Immunohistochemical Pitfalls

Common Mistakes in the Evaluation of Lynch Syndrome

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KEYWORDS

• Lynch syndrome • Immunohistochemistry • Pitfalls • Staining pattern

Key points

- A diagnostic algorithm for screening newly diagnosed colorectal cancer for Lynch syndrome is discussed.
- Usual staining patterns of mismatch repair protein immunohistochemistry are discussed.
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- Pitfalls in interpreting mismatch repair protein immunohistochemistry are discussed.

ABSTRACT

At least 15% of colorectal cancers diagnosed in the United States are deficient in mismatch repair mechanisms. Most of these are sporadic, but approximately 3% of colorectal cancers result from germline alterations in mismatch repair genes and represent Lynch syndrome. It is critical to identify patients with Lynch syndrome to institute appropriate screening and surveillance for patients and their families. Exclusion of Lynch syndrome in sporadic cases is equally important because it reduces anxiety for patients and prevents excessive spending on unnecessary surveillance. Immunohistochemistry is one of the most widely used screening tools for identifying patients with Lynch syndrome.

OVERVIEW

Lynch syndrome is the most common hereditary colorectal cancer syndrome; it accounts for approximately 3% of colorectal cancers and affects approximately 1 in 35 unselected patients with colorectal cancer.[1–3] Patients with Lynch syndrome carry a germline mutation in one of the mismatch repair genes (*MLH1*, *PMS2*, *MSH2*, *MSH6*) or an *EPCAM* mutation.[4] In the latter situation, germline deletion of the 3′ end of *EPCAM* silences *MSH2* from transcription; *EPCAM* is located just upstream to *MSH2*, and its inactivation leads to methylation and inactivation of *MSH2*. Patients with this genetic alteration have Lynch syndrome and loss of immunostaining for MSH2 and MSH6, as discussed later.

Patients with Lynch syndrome are at an increased risk for several other types of malignancy, including endometrial, gastric, ovarian, pancreas, ureter, renal pelvis, biliary tract, and brain tumors.[5] Universal screening of patients with colorectal carcinoma for Lynch syndrome is recommended by multiple sources, including Evaluation of Genomic Applications in Practice and Prevention,[6] National Comprehensive Cancer Network,[7] US Multi-Society Task Force,[8] the

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American College of Gastroenterology,[9] and the American Society of Clinical Oncology.[10] Screening for Lynch syndrome is cost-effective for the US health care system[11–13] and helps determine appropriate lifetime screening regimens for patients and their family members. Identification of microsatellite instability (MSI) is also important because cancers with MSI do not respond well to 5-fluorouracil[14] and may be more amenable to anti–programmed cell death 1 immunotherapy.[15]

Families are smaller than in the past; many patients undergo preventive colonoscopy with polypectomy, so family and personal history of cancer do not reliably detect all affected patients. In fact, approximately 50% of patients with Lynch syndrome are not detected by Amsterdam and Bethesda criteria.[2] Histologic features, including tumor-infiltrating lymphocytes, mucinous or high-grade features, and a Crohnlike peritumoral lymphocytic response, are suggestive of MSI but are not entirely sensitive or specific.

MISMATCH REPAIR PROTEIN IMMUNOHISTOCHEMISTRY AND MICROSATELLITE INSTABILITY

Analysis for MSI by polymerase chain reaction (PCR) and mismatch repair protein immunohistochemistry facilitates screening for mismatch repair deficiency, but each method has advantages and disadvantages.[16,17] If only one test is used, immunohistochemistry is preferred by most because it is more cost-effective and readily available than PCR and the results can be used to guide further testing of the germline. However, it is likely and may be true in some cases that decreasing costs of next-generation sequencing will reach the point at which the cost of analyzing multiple genes is comparable with that of single-gene testing. If this time comes, then solid tumor immunohistochemistry and MSI analysis may become largely obsolete for Lynch syndrome screening.

There is a high degree of concordance (>90%) between mismatch repair deficiency by immunohistochemistry and MSI,[2,18–20] although tumors with *MSH6* mutations may not show MSI, particularly if the Bethesda panel is used. Immunohistochemical stain results implicating deficient MSH2, MSH6, and PMS2 proteins generally suggest Lynch syndrome. However, results showing MLH1 deficiency are not specific for Lynch syndrome; most cases are sporadic and result from *MLH1* hypermethylation.[16,21] Tests for *BRAF* V600E mutations and *MLH1* methylation are used to identify these sporadic tumors, as shown in the algorithm later.

DIAGNOSTIC ALGORITHM FOR SCREENING NEWLY DIAGNOSED COLORECTAL CANCER FOR LYNCH SYNDROME

Multiple algorithms are available to screen for Lynch syndrome, but most are fairly similar. Loss of staining for one or more mismatch repair proteins indicates the need for additional testing. **Fig. 1** demonstrates the authors' algorithm:

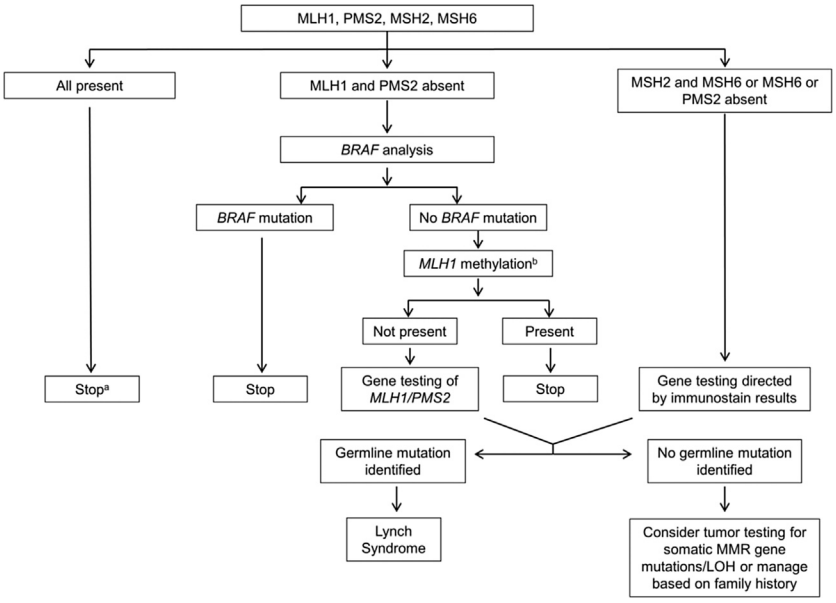

Fig. 1. Diagnostic algorithm for screening newly diagnosed colorectal cancer for Lynch syndrome. [a]Consider referral to genetics and MSI testing if concerning family history and age. [b]Consider gene testing rather than methylation if suspicious for Lynch syndrome by age or patient history LOH, Loss of heterozygosity.

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