xylene and a series of graded alcohol. Endogenous peroxidase activity was blocked in 0.3% H₂O₂ in methanol for 20 min. Slides were submerged in citrate buffer (0.01 M; pH 6.0) and heated in a temperature-probe-controlled microwave oven for 10 min at 100°C. After cooling for 20 min, 10% normal goat serum in PBS was applied for 20 min. The sections were subsequently incubated for 1 h at 37°C with the primary antibodies. A monoclonal mouse antihuman hMLH-1 (PharMingen International, CA) was used at a dilution of 1:20 in PBS.
monoclonal mouse anti-human hMSH-2 (Calbiochem, CA) was used at a dilution of 1:100 in PBS. After washing, biotinylated goat antipolyvalent antibody (Lab Vision Corporation, CA) in PBS (1:1) was applied for 15 min, followed by streptavidin peroxidase in PBS (1:1) for 15 min. The peroxidase activity was visualized using 3,3′-diaminobenzidine (1:20) in Tris-HCl, 0.05 M, with 0.1% H₂O₂ for 10 min. Counterstaining of the nuclei was done with hematoxylin. Adjacent normal tissue in each sample served as the positive control. The primary antibody was replaced by PBS as the negative control.

Stained slides were evaluated for the presence of expression of hMLH-1 or hMSH-2 in the tumor by two independent observers (G. J. A. O. and J. J. K.).

Statistics. Comparisons between groups were statistically evaluated using the Fisher’s exact test or Mann-Whitney U test, whichever was appropriate.

RESULTS

Including the index patient, tumor samples of 13 MTS patients and 8 sporadic SGC patients were collected. In the MTS group, the average age of onset of the first malignancy was 58.1 years (range, 34–77). The average age of onset of SGC in the MTS group was 65.3 years (range, 46–83) compared with 65.1 years (range, 16–83) in the sporadic group (Table 1). In three MTS patients, SGC followed an internal malignancy, but preceded or presented concomitantly with a (additional) visceral malignancy.

MSI. MSI was analyzed in 10 samples of SGC and 11 samples of CRC from 13 patients with the clinical diagnosis of MTS (index patient included). In three MTS patients, only CRC tissue was available. MSI was also determined in SGCs of eight patients without a history of internal malignancies, indicated as sporadic SGC.

In the MTS group, MSI was present in samples of 9 of 13 (69%) MTS patients (Table 1; Table 2). The average age of onset of gastrointestinal carcinoma in the MSI-positive group was 58 years (range, 36–76) compared to 69.8 years (range, 60–80) in the MSI-negative MTS patients (P = 0.17). In all four patients (patients 9, 12, 18, and 21) from whom SGC and CRC tissue was available, both tissue types showed a concordant MSI status. In the index case, all carcinomas showed MSI. In the sporadic SGCs, none of the samples showed MSI for any of the markers. The difference in MSI status between the MTS and sporadic groups was statistically significant (P = 0.002; Fisher’s exact test). When MSI was present (Fig. 1), BAT-40, BAT-26, and BAT-25 showed shifts in all samples (n = 9), marker D17S250 showed shifts in seven samples, and marker D2S123 showed shifts in eight samples.

Expression of MLH-1 and MSH-2. IHC for the expression of hMLH-1 and hMSH-2 was performed on all available SGCs from both the MTS group (n = 10) and the sporadic group (n = 8; Fig. 2). In addition, CRC tissue of three patients in the MTS group from whom no SGC tissue was available was used. All three CRCs that were used for IHC showed MSI.

In the MTS group, eight of nine tumors with MSI showed MMR deficiency: four samples showed loss of expression of hMLH-1; and four samples had loss of expression of hMSH-2. In one sample of CRC, IHC was inconclusive, presumably attributable to technical error. All MSI-negative SGCs from MTS patients (n = 4) showed expression of both hMLH-1 and hMSH-2. (Table 2). All sporadic SGCs also showed expression of both hMLH-1 and hMSH-2.

DISCUSSION

SGCs are rare skin tumors that can occur sporadically or as a characteristic phenotypic feature of MTS. MTS patients are prone to multiple malignancies throughout life, most commonly CRC, and require close surveillance (3, 4). Therefore, differentiation between patients with MTS and sporadic SGC has important ramifications. Clinically, MTS can be defined as the presence of an internal malignancy and a sebaceous gland tumor, which is SGC in 30% of the cases (3). In patients with a SGC and a history of CRC, the diagnosis of MTS is clear. However, in patients with SGC as the initial malignancy, the distinction between sporadic SGC and MTS cannot be made on clinical grounds, although a positive family history for SGC or CRC can be considered as indicative for MTS.

MSI is a phenotypic feature of HNPCC-associated tumors, and it has been described in MTS malignancies (11, 12). MSI occurs infrequently in most sporadic carcinomas, including skin cancer (7, 13–16). However, no MSI data for sporadic SGC are available. In our study, sporadic SGC did not show MSI. In contrast, malignancies from 9 of 13 (69%) MTS patients showed MSI. 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 tumors of patients with a germ-line

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Tumor site</th>
<th>Age</th>
<th>MSI status</th>
<th>hMLH-1/ hMSH-2</th>
</tr>
</thead>
<tbody>
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<td>Eye</td>
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<tr>
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<td>m</td>
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<tr>
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<td>m</td>
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<tr>
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<td>Back</td>
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<td>+/+</td>
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<tr>
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<td>+/+</td>
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<tr>
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<td>m</td>
<td>Eye</td>
<td>83</td>
<td>No MSI</td>
<td>+/+</td>
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<tr>
<td>8</td>
<td>m</td>
<td>Eye</td>
<td>71</td>
<td>No MSI</td>
<td>+/+</td>
</tr>
</tbody>
</table>

a Average age of onset is 65.1 years.
Table 2 Gender; site of sebaceous gland carcinoma (age of onset), other malignancies (age of onset), MSI status (number of shifts/number of markers used), and expression of hMLH-1 and hMSH-2 from patients with MTS

MSI status and expression of hMLH-1 and hMSH-2 were determined in SGCs, except for patients 15, 16, and 17, from whom only CRC samples were available. Nine of 13 patients showed MSI (69%); four patients did not show MSI (31%). Average onset age of primary tumors in the MSI positive cases was 57.7 years; average onset age of primary tumors in the MSI negative cases was 59.0 years.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Site SGC (age)</th>
<th>Site of other tumors (age)</th>
<th>MSI (shifts)</th>
<th>hMLH-1/hMSH-2</th>
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<td>9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>m</td>
<td>Back&lt;sup&gt;b&lt;/sup&gt; (61)</td>
<td>Cecum&lt;sup&gt;b&lt;/sup&gt; (36)/colon&lt;sup&gt;n&lt;/sup&gt; (41)/rectum&lt;sup&gt;b&lt;/sup&gt; (59)</td>
<td>MSI + (5/5)</td>
<td>−/+</td>
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<tr>
<td>10</td>
<td>m</td>
<td>Eye&lt;sup&gt;b&lt;/sup&gt; (46)</td>
<td>Colon (45)</td>
<td>MSI + (5/5)</td>
<td>−/+</td>
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<tr>
<td>11</td>
<td>m</td>
<td>Back&lt;sup&gt;b&lt;/sup&gt; (58)</td>
<td>Stomach (58)/bladder (57)</td>
<td>MSI + (4/5)</td>
<td>+/−</td>
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<tr>
<td>12</td>
<td>f</td>
<td>Back&lt;sup&gt;b&lt;/sup&gt; (69)</td>
<td>Colon&lt;sup&gt;b&lt;/sup&gt; (63)</td>
<td>MSI + (5/5)</td>
<td>−/+</td>
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<tr>
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<td>m</td>
<td>Front head&lt;sup&gt;b&lt;/sup&gt; (72)</td>
<td>Esophagus (70)/basal cell (72)</td>
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<td>+/−</td>
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<tr>
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<td>m</td>
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<td>Colon (74)</td>
<td>MSI + (4/5)</td>
<td>−/+</td>
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<td>m</td>
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<td>Colon&lt;sup&gt;b&lt;/sup&gt; (49)</td>
<td>MSI + (5/5)</td>
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<td>m</td>
<td>Face (61)</td>
<td>Colon&lt;sup&gt;b&lt;/sup&gt; (51)</td>
<td>MSI + (4/5)</td>
<td>NC&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>f</td>
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<td>MSI + (5/5)</td>
<td>−/+</td>
</tr>
<tr>
<td>18</td>
<td>f</td>
<td>Eye&lt;sup&gt;b&lt;/sup&gt; (59)</td>
<td>Cecum&lt;sup&gt;b&lt;/sup&gt; (60)/cervix (34)</td>
<td>No MSI</td>
<td>+/+</td>
</tr>
<tr>
<td>19</td>
<td>m</td>
<td>Eye&lt;sup&gt;b&lt;/sup&gt; (62)</td>
<td>Sigmoid (67)</td>
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<td>+/+</td>
</tr>
<tr>
<td>20</td>
<td>m</td>
<td>Face&lt;sup&gt;b&lt;/sup&gt; (74)</td>
<td>Cecum (72)/basal cell (63)</td>
<td>No MSI</td>
<td>+/+</td>
</tr>
<tr>
<td>21</td>
<td>m</td>
<td>Face&lt;sup&gt;b&lt;/sup&gt; (77)</td>
<td>Rectum&lt;sup&gt;b&lt;/sup&gt; (80)</td>
<td>No MSI</td>
<td>+/+</td>
</tr>
</tbody>
</table>

<sup>a</sup> Index case.

<sup>b</sup> Tumors from which available tissue was used for analysis.

<sup>c</sup> Immunohistochemistry inconclusive for expression of hMLH-1 and hMSH-2. Carcinoma stained negative for both hMLH-1 and hMSH-2. However, importantly, normal tissue also stained negative in both hMLH-1 and hMSH-2, indicating a technical error.

Fig. 1 Marker shifts attributable to MMR deficiency in a SGC from a patient with the MTS phenotype. We compared normal (N) to tumor (T) tissue. Markers D17S250 (A), BAT-25 (B), BAT-26 (C), and D2S123 (D) are displayed.

hMSH-6 mutation (23), or a MMR-independent pathway. Because SGCs are very rare (~0.2% of all skin malignancies are SGCs; Ref. 24), a coincidental occurrence with CRC in all MSI-negative MTS cases appears unlikely, although this possibility cannot be completely excluded.

Our results are in agreement with Honchel et al. (11), who reported MSI in 46% of carcinomas of MTS patients (compared to 69% in our study). These investigators also found longer survival, earlier age of onset of visceral malignancies, and higher numbers of internal malignancies in MSI-positive patients compared to the MSI-negative group. Based on clinical and genetic differences, Honchel et al. (11) suggested different subgroups of MTS patients, a concept supported by our data.

The data points to two variants of MTS: one sharing its pathophysiology and genetic cause with HNPCC, characterized by early age CRC and a strong family history of at least CRC; and a second, MSI-negative variant of MTS, with late onset cancer and a less pronounced family history. The molecular mechanism underlying the latter variant has still to be determined. In the study of Kruse et al. (17), MSI was found in all MTS patients, suggesting a 100% correlation between MTS and HNPCC. The 69% rate of MSI in our study could be related to different patient selection methods.

The association between HNPCC and MTS has been confirmed by studies showing germ-line mutations in the MMR genes, hMLH-1 and hMSH-2, in MTS patients. In our study, MSI-positive patients had loss of expression of hMLH-1 (n = 4) or hMSH-2 (n = 4), whereas all MSI-negative and sporadic SGC showed full expression of both. In one MSI-positive tumor sample, IHC was inconclusive, possibly attributable to fixation conditions. These results indicate that MSI and immunohistochemical loss of expression of hMLH-1 or hMSH-2 have the same value as the marker for MTS; with 100% specificity. Presently, only two MTS families with an hMLH-1 mutation have been described in the literature, compared to many reports linking MTS to a germ-line hMLH-1 mutation. However, no family history is available, and not all patients may be independent. Therefore, our findings concerning the occurrence of hMLH-1 or hMSH-2 mutations in MTS cannot be generalized.

In this investigation, MSI was only seen in those with a history of both SGC and intestinal carcinomas. But patients with apparently sporadic SGC could have MTS. Previous
studies show that 41% of the MTS patients have SGC as the initial malignancy; alone or concomitant with an internal neoplasm. Our study indicates that MSI or loss of expression of hMLH-1 or hMSH-2 in SGC predicts the presence of MTS. It is likely that the MSI status of other MTS-related skin tumors (such as sebaceous adenomas and sebaceous epitheliomas) might also predict the presence of MTS. Identification of MTS has important practical consequences (e.g., genetic follow-up and counseling) for the patient and family. Close follow-up of MTS patients is needed in both the MSI-positive and MSI-negative subgroups. Patients with an MSI-positive tumor or immunohistochemical loss of expression of one of the MMR genes should be offered MMR gene germ-line mutation analysis in a specialized center. Further studies are needed to identify the molecular mechanism leading to the MSI-negative variant of MTS.

Fig. 2  hMSH-2 and hMLH-1 immunohistochemical staining of CRC, SGC, and adjacent normal epithelium. Carcinoma is marked with c, and normal epithelium is marked with n. A and B, hMLH-1-negative CRC. A, adjacent normal epithelium shows full expression of hMLH-1. B, hMSH-2 is expressed in both CRC and normal tissue of the same sample. C, hMLH-1-negative SGC with positive staining of normal epithelium. D, hMSH-2 staining is positive in both SGC and normal epithelium. E, hMLH-1 expression is present in normal epithelium and SGC. MSH-2 expression is absent in the same SGC. F, there is positive hMSH-2 staining of adjacent normal epithelium.
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