Primary gastric combined adeno-small cell neuroendocrine carcinoma

Case report

A 66-year-old man presented with intermittent upper abdominal pain (epigastralgia) for a few months associated with heartburn, intermittent nausea and bloating. The patient denied vomiting, dysphagia or odynophagia. There was no history of significant weight loss, anorexia, overt gastrointestinal bleeding or alterations in bowel movements. His past medical history included type 2 diabetes mellitus, hypertension and hypothyroidism. He was a former smoker with 20 pack-year smoking history, and drank alcohol occasionally. Family history was notable for his sister and two nieces with breast cancer. The patient's symptoms were attributed to gastro-oesophageal reflux disease (GERD) and were empirically treated with proton pump inhibitor (PPI)—omeprazole. However, his symptoms continued to worsen and he was referred for endoscopic evaluation. Physical examination was significant only for mild epigastric tenderness. There was no hepatosplenomegaly, ascites or lymphadenoapthy. Initial laboratory investigations were unremarkable.

Oesophagogastroduodenoscopy (EGD) was performed, which revealed a 20 mm semi-sessile polyp on the greater curvature in the fundus of the stomach (**Figure 1**). Histopathology of the gastric biopsies from this polypoid mass showed solid proliferation of small-sized tumour cells with scanty cytoplasm and hyperchromatic nuclei, positive for immunostaining with anti-chromogranin A and anti-synaptophysin (**Figures 2, 3A1, 3A2**). There was also a minor

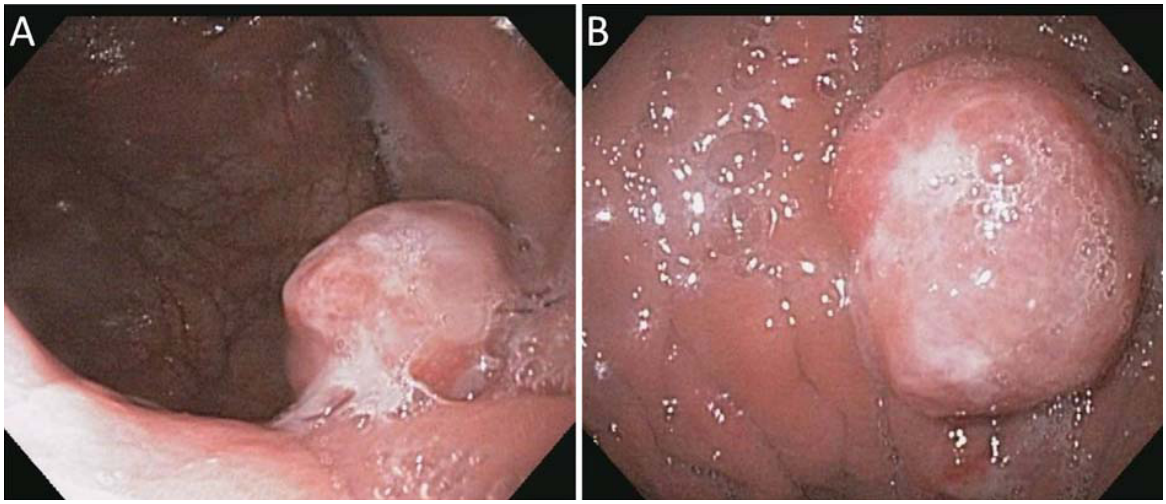

Figure 1: Oesophagogastroduodenoscopy (EGD) showing a 20 mm semi-sessile polyp in the gastric fundus (A: side view, B: top view).

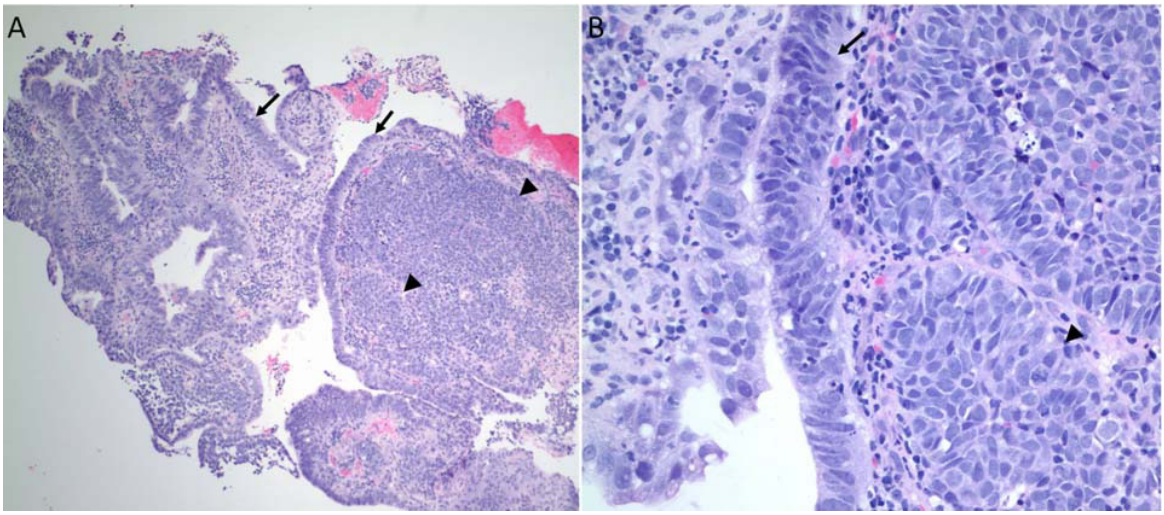

Figure 2: H&E stain (A: 100X, B: 400X magnification) showing a combined tumour exhibiting two morphologies—neuroendocrine mixed with an adenocarcinoma component. Predominant small cell neuroendocrine (large arrowhead) component showing prominent nucleoli and open chromatin. The adenocarcinoma (small arrow) component showing features of columnar epithelium with tall, elongated, and pseudostratified nuclei.

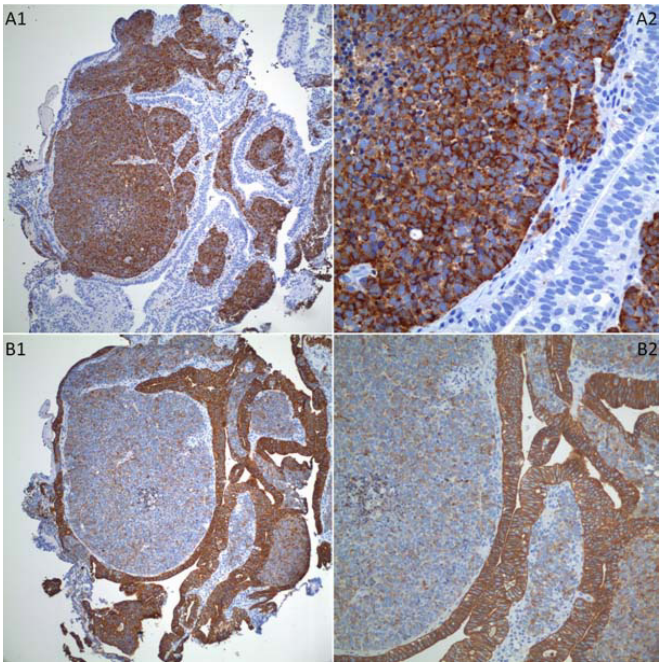

Figure 3: Immunohistochemical staining for chromogranin (A1: 100X, A2: 400X magnification) showing strong positivity in a granular cytoplasmic pattern seen in small cell carcinoma that indicates neurosecretory granules of this cell origin. Synaptophysin (which is not shown) showed similar and as intense staining. Immunostaining for cytokeratin (B1: 100X, B2: 400X magnification) showing intense positivity in the glandular epithelium seen in adenocarcinoma, and perinuclear dot-like positivity in the small cell component.

component of neoplastic cells with gland formation being positive for anti-cytokeratin (**Figures 2, 3B1, 3B2**). Based on these findings, a diagnosis of combined gastric small cell neuroendocrine carcinoma–adenocarcinoma was established. Immunostaining for MIB1 showed high proliferation index in both the neoplastic components. Subsequent, computed tomography (CT) scan of the chest, abdomen and pelvis showed a 2 cm polypoid mass in the gastric fundus with enlarged regional lymph nodes (largest 3 cm coeliac lymph node, , but no evidence of visceral metastasis or disseminated disease. Magnetic resonance imaging (MRI) of the brain did not show metastasis. A positron emission tomography (PET)-CT scan showed no focal [18F]-fluorodeoxyglucose (FDG) uptake in the stomach, or lymph nodes and no other focus of the disease.

Neoadjuvant chemotherapy followed by radiotherapy and surgical resection was planned. He has completed four out of total six cycles of combination chemotherapy consisting of etoposide 100 mg/m^2 on days 1–3 and carboplatin AUC-5 on day 1 of a 28-day cycle. Follow-up imaging showed significant regression of abdominal lymphadenopathy and the gastric mass was no longer visible. The patient reported symptomatic improvement and continues to do well without any complications.

Discussion

Small cell carcinomas (SmCC) are among the most aggressive, poorly differentiated and highly malignant of the neuroendocrine tumours (NETs).[1] SmCC predominantly affect the lung; only about 5% of SmCC have an extrapulmonary origin.[2] Extrapulmonary SmCC have been reported in various organs such as the oesophagus, colon, rectum, pancreas, uterine cervix, urinary bladder, prostate, kidneys and salivary glands.[3] Primary SmCC areextremely rare in the stomach, representing <0.1% of all primary gastric cancers.[4] A majority of the cases have been reported among Asians with a minority of case reports from western countries. These occur more frequently in the sixth to seventh decade of life and in men.[2]

The most frequent location in the stomach is the upper third (45.2%), followed by the antrum (35.2%) and middle third (19.2%).[2] Progressive dysphagia and weight loss are often the first symptoms of the disease, similar to other gastric malignancies. In the World Health Organization (WHO) classification of gastrointestinal tumours, SmCC of the stomach have been recognized as an "independent entity affecting the stomach". There are two types of SmCC—a "pure type" and a "composite or combined-type" admixing glandular and/or squamous differentiation. In the reported cases, a higher prevalence of "pure-type" (60%) than "composite-type" (40%) have been found. [2]

The exact histogenesis of SmCC of the stomach remains unclear. It has been proposed to originate from either the argyrophilic Kulchitsky cells found in the bronchial and gastric mucosa (amine precursor uptake and decarboxylation [APUD] cells) or from an endodermal origin.[2] Synaptophysin, chromogranin A, CD56 and other immunohistochemical markers have been described as reliable markers for detecting neuroendocrine differentiation. the CD56 marker is also helpful in differentiating between SmCC and large cell carcinomas.[4] The biological features of gastric SmCC resemble those of pulmonary SmCC, which is consistent with the histological and immunohistochemical similarity of the two tumours.[2]

Gastric SmCC has a poor prognosis with a mean survival of 7 months.[5] This neoplasm shows a high propensity to distant metastasis and locoregional involvement.[1] The choice of

treatment for gastric SmCC remains controversial. The surgical approach follows the same criteria of adenocarcinoma as it is linked to the primary tumour location in the stomach.[2] Because of similarity in the biological and clinical characteristics of gastric and pulmonary SmCC, some authors affirmed that the validity of chemotherapy with a regimen specific for pulmonary SmCC may be suitable for the treatment of this tumour.[5] The combination chemotherapy usually consists of cisplatin and etoposide or irinotecan.[2] Multimodality approaches are promising but more studies are needed before any single combination can be recommended.[1]

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Chronic hepatic abscess due to gallbladder perforation: three cases and exact nomenclature

Introduction

Gallbladder perforation is a rare cause of secondary peritonitis in the Eastern hemisphere, with a higher mortality rate than that caused by perforation of other hollow viscera.[1,2] Owing to prompt management of symptomatic cholelithiasis, the incidence of gallbladder perforation has also declined worldwide in patients of acute cholecystitis (~1%).[3,4] Niemeier in 1934[5] classified gallbladder perforation into three types: type I—chronic perforation with the presence of a fistulous communication between the gallbladder and some other viscus; type II—subacute perforation where the perforated gallbladder is surrounded by an abscess walled off by adhesions from the general peritoneal cavity; and type III—acute perforation of the gallbladder into the free peritoneal cavity without protective adhesions. Though this classification has withstood the test of time, there is some debate regarding its modification, especially about inclusion of specific types such as cholecystohepatic or cholecystobiliary fistulae.[6–8]

Type II is the most common type (40%–63% cases) of gallbladder perforation. Most cases present with signs of localized peritonitis such as pain, fever, tenderness, and, leukocytosis.[9,10] Among type II, however, hepatic abscess with gallbladder perforation is very rare and has been reported in only a few cases.[8,11–13] We present three cases of gallbladder perforation with hepatic abscess formation. In all three patients, the presentation was insidious, with minimal symptoms. We wish to emphasize the unexpected location of the pathology as well as the uncommon presentation. The merits of modification of the Niemeier's classification are also discussed.

Case 1

An 18-year-old boy presented with mild upper right quadrant abdominal pain of 3 weeks' duration. There was no history of jaundice, acute pain, vomiting, fever, or other significant complaints. On examination, the boy was found to be afebrile and moderately-nourished with no abnormal signs. Ultrasound abdomen was suggestive of irregular thickening of the gallbladder with multiple calculi in the lumen, along with a hypoechoic septate subcapsular hepatic collection abutting the right anterior lower chest wall. Computed tomography (CT) scan revealed an irregularly thickened gallbladder wall with a defect in the fundal region, communicating with a localized subcapsular hepatic septate collection (**Figures 1a, 1b**). The gallbladder was also filled with sludge and calculi, and there