



Primary Gastric Invasive Micropapillary Carcinoma: A Case Report

Primer Mide İnvaziv Mikropapiller Karsinomu: Olgu Sunumu

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ABSTRACT

Invasive micropapillary carcinoma is a recently identified neoplasm. A 77-year-old-female was admitted to the hospital due to progressive loss of weight and nausea. Endoscopic biopsy of the antral/prepyloric located mass was diagnosed as moderately differentiated adenocarcinoma. Subtotal gastrectomy and regional lymph node resection were performed. The tumor was composed of moderately differentiated cells arranged in micropapillary structures with only a few poorly formed glandular foci in lamina propria. Immunohistochemically, neoplastic cells of micropapillary and focal conventional adenocarcinoma areas were diffusely positive for pancytokeratin, cytokeratin 7 and epithelial membrane antigen. In micropapillary areas, membranous and peripheral cytoplasmic positivity with epithelial membrane antigen in outside of the cell clusters called "inside-out polarity" pattern that is characteristic for invasive micropapillary carcinoma were seen. Invasive micropapillary carcinoma is very rare in the stomach in the English literature.

Key Words: Stomach neoplasms, Gastrointestinal neoplasms, Papillary carcinoma

ÖZ

İnvaziv mikropapiller karsinom yeni tanımlanan bir tümördür. Progressif kilo kaybı ve bulantı nedeniyle hastaneye yatırılan 77 yaşındaki kadın hastanın endoskopik biyopsisinde antral/prepilorik yerleşimli, orta derecede diferansiye adenokarsinom saptandı. Sonrasında subtotal gastrektomi ve lenf düğümü rezeksiyonu yapıldı. Tümör, orta derecede diferansiye hücrelerin oluşturduğu mikropapiller ve az sayıda glandüler yapılardan oluşmaktaydı. İmmunohistokimyasal olarak mikropapiller ve glandüler alanlarda pansitokeratin, sitokeratin 7 ve epitelyal membran antijen pozitifliği. Mikropapiller alanlarda, hücre kümelerinin çevresinde periferik lokalizasyonda epitelyal membran antijen ile invaziv mikropapiller karsinom için karakteristik membranöz, sitoplazmik pozitiflik saptandı. Literatürde mide yerleşimli invaziv mikropapiller karsinom oldukça nadirdir.

Anahtar Sözcükler: Mide neoplazileri, Gastrointestinal neoplaziler, Papiller karsinom

INTRODUCTION

Invasive micropapillary carcinoma (IMPC) has been recently identified as a characteristic variant of carcinoma composed of small clusters of tumor cells located within clear spaces (1-8). Initially, it was described as an architecturally different variant of invasive breast carcinoma (2). In addition to highly interesting histological and immunohistochemical features, this type of tumor has a poor clinical prognosis due to the unique high incidence of lymphatic invasion and axillary lymph node metastases (2). This entity has been reported in various sites other than breast, including urinary bladder, lung, colon and major salivary glands (3-6). IMPC of the bladder more often appears in combination with conventional carcinoma rather than a pure histological component (3). Herein

we report a case of gastric IMPC, rarely reported in the literature previously.

CASE REPORT

A 77-years-old-female who had been followed up for hypertension and coronary arterial disease in outpatient clinic for ten years, was admitted to hospital with the complaints of nausea and loss of weight. In the gastric endoscopy, an antral/prepyloric, ulcerated mass, 5 cm in largest diameter has been observed and biopsied. Endoscopic biopsy was diagnosed as moderately differentiated adenocarcinoma. Among the tumor markers, only carcinoembryonic antigen (CEA) was increased (CEA:39.26 mg/dl., normal value: <2.5 mg/dl.). Upper abdominal and pelvic ultrasonography (US) and

(Türk Patoloji Derg 2015, 31:219-222)

Received : 18.11.2011 Accepted : 06.02.2012

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thorax computerized tomography revealed no metastatic lesion, preoperatively. Distal subtotal gastrectomy and regional lymph node resection were performed. Adjuvant chemotherapy were planned due to the presence of residual tumor in peritoneum, but could not be applied due to advanced age and cardiac problems. The patient is being followed up by US and CEA levels for eight months.

Macroscopically, the 5 cm ulcerated tumor was located in the antral and pyloric transition region with an irregular border. Microscopically, it was composed of moderate to severe cytological atypical carcinoma cells, arranged in micropapillary structures. In superficial areas of ulcerated

mass, transition from classical adenocarcinoma to IMPC areas were seen abruptly (Figure 1). However over 90% of the tumor was composed of micropapillary structures (Figure 2) except for several foci of poorly differentiated adenocarcinoma. Neoplastic cells invaded the muscularis propria and subserosal adipose tissue and also foci of lymphatic invasion were observed. Two of two lymph nodes along the greater curvature, and six of nine lymph nodes along the lesser curvature revealed metastases composed of a mixture of micropapillary and conventional adenocarcinoma morphologically contrary to primary tumor (Figure 3).

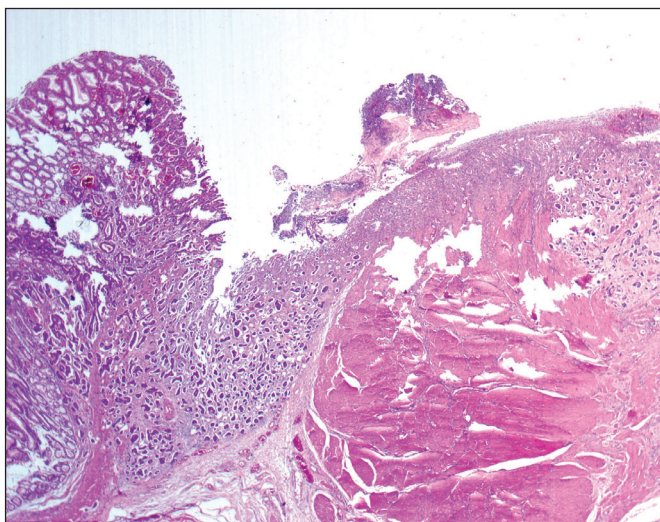


Figure 1: Ulcerated surface, submucosal and muscularis propria invasion were seen in adjacent to normal gastric glandular epithelium (H&E; x20).

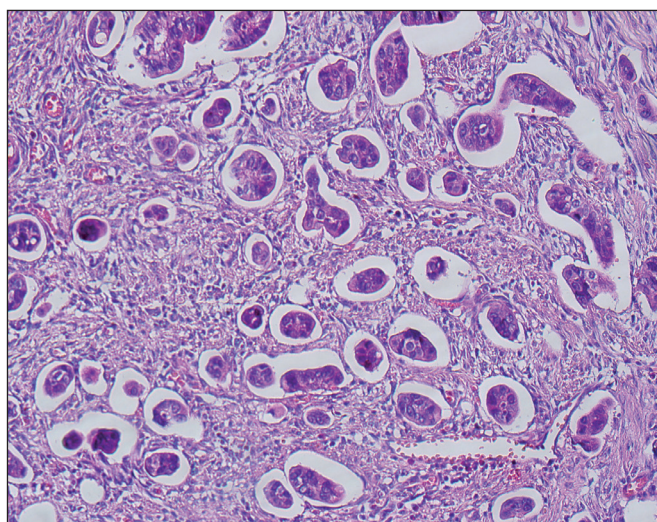


Figure 2: High-power view showing micropapillary small clusters of neoplastic cells lying within clear spaces. (H&E; x200).

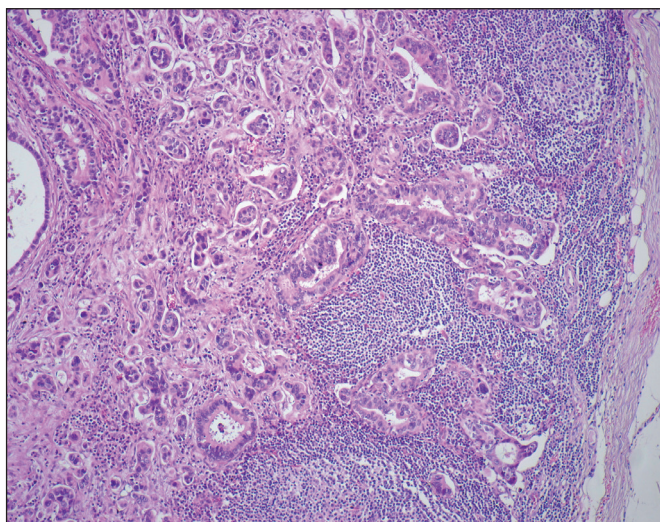


Figure 3: Mixture of classical adenocarcinoma and micropapillary carcinoma areas in metastatic lymph node (H&E; x100).

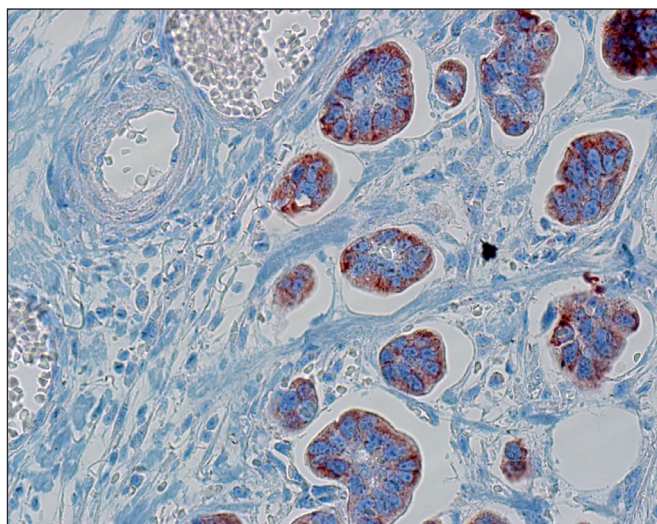


Figure 4: Characteristic inside-out polarity staining pattern were seen in immunohistochemistry for epithelial membrane antigen (EMA; x400).

Table I: Primary antibodies and staining methods

Antibody	Clone	Source	Result
Cytokeratin 7	OVTL 12/30	Biogenex (Ready to use)	+
Cytokeratin 20	KS20.8	Biogenex (Ready to use)	-
Epithelial membrane antigen	Mc5	Biogenex (Ready to use)	+
E-cadherin	36B5	Novocastra (Ready to use)	-
Gross cystic disease fluid protein-15	23A3	Novocastra (Ready to use)	-
Estrogen receptor	6F11	Novocastra (Ready to use)	-
Progesterone receptor	16	Novocastra (Ready to use)	-
c-erbB-2 oncoprotein	CB11	Novocastra (Ready to use)	-
Thyroid transcription factor-1	SPT24	Novocastra (Ready to use)	-
Ki-67 antigen	MM1	Novocastra (Ready to use)	+

Neoplastic cells of micropapillary and conventional adenocarcinoma components were diffusely positive for pancytokeratin, cytokeratin 7 (CK7) and EMA. On the contrary of the positivity of EMA that was predominantly observed in luminal surface and cytoplasm of glandular structures in ordinary adenocarcinoma areas; outside membranous and peripheral cytoplasmic positivity were seen in micropapillary areas (Figure 4). This kind of staining pattern is called “inside-out polarity” and is considered highly characteristic for micropapillary carcinoma. The possibility of fixation artefact versus vessel invasion was verified by CD34 and factor VIII related antigen negativity. Results of other immunohistochemical antibodies were given in Table I. Approximately 35% of the neoplastic cells were positive for Ki-67 antigen.

DISCUSSION

IMPC is a rare entity, the most characteristic feature of which is tufts of tumor cells arranged in pseudopapillary patterns without fibrovascular cores. The tufts are characteristically surrounded by clear spaces (1-6). The “inside-out” growth structure has been explained with the rotation of cell polarization whereas the stroma-facing surface of the cells obtaining apical properties (3). In the present case, inside-out growth pattern has been proved immunohistochemically with the anti-EMA antibody. It is hypothesized that this reverse polarization in IMPC activates the secretion of some molecules by the tumor cells, such as metalloproteinases, which are suspected to be responsible for stromal and vascular invasion, and propensity to easier dissemination of tumor cells and a higher risk for lymph node metastases (2).

The main differential diagnosis of primary IMPC of the stomach is conventional gastric carcinomas showing

extensive lymphatic invasion or metastatic invasive micropapillary carcinomas (8). In our case, lymphovascular invasions have been ruled out with CD34 negativity in lining cells in inner surface of spaces. We used three criteria to distinguish the primary IMPC from a metastatic carcinoma. Firstly, the presence of foci of ordinary adenocarcinoma originated from the gastric mucosa and the transition between classical adenocarcinoma and IMPC areas. Secondly, absence of any radiologically detected solitary or multiple masses compatible with possible primary focus. And finally, immunohistochemical staining profile of neoplastic cells which demonstrated CK7 positivity, CK20, estrogen, progesteron, GCDPF-15 and cerbB-2 negativity pointing out the stomach as the most possible primary site. Clinicopathological stage of stomach IMPC is usually reported to be higher, that most of the patients have invasion in gastric subserosal tissue in addition to muscularis propria invasion and lymph node metastasis similar to our case (7-10). But, on the contrary, Roh et al. suggested that the prognosis of the patients with IMPC of the stomach were not different than the patients with ordinary adenocarcinoma of the stomach (11). Our patient was under follow-up without any therapy due to major cardiovascular problems. Although a minimum increase of the CEA level (CEA:39.26 mg/dl. to 43.19 mg/dl.) was observed in blood during follow-up, the patient remained alive without further metastasis for eight months, after the operation. But it is very early to judge about the survival of the case for the limited follow up period.

The E-cadherin gene has been described as an invasion-suppressor gene (12) and the loss of E-cadherin expression is considered to be associated with tumor invasion in gastric adenocarcinomas. E-cadherin loss has also been reported in primary gastric IMPC and one of the reported case also

had a 23.5 % Ki-67 expression rate as a predictive marker of poor prognosis (12, 13). In our case, loss of E-cadherin expression was observed in both IMPC and poorly differentiated component of the tumor similar to reported by Shimoda et al (8). Ki-67 index was 35% in neoplastic cells and was similar again to results published in literature. Aggressive nature and high morbidity and mortality ratio of the entity in stomach were also described in a recently published paper by Ushiku et. al (14). However larger series with IMPC component is necessary to determine the actual importance of the ratio of IMPC component and its impact on the prognosis of gastric cancer.

In conclusion, the diagnosis of IMPC should be kept in mind and needs to be carefully analyzed to understand its etiopathogenesis and effect on clinical behaviour.

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