

Retrospective Study

Phagocytosis (cannibalism) of apoptotic neutrophils by tumor cells in gastric micropapillary carcinomas

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ascertain relative frequency and document clinicopathological characteristics by reviewing gastric carcinomas.

METHODS: One hundred and fifty-one patients diagnosed with gastric cancer who underwent gastrectomy were retrospectively studied and the presence of a regional invasive micropapillary component was evaluated by light microscopy. All available hematoxylin-eosin (HE)-stained slides were histologically reviewed and 5 tumors were selected as putative micropapillary carcinoma when cancer cell clusters without a vascular core within empty lymphatic-like space comprised at least 5% of the tumor. Tumor tissues from these 5 invasive gastric carcinomas were immunostained using an anti-mucin 1 (MUC1) antibody (clone MA695) to detect the characteristic inside-out pattern and with D2-40 antibody to determine the presence of intratumoral lymph vessels. Detection of intraepithelial neutrophil apoptosis was evaluated in consecutive histological tissue sections by three independent methods, namely light microscopy with HE staining, the conventional terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end-labeling (TUNEL) method and immunohistochemistry for activated caspase-3 (clone C92-605).

RESULTS: Among 151 gastric cancers resected for cure, 5 (3.3%) were adenocarcinomas with a micropapillary component. Four of the patients died of disease from 6 to 23 mo and one patient was alive with metastases at 9 mo. All patients had advanced-stage cancer (\geq pT2) and lymph node metastasis. Positive MUC1 immunostaining on the stroma-facing surface (inside-out pattern) of the carcinomatous cluster cells, together with negative immunostaining for D2-40 in the cells limiting lymphatic-like spaces, confirmed the true micropapillary pattern in these gastric neoplasms. In all five cases, several micropapillae were infiltrated by neutrophils. HE staining, TUNEL assay and immunostaining for caspase-3 demonstrated apoptotic

Abstract

AIM: To identify those with a micropapillary pattern,

neutrophils within cytoplasmic vacuoles of tumor cells. These data suggest phagocytosis (cannibalism) of apoptotic neutrophils by micropapillary tumor cells. Tumor cell cannibalism is usually found in aggressive tumors with anaplastic morphology. Our data extend these observations to gastric micropapillary carcinoma: a tumor histotype analogously characterized by aggressive behavior and poor prognosis. The results are of interest because they raise the intriguing possibility that neutrophil cannibalism by tumor cells may be one of the mechanisms favoring tumor growth in gastric micropapillary carcinomas.

CONCLUSION: This is the first study showing phagocytosis (cannibalism) of apoptotic neutrophils by tumor cells in gastric micropapillary carcinomas.

Key words: Gastric cancer; Micropapillary pattern; Mucin 1; Caspase-3; TUNEL assay

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Core tip: Five rare cases of micropapillary carcinoma of the stomach are reported. Phagocytosis (cannibalism) of apoptotic neutrophils by tumor cells is demonstrated for the first time in micropapillary components of gastric carcinomas. These unique features might help us to better understand the aggressive behavior and poor prognosis of this rare entity.

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INTRODUCTION

Micropapillary carcinoma was originally described by Siriaunkgul and Tavassoli^[1] as a rare subtype of invasive ductal carcinoma of the breast, characterized by pseudopapillary cell clusters devoid of fibrovascular cores and surrounded by empty and clear spaces. Then, this neoplastic architectural pattern was identified as a distinct entity in other organs, including the bladder^[2], lung^[3], pancreas^[4], parotid gland^[5], gallbladder^[6] and colorectum^[7,8]. Ultrastructural studies performed on breast micropapillary carcinomas demonstrated the presence of microvilli on the external surface of tumor cells facing the surrounding stroma^[9,10]. Immunohistochemical studies confirmed these data, showing mucin 1 (MUC1), EMA, CD10 and villin, normally expressed at the apical surface (luminal surface) on the cells in normal glandular epithelium, exclusively on the basal surface of micropapillary clusters^[11]. These findings suggest that micropapillary

growth pattern is due to abnormal inversion of tumor cell polarity where the stroma-facing (basal) surface of the cells acquires apical secretory properties^[12]. This inversion of cell polarity has been defined as the "inside-out" pattern and is considered a diagnostic feature of micropapillary carcinoma^[12].

MUC1 is a glycoprotein that plays a key role in lumen formation and prevents interaction between cell and stroma^[12,13]. The "inside-out" pattern of MUC1 expression may explain the aggressive behavior and high metastatic potential of micropapillary carcinoma^[12]. Furthermore, MUC1 is one of the epithelial tissue-specific genes repressed in tumor cells during epithelial-mesenchymal transition, a process by which epithelial cells acquire the potential to migrate through the extracellular matrix, similarly to mesenchymal cells^[14].

A micropapillary component is usually found at the invasive front of the tumor, where it may share morphological features with the histological appearance of the tumor budding of many colorectal carcinomas. Recently, we showed the characteristic "inside-out" pattern of MUC1 expression in the so-called "poorly differentiated clusters" of colorectal carcinomas^[15]. Therefore, we suggested that a micropapillary component and "poorly differentiated clusters" are the same biological phenomenon during epithelial-mesenchymal transition in colorectal cancer^[15]. Several immunohistochemical variants of the "inside-out" pattern of MUC1 expression have been reported in the recent literature. In particular, an incomplete "inside-out" pattern defined as the presence of tumor cell clusters partly but not completely decorated with EMA or MUC1 immunostaining has been described in breast carcinoma^[16]. Moreover, neutrophils may favor a micropapillary phenotype *via* elastase that degrades E-cadherin on pancreatic tumor cells^[17]. Overall, these data suggest that the micropapillary phenotype is a complex phenomenon that has been only partially explored.

The invasive micropapillary variant of gastric carcinoma has been the subject of recent review as well as publications and case reports describing about 144 cases^[11,18-27]. These series reported clinicopathological and immunohistochemical features of this entity. In this work, gastric carcinomas were reviewed to identify those with a micropapillary pattern, ascertain relative frequency and document clinicopathological characteristics. We also analyzed the relationship between neutrophils and tumor cells and found phagocytosis (cannibalism) of apoptotic neutrophils by micropapillary carcinoma cells.

MATERIALS AND METHODS

Case selection

A consecutive series of 151 patients with gastric adenocarcinomas who underwent gastrectomy at the University Hospital of Messina (Italy) between January 2001 and July 2005 were retrospectively analyzed. All

Table 1 Clinicopathological features of the 5 patients

Case No.	Age (yr)	Sex	Location	Histology	Tnm	Outcome
1	55	Male	Antrum	Papillary	T3N2	DOD, 6 mo
2	47	Male	Antrum	Papillary	T2N3	DOD, 10 mo
3	62	Male	Antrum	Papillary	T3N1	DOD, 23 mo
4	58	Male	Body	Papillary	T3N2	DOD, 7 mo
5	75	Female	Body	Papillary	T2N2	AWD, 9 mo

DOD: Dead of disease; AWD: Alive with disease (metastases).

samples were fixed in 10% neutral formalin for 24–36 h at room temperature and then embedded in paraffin at 56 °C. Gastric carcinoma was classified according to the World Health Organization classification^[28]. All available slides were histologically reviewed and 5 tumors were selected as putative micropapillary carcinoma when cancer cell clusters without a vascular core within an empty lymphatic-like space comprised at least 5% of the tumor.

Immunohistochemistry

Four micrometer thick consecutive sections were cut from the paraffin blocks of the 5 putative micropapillary carcinomas and submitted to the immunohistochemical procedure against MUC1, D2-40 and caspase-3. Antigen retrieval was performed prior to the addition of the primary antibody by heating slides placed in 0.01 mol/L citrate buffer at pH 6.0 in a microwave oven (750 W) for three 5 min cycles. Sections were successively incubated with the primary monoclonal antibody against MUC1 (clone Ma695, 1:100 w.d.; Novocastra Laboratories, Newcastle, United Kingdom), D2-40 (clone M3612; 1:200 w.d.; DakoCytomation, Copenhagen, Denmark) and caspase-3 (clone C92-605, 1:100 w.d.; BD Biosciences). The bound primary antibodies were visualized by using the LSAB kit (Dako Cytomation, Glostrup, Denmark) according to the manufacturer's instructions. To reveal the immunostaining, the sections were incubated in darkness for 10 min with 3,3'-diaminobenzidine tetrahydrochloride (Sigma Chemical Co., St Louis, MO, United States) in the amount of 100 mg in 200 mL 0.03% hydrogen peroxide in phosphate-buffered saline solution. Nuclear counterstaining was carried out by using Mayer's hemalum. The immunohistochemical procedures were carried out automatically by using Dako Autostainer Link 48 (Dako Cytomation, Glostrup, Denmark) according to the manufacturer's instructions.

TUNEL assay

TUNEL assay was conducted by using a TUNEL detection kit according to the manufacturer's instruction (Apotag, HRP kit DBA, Milan, Italy). Briefly, sections were incubated with 15 µg/mL proteinase K for 15 min at room temperature and then washed with PBS. Endogenous peroxidase was inactivated by 3% H₂O₂ for 5 min at room temperature and then washed with PBS. Sections were immersed in terminal

deoxynucleotidyl transferase (TdT) buffer containing deoxynucleotidyl transferase and biotinylated dUTP in TdT buffer, incubated in a humid atmosphere at 37 °C for 90 min and then washed with PBS. The sections were incubated at room temperature for 30 min with anti-horseradish peroxidase-conjugated antibody and the signals were visualized with diaminobenzidine. Sections of human tonsil and human small intestine, as well as a control tissue provided with the Apo Tag Kit, were the positive controls.

Statistical analysis

No statistical analysis was performed.

RESULTS

Clinicopathological features of the 5 patients are summarized in Table 1. There were 4 males and 1 female. Ages ranged from 47 to 75 years (median, 58 years). Two patients had a clinical stage T2 tumor and 3 had stage T3 disease (Table 1). All patients had lymph node metastases. Follow-up data after surgery were available in all 5 cases (range: 6–23 mo). Four of patients died of disease from 6 to 23 mo and one patient was alive with metastases at 9 mo.

At histology, in all 5 cases there was a papillary adenocarcinoma in the superficial portion of the tumor and an invasive micropapillary component at the deep invasive cancer front. In one case, the micropapillary phenotype was greater than 80% of the tumor. In all of the investigated cases, the invasive micropapillary component was characterized by cancer cell clusters without a vascular core within an empty lymphatic-like space (Figure 1A). Cluster cells demonstrated a moderately abundant eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli. At immunohistochemistry, clusters cells were reactive for MUC1 on the stroma-facing surface, demonstrating an inside-out pattern (Figure 2). In addition, immunostaining for D2-40 was negative in the cells limiting the lymphatic-like spaces, which ruled out the possibility of lymphatic vessel invasion. Several micropapillae were infiltrated by numerous neutrophils (Figure 1B). Tumor necrosis was absent. Neutrophils were mainly intraepithelial and less frequently were found in the tumor stroma (Figure 1A). Some intraepithelial neutrophils were observed within cytoplasmic vacuoles of micropapillary tumor cells

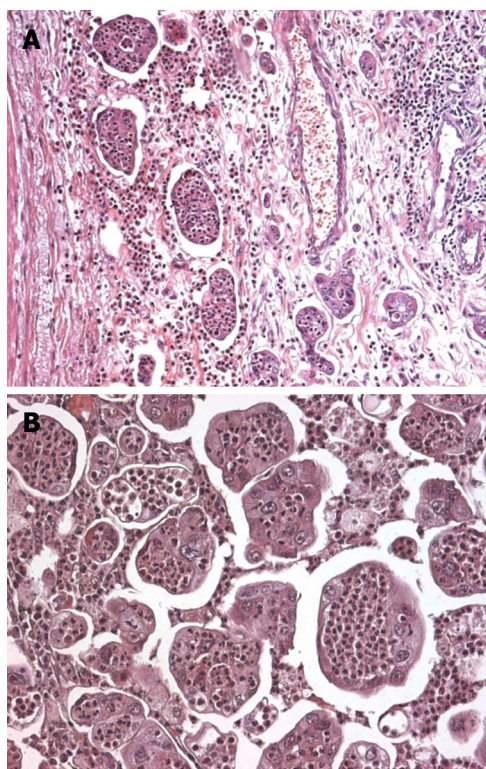


Figure 1 Invasive micropapillary carcinoma characterized by cell clusters surrounded by lacunar spaces and fibrous stroma (A) and several micropapillae infiltrated by numerous neutrophils. A: HE staining, magnification $\times 100$; B: HE staining, magnification $\times 400$.

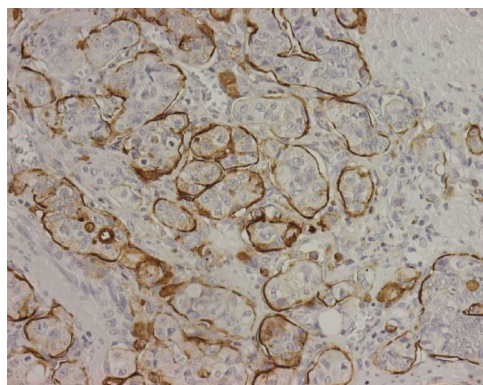


Figure 2 Micropapillary clusters were characteristically MUC-1 immunoreactive on the stroma-facing surface (“inside-out” pattern). Magnification $\times 200$.

and showed the characteristic morphological findings of apoptotic death, such as chromatin condensation and cell shrinkage (Figure 1B). They exhibited TUNEL-positive nuclei (Figure 3) and cytoplasmic immunoreactivity for caspase-3 (Figure 4).

DISCUSSION

The aim of the current retrospective study was to identify the incidence as well as clinicopathological characteristics of gastric micropapillary carcinomas. Of 151 gastric carcinomas resected for cure at the

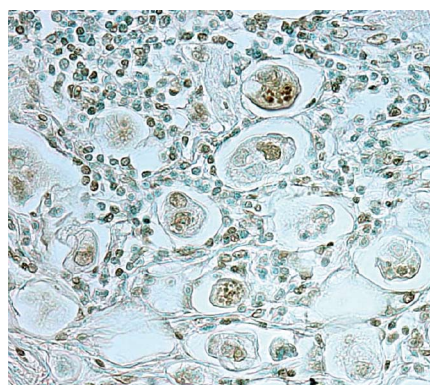


Figure 3 Intraepithelial neutrophils showing TUNEL-positivity. Magnification $\times 200$.

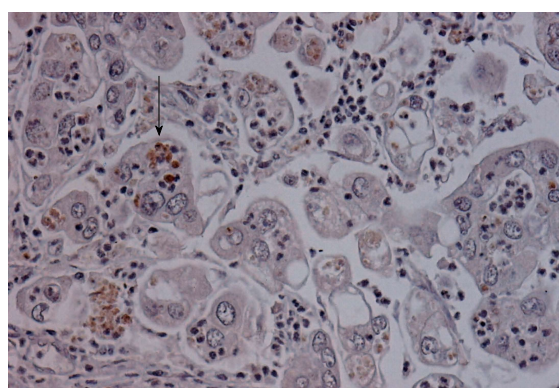


Figure 4 Neutrophils showing cytoplasmic immunoreactivity for caspase-3 are found within cytoplasmic vacuoles of tumor cells (arrow). Magnification $\times 200$.

University Hospital of Messina (Italy) from 2001 to 2005, 5 fulfilled the criteria of gastric micropapillary carcinomas. The frequency of gastric micropapillary carcinoma was 3.3% in our study. Based on the limited number of cases in this study, gastric micropapillary carcinoma is characterized by a particularly aggressive clinical outcome. In the present study, patients died of the disease or were alive with metastases less than 2 years from initial diagnosis.

In our study, positive MUC-1 immunostaining on the stroma-facing surface (inside-out pattern) of the carcinomatous cluster cells, together with negative immunostaining for D2-40 in the cells limiting the lymphatic-like spaces, confirmed the true micropapillary pattern in these gastric neoplasms.

Neutrophil infiltration has been described in a series of invasive micropapillary carcinomas of the pancreas^[4] and periampullary region^[29], as well as in a case of colorectal micropapillary carcinoma^[30]. In our five cases, we showed intraepithelial apoptotic neutrophils in several micropapillary components of gastric tumors for the first time. To investigate neutrophil apoptosis, we chose three independent techniques: light microscopy with hematoxylin-eosin staining, TUNEL and caspase-3 immunohistochemistry.

At the light microscopic level, some intraepithelial neutrophils were found within cytoplasmic vacuoles and showed morphological signs of apoptosis, such as pyknotic nuclei and cell shrinkage. TUNEL staining and caspase-3 immunoreactivity confirmed the apoptotic nature of these neutrophil changes. These findings are similar to that described in tumor cell cannibalism both in cytological or histological samples of human tumors where it is possible to detect cells with one or more vacuoles, possibly containing cells under degradation, that push the nucleus to the cell periphery^[31,32]. Taken together, our data show phagocytosis (cannibalism) of apoptotic neutrophils by micropapillary carcinoma cells.

Tumor cell cannibalism is described as the ability of tumor cells to cannibalize their siblings as well as cells from the immune system^[32]. Neutrophil cannibalism by tumor cells must be distinguished from other “cell-in-cell” phenomena, such as emperipolesis and entosis. Emperipolesis has been defined as a random passage of different types of cells through the cytoplasm of another cell without any important change in either the host or invading cells^[33]. We ruled out the possibility that the presence of neutrophils within micropapillary tumor cells is merely due to emperipolesis as these neutrophils were apoptotic. Entosis is a term coined by Overholtzer *et al.*^[34] to describe a form of cell engulfment involving the cells that resembles emperipolesis. However, the entosis may be characterized by a non-apoptotic cell death of the internalized cell, whereas in our cases of micropapillary carcinomas we showed apoptotic mechanisms of neutrophil death.

While phagocytic behaviors have been reported for most forms of human cancer, not all cancer cells within a tumor are phagocytic. For most of the tumors described, phagocytic/cannibalistic behavior was restricted primarily to those cells that are highly invasive and metastatic, such as pleomorphic giant cell carcinoma of the lung, gall bladder, pancreas and intestine^[33]. In addition to pleomorphic giant cell carcinoma, our cases of gastric micropapillary carcinomas represent a further example of adenocarcinoma with aggressive behavior associated with neutrophil tumor cell phagocytosis.

Our findings of neutrophil cannibalism by tumor cells may suggest several intriguing hypotheses. First, this phenomenon may be interpreted as a sort of “feeding” activity necessary to sustain survival of tumor cells independent of the microvasculature^[35]. Second, the presence of cannibalized cells may interfere with cell division, leading to non-genetic polyploidy^[36]. Finally, recent studies have demonstrated that horizontal DNA transfer between mammalian cells can occur through the uptake of apoptotic bodies, where genes from the apoptotic cells were transferred to neighboring cells phagocytosing the apoptotic bodies^[37-39]. It has been suggested that horizontal transfer of DNA from apoptotic bodies could be one explanation for the chromosomal instability and aneuploidy observed in cancer cells^[39]. Cannibalism-mediated chromosomal

instability and aneuploidy could be one of the reasons for aggressive behavior of micropapillary carcinoma but further studies are needed to verify these hypotheses.

COMMENTS

Background

Micropapillary carcinoma has been recently characterized as a rare but distinctive variant of adenocarcinoma in several organs. From a histopathological viewpoint, it is formed by small papillary cell clusters surrounded by lacunar spaces resembling lymphatic channels. This tumor histotype is associated with frequent lymphovascular invasion and poor clinical outcome.

Research frontiers

The phenomenon of tumor cell cannibalism, a morphological feature mainly seen in highly malignant tumors, is characterized by the ability of tumor cells to cannibalize their siblings as well as cells from the immune system, such as neutrophils and lymphocytes. Although cell cannibalism is a morphological marker of aggressive biological behavior, it has not been studied in micropapillary carcinoma, a tumor histotype also characterized by a dismal prognosis.

Innovations and breakthroughs

Previous studies have documented the mere presence of intraepithelial neutrophils in micropapillary carcinomas of the colon, as well as of the pancreas and periampullary region. The phenomenon of neutrophil cannibalism by tumor cells must be distinguished from emperipolesis, where the invading cell appears normal, or from entosis, where the invading cell undergoes non-apoptotic cell death. In order to characterize the necrotic changes of cannibalized neutrophils, we performed three independent techniques: light microscopy with hematoxylin-eosin, TUNEL and caspase-3 immunohistochemistry. The authors showed apoptotic neutrophil cannibalism by tumor cells in 5 cases of micropapillary gastric carcinomas for the first time.

Applications

The presence of cannibalistic tumor cells is a further morphological feature associated with the high-grade malignancy of gastric micropapillary carcinomas. A study evaluating this phenomenon in a series of micropapillary carcinomas in relation to diagnostic purpose, frequency, stage and biology may be of value.

Terminology

Micropapillary carcinoma is a recently recognized type of adenocarcinoma with an aggressive behavior, as shown by local recurrence and extensive nodal involvement. Cellular cannibalism is generically defined as a large cell enclosing a slightly smaller one within its cytoplasm. Neutrophil-tumor cell cannibalism is a particular form of cannibalism where apoptotic neutrophils are shown in tumor cell cytoplasm by HE staining, TUNEL assay and specific immunohistochemical methods.

Peer-review

This topic is very interesting and the significance of apoptotic neutrophils in the micropapillary tumor cells should be further studied.

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