CASE REPORT

Pancreatic metaplasia of gastric mucosa associated with gastroduodenal ulcer

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Abstract

Metaplasia represents the process of transforming a well-differentiated adult tissue into another type of adult tissue. Pancreatic metaplasia of the gastric mucosa represents the process in which the normal mucosa of the stomach is replaced with pancreatic formations, which mimic the structure of pancreatic acini. We describe the case of a male patient aged 39 who was admitted for abdominal pain, vomiting, hematemesis, melena, pale teguments, intense perspiration and nausea. The patient underwent surgery for suturing a perforated duodenal ulcer five years prior to this episode (2002). A gastric ulcer complicated with superior digestive bleeding and a chronic duodenal ulcer complicated with partial stenosis and perivisceritis were found during surgery. Gastric wall fragments were harvested and underwent usual histological techniques and immunohistochemistry. We found an ulceration from the gastric mucosa to the submucosa, covered by fibrino-leukocytic detritus. In the mucosal chorion we found numerous round or oval shaped nested formations which occupied the lower two thirds of the chorion, to the muscularis mucosae. Some metaplasic acini contain cells variable in shape, color and immunophenotype. Surrounding the nested acini we found tubular formations, formed of cubic shaped cells, representing excretory canals which were continued by gastric glands or opened directly in the crypts of the gastric epithelium.

***Keywords*:** pancreatic metaplasia, gastric mucosa, gastroduodenal ulcer, acinar pancreatic cells.

Introduction

Pancreatic metaplasia of the gastric mucosa represents the process in which the normal mucosa of the stomach is replaced with pancreatic formations, which mimic the structure of pancreatic acini.

Currently, intestinal metaplasia is the most common type of gastric mucosal transformation. It can contain both sialomucin secreting goblet cells and non-secretory absorptive cells. Sometimes the transition from the normal gastric mucosa to the intestinal type occurs abruptly, both types of cells appearing concomitantly; in other cases, it is a progressive transition. In the latter case columnar cells with increased sulphomucin secretion and goblet cells that can secret either sialomucin or sulphomucin can be found [1, 2].

In recent years, there have been an increased number of reports concerning cases of pancreatic metaplasia appearing in chronic atrophic gastritis and autoimmune gastritis [3–5]. This type of metaplasia mainly consists of nested acin formations that can be found in the lower thirds of the gastric chorion. They are usually accompanied by tubular cell clusters that resemble glandular ducts that usually reach the gastric crypts or are continued by gastric fundic glands [3, 5].

Patient and Methods

We describe the case of a male patient (CP) aged 39, coming from a rural environment, who was admitted in the Emergency Ward in August 2007 in the 2nd Surgery Clinic at the Emergency County Hospital of Craiova. He presented a deteriorated condition, intense abdominal pain, vomiting, hematemesis, melena, pale teguments, intense perspiration and nausea. The acute symptoms debuted five days prior to admission, following several abundant meals accompanied by large alcohol intake. During anamnesis, we found out that the patient was suffering from an older gastric condition, five years prior to this episode (2002) being admitted and treated by surgery for a perforated duodenal ulcer, when the suture of said ulcer was performed.

Clinical examination revealed an underweight patient, with pale teguments and mucosae, little adipose tissue, presenting diffuse abdominal pain, both spontaneous and on palpatory examination.

Endoscopic examination showed intense brown-colored sanguinolent secretions (hematemesis debris) in the esophagus, and an ulcer of about 3–4 cm bleeding ulcer situated on the incisura angularis, on the lesser curvature, having prominent margins, with great malignisation potential. A large quantity of blood and secretions was found in the gastric cavity (hematemesis).

Laboratory tests showed normal, except a moderated anemia (Hemoglobin level 10.24 g/L), anizocytosis with anisochromia and hypokalemia with hyponatremia.

After correcting the hydroelectrolitic imbalance and hemostatic treatment, surgery was performed, finding a double ulcer (gastric ulcer complicated with superior digestive bleeding and a chronic duodenal ulcer

complicated with partial stenosis and perivisceritis). Two-thirds gastric resection was performed, followed by gastroduodenal Péan-type anastomosis.

For the histopathology study we harvested gastric wall fragments from the lesion site, three centimeters above (line of gastric resection), from the antral area and from adjacent ganglia on the lesser curvature. All biologic material was fixated in neutral 10% formaldehyde solution for 48 hours, followed by paraffin inclusion. After performing 3–5 micrometer thick sections, some of the histologic cups were stained with Hematoxylin–Eosin and PAS–Hematoxylin dyes.

For the immunohistochemistry study, sections placed on poly-Lysine slides were deparaffinated and rehydrated. Antigenic retrieval was performed according the producers specifications (Table 1).

Table 1 – ***Characteristics of the antibodies used in the present study***

Antigen	Host	Clonality	Antigenic retrieval	Dilution	Produced by
Alpha 1 antitrypsin	Rabbit	Polyclonal	Digestion with K proteinase, 5 minutes at 37^0C	1:2000	Dako, A0012
Cytokeratin 7	Mouse	Monoclonal	Boiling in citrate buffer, pH 6	1:50	Dako, M7018
Cytokeratin 18	Mouse	Monoclonal	Boiling in EDTA buffer, pH 9	1:50	Dako, M7010
Cytokeratin 20	Mouse	Monoclonal	Boiling in citrate buffer, pH 6	1:50	Dako, M7019
E-cadherin	Mouse	Monoclonal	Boiling in citrate buffer, pH 7	1:100	Dako, M7361
Lysozyme	Rabbit	Polyclonal	Digestion with K proteinase, 5 minutes at 37^0C	1:400	Dako, A0099

Endogenous peroxidase was inactivated by incubating in oxygenated water 1%; afterwards non-specific antigen situs were blocked with 1% non-fat milk solution. The primary antibody was added in optimal dilution, and sections were incubated at 4^0C overnight. On the second day, after washing the excess primary antibody, sections were incubated with secondary polyclonal polymeric antibodies labeled with peroxidase (EnVision, Dako).

Actual staining was performed using Diaminobenzidine (DAB) under the optic microscope for each section. Afterwards, sections were counterstained with Hematoxylin, dehydrated, clarified and mounted in DPX (Merck) mounting environment.

For the histology and immunohistochemistry study, we used the Nikon 55i microscope.

Results

The histopathology exam of the gastric wall at ulcer level and the surrounding area evidentiated the existence of an ulceration reaching from the gastric mucosa to the submucosa, covered by fibrino-leukocytic detritus, underneath which we found granulation tissue. At the level of the gastric corpus, at a distance of about 3 cm from the ulcerous lesion, we found hypertrophic mucosa with a rich inflammatory infiltrate containing polymorphonucleated cells in the chorion (lamina propria) and moderated vascular congestion.

Study of the gastric mucosa fragments coming from the antral region showed an atrophic mucosa, with fewer and smaller glandular crypts and small and rare glands.

In the mucosal chorion we found numerous round or oval shaped nested formations, with diameters between 150 and 350 microns, which occupied the lower two thirds of the chorion, to the muscularis mucosae (Figure 1). These formations were separated by variable amounts of lax conjunctive tissue with rare vascular vessels, conjunctive fibers and cells (Figures 2 and 3).

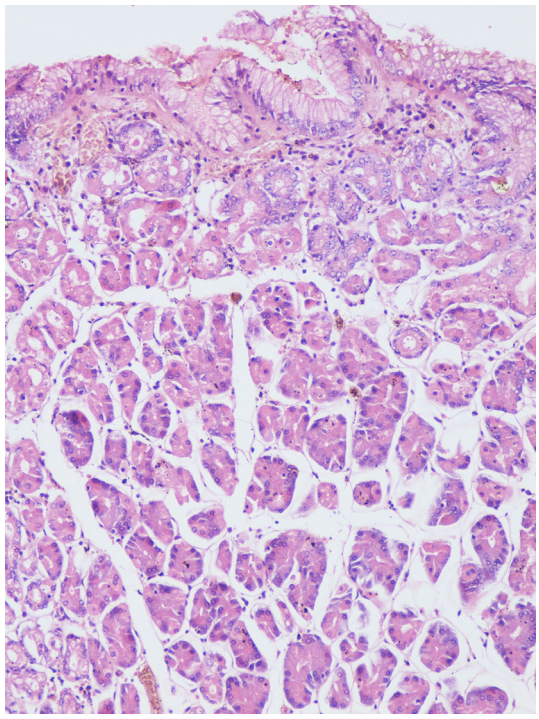

Figure 1 – ***Overview image of gastric mucosa with pancreatic metaplasia (HE staining, ×100).***

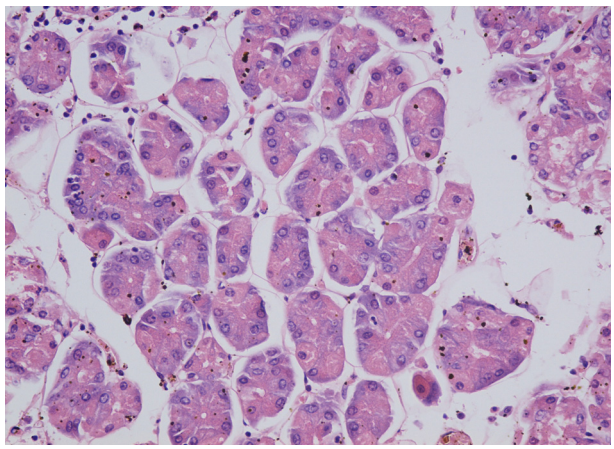

Figure 2 – ***Nest of metaplasic pancreatic acini (HE staining, ×200).***

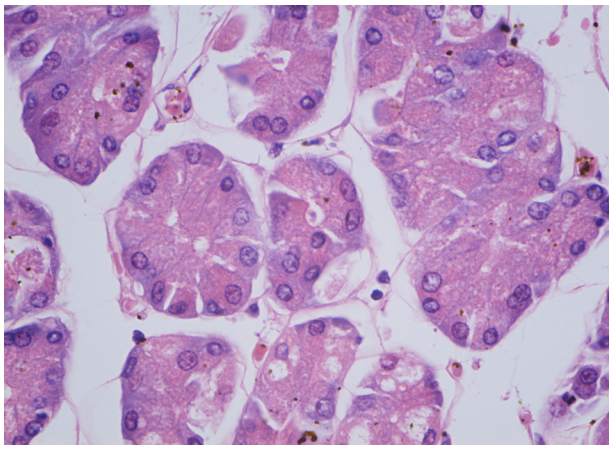

Figure 3 – ***Metaplasic pancreatic acini (HE staining, ×400).***

To evidentiate the shape of the cells in these acinar formations we marked the cellular limits with E-cadherin and contrasted with Hematoxylin–Eosin, knowing that E-cadherin or epithelial cadherin is an intercellular adherence glycoprotein made up of a long extracellular domain, a transmembranary domain and a short intracellular domain. They form homotypical extracellular interactions, creating a functional link between epithelial cells. Hence, immunostaining of E-cadherin will mark the external surfaces of epithelial cells.

As it can be seen in our images (Figure 4), the acinar formations were formed by pyramid or pyramid body shaped cells with slight basophilic cytoplasm, fine granules, with round nuclei frequently found in the basal region, with distinct nucleoli. Cells were delimited by a thin basal membrane which continuated with the basal membrane of the gastric glands. Acinar cells have delimited a small round or star shaped lumen at their apical pole.

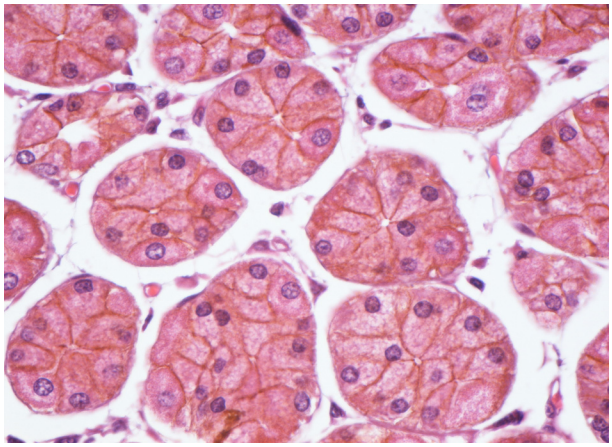

Figure 4 – ***Metaplasic pancreatic acini (immunostaining with E-cadherin; counterstaining with HE, ×400).***

The PAS–Hematoxylin staining revealed acinar cells, numerous small acidophilic granules, usually found in the middle third and apical regions. We have to account for the fact that the PAS reaction was not homogenous between acini, hence the number of granules found in each acinar cell was different (Figure 5).

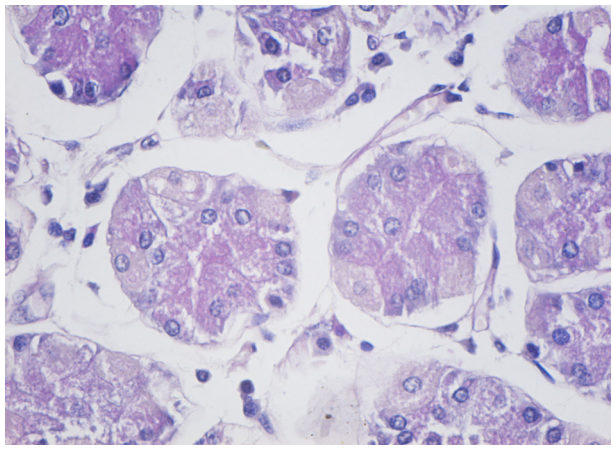

Figure 5 – ***Metaplasic pancreatic acini with PAS-positive granules in the apical two thirds (PAS–Hematoxylin staining, ×400).***

Immunohistochemistry showed a positive, nevertheless variable reaction to alpha-trypsin between acini (Figure 6), while reactions to cytokeratins 7, 18 and 20 and lysozyme were negative.

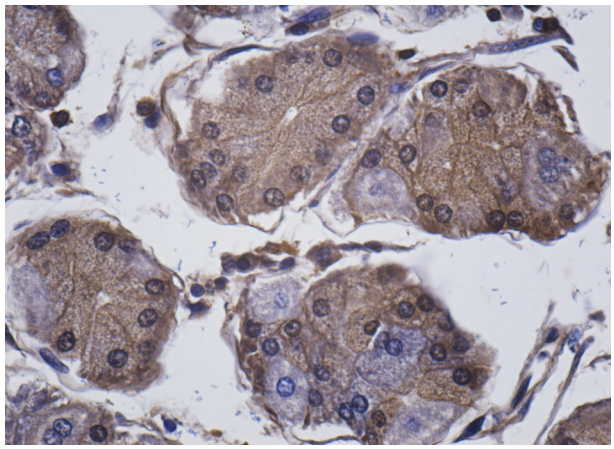

Figure 6 – ***Metaplasic acini. Positive immunostaining with alpha-trypsin, ×400.***

On some slides, histology staining as well as immunostaining for alpha-trypsin allowed us to evidentiate the fact that some metaplasic acini contain cells variable in shape, color and immunophenotype. Therefore, in the structure of some acini we identified oval shaped cells, with a round, central nucleus, more hypochromic cytoplasm, which can be either endocrine or oxyntic cells (Figure 6), while other cells had columnar shapes, clear cytoplasm, basal nuclei, aspect similar to that of mucinous cells found in the epithelium of the neck of pyloric glands (Figure 7). Additionally, we found cells with two or even three nuclei in the acinar structure.

Surrounding the nested acini, we found tubular formations 80–120 microns in diameter, formed of cubic shaped cells, which paved a lumen of approximately 25–40 microns in diameter, representing excretory canals of these acin formations. These tubular shapes were continued by gastric glands or opened directly in the crypts of the gastric epithelium. Unlike pancreatic canalicules, these canals did not have other cellular of fibrillary structures surrounding them (smooth muscle cells or collagen fibers).

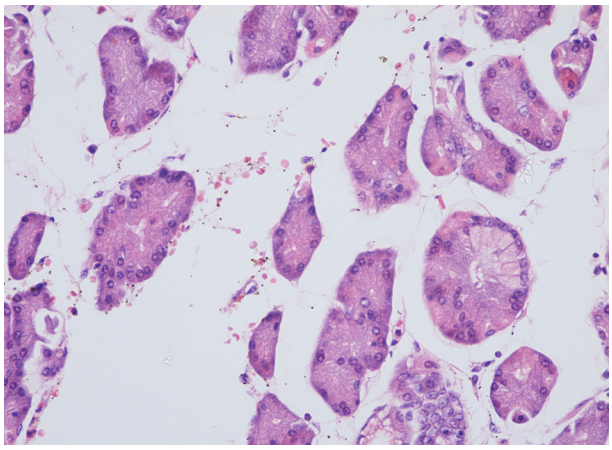

Figure 7 – ***Metaplasic acin containing numerous cells with clear cytoplasm (HE staining, ×200).***

Discussion

Metaplasia represents the process of transforming a well-differentiated adult tissue into another type of adult tissue. The term of metaplasia signifies that the transformation process takes place in postnatal life, that it consists of a tissue that appears in a place it is not normally found and that it can be part of both physiological and pathological processes. Some researchers consider it a process of adapting structures to new conditions in the local environment. In experimental biology, the term of metaplasia is often replaced with "transdifferentiation" [1]. In histopathology, for humans, metaplasic processes are frequently encountered. They always occur in tissue that has been subjected to chronic trauma, infections or hormonal stimulations, therefore places that are subject to a continuous process of regeneration. In some processes, it is unclear whether the metaplasic tissue has occurred because of local cellular differentiation or has migrated from elsewhere [2].

Metaplasia of gastric mucosa is frequently encountered in chronic inflammatory processes (gastritis), ulcer or gastric cancer. The one most often quoted is intestinal metaplasia that consists of replacing gastric epithelium with enterocytes, caliciform cells and Paneth cells.

Pancreatic metaplasia is much rarer than the intestinal one. According to some authors, Doglioni C *et al.* (1993) [3], it is present in approximately 12% of patients with autoimmune gastritis, usually occurring in the cardia region and co-existing with other types of metaplasia [4]. Jhala NC *et al.* (2003) [5] offer similar data and consider that pancreatic acinar cells metaplasia mainly occurs in patients with autoimmune gastritis.

Jhala NC *et al.* (2003) [5], while investigating the presence of pancreatic metaplasia at the level of the oxyntic mucosa on fragments of gastric biopsy from adult patients, finds an incidence of 11%, out of which 9% is found in patients with autoimmune gastritis, 1% in patients with multifocal atrophic chronic gastritis and 1% in a patient with normal gastric mucosa.

Pancreatic metaplasia has been evidenced in children. Thus, Integlia MJ *et al*. (1997) [6] has shown through studies of histology and immunohistochemistry the presence of islands of exocrine pancreas within the gastric mucosa on a number of eight children aged between 8 and 18 years, who presented digestive symptoms. If pancreatic metaplasia in adults is associated with atrophic or autoimmune gastritis phenomena, it is considered for children that the presence of pancreatic metaplasia is caused by developing and differentiating problems of the gastric mucosa.

Other authors [7] consider that pancreatic acinar cells can also develop within the gastric mucosa of the antral region and is often associated with intestinal metaplasia or gastric atrophy. These focal points of metaplasia contain isolated or multiple nests of acini or lobules, measuring up to 1.7 mm in diameter. More rarely, acinar cells appear isolated or in small cellular nests amongst the gastric glands.

Our study aimed at demonstrating that pancreatic metaplasia can be localized in the antral mucosa and can be associated with grave pathologies of the stomach. On some histological cups, we remarked that metaplasic tissue merges imperceptibly with gastric glands in which it sends synthesized products, but larger lobules contain collector tubes, which communicate with gastric crypts.

Leys CM *et al*. (2006) [8] showed that both pancreatic metaplasia and gastric endocrine cells hyperplasia are associated with atrophic gastritis of the gastric body.

A study performed by Doglioni C *et al.* (1993) [3] showed that metaplasic acinar cells are localized within the same basal membrane and are joined with gastric cells through desmosomes, which might be a hint that progenitor cells for pancreatic metaplasia are part of normal gastric epithelium. Authors have also observed a striking similarity between parietal and metaplasic cells.

We consider that the diagnosis of pancreatic metaplasia is quite difficult on gastric biopsies, especially when the inflammatory process is abundant, because acinar cells can be mistaken with parietal cells from the bottom of gastric glands. In these situations, immunohistochemistry techniques can bring a considerable advantage, highlighting the presence of enzymes characteristic to pancreatic acinar cells. All authors agree that the islands of acinar epithelial cells produce pancreatic enzymes like amylase, lipase and trypsinogen [3]. Molecular pathogenesis of pancreatic metaplasia is insufficiently known. Metaplasic cells probably result from an aberrant differentiation of stem cells present at the neck of gastric glands [9].

Our study confirms that hypothesis as we observed a direct continuation between the acin pancreatic structures and cells from gastric glands or crypts.

Johansson J *et al.* (2010) [10], while examining biopsies coming from eso-gastric junctions of 644 patients, found pancreatic acinar metaplasia in 19% of the patients, out of which 8% in the esophageal mucosa, associating Barrett esophagus, and 11% on gastric mucosa surrounding the cardia. Pancreatic acin metaplasia above the eso-gastric junction was associated with the female gender, while the one below the junction positively correlated with the presence of Helicobacter pylori. The author considers that eso-gastric pancreatic metaplasia may be an age-dependent lesion, associated with *Helicobacter pylori*, female gender and gastro-esophageal reflux. However, the nature of the metaplasia at this level remains obscure.

In recent years, through studies of molecular biology, a series of key factors in pancreatic organogenesis were characterized [11]. The transcription factor PDX-1 (pancreatic duodenal homeobox-1), also named IPF-1, could be considered a major factor in the exocrine and endocrine gland differentiation in the pancreas. In the stomach, PDX-1 was demonstrated to be essential in differentiating endocrine cells in the antropyloric region in mice, and eliminating PDX-1 induced a severed impairment of the development of gastrin–secreting cells in the antrum [12]. Transcription factor PDX-1 is expressed both in adult pancreatic cells, and in cells of the gastric antrum and duodenal mucosa. Expression of PDX-1 is associated with intestinal metaplasia but not with pseudopyloric metaplasia [8]. Gastrointestinal metaplasic cell lines represent precursor states of gastric neoplasia. Two types of metaplasia are associated with gastric cancer: intestinal metaplasia characterized by goblet cells, and pseudopyloric metaplasia.

Buettner M *et al.* (2004) [7] showed through immunohistochemistry studies that gastric parietal cells surrounding the nests of pancreatic metaplasia presented a strong cytoplasmatic staining for PDX-1, contrasting with parietal cells of the normal mucosa of the corpus, which were not reactive. This might indicate that an insufficient differentiation on the parietal cell line could be responsible for pancreatic metaplasia.

Nuclear expression of PDX-1 was primarily found in the periphery of metaplasic areas or in gastric cells adjacent to pancreatic metaplasia sites. This indicates that PDX-1 plays a role in the initiation of the metaplasia at the gastric mucosa level.

These metaplasic areas, in which PDX-1 was poorly expressed, would represent more pronounced lesions of pancreatic acini in adults, which are also PDX-1 negative [13, 14].

Conclusions

Pancreatic metaplasia of gastric mucosa can be localized at an atral level and can associate gastroduodenal ulcers. Metaplasic cells, through the secretions they produce, can alter the local pH level and can favor the apparition of gastritis and even ulcers.

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