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Editorial

Algorithmic approach of immunohistochemistry in metastatic carcinoma of unknown primary site

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ABSTRACT

Cancers of unknown primary site (CUPs) are histologically confirmed metastatic carcinoma for which primary site cannot be identified after standard diagnostic approach. It comprises 3-4% of all malignant neoplasms. The broad tumour type for CUPs is carcinoma. Metastatic tumours are more difficult to classify than primaries by Immunohistochemistry (IHC). Integration of morphology & IHC is the gold standard at diagnosing CUP. It is important to be aware of possible pitfalls of IHC and pay attention to correct interpretation. One should have a working algorithmic approach to identifying and classifying CUPs.

1. Introduction

Cancers of unknown primary site (CUPs) are histologically confirmed diverse group of metastatic cancers for which primary tumor site cannot be identified after extensive multidisciplinary investigations.[1] At present, along with IHC and molecular assay, genetic profiling is guiding the clinicians to diagnose and initiate individualised therapy to the patient with CUPs.[2] A step-wise histopathological diagnosis based on morphology followed by application of IHC is to exclude the treatable malignancy like lymphoma, sarcoma and melanoma and also to further confirm the diagnosis of carcinoma.[3] So the basic panel of IHC which include pancytokeratin, Vimentin, LCA, S-100, Melan-A and GFAP.[4]

Cytokeratins are intermediate filament proteins expressed in epithelial cells. There are around 54 functional keratin genes. Low molecular weight (LBW) keratins (CK8 and CK18) positivity is seen in adenocarcinoma and hepatocellular carcinoma. High molecular weight keratins (CK5 & CK14) are helpful to confirm squamous cell carcinoma and urothelial carcinoma. CK7 and CK20 have been most widely used to detect the primary site of the tumor. The CK7 is expressed by simple epithelia like lung pneumocytes and breast acinar epithelium. The CK20 is limited to the epithelium of the gastrointestinal tract, especially colorectum, the urothelial umbrella cells, and Merkel cells of the epidermis. This has been useful in the identification of the primary site of carcinomas. A broad-spectrum cytokeratin cocktail (AE1/3 and CAM 5.2), CK7, CK20 along with organ-specific markers should be used in the initial panel (Table 1).[3,5,6]

The sub-classification of carcinoma is gaining importance due to the recent advances in the targeted therapy. It is difficult to subclassify based on morphology on routine haematoxylin and eosin stained sections. At the same time, use of numerous markers in aiding the diagnosis can increase the burden on the patient. A wide range of carcinoma can be positive for CK7 and negative for CK20. A various number of organ-specific markers are available with varying sensitivity and specificity. In view of common site of origin of CUPs, the markers like TTF-1, GATA3, PAX8, WT1 can be used in CK7 positive carcinoma.[7] CK20 positivity can be seen in co; orectal

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Table 1: Distribution of cytokeratin 7 and 20 immunophenotype in various carcinoma

CK7+/CK20–	CK7+/CK20+	CK7–/CK20+	CK7–/CK20–
Breast carcinoma	Urothelial carcinoma	Colorectal adenocarcinoma	Prostate adenocarcinoma
Lung adenocarcinoma	Pancreatic adenocarcinoma	Merkel cell carcinoma	Renal (clear cells) Carcinoma
Endometrial Adenocarcinoma	Ovarian mucinous carcinoma	Gastric adenocarcinoma	Hepatocellular carcinoma
Endocervical Adenocarcinoma	Bladder adenocarcinoma		Adrenocortical carcinoma
Ovarian (serous) ca			Non-seminoma germ cell tumours
Cholangiocarcinoma	Gastric adenocarcinoma		Mesothelioma
Small cell lung ca	Cholangiocarcinoma		Small cell lung carcinoma
Mesothelioma			
Thyroid carcinoma			Gastric adenocarcinoma
Salivary gland tumours			
Kidney (papillary) Urothelial ca(subset)			
Pancreatic adenocarcinoma			
Gastric adenocarcinoma			

carcinoma which can be further confirmed by CDX-2.[8] The diffuse or focal CK7+ and CK20+ is seen in urinary bladder carcinoma, mucinous carcinoma of ovary and lung, pancreatic and intrahepatic cholangiocarcinoma, small intestinal carcinoma and NUT carcinoma.[9] Many of the CUPs can be CK7 and CK20 negative and few of the carcinoma which commonly present as both CK7 and CK20 negative are prostatic, renal, hepatic, adrenocortical and germ cell tumors.[5]

2. Conclusion

CUPs are the diverse group of metastatic carcinomas for which subclassification is difficult on morphology. Application of immunohistochemistry in a step-wise manner can help to detect the origin of tumor tissue. The sub-classification is very important in the era of targeted therapy which indeed can improve the survival rate of cancer patients. Immunohistochemistry is a composite diagnostic procedure, where each step is important for final results. Interpretation should be done after analysing the pitfalls, morphology and clinical information.

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