Editorial

Limitations of Dermatopathology: Muir-Torre Syndrome as an Example

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In the current state of the US economy and health care system, dermatologists need to be ever vigilant in ensuring that the tests we order are relevant to disease diagnosis, management, and/or treatment. Several articles in the literature have suggested that routine immunohistochemical staining of sebaceous neoplasms is an important screening tool for Muir-Torre syndrome.[1-3] Although immunohistochemistry can play a role in evaluating for Muir-Torre syndrome in certain situations, testing is not a requisite for the diagnosis of this disease; rather it is a clinical diagnosis based on the presence of at least 1 sebaceous neoplasm and a personal history of internal malignancy.[4] This definition of the syndrome obviates the need for immunohistochemical testing in patients who meet these 2 criteria; clinical history is sufficient in these cases.

Muir-Torre syndrome is sporadic or inherited in an autosomal-dominant fashion (sometimes a subset of Lynch syndrome).[5] In cases of autosomal-dominant inheritance, extensive screening (eg, colonoscopy beginning at 25 years of age, endometrial biopsy, renal ultrasonography) is recommended for patients and their family members.[6] Colon cancer and genitourinary cancers in particular are overrepresented. Notably, a family history of colon cancer in 2 or more relatives in a patient with 1 sebaceous neoplasm has a 92% sensitivity and 99% specificity for Muir-Torre syndrome.[4] The vast majority of cases of inherited Muir-Torre syndrome are secondary to mutations in the mismatch repair protein MSH2.[7]

Because internal malignancy often can be detected concurrently with or subsequently to (approximately 22% and 6% of cases, respectively) the identification of a sebaceous neoplasm,[8] immunohistochemistry or other ancillary tests can be useful in diagnosing these patients. In these scenarios, Muir-Torre syndrome, or even Lynch syndrome, are in the differential and should be ruled out. Suspicion for either syndrome should be heightened if certain clues are present, such as younger age (<50 years); a sebaceous neoplasm in a non–head and neck location; more than 1 sebaceous neoplasm; and histopathologic features that include tumor-infiltrating lymphocytes, peritumoral lymphocytes, cystic or keratoacanthoma-like architecture, and immunohistochemical loss of mismatch repair proteins.[9] Suspicion also should be increased if the patient has a strong family history of internal malignancy.[4]

The value of immunohistochemistry is limited by sensitivity and specificity for detecting Muir-Torre syndrome (85% and 48%, respectively). The positive predictive value for Muir-Torre syndrome when immunohistochemical loss of mismatch repair protein(s) is observed is only approximately 22%.[4] Forty percent of sebaceous neoplasms can show loss of mismatch repair protein staining in the absence of any syndrome.[10] Furthermore, some cases of sebaceous neoplasms arising in patients with Muir-Torre syndrome show retention of staining with mismatch repair proteins.[11] Therefore, immunohistochemical staining results are only data points that need to be evaluated in the context of the patient's presentation as a whole.

Thus it is important for clinicians rather than dermatopathologists to ultimately decide when to order immunohistochemical staining for mismatch repair proteins (or other mismatch repair testing). Dermatopathologists rarely have enough history to determine if a patient fulfills the clinical criteria for Muir-Torre syndrome. In patients who already fulfill the clinical criteria, immunohistochemistry may be a waste of resources. Additionally, it is important to keep in mind that as loss of MSH2 sometimes does correlate with genetic mutations in the mutS homolog 2 gene, *MSH2*, and is arguably a surrogate of genetic testing,[11] it is notable that some patients refuse genetic sequencing. Patients should receive proper counseling by their physicians before genetic studies are performed.

Dermatopathologists and dermatologists are key players in directing the proper sequence of events. In summary, immunohistochemical staining of all sebaceous neoplasms can be (too) easily performed; performing such staining should be limited by clinical correlation and discussion with the clinician.

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