CASE REPORT

An unusual cause of obstructive jaundice

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Small-cell carcinomas of lung origin have been well characterised for their clinico-histopathological features. However, extrapulmonary small-cell carcinomas are rare, and in particular, they are extremely rare at the ampullary region. We report herein a case of small-cell carcinoma of ampulla of Vater and review its clinical, histological, and immunohistochemical features.

Introduction

Small-cell carcinoma of extra-pulmonary origin is rare and accounts for less than 2% of ampullary malignancies. It is a neuroendocrine tumour and confers a poor prognosis associated with its poorly differentiated histology, which differs from carcinoid, another neuroendocrine tumour of a more benign nature. We present a case of small-cell carcinoma of ampullary of Vater.

Case report

A 52-year-old man was admitted to hospital with a history of passing tarry stools and epigastric pain for 3 weeks. On examination, he was deeply jaundiced but had no stigmata of chronic liver disease. Laboratory data of the patient are shown in the Table. Upper gastrointestinal endoscopy revealed a huge friable ulcerative tumourous growth at the ampullary region. It occupied most of the duodenal lumen and the cholangiogram showed a long distal common bile duct stricture with proximal dilatation (Figs a and b). A plastic stent (10-French size, 12 cm long) was inserted to bypass the stricture and a mucinous discharge emanating from the stent was immediately noted. Papillary biopsy revealed the tumour was small-cell carcinoma of the ampulla of Vater. The lesion was characterised by sheets of oval cells having scanty cytoplasm, and hyperchromatic nuclei. Immunohistochemical studies demonstrated focal positive staining for cytokeratin, weakly positive for synaptophysin, whilst staining for chromogranin, leukocyte common antigen, and myeloperoxidase was negative, thus supporting the neuroendocrine lineage of the lesion (Figs c and d). Computed tomography (CT) showed the tumour was widely metastasised to both lobes of the liver, lymph nodes in the para-aortic and mediastinal region, but there was no focal lung mass or pleural effusion (Fig e). Further relevant blood tests revealed an alpha-fetoprotein level of 1.9 ng/mL (reference level, <6 ng/mL), carcinoembryonic antigen (CEA) level of 1.6 ng/mL (reference level, <4 ng/mL in non-smokers and <8.9 ng/mL in smokers) and cancer-associated antigen (CA) 19-9 level of 11 071 U/mL (reference level, <37 U/mL). The patient's liver function did not improve after endoscopic biliary drainage, so bypass surgery (choledochogastro-jejunojejunostomy) was performed to achieve good biliary drainage and the serum total bilirubin level decreased to 16 μmol/L. Cyclical intravenous chemotherapy (etoposide 170 mg for 3 days combined with carboplatin 500 mg for 1 day) was given 3 weeks afterwards. However, the patient

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TABLE. Laboratory data of the patient

	Data	Reference range
Haemoglobin (g/L)	114	134-172
Mean cell volume (fl)	91	83-98
Total bilirubin (μmol/L)	167	5-20
Alkaline phosphatase (IU/L)	348	46-127
γ-Glutamyl transpeptidase (IU/L)	750	12-57
Alanine aminotransferase (IU/L)	161	10-57
Iron saturation (%)	33	20-55

deteriorated rapidly after the fourth cycle of the chemotherapy, whereupon CT revealed multiple, enlarging lymph nodes involving the mediastinum, upper abdomen, and hepatic regions. The patient succumbed 6 months after the diagnosis.

梗阻性黃疸的一個罕見病因

小細胞肺癌的臨床組織病理學特徵早已為人熟悉。可是肺外小細胞癌卻很罕見，尤其是發生在壺腹區的更為罕見。本文報告一宗壺腹乳頭癌上小細胞癌的病例，並探討其臨床、組織學及免疫組織化學特徵。

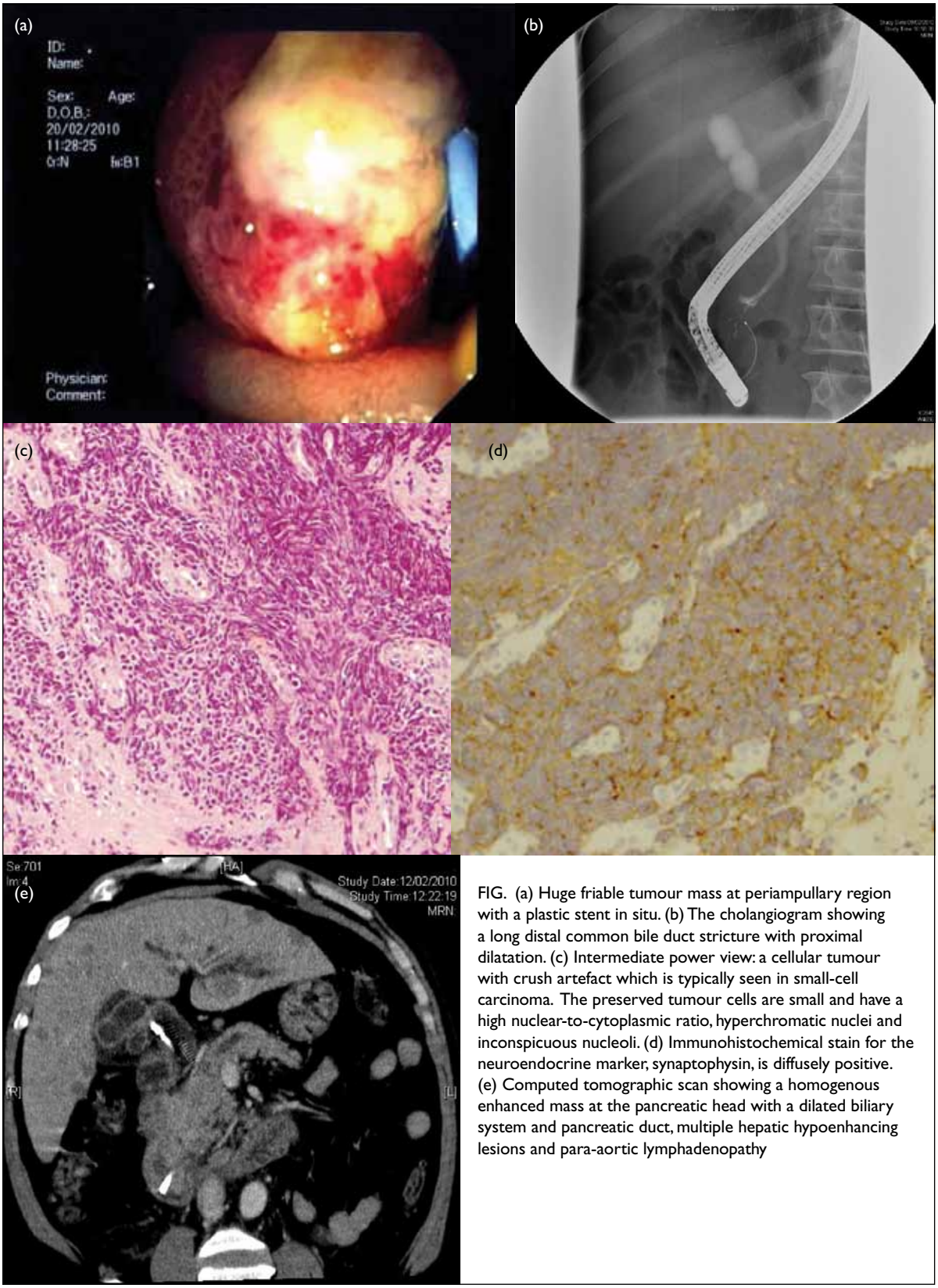

FIG. (a) Huge friable tumour mass at periampullary region with a plastic stent in situ. (b) The cholangiogram showing a long distal common bile duct stricture with proximal dilatation. (c) Intermediate power view: a cellular tumour with crush artefact which is typically seen in small-cell carcinoma. The preserved tumour cells are small and have a high nuclear-to-cytoplasmic ratio, hyperchromatic nuclei and inconspicuous nucleoli. (d) Immunohistochemical stain for the neuroendocrine marker, synaptophysin, is diffusely positive. (e) Computed tomographic scan showing a homogenous enhanced mass at the pancreatic head with a dilated biliary system and pancreatic duct, multiple hepatic hypoenhancing lesions and para-aortic lymphadenopathy

Discussion

Our patient presented with acute upper gastro-intestinal bleeding caused by a small-cell carcinoma of the ampulla, which is a neuroendocrine cell (NEC) tumour. In fact, NEC carcinomas of the gastro-intestinal tract account for less than 5% of all alimentary tract tumours.[1] It is suggested that they originate from pre-existing non-neoplastic multipotent stem cells, because of consistent expression of cytokeratins and CDX2.[2] Nearly all tumours arise sporadically, but in some patients there is a background of an inherited neoplastic syndromes such as multiple endocrine neoplasia type 1 and type-1 neurofibromatosis. According to the World Health Organization classification published in 2000, NECs can be categorised into well-differentiated relatively benign tumours (eg carcinoid), well-differentiated carcinomas of low-grade malignancy (eg atypical carcinoids) and poorly differentiated carcinomas of high-grade malignant potential (eg small- and large-cell carcinomas).[3] The criteria for these categories depend on histological differentiation, size, extension into surrounding tissues, angio- or peri-neural invasion and the presence of metastases.[4] This classification has considerable clinical relevance, in that well-differentiated benign tumours can be treated conservatively while poorly differentiated carcinomas usually require more aggressive therapy.[1]

These NECs account for less than 2% of ampullary malignancies (ie adenocarcinoma contribute more than 90%), whilst small-cell carcinoma is extremely rare.[5] Microscopically, these tumours are sheets and nests of tightly packed, small, round-to-fusiform tumour cells with scanty cytoplasm, hyperchromatic nuclei and a high nuclear-to-cytoplasmic ratio. Immunohistochemically, most are immunoreactive for neuroendocrine markers such as neuron-specific enolase, chromogranin A, synaptophysin and Leu7, as well as some epithelial markers such as CEA and CA 19-9.

Management of this disease depends on its staging; pancreatoduodenectomy with local lymph node dissection is the only standard treatment for limited disease.[6] Combined chemotherapy with cisplatin and etoposide has been employed as first-line chemotherapy because the genetic, pathological, and clinical features of small-cell carcinoma of the ampulla overlap with those of small-cell lung cancer (SCLC). However, thus far it does not reveal any survival benefit.[7] This is because at the molecular level there are several differences between NECs and SCLCs.[8] Unlike SCLCs, NECs show retention of both short arms of chromosome 3, whilst Bcl-2 overexpression is not at all common in NECs (33% vs 75-95% in SCLC). Histologically some NECs may have other components such that those arising from the gastric, colorectal, pancreatic and oesophageal regions may have features of adenocarcinoma and squamous cell carcinoma, whereas this does not happen in SCLC. Our patient had a rapid downhill course with about 6 months of survival after diagnosis. As compared to ampullary adenocarcinoma, the prognosis of small-cell carcinoma of ampulla is very poor, early metastases to the liver and regional lymph nodes being common.[9,10] The median survival of patients with small-cell carcinoma of the ampulla is about 5.8 months whereas that of ampullary adenocarcinoma is 30 to 50 months.[11] Because of the extremely poor prognosis and unsatisfactory responses to combined chemotherapy with cisplatin plus etoposide, there is a pressing need to develop novel forms of treatment.

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