

## COMMENTARY

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the “cancer family syndrome,” we contacted several of these authors to request additional information about their cases, specifically, whether any of their data were consistent with HNPCC. One of the authors, a dermatopathologist, kindly advised us about his patient with MTS cutaneous signs and visceral cancer who, after considerable discussion, had stated that she was a member of a very large extended family, namely, “Family G of Warthin,” which we were studying. This family has been under investigation for more than 100 years (Douglas *et al.*, 2005; Lynch and Krush, 1971; Warthin, 1913). As far as we are aware, this report provided the first description of MTS in HNPCC (Lynch *et al.*, 1981).

For more than 20 years, sebaceous skin tumors and keratoacanthomas have been known to be characteristic, albeit uncommon, features of HNPCC. Since the discovery that germline mutations in members of the mismatch repair (MMR) family of genes are responsible for HNPCC, a variety of related findings have made the central role of family history less critical to the clinical diagnosis of HNPCC. Important among these has been the recognition that the vast majority of tumors in HNPCC patients show evidence of microsatellite instability (MSI). In turn, MSI has been found to correlate very strongly with immunohistochemical (IHC) abnormalities, specifically loss of staining in tumors of those proteins corresponding to specific MMR genes. Initially, most of these correlations, both MSI and IHC, were identified in colorectal cancers. More recently it has been observed that many of the associated tumors also show MSI and loss of expression with MMR IHC staining. When the family history (for example, Amsterdam I or II Criteria, or Bethesda Guidelines; see Supplementary Table S1), clinical picture (early age at onset, right colon predominance), or histologic features (poor differentiation, extracellular mucin, tumor-infiltrating lymphocytes) are suggestive of HNPCC, performance of MSI testing or IHC is warranted. When informative, MSI and IHC can lead to effective germline mutation testing.

Ponti *et al.* (2006, this issue) describe a series of HNPCC families in which a small number of cases, about 1%, had

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## Sebaceous Skin Lesions as Clues to Hereditary Non-Polyposis Colorectal Cancer

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**Cutaneous lesions consonant with Muir–Torre syndrome strongly suggest hereditary non-polyposis colorectal cancer (HNPCC). Ponti *et al.* discuss the importance of combining molecular genetic features of the sebaceous neoplasms, including microsatellite instability and immunohistochemistry, with family history, to determine the likelihood of HNPCC. Proof of diagnosis is identification of one of the mismatch repair germline mutations.**

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The rarely occurring Muir–Torre syndrome (MTS) is a cancer-associated genodermatosis characterized by sebaceous adenomas, sebaceous carcinomas, and multiple keratoacanthomas in the presence of visceral cancers integral to hereditary non-polyposis colorectal cancer (HNPCC), also known as the Lynch syndrome. Muir *et al.* (1967) and Torre (1968) were the first to describe MTS, although they gave no mention

of the presence or absence of a family history. Subsequent reports of MTS involved patients with the above manifestations, but family histories were not routinely investigated.

Because of our interest in the pattern and natural history of multiple primary cancers identified in some of these published case reports, including carcinoma of the colorectum and endometrium and other HNPCC tumors, then known as

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characteristic MTS skin lesions. This is probably very conservative, as it was not shown that all evaluated subjects were, in fact, mutation carriers. In addition, it was noted that meticulous skin examinations were not performed on all subjects. Nevertheless, the key point was that in all of the characteristic skin lesions, MSI and IHC were informative. In another report by these authors (Ponti *et al.*, 2005), an algorithm was described by which sebaceous tumors would be subjected to MSI and IHC. Informative cases would then undergo mutational testing after family-history

### Sebaceous carcinomas are among tumors that should be tested for microsatellite instability

characterization. Subjects with microsatellite-stable tumors but with positive family history would be screened clinically for visceral tumors.

Importantly, a question to consider is whether, given the relative infrequency of such lesions, routine testing for MSI and IHC may be warranted for any sebaceous tumor or keratoacanthoma. If the issue were testing of colorectal cancer, a very common visceral malignancy, the answer would be that universal testing for MSI and IHC is not warranted. Population studies have shown that although about 15% of colorectal cancers show MSI, most do so because of somatically acquired hypermethylation of the MLH1 promoter and thus are not indicative of HNPCC (Hampel *et al.*, 2005). So in this setting, MSI and IHC point to the presence of HNPCC only when some additional clinical information is present (for example, when the Bethesda Guidelines are met; see Supplementary Table S1). But sebaceous skin tumors are sufficiently uncommon that it is unlikely that events such as hypermethylation of the MLH1 promoter would lead to a high rate of "false positives."

A second question deals with the utility of detailed family-history evalua-

tion in such patients. We have already mentioned that when the Bethesda Guidelines are met in a patient with colorectal cancer, the positive predictive value of MSI and IHC testing is much improved. How much the addition of clinical information such as positive family or personal history of visceral malignancy helps in patients with sebaceous skin tumors is less clear. Obviously a positive family history is helpful, but this really begs the question of whether any family history is needed to support MSI and IHC in the patient with sebaceous skin tumors.

Perhaps an analogy would prove helpful. Familial adenomatous polyposis (FAP), including its attenuated variant (AFAP), and HNPCC carry an increased risk of duodenal adenomas and cancer, tumors that are otherwise quite rare in the general population. If an endoscopist identifies a duodenal adenoma or cancer in a patient undergoing upper gastrointestinal endoscopy for any reason (for example, dyspepsia or heartburn), then colonoscopy is generally recommended, on the small chance that FAP, AFAP, or HNPCC may be present. The yield is generally not great in this setting. However, because so few patients have duodenal neoplasia, and because our threshold for recommending colonoscopy for any risk factor is low, the approach is not hard to rationalize. So the argument follows this line of reasoning for patients with sebaceous lesions: (1) sebaceous tumors are rare; (2) they are commonly associated with HNPCC; (3) MSI and IHC are informative at least 10% of the time, a reasonable cutoff for deciding to follow through with the appropriate laboratory assessment; (4) whether or not MSI and IHC are done or are informative, colonoscopy screening is warranted.

Lack of awareness of the MTS cutaneous findings may be the most important reason for underreporting of MTS. Ponti *et al.* (2006) clearly state that underestimation of MTS is probably due to the scarce importance assigned to research on the subject, with corresponding inattention to sebaceous gland tumors in personal and fam-

ily anamnestic surveys. These authors appropriately wish to include sebaceous carcinomas among tumors that should be tested for MSI (Umar *et al.*, 2004). They contend that these rare lesions should be carefully examined through these molecular tests even when they appear in individuals without evidence of visceral malignancy, a contention that we also support.

#### CONFLICT OF INTEREST

The authors state no conflict of interest.

#### SUPPLEMENTARY MATERIAL

**Table S1.** Amsterdam I and Amsterdam II Criteria and Bethesda Guidelines.

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