BT9

A Practical Method to Determine the Site of Unknown Primary in Metastatic Neuroendocrine Tumors

Jessica E. Maxwell MD, MBA[1], Scott K. Sherman, MD[1], Kristen M. Stashek, MD[2], Thomas M. O'Dorisio, MD[3], Andrew M. Bellizzi, MD[4], James R. Howe, MD[1]

[1]Department of Surgery, University of Iowa Carver College of Medicine, Iowa City, IA, 52242
[2]Department of Pathology, Hospital of the University of Pennsylvania, Philadelphia, PA, 19104
[3]Department of Medicine, University of Iowa Carver College of Medicine, Iowa City, IA, 52242
[4]Department of Pathology, University of Iowa Carver College of Medicine, Iowa City, IA, 52242

Background: The primary tumor site is unknown in approximately 20% of small bowel (SBNET) and pancreatic (PNET) neuroendocrine tumors despite optimal workup. Biopsies of PNET and SBNET metastases are histologically similar, yet knowing the primary site has important therapeutic and prognostic implications. We compared the utility of a three-marker immunohistochemistry (IHC) panel to our previously defined gene expression classifier (GEC) to determine the primary site of NET metastases.

Methods: RNA was extracted from 109 SBNET and PNET liver and lymph node metastases, and gene expression determined using qPCR. The GEC uses expression of *BRS3* and *OPRK1* in metastases to determine site of origin. The IHC algorithm uses CDX2, PAX6 and ISLET-1 to differentiate between tissues. It was evaluated in 86 primary SBNETs and PNETs and 37 metastases. NETs negative for all three markers were considered indeterminate. IHC was assessed by a pathologist blinded to the primary site, and results compared to those of the GEC.

Results: The GEC correctly identified the primary site in 76/78(97%) SBNET and 27/31(87%) PNET metastases. IHC correctly classified 83/86(97%) primary SBNETs and PNETs. In metastases, IHC called 33/37(89%) correctly, with 4 indeterminate. In the 27 metastases tested by both GEC and IHC, 26/27(96%) were correctly classified by GEC. IHC correctly classified 23/27(85%) samples, while the remaining 4 had "indeterminate" staining. All NETs missed by one method were correctly classified by the other.

Conclusion: Three-marker IHC is a simple and accurate initial test to determine the primary site from NET metastases. Although it made no incorrect classifications, 15% of metastases were indeterminate, necessitating a supplemental test. Our GEC demonstrates excellent overall accuracy (94%), and identified the primary tumor site in all cases where IHC failed. This suggests that performing IHC, followed by GEC for indeterminate cases, will identify the primary site of SBNET and PNET metastases in virtually all patients.