Evaluation of Carcinoma of Unknown Primary on Cytologic Specimens

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KEYWORDS

• Carcinoma • Unknown primary • Cytology • Immunohistochemistry • Molecular profiling

Key points

- Carcinoma of unknown primary is a distinct entity defined as metastatic carcinoma without a clinically obvious primary tumor.
- Determining the tissue of origin in patients diagnosed with carcinoma of unknown primary is important so site-directed therapy can be given, which may improve patient outcomes.
- Immunohistochemistry is the most widely used tool for the work-up of metastases, but molecular profiling assays are now also available for this purpose.
- This review provides an overview of helpful immunohistochemical stains used in the work-up of metastatic carcinoma, with a focus on newer site-specific markers, and discusses the role of gene expression profiling assays for determining tissue of origin.
- The utility of cytopathology specimens in the evaluation of carcinoma of unknown primary also is highlighted.

ABSTRACT

Carcinoma of unknown primary is defined as metastatic carcinoma without a clinically obvious primary tumor. Determining the tissue of origin in carcinoma of unknown primary is important for site-directed therapy. Immunohistochemistry is the most widely used tool for the work-up of metastases, but molecular profiling assays are also available. This review provides an overview of immunohistochemical stains in the work-up of metastatic carcinoma, with a focus on newer site-specific markers, and discusses the role of gene expression profiling assays for determining tissue of origin. The utility of cytopathology specimens in the evaluation of carcinoma of unknown primary also is highlighted.

OVERVIEW

Carcinoma of unknown primary (CUP) is defined as metastatic carcinoma without a clinically obvious primary tumor and is diagnosed only after a thorough clinical history and physical examination, imaging studies, and serum tumor marker analysis fail to elucidate a primary site.[1,2] CUP accounts for approximately 3% to 5% of all carcinomas,[1,3,4] and comprises a heterogeneous collection of tumors, including poorly differentiated carcinoma, adenocarcinoma, squamous cell carcinoma, and neuroendocrine carcinoma. Although a majority of patients with CUP have unfavorable outcomes and an aggressive clinical course, some clinically recognized subgroups of patients have more favorable outcomes, including women with isolated metastases to the axillary

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lymph nodes, patients with metastatic squamous cell carcinoma to neck lymph nodes, and men with bone metastasis and elevated prostate-specific antigen (PSA); these patients may be given locoregional treatment based on the most likely primary site.[1,4] Patients with unfavorable outcomes tend to have widely metastatic disease and adenocarcinoma histology[1,4,5] and are often treated with platinum-based combination chemotherapy.[6] In autopsy-based studies, a small, clinically undetectable primary is found in up to 73% of patients with CUP, mostly from the lung and pancreas.[7]

Key Points
Carcinoma of Unknown Primary

- CUP is a clinical entity defined as metastatic carcinoma without a clinically apparent primary site.
- Because therapeutic strategies are based primarily on site of origin and histologic features, pathologists have an important role in assigning a primary site in cases of CUP.
- Immunohistochemistry (IHC) is the most widely used and cost-effective method to evaluate CUP, but molecular profiling assays are also commercially available for determining site of origin.
- Even after IHC and/or molecular analysis, a primary site is not identified in a significant proportion of CUP cases.

Management of patients with carcinoma is dependent on the anatomic site and histologic classification of the tumor. Attempts by a pathologist to identify the site of origin in patients with CUP are made with the hopes that tumor site-specific therapy will be the best treatment of the patient; furthermore, on identifying a primary site, tumor-specific molecular testing can be performed to guide therapy (ie, personalized or targeted therapy). The clinical utility of assigning a primary site is based on the assumption that the CUP would behave as the assigned primary tumor, but it is not known if CUP has distinct biology from tumors of known primary origin or if outcomes in patients with CUP will improve from receiving site-specific therapy.[6] In a study by Hainsworth and colleagues,[8] patients with CUP who received anatomic site-directed therapy had longer median survival than patients given empiric CUP regimens.

IHC is the most widely used tool by pathologists to identify a likely primary site based on tumor expression of site-specific markers. In recent years, the utility of IHC has been bolstered by new lineage-specific transcription factors that have greater sensitivity and specificity than traditional cytoplasmic markers for identifying likely primary sites.[9] In addition, new gene expression profiling assays have been developed for identifying tissue of origin in patients with CUP; these assays have gained popularity with clinicians, although they are less familiar to the average practicing pathologist, despite their reportedly superior accuracy over IHC in identifying a primary site.[10,11]

From a pathologist's point of view, tumors that fall into the category of CUP are not always easy to recognize, and whether or not a tumor needs to be worked up extensively by IHC is not always clear. Pathologists may not be privy to all of the available clinical information; furthermore, the clinical work-up may be incomplete at the time of the initial biopsy. In many cases, limited IHC panels are used to confirm clinically suspected primary sites. It is not uncommon, however, for a pathologist to need to perform an extensive work-up; common scenarios include patients with widely metastatic disease and no obvious dominant mass, patients who have a history of more than 1 primary carcinoma, or patients in whom there is a remote history of carcinoma. Even after a thorough IHC work-up, a primary site is unable to be identified in up to a third of metastatic carcinomas.[12]

This review provides an overview and update of useful immunohistochemical stains for the work-up of CUP and discusses the current molecular approaches that are commercially available for identifying tissue of origin. The term CUP is used broadly to include situations where at least initially there is no clinically known primary, and the pathologist is asked to try to identify a primary site by morphology and IHC, while recognizing that "true" CUPs are often morphologically and immunohistochemically ambiguous. In addition, issues specific to cytopathology specimens are discussed, because these specimens are increasingly used in the work-up of these patients.

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Most of the data on the use of IHC are from the surgical pathology literature. Over the past few