

## Case Report

# Ck7 Negative, Ck20 Positive Gastric Cancer: More Common than you Might Think

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## Introduction

Metastatic carcinomas of unknown primary site are frequently encountered in clinical practice. Determination of the origin is often essential because accurate diagnosis is needed to devise the proper treatment and affects patient prognosis [1]. In addition to the use of clinical and histological data, the discovery and subsequent incorporation of cytokeratin immunohistochemical stains over the past decade have revolutionized the workflow and improved the diagnostic accuracy for metastatic diseases. Tumor phenotyping with cytokeratins 7 (CK7) and 20 (CK20) have been the single most useful diagnostic tool. The differential and concordant expression of these immunohistochemical markers have proved invaluable in determining the primary site from which a tumor originated.

In the work-up of metastatic carcinomas of probable gastrointestinal origin, many hold a common misconception that metastatic gastric adenocarcinomas have concordant positive expression of CK7 and CK20. Based on the observation of various cases received at this institution, we conclude that metastatic gastric adenocarcinomas do not exhibit CK7/20 concordant immunopattern. Rather, the expressions of these two markers are highly variable. As such, we present three cases that characterize the variable immunopattern expressed by metastatic gastric adenocarcinomas.

### Case 1

A 77 year-old woman with no reported medical history and minimal information in the electronic medical record system underwent an exploratory laparotomy for unknown reasons, and was found to have a peritoneal carcinomatosis. Biopsy of the pelvic side-wall revealed adenocarcinomas with signet-ring features. Immunohistochemical studies were performed and showed the malignant cells staining strongly and diffusely positive for CK20, negative for CK7 and TTF-1.

Prior to finalizing the diagnostic report with a suspected differential diagnosis of colon cancer based on the result of the immunohistochemical studies, the surgeon was contacted to obtain further information. The patient had been hospitalized at an outside institution for failure to thrive, weakness, nausea, vomiting, weight loss, and mid-epigastria pain. A subsequent abdominal CT image showed thickening of the gastric wall, and endoscopy revealed a large circumferential mass, involving two-thirds of the stomach, sparing the

antrum and duodenum. Biopsy (performed at the outside institution) of this lesion revealed poorly differentiated, signet-ring type adenocarcinomas of the stomach. Positron Emission Tomography (PET) scan revealed no other mass lesions. Given the clinical history and histomorphology of the tumor, metastatic adenocarcinomas from a gastric primary were favored.

### Case 2

A 39 year-old woman with no significant medical history presented with rapid abdominal distention and associated abdominal discomfort. She endorsed a three-year history of intermittent abdominal discomfort, which gradually progressed to a persistent feeling of having a “mango ball” in the right lower quadrant, and a 15-pound weight loss over the three months leading up to admission. An abdominal CT image demonstrated enlarged bilateral ovarian lesions with ascites, mesenteric and retroperitoneal lymphadenopathy, raising suspicion for peritoneal carcinomatosis with primary ovarian tumor versus Krukenberg metastasis. Multiple bilateral pulmonary nodules (<5 mm) were found on chest CT image. The patient subsequently underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy. The left and right ovaries revealed partially signet-ring type adenocarcinomas. The tumor cells were positive for CK7, CK20, CDX2, and CA19-9; negative for CA-125, chromogranin, CD56, inhibin and SMA. This finding favored metastatic adenocarcinomas from a gastrointestinal primary such as stomach or colon.

### Case 3

A 48 year-old man with chronic hepatitis C virus infection and alcohol abuse presented with a six-month history of progressive dysphasia, and unintentional weight loss of 50 pounds. An initial abdominal CT image showed cirrhosis with no focal lesions, and a 4.2 cm anterior abdominal wall mass. Endoscopic evaluation of the upper gastrointestinal tract revealed a friable, irregular, ulcerated mass, extending from the Gastro Esophageal junction (GEJ) along the lesser curvature of the stomach. In addition, the study detected a previously unknown astral nodule with a centrally umbilicated ulcer. Colonoscopy showed large, ulcerated masses at hepatic and splenic flexures. The findings were suggestive of metastatic cancer arising from the stomach or colon. Biopsies of the masses at the GEJ, antrum, and hepatic flexure all revealed poorly differentiated adenocarcinomas with signet-ring features. Immunohistochemical studies showed the tumor cells to be strongly and diffusely positive for CK20 and negative for CK7. In addition, CK20-positive, CK7-negative intestinal metaplasia with associated dysplasia was noted in the biopsy of the astral lesion.

The three described cases highlight important but often overlooked concepts in the practice of surgical pathology:

1. Immunopattern are variable, and many cases often deviate from the expected “classic” staining patterns

2. Any question regarding a patient's medical history must be addressed by contacting the clinician. Patient care is of utmost importance – discussion among all physicians involved in a patient's care including the pathologist should be encouraged.

3. Do not forget that CK7- CK20+ gastric carcinomas are just as common as CK7+ CK20- ones.

## Discussion

Cytokeratins are proteins that comprise the intermediate filaments of cytoskeleton. These proteins are considered markers of epithelial differentiation with specific expression in both normal and tumor tissues. [2]. Gastric adenocarcinomas can present as either an intestinal-type or diffuse-type (signet-ring cell carcinoma), with similar immunohistochemical staining patterns. Gastric adenocarcinomas stain diffusely and strongly with many cytokeratins including AE1/AE3, CAM 5.2, CK18, and CK19.1 CK7 is absent in normal gastric mucosa but expression is observed with chronic mucosal irritation and the majority of gastric adenocarcinomas, with up to 50% of tumors staining strongly positive in a diffuse or patchy pattern. However, 20% of gastric adenocarcinomas stain weakly positive or negative for CK7. CK20 is normally expressed only by foveolar cells of the superficial gastric epithelium as well as 40% of gastric adenocarcinomas. 20% of gastric adenocarcinomas stain weakly positive and 40% are negative for CK20 [4,3].

Adenocarcinomas of non-gastric origin e.g. colon and breast, usually express a uniformly concordant staining pattern between CK7 and CK20. In contrast, gastric adenocarcinomas, regardless of the subtype, often show heterogeneous CK7/20 staining patterns. CK7+/

CK20- and CK7+/CK20+ immunopattern are more common than CK7-/CK20+ and CK7-/CK20- (suggestive of undifferentiating). This particular finding may be secondary to the lack of definitive threshold at which staining is classified as positive or negative [4,3].

The three described cases of gastric adenocarcinomas demonstrate that, unlike other adenocarcinomas of the gastrointestinal origin that demonstrate a more concordant CK7/20 staining pattern, immunohistochemical studies with CK7 and CK20 should not be the sole method for characterizing suspected primary and metastatic gastric adenocarcinomas, especially with the signet-ring cell type. Clinical and histopathological correlation is crucial for making an accurate diagnosis. Should there be any confusion or doubt, especially when minimal or no clinical history is available, the clinician must be contacted to serve in the best interest of the patient.

## References

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