A rare case of signet-ring cell carcinoma associated with poorly differentiated adenocarcinoma of the non-ampullary duodenum

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Abstract
Primary duodenal cancer is a rare entity accounting for only 0.3% of all gastrointestinal cancers. Histopathologically, most duodenal cancers are mucin-producing adenocarcinomas, 34% being poorly differentiated. Signet-ring cell (SRC) carcinoma is extremely uncommon in the duodenum. Herein, we report a rare case of SRC carcinoma associated with poorly differentiated adenocarcinoma of the non-ampullary duodenum in a 74-year-old woman. The patient was admitted to the hospital for persistent epigastric pain, significant weight loss and hypochromic microcytic anemia. Esophago-gastro-duodenoscopy revealed a protruded lesion, with ulceration in the second portion of the duodenum, above the papilla. The patient was referred to surgery and pancreatico-duodenectomy with lymph node dissection was performed. The tumor consisted predominately of SRCs, Periodic Acid Schiff (PAS)–Alcian blue positive. The tumor cells were CDX2, cytokeratin (CK) 7 and CK 18/8 positive, which suggested a primary upper gastrointestinal tract site of origin. Immunostaining for mucin (MUC) 2 and MUC5AC was also positive demonstrating the duodenal goblet cells differentiation with a mixed gastric-foveolar and intestinal phenotype. Based on the morphological features and the immunohistochemical profile, a diagnosis of SRC carcinoma associated with poorly differentiated adenocarcinoma of the non-ampullary duodenum was set.

Keywords: signet-ring cell carcinoma, duodenum, goblet cell.

Introduction
Signet-ring cell (SRC) carcinoma is uncommon in the small intestine, colon and rectum, with a reported incidence of only 0.1–0.9% [1, 2]. More than 96% of SRC carcinomas occur in the stomach. However, rarely, other organs might be affected, including breast, gallbladder, pancreas, urinary bladder and large bowel [3]. To our knowledge, only 20 cases of SRC carcinoma of the duodenum have been reported [4, 5] in the literature up to present date.

Familial adenomatous polyposis, hereditary non-polyposis colorectal cancer syndrome, Peutz–Jeghers syndrome, Crohn’s disease, celiac disease, cystic fibrosis and cholecystectomy are among the identifiable risk factors for developing small intestinal adenocarcinoma [6, 7]. SRC tumors generally carry a poor prognosis regardless the site of origin with advanced (stage III of IV) disease [8, 9]. The most frequent clinical symptoms of duodenal cancer include epigastric pain, nausea, vomiting, postprandial bloating, weight loss [10–12].

Herein, we report a rare case of SRC carcinoma associated with poorly differentiated adenocarcinoma of the non-ampullary duodenum in a 74-year-old woman, aiming to highlight the important diagnostic challenges raised by this rare entity.
specimen showed a 40 mm diameter ulcer-infiltrative tumor, 14 mm in thickness, located in the second part of the duodenum (at 25 mm proximal to the ampulla, 90 mm from the proximal resection margin and 120 mm from the distal resection margin), infiltrating the pancreas. Ten lymph nodes were also evaluated (five peripancreatic, four in the celiac trunk and one in the hepatic hilum). The specimen was fixed in 10% buffered formaldehyde; the tumor was extensively sampled (one block per cm) and further processed according to routine practice guidelines. Five-μm-thick sections were stained with Hematoxylin–Eosin (HE). Immunohistochemistry was performed on 4-μm-thick sections using the labeled Streptavidin–Biotin–peroxidase complex system. The antibodies (clone, source) included: cytokeratin 7 (CK 7, mouse monoclonal, OV-TL 12/30, Cell Marque), cytokeratin 8/18 (CK 8/18, mouse monoclonal, B22.1 & B23.1, Cell Marque), mucin (MUC) 5AC (mouse monoclonal, MRQ-19, Cell Marque), Ki67 (rabbit monoclonal, SP6, Cell Marque), estrogen receptor (ER) (rabbit monoclonal, SP1, Cell Marque), CDX2 (rabbit monoclonal, EPR2764Y, Cell Marque), MUC2 (mouse monoclonal, MRQ18, Cell Marque). Pre-treatment using the antigen retrieval technique was performed for all antibodies. Appropriate positive controls ran simultaneously for all tested antibodies. In addition, structures within the examined section known to express the detected antigen also served as an internal positive control. Histochemical stainings with PAS–Alcian blue were also performed. At the microscopic evaluation, approximately 60% of the tumor was composed of SRC carcinoma; the tumor cells revealed the characteristic “signet-ring cell appearance”, showing a central, optically clear, globoid droplet of cytoplasmic mucin with an eccentrically placed nucleus and extracellular mucin. The remaining 40% tumor component was poorly differentiated (non-SRC type) with atubular, cribriform architecture, and included goblet cells. The nuclei were large and markedly hyperchromatic with a high mitotic index (Figure 3). The tumor cells were diffusely positive for PAS–Alcian blue (Figure 4).

On immunohistochemical (IHC) evaluation, the tumor cells stained strongly and intensely positive for CDX2 (nuclear staining), and CK 18/8 (cytoplasmic staining). Immunostaining for MUC2 and MUC5AC were also
positive (cytoplasmic staining). IHC staining for CK 7 and ER were negative.

Based on the morphological features and the IHC profile, a diagnosis of SRC carcinoma associated with poorly differentiated adenocarcinoma of the non-ampullary duodenum was set.

The positive CDX2 and CK 18/8 expression (with negative CK 7 profile) suggested a site of origin in the upper gastrointestinal tract. The positive cytoplasmic staining for MUC2 and MUC5AC advocated for the duodenal origin of the goblet cells, with a mixed gastric-foveolar and intestinal phenotype (Figures 5–11).
Primary duodenal carcinomas are rare tumors (about 0.3% of all malignant tumors of the gastrointestinal tract) [13], and adenocarcinomas represent the most frequent histological type [14]. The tumors are mainly located in the third and forth portion of the duodenum (45%), followed by the second part of the duodenum (40%), and the duodenal bulb (15%) [15].

Due to the local anatomy, the diagnosis of primary tumors arising from the third or forth portion is much easier to be set than the diagnosis of the tumors located in the first or second part of the duodenum. Differential diagnosis with duodenal invasion from a pancreatic cancer, distal bile duct cancer, and gastric cancer should be considered when duodenal tumor is located in the first or second part of the duodenum. The development of advanced endoscopic and imagistic methods, as well as an accurate histological examination, allows a better preoperative characterization of duodenal tumors. Histologically, the origin of SRC remains unknown. One theory regarding the etiology is that the SRCs are thought to originate in ectopic gastric mucosa found in the duodenum. Another theory is that SRC carcinoma arises from gastric type metaplastic epithelium [8, 9, 16]. The best known tumor of this type is the Krukenberg tumor of gastric origin [14] and carcinomas of the colon, appendix and breast are the next most common site of origin [17].

A study by Terada showed a tendency for the MUC immunoreactivity to be strong and diffuse in primary gastric SRC carcinomas with a high expression percentage (MUC5AC: 67%), and for the MUC immunoreactivity to be weak and focal in those with a low expression percentage (MUC2: 13%). In addition, there was a tendency for the MUC immunoreactivity to be strong and diffuse in primary colorectal SRC carcinomas with a high expression percentage (MUC2: 92%), for the MUC5AC immunoreactivity to be weak and focal with a low expression percentage (33%) [18, 19]. Walsh et al. reported on the similar phenomenon and the expression of MUC5AC and MUC2 in 100% of the SRC carcinomas from the colorectal region, where there is intestinal epithelium similar to the small intestine (duodenum) [20].

In our case, the expression of MUC2 was mainly seen in the goblet cells, while the expression of MUC5AC was positive only in the gastric foveolar epithelial cells. Accordingly, the MUC apomucin profile of this tumor corresponded to neither primary gastric SRC carcinoma nor primary colorectal ring cell carcinoma. This tumor had cells that were consistent with mixed gastric foveolar and intestinal phenotypes. The similarity in MUC apomucin profiles of this tumor and goblet cells may indicate that this tumor derived from duodenal goblet cells with MUC5AC expression.

Regarding the incidence of primary duodenal carcinomas, the data vary in different reports: 3.7 cases per one million persons per year in USA [21]. A publication of the American Association for Cancer Research (cosponsored by the American Society of Preventive Oncology), reported 5.9 cases in a Swedish study [22] and 5.4 cases in a recent Danish report [14]. Pancreatectoduodenectomy represents the therapy of choice for tumors located in the first and second part of the duodenum, while segmental resection is performed for tumors located in the third or forth part of the duodenum [23].

SRC tumors generally carry a poor prognosis regardless of site of origin, with over 80% of SRC diagnoses presenting with advanced (stage II of IV) disease [8, 9]. The oncological evaluation of patients is advisable for a proper therapy. However, the role of oncological treatment is still under debate. According to published data, it seems that adjuvant chemoradiotherapy does not improve survival [24–26]. On the other hand, lymph nodes involvement of, as well as curative resection of tumor, have an impact in patient’s survival [27]. Also, the localization of the duodenal neoplasia may affect survival. Proximal location is associated with a worse survival, compared with distal location [23, 24].

Herein, we report a rare case of duodenal SRC carcinoma associated with a poorly differentiated adenocarcinoma component, considered to have arisen de novo from the non-ampullary duodenal mucosa with a gastric foveolar and intestinal phenotypes. Although rare, knowledge and recognition of this entity is important as it may raise important diagnostic challenges in daily practice. The differential diagnosis of the tumor includes metastases from the stomach, colon, pancreas/biliary tract, appendix and ovary.

**Conclusions**

The authors declare no conflict of interests.

**Informed consent**

On admission, written informed consent was obtained from patient who participated in this study.

**Ethics Committee approval**

Hospital Ethics Committee approval was obtained.

**Financial disclosure**

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