MSI and IHC tumor testing for Lynch syndrome

This month’s posting focuses on the use of tumor analysis as a possible pathway to identifying cancer patients needing testing for Lynch syndrome.

**What is the role of MSI/IHC in testing for Lynch syndrome?**

While many patients are identified as appropriate for genetic testing for Lynch syndrome based on personal and/or family history, tumor analysis provides an additional means for identifying cancer patients at risk for Lynch syndrome. Microsatellite instability (MSI) and immunohistochemistry (IHC) are screening tests performed on tumor tissue; neither test is diagnostic for Lynch syndrome. If the tumor screen is abnormal, NCCN recommends that germline (constitutional) genetic testing for Lynch syndrome should be offered to the patient; either comprehensive testing for an MSI-high result, or gene-specific testing for one or more of the Lynch syndrome genes (MLH1, MSH2, MSH6, PMS2 or EPCAM) if IHC shows absence of staining.

**What are MSI and IHC tests?**

Lynch syndrome tumors tend to show variability in the lengths of repeated DNA sequences called microsatellites. This is a reflection of the underlying deficiency of “mismatch repair” that occurs in the presence of a mutation in one of the Lynch syndrome genes. The MSI test measures whether the microsatellite repeat sizes are stable (MSS) or unstable (MSI-high). IHC detects the presence or absence of the mismatch repair proteins in tumor tissue. Absence of staining for a particular protein suggests the possibility of a mutation in the gene producing that protein.

**What tissue can be used for MSI/IHC analysis?**

MSI and IHC are typically performed on colorectal or endometrial tumors, or advanced colorectal adenomas, obtained from biopsy or surgical resection.

**What are the advantages of MSI/IHC screening for Lynch syndrome?**

- 55-95% of Lynch syndrome-associated tumors exhibit microsatellite instability (MSI-high) or loss of staining on IHC, making the tests useful screens.\(^2\,^5\)
- MSI/IHC can be helpful when a patient with a high suspicion of Lynch syndrome has been found not to have a germline mutation, because an abnormal screen would suggest the presence of a mutation that is undetectable by current technology.\(^8\)
- Abnormal IHC screening can indicate which gene(s) to target for germline testing.

**What are the limitations of MSI/IHC screening for Lynch syndrome?**

- A tumor sample is not always available, for example, a patient who has not had cancer.
- False negative results are possible, for example, certain types of mutations are less likely to exhibit microsatellite instability or abnormal IHC staining.\(^3\)
- False positive results are possible, for example, approximately 15% of sporadic colorectal cancer will be microsatellite unstable, unrelated to Lynch syndrome.\(^3,^5\)
- The tests may not be possible on all biopsy samples, are less reliable on adenomas, and cannot be performed on irradiated rectal tumors.
- MSI testing is not available in most pathology labs.
- Technical artifacts and subjective interpretation impact the reliability of IHC.

**What is the role for “universal” screening of all colorectal tumors?**

In addition to the clinical evaluation of patients for family history, young age at cancer diagnosis, or multiple primary cancers, several groups have recommended universal screening of all colorectal tumors by MSI or IHC demonstrating it to be cost effective.\(^3\) The recent Jerusalem Workshop recommended screening all colorectal tumors at least under age 70.\(^4\) Limiting tumor analysis to patients who meet Bethesda or Amsterdam criteria misses 28% or 50% of Lynch syndrome cases respectively.\(^5\)
NCCN recommends that a patient whose tumor is identified as MSI-high or shows absent staining for one or more mismatch repair proteins on IHC should be offered germline genetic testing for Lynch syndrome. If MSI and IHC analyses are normal, then it is important to consider the patient’s age at diagnosis, personal history of additional cancers and family history when determining whether or not to proceed with germline testing and when planning medical management.

REFERENCES:

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