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Case Report

Invasive Micropapillary Carcinoma of the Sigmoid Colon: Distinct Morphology and Aggressive Behavior

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Abstract: We report a case of invasive micropapillary carcinoma of the sigmoid colon in a 72-year-old female with anemia and abdominal pain. Grossly, the tumor demonstrated a deeply invasive, ulcerated fungating mass. Microscopically, the carcinoma was predominantly composed of micropapillae with reversed cell polarity, abundant neutrophils, and surrounded by clear spaces. Multifocal lymphovascular invasion was present with extensive lymph node metastasis. Immunohistochemically, the carcinoma cells were positive for CDX2, CK20 and monoclonal carcinoembryonic antigen. They were negative for CK7. The stroma-facing surface of the micropapillae was positive for CD10 and villin, confirming the inside-out growth pattern characteristic of micropapillary carcinoma. Work-up for distance metastasis was negative. The patient was alive and well 1.5 years after sigmoidectomy and postoperative chemotherapy.
Key Words: Adenocarcinoma, micropapillary, invasive, metastasis, colon

Introduction

Invasive micropapillary carcinoma (IMPC) has been recently recognized as a rare but distinctive variant of adenocarcinoma in several anatomic sites, including breast [1, 2] , urinary bladder [3], lung [4], the major salivary glands [5] and pancreas [6]. Morphologically, it is characterized by small, tight round to oval clusters of neoplastic cells surrounded by clear spaces resembling lymphatic channels. However, vigorous immunohistochemical staining for endothelial or lymphatic markers has been negative [1, 3]. The micropapillary pattern is usually maintained in the lymphovascular invasion and lymph node metastases. In most cases, there is a variable component of conventional carcinoma. Patients with IMPC usually present with higher-stage disease with extensive lymphovascular and lymph node metastases, and have a poorer clinical outcome compared to those with conventional carcinoma arising in the same organ site [7]. Here we report a case of IMPC of the sigmoid colon with immuno-histochemical studies. To the best of our knowledge, there has been only one report on IMPC of the colon in the English literature [8].

Case History

A 72-year-old woman presented to a regional hospital with anemia and abdominal pain. Colorectal endoscopic examination revealed a 3.5 cm fungating mass in the sigmoid colon. Whole body positron emission tomography (PET) and computerized tomography (CT) scans were negative for metastatic disease. No family history of colon cancer was reported. Past medical and surgical history was unremarkable. She underwent sigmoidectomy. Postoperatively, she was treated with 5-fluorouracil (5-FU), oxaliplatin and leucovorin. After a total of 14 months of chemotherapy, repeat MRI and PET scans showed no evidence of metastatic disease. However, the patient had slightly elevated serum carcino-embryonic antigen (CEA) at 40 ng/mL. Patient was alive and well one and a half years after surgery.

Pathologic and Immunohistochemical Findings

In the 11-cm segment of sigmoid colon, an ulcerated fungating mass measuring 3.5 x 1.3 x 1.0 cm was found. The tumor invaded through the muscularis propria into subserosal

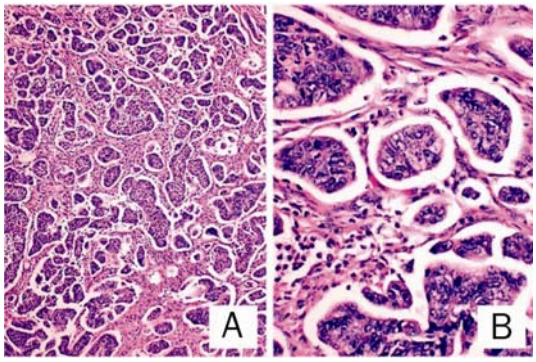

Figure 1 The neoplastic cells form micropapillae with reserved polarity without central fibrovascular core. **A**. Low magnification showing micropapillae, singly or in small groups, surrounded by lacular-like clear spaces (H&E, x200). **B**. High magnification showing reserved polarity with smooth terminal bar-like surface of the microvilli facing the lacunar-like spaces (H&E, x400).

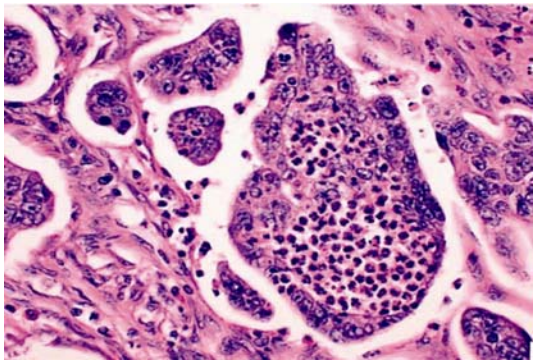

Figure 2 Collections of neutrophils infiltrating the micropapillae and occasionally spilling into the lacunar-like spaces, mimicking microabscess (H&E, x400). Overt "dirty necrosis" is not seen.

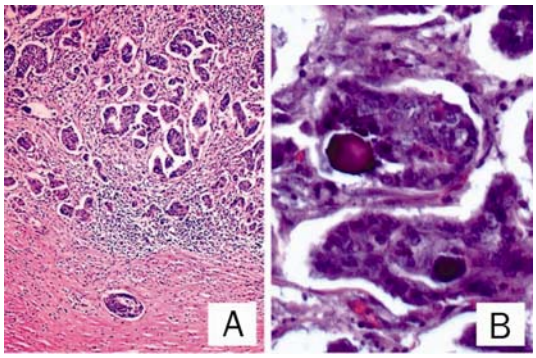

Figure 3 Metastatic carcinoma with micropapillae (**A**, H&E, x200) and psammoma bodies (**B**, H&E, x400) in a lymph node.

adipose tissue and had negative resection margins. Microscopically, it was predominantly composed of tumor cells forming micropapillae surrounded by lacunar-like clear spaces. One or several micropapillae found in each space (**Figure 1A**). No fibrovascular core was noted in the micropapillae. The tumor cells were columnar, oval, or round with moderate amphophilic cytoplasm, vesicular nuclei with conspicuous nucleoli. Unlike conventional colorectal carcinoma, the micropapillae had terminal bar-like surface facing the stroma or lacunar-like spaces (**Figure 1B**). Furthermore, abundant neutrophils were frequently found mainly within and occasionally surrounding the micropapillae, forming microabscess but not "dirty necrosis" that is typically associated with conventional colorectal carcinoma (**Figures 2A** and **2B**). No mucin production or peritumoral Crohn-like reaction was noted. Fourteen of 15 mesenteric lymph nodes were positive for metastasis, 11 of which maintained micropapillary morphology and four had conventional colonic adenocarcinoma. Interestingly, psammoma bodies were occasionally found in the lymph nodes with metastatic carcinoma (**Figures 3A** and **3B**) but absent in the primary site. Immunohistochemically, as in conventional colorectal carcinoma, the tumor cells were positive for CDX2, CK20, monoclonal CEA, CD10, and villin; and negative for CK7. Furthermore, reversed polarity was demonstrated by positive CD10 and villin immunostaining on the stroma-facing surfaces of the micropapillae (**Figures 4A** and **4B**). CD31 immunohistochemical staining showed no positive endothelial lining in the lacunar-like clear spaces but positive in true lymphovascular invasion (**Figures 5A** and **5B**). To test if this tumor displayed microsatellite instability, immunohistochemical stains for the mismatch repair proteins (MLH1, MSH2, MSH6 and PMS2) were performed. The tumor cells were positive for all the four markers tested (**Figures 6A** and **6B** showed MLH1 and MSH2 immunostaining results, respectively; MSH6 and PMS2 data not shown).

Discussion

IMPC has been described in breast, urinary bladder, lung, and salivary gland tissues [7]. The incidence of breast IMPC varies from 0.9% (in pure form) to 7% (mixed with other types of breast carcinoma) [9-10]. Breast IMPC tends to have higher percentage of estrogen,

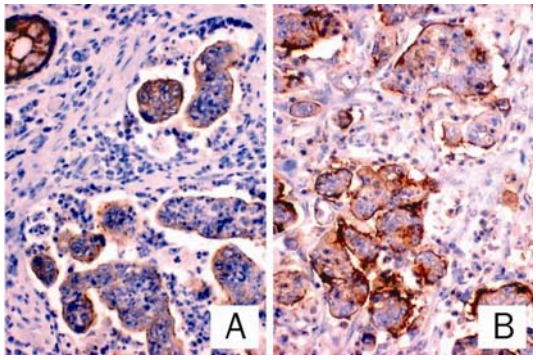

Figure 4 Reversed polarity of the micropapillae demonstrated by immunostaining for villin (**A**) and CD10 (**B**) (original magnification x 100).

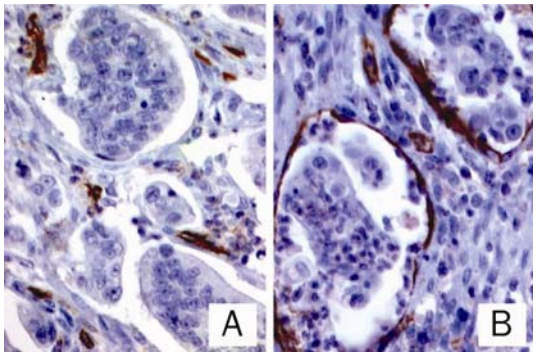

Figure 5 Negative CD31 mmunostaining of the lacunar-like spaces with tumor micropapillae (**A**, x400) but positive immunostaining of the lymphovascular channels with metastatic tumor (**B**, x400).

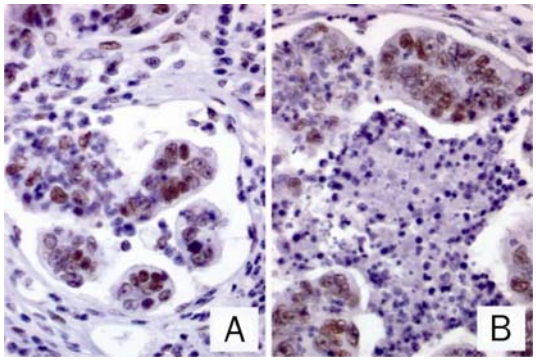

Figure 6 Positive nuclear staining of the tumor cells for MLH1 (**A**) and MSH2 (**B**) (original magnification, x 400)

progesterone and *Her2/neu* oncoprotein positivity, higher expression of p53 and N-cadherin, high lymph node metastasis and high local recurrence, which may explain its aggressiveness of this tumor [10-13]. The IMPC is a special type of adenocarcinoma with characteristic morphologic features and poorer prognosis regardless of anatomic location. The neoplastic cells form small tight round to oval clusters that are surrounded by clear spaces and are devoid of fibrovascular cores. All IMPCs have a typical inside-out growth pattern with reversed polarity where the stromal-facing (basal) surface of the tumor cells acquire apical secretory properties as demonstrated by MUC1 imunohistochemical staining on the surface [6] and electron microscopic examination revealing microvilli at the surface of the cells facing stroma [2]. An earlier study showed that the clear spaces represent tissue retraction that is not seen in frozen sections [8]. However, the reversed polarity with apical properties on the stromal-facing surfaces may also contribute to the clear spaces around the tumor cell nests [6]. Although IMPC of different anatomic sites shares histomorphology, the site-specific immunohistochemical profile is still maintained, which is helpful to determine the primary of metastatic IMPC [14]. Our case is among the first reported cases of IMPC variant of the colorectal adenocarcinoma in the literature. The histomorphological and immunostaining pattern all supports that this is a true invasive micropapillary carcinoma of the colorectal origin. The inside-out growth pattern or reversed polarity of the micropapillae was demonstrated by polarized positive CD10 and villin immunostaining on the stroma-facing surfaces of the micro-papillae. The component of conventional colorectal carcinoma and typical immuno-phenotype (i.e., positive CK20, CDX2, and villin; negative CK7) support a colorectal primary for the carcinoma. In addition, as reported in IMPC of other sites, CD31 immunohistochemical staining demonstrated the lacunar-like spaces were negative for endothelial lining and confirmed widespread lymphovascular invasion. However, unlike previous reports on IMPC, our case uniquely showed abundant neutrophils within and around micropapillae. We believe that this is analogous to “dirty necrosis” characteristically associated with colorectal carcinoma. However, in the micropapillae the neutrophilic infiltrate manifested more like microabscesses rather than “dirty necrosis”.

In summary, our case is among the first reported cases of invasive micropapillary carcinoma of the colorectal adenocarcinoma in the literature. It is a rare but distinct variant

of adenocarcinoma that shares histologic and immunohistochemical features of IMPC in other documented sites. Also as in other sites, it has high rate of lymphovascular invasion and presented at high stage (multiple positive lymph nodes), but large series study of colorectal IMPC is needed to further characterize if this entity has poorer prognosis compared to conventional colonic adenocarcinoma.

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