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Differentiating breast carcinoma with signet ring features from gastrointestinal signet ring carcinoma: assessment of immunohistochemical markers☆,☆☆

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Summary Signet ring morphology is recognized throughout the gastrointestinal tract. However, this pattern may be observed in other primary sites giving rise to diagnostic challenges in the work-up of metastases. Relatively newer immunohistochemical markers have not been evaluated in this context. We assessed expression patterns of several common immunohistochemical markers in tumors with Signet ring morphology to delineate a pragmatic approach to this differential diagnosis. Primary breast and gastrointestinal carcinomas showing Signet ring features were reviewed. Non-mammary and non-gastrointestinal tumors with this morphology were included for comparison. Estrogen receptor (ER), progesterone receptor (PR), E-cadherin, CK7, CK20, GCDFP-15, mammaglobin, CDX2, GATA-3, and HepPar-1 immunohistochemistry was performed. Expression patterns were compared between breast and gastrointestinal tumors as well as lobular breast and gastric tumors. Ninety-three cases were identified: 33 breast carcinomas including 13 lobular, 50 gastrointestinal tumors including 23 gastric, and 10 from other sites. ER (sensitivity=81.8%, specificity = 100%, positive predictive value (PPV) = 100%, negative predictive value (NPV) = 89.3%) and GATA-3 (sensitivity = 100%, specificity = 98%, PPV = 96.8%, NPV = 100%) expression were associated with breast origin. CK20 (sensitivity = 66.7%, specificity=93.3%, PPV = 94.1%, NPV = 63.6%) and CDX2 (sensitivity = 72%, specificity = 100%, PPV = 100%, NPV = 68.9%) demonstrated the strongest discriminatory value for gastrointestinal origin. These markers exhibited similar discriminatory characteristics when comparing lobular and gastric signet ring carcinomas. In a limited trial on metastatic breast and gastric cases, these markers successfully discriminated between breast and gastric primary sites in 15 of 16 cases. ER and GATA-3 are most supportive of mammary origin and constitute an effective panel for distinguishing primary breast from primary gastrointestinal Signet ring tumors when combined with CK20 and CDX2 immunohistochemistry.

1. Introduction

Tumors with Signet ring morphology are most commonly recognized throughout the gastrointestinal tract. This pattern has also been observed in adenocarcinomas arising from other sites such as the breast, lung, pancreaticobiliary tract, Mullerian tract, and other less common sites. In the breast, Signet ring carcinoma is not typically recognized as a specific entity

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although the morphology may give rise to diagnostic challenges in certain situations [1-3].

Breast carcinoma is recognized to metastasize to the stomach with clinical and pathologic features mimicking a gastric primary [4-6]. Presently, this diagnostic issue has been explored predominantly in the form of case reports in the literature [1,3]. In some instances, gastric metastases may be detected prior to identification of the breast primary [7]. Conversely, gastric primary Signet ring carcinomas have been reported to metastasize to the breast [8]. Tumors arising from both breast and the GI tract may metastasize to other similar locations [9]. For example, both lobular breast and gastric Signet ring carcinomas are recognized to cause peritoneal carcinomatosis and show similar patterns of infiltrative growth [10]. Given this overlap in locations and morphology, the distinction between these tumors is an important diagnostic challenge as the available management options depend on identification of the primary site.

Immunohistochemistry (IHC) is often utilized for determination of a suspected primary location. Markers such as CK20, CK7, and estrogen receptor (ER), have been employed in the differential diagnosis of signet ring tumors [11]. Chu and Weiss previously evaluated Signet ring carcinomas from the breast, stomach, and colon in a series of 60 cases for expression of a variety of markers. They found ER, MUC1 (EMA), hepatocyte paraffin 1 (HepPar-1), and CDX2 to be useful in distinguishing breast from gastric primaries while ER, CDX2, MUC2, and MUC5AC were useful for breast versus colonic primaries [12]. Relatively newer markers such as GATA-3 and mammaglobin have not been evaluated as part of a panel in this context.

We assessed staining patterns of several common immunohistochemical markers including ER, PR, E-cadherin, cytokeratin 7 (CK7), cytokeratin 20 (CK20), gross cystic disease fluid protein 15 (GCDFP-15), mammaglobin, CDX2, GATA-3, and HepPar-1 in the Signet ring component of tumors with known breast and gastric origin. We also compared expression to some tumors showing Signet ring morphology from extra-mammary and extra-gastrointestinal sites. Using our findings, we delineate a pragmatic immunohistochemical work-up for the distinction between these tumors.

Table 1 Characteristics of primary antibodies

Antibody	Source	Host and clone	Antigen retrieval buffer and parameters	Dilution	Detection method
CK7	Dako, Carpinteria, CA	Mouse monoclonal OV-TL 12/30	pH9 EDTA 97°C 30 min	Ready-to-Use	EnVision FLEX, Dako Omnis Autostainer
CK20	Dako	Mouse monoclonal Ks20.8	pH9 EDTA 97°C 30 min	Ready-to-Use	EnVision FLEX, Dako Omnis Autostainer
E-cadherin	Dako	Mouse monoclonal NCH-38	pH9 EDTA 97°C 30 min	Ready-to-Use	EnVision FLEX, Dako Omnis Autostainer
GCDFP-15	Dako	Mouse monoclonal 23A3	pH9 EDTA 97°C 30 min	Ready-to-Use	EnVision FLEX, Dako Omnis Autostainer
Mammaglobin	Cell Marque, Rocklin, CA	Mouse/Rabbit cocktail 304-1A5/31A	pH9 EDTA 97°C 30 min	1:100	EnVision FLEX, Dako Omnis Autostainer
ER	Ventana, Tucson, AZ	Rabbit monoclonal SP-1	pH9 EDTA 97°C 30 min	Ready-to-Use	EnVision FLEX, Dako Omnis Autostainer
PR	Ventana	Rabbit monoclonal 1E2	pH6 Citrate 97°C 30 min	Ready-to-Use	EnVision FLEX, Dako Omnis Autostainer
GATA-3	Biocare, Concord, CA	Mouse monoclonal L50-823	pH9 EDTA 97°C 30 min	1:250	EnVision FLEX, Dako Omnis Autostainer
CDX2	Dako	Mouse monoclonal DAK-CDX2	pH9 EDTA 97°C 30 min	Ready-to-Use	EnVision FLEX, Dako Omnis Autostainer
HepPar-1	Dako	Mouse monoclonal OCH1E5	pH9 EDTA 97°C 30 min	Ready-to-Use	EnVision FLEX, Dako Omnis Autostainer