Amphicrine (mixed adenoneuroendocrine carcinoma) of the duodenum and coexistent metastatic well differentiated neuroendocrine tumour

Stefano Serra

Runjan Chetty

Abstract

A 56-year-old man with a clinical history of pancreatitis was diagnosed with a periampullary carcinoma during investigation for increase of liver enzymes. Biopsies confirmed an adenocarcinoma. A Whipple resection showed an amphicrine carcinoma and a metastatic neuroendocrine tumour to the peripancreatic lymph nodes. High-grade amphicrine carcinoma did not spread to nodes. It is unlikely that the well differentiated tumour is part of the duodenal amphicrine carcinoma but rather from a separate, undetected well differentiated neuroendocrine carcinoma located elsewhere.

This case highlights an unusual combination of neuroendocrine tumours.

Keywords adenoneuroendocrine carcinoma; amphicrine; duodenum; neuroendocrine

Case report

A 56-year-old man with a clinical history of pancreatitis due to pancreatic stones presented with an increase of liver enzymes. An ERCP was performed and a friable area adjacent to the ampulla of Vater was noted. Multiple biopsies were taken. A cholangiogram revealed a dilated biliary tree with an obstructive so a stent was inserted. The periampullary biopsies revealed the presence of an adenocarcinoma compatible with pancreatobiliary origin; the common bile duct brushing was reported as suspicious for adenocarcinoma. A computed tomography scan did not clearly identify the tumour in the periampullary area. However, multiple enlarged peripancreatic lymph nodes were identified. Intrahepatic biliary duct dilation with associated pneumobilia was also seen. The pancreatic duct was diffusely dilated, containing a 9 mm calcification within the proximal portion of the duct. There was no evidence of involvement of the superior mesenteric artery or vein or the portal vein. The gallbladder contained small calcified stones. The spleen, kidneys and adrenal glands were unremarkable. The patient underwent a Whipple resection.

Pathologic findings

Macroscopic examination revealed an ill-defined, firm tan area in the duodenal mucosa adjacent to the ampulla, measuring 1.5 × 1.0 × 1.0 cm. The tumour extended into adjacent distal common bile duct wall. In addition, 25 regional lymph nodes were dissected.

Microscopically, the lesion consisted of small glands, as well as irregular nests and cords of atypical cells infiltrating a desmoplastic stroma (Figure 1). The atypical cells showed large nuclei with "salt and pepper" chromatin and granular eosinophilic cytoplasm. Frequent goblet cell differentiation and occasional extracellular mucin pools were also seen (Figure 2). In other areas, distinct well-formed malignant glandular structures were also present (I think that the morphological features were uniform, similar all over the tumour). Perineural and lymphovascular invasion were present. The lesion extended focally into the underlying pancreas and ampulla. The adjacent duodenal mucosa showed evidence of intraepithelial high-grade dysplasia.

The tumour was focally immunoreactive for chromogranin (Figure 3) and synaptophysin (approximately 30% of the tumour cells), diffusely positive for CK7, CK20, CK19 and CDX2. These features were in keeping with amphicrine carcinoma (mixed adenoneuroendocrine carcinoma, intermediate grade using WHO 2010 terminology). The MIB1 index was approximately 60%.

Electron microscopy was performed and the tumour cells contained variably sized and shaped membrane bound dense-core neurosecretory granules of type. Also round to oval, electron-lucent membrane-bound secretory mucin-type exocrine granules were also present in the same cells (Figure 4).

In addition, a second lesion was present, which appeared to be in peripancreatic lymph nodes only. It consisted of large round to oval cells with "salt and pepper" chromatin and abundant eosinophilic cytoplasm, arranged in large nests (Figure 5). A total of 5 of 25 lymph nodes were involved by this lesion. The metastatic tumour was diffusely and strongly immunoreactive for synaptophysin (Figure 6), chromogranin and focally positive for gastrin; but negative for insulin, glucagon, somatostatin, serotonin, VIP, PP, CK19, CDX2 and TTF1. The MIB 1 index was approximately 1%. The findings were in keeping with metastatic well-differentiated, grade 1, neuroendocrine tumour according to the WHO 2010. A primary lesion of a similar morphology was not found anywhere else in the specimen.

Discussion

In 1924, Cordier reported gastrointestinal tumours with exocrine and endocrine components. The term "amphicrine" was advocated by Ratzenhofer in 1977 for cells which synchronously displayed exocrine and endocrine differentiation.[1]

Amphicrine cells have been divided into two subgroups[2,3]: cells which have the endocrine and exocrine component separated in the cytoplasm (apical mucus granules and basal neuroendocrine granules) and, cells which have both components

Stefano Serra *MD Department of Pathology, Laboratory Medicine Program, University Health Network/University of Toronto, Toronto, Canada. Conflicts of interest: none declared.*

Runjan Chetty *MB BCh FRCPath Department of Pathology, Laboratory Medicine Program, University Health Network/University of Toronto, Toronto, Canada. Conflicts of interest: none declared.*

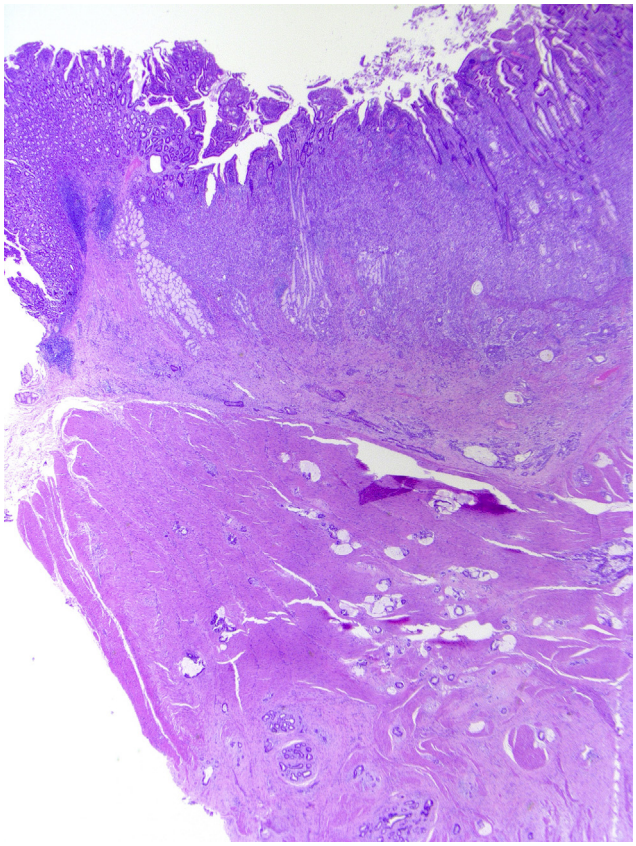

Figure 1 A tumour originating in duodenal mucosa and extending into the ampulla of Vater.

mixed in the cytoplasm. In 1987, Lewin suggested classifying exocrine tumours with neuroendocrine features into three groups: collision tumours, combined tumours and amphicrine tumours. The 2000 WHO classification of neoplasm of the gastrointestinal tract defined these neoplasms as mixed exocrine–endocrine tumours when each component represented at least 30% of the tumour. In 2010, the new WHO classification defines these neoplasms as "mixed adenoneuroendocrine carcinomas" (MANECs).[4] The routine use of immunohistochemical stains has

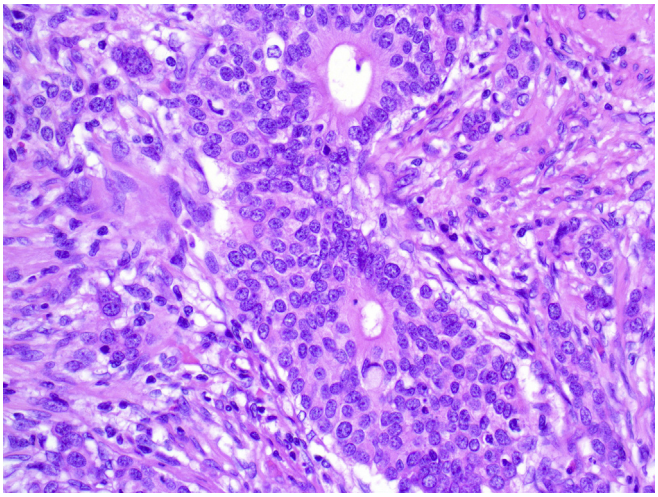

Figure 2 The tumour is arranged in cords, nests and occasionally, well-formed glandular structures.

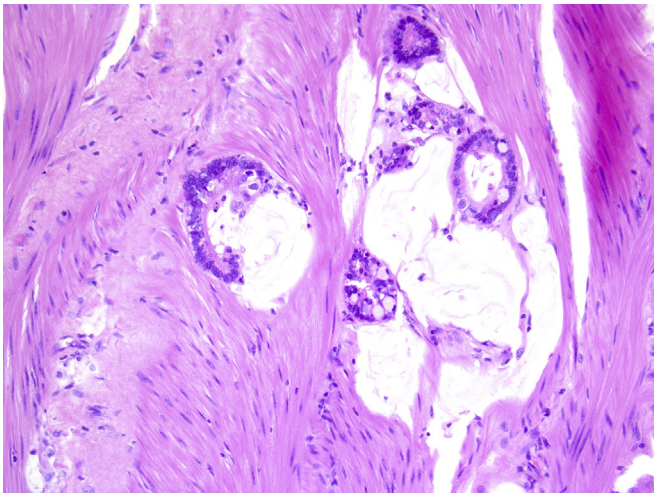

Figure 3 In areas there was extracellular mucin and goblet cell like areas, resembling a goblet cell carcinoid from the appendix.

shown that neuroendocrine cells are frequently identified in non-neuroendocrine neoplasms. Conversely, the presence of an exocrine component in neuroendocrine neoplasm has also been reported especially in high grade neuroendocrine carcinomas. Thus, there is a spectrum of combinations of exocrine and neuroendocrine neoplasms with a spectrum of change: adenocarcinomas with a neuroendocrine component at one end, and neuroendocrine neoplasms with an exocrine component at the other end. In the middle of this spectrum, there are the mixed exocrine–neuroendocrine neoplasms with at least 30% of either the endocrine or exocrine component. In addition, both the exocrine and neuroendocrine components can show variable morphological features, as well as different degrees of differentiation. However, mixed exocrine–neuroendocrine tumours are rare entities. The mixed adenoneuroendocrine carcinomas are characterized by both gland formation and neuroendocrine features and are defined as carcinomas since both components are malignant. In some MANECs, the exocrine and the neuroendocrine component are confined to separate areas of the same neoplasm (composite or collision neoplasms); whereas, in other

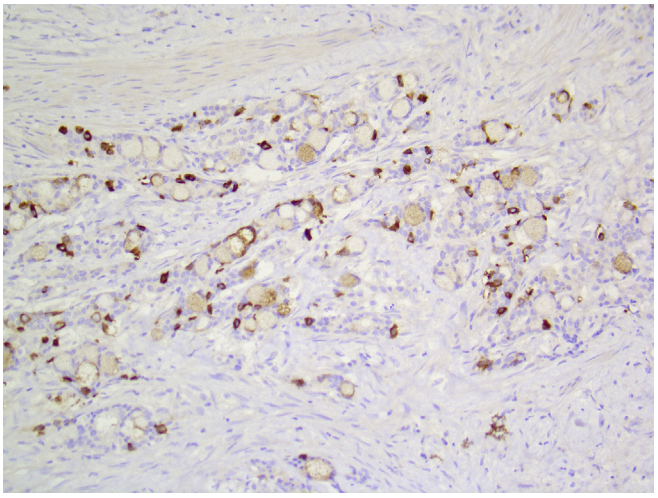

Figure 4 Strong chromogranin immunoreactivity of the tumour cells.