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Primary giant hepatic neuroendocrine carcinoma: A case report

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ABSTRACT

Carcinoid tumours arise from neuroendocrine cells and may develop in almost any organ. These type of tumours actually are correctly termed neuroendocrine tumours. Hepatic neuroendocrine carcinomas rarely arise as primary tumour; in fact on 100 cases reported in literature just a few of these are of primary nature. We report the case of a giant hepatic neuroendocrine carcinoma in a 55-year-old man. The symptoms were only recurrent hypoglycemia and an abdominal mass. Diagnosis was performed by blood analysis, ultrasonography, TC scan and In111-DTPA-octreotide scan. Surgical treatment occurred by an en bloc removal of the mass and a wide resection with free margins. Histological examination confirmed diagnosis. Clinical and instrumental diagnostic follow-up show the patient still alive, in very good conditions and disease free two years after surgery.

1. Introduction

Primary hepatic carcinoids actually termed neuroendocrine carcinomas are rare tumours that are often diagnosed at a locally advanced stage. Despite about 100 reports in the literature very little information are known of primary hepatic carcinoids [1–8]. Several different investigations and long-term follow-up are necessary to ascertain the primary nature of these lesions. The majority is discovered accidentally when the tumour is already big and developed. They often present a large size and central liver localization but despite these discouraging resection approaches aggressive surgical treatment remains the gold standard therapy. Tumours not amenable to liver resection should be treated by chemotherapy or liver transplantation. Surgical treatment outcome data are not clear but long-term survival of most patients justify an aggressive surgical approach. We present a case of a 55 years old man who had a 30 cm tumour of the left liver, who is still alive and disease free two years after surgery.

2. Case report

A 55-year-old man in good state of health complained of recurrent hypoglycemia. There was no history of liver failure, haematemesis, flushing, or diarrhoea. Hypoglycemic status induced patient to come at our emergency room. Clinical examination showed a palpable hepatomegaly and large mass in epigastrium and left hypochondrium. Abdominal ultrasound scan revealed a heterogeneous 30 cm left lobe focal liver lesion. Contrast enhanced CT performed three days later showed a solid 183 × 158 × 214 cm little wing liver mass with a soft enhancement, an hypodense core with large colliquative areas and minute central calcifications. Laboratory data showed normal blood tests except for low levels of serum albumin 2.8 g/dl, and potassium 2.4 mEq/l. Hepatitis B and C serologies were negative. Serum tumour markers including CEA, AFP, CA 12.5, CA 19.9, gastrin and NSE were in the range level, while Chromogranin A were 3972 U/L with a range value 2.0–18.0. Chest CT didn't show any pathological sign or marker of metastasis linked to lung or linfonodes. We performed also an oesophagus–duodenum–gastroscopy which showed widespread and severe gastropathy interested gastric fundus and body. Compression ab exstriseco of the bulb and of duodenum. Liver biopsy confirmed suspect of NET (neuroendocrine tumour), it was positive for synaptophysin, CD 56, Ki67 proliferation index of 10% with diagnosis of

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NET G2 according to WHO-2010. Before operation we decided to perform also In111-DTPA-octreotide scan, which confirm a hyper intense accumulation of the marker at the known massive hepatic neoplasm. No other site of accumulation were found. During laparotomy we found a mass of 30 cm interesting IIs, IIIs, IVs, and which arrives since umbilical line thorough exploration of the abdominal cavity, small bowel, and mesentery was performed. We performed also intraoperative ultrasound scan which showed that the mass compresses the middle hepatic vein, while the right hepatic vein is pervious, but moved posteriorly. Ultrasounds confirmed that right lobe was free from disease. Left hepatic resection and colecistectomy were performed. When we removed the giant mass during surgical procedure the patient had a hypotensive crisis with severe bradycardia, but drug therapy saved immediately the patient. The patient went back home in good condition about 10 days later. Tc scan and blood exams didn't reveal any abnormalities. The resected specimen was almost entirely occupied by a 24 × 23 × 20 cm solid mass. Lesion was 3 cm far from resection margin. Neoplasia is organized in trabeculae, consisting of cells with eosinophilic cytoplasm (Fig. 1). At immunohistochemical examination neoplasia expressed synaptophysin, CD 56, Chromogranin A, is negative for hepatocyte antigen. The Ki 67 is expressed in about 5% of the neoplastic cells (Fig. 2). Immunohistochemical data are summarized in Table 1. Final diagnosis was neuroendocrine tumour NET G2 according to WHO 2010. Differential diagnosis was made to hepatocellular carcinoma, cholangiocellular carcinoma, hypervascularized metastasis, angiosarcoma, hemangiopericytoma, and a neuroendocrine tumour. At 36-month follow-up the patient shows no signs of liver recurrence or appearance of a primary tumour or secondary extrahepatic tumour. He is asymptomatic and fully functional. He performs only a monthly administration of somatostatin.

3. Discussion

Carcinoid tumours actually known as well-differentiated neuroendocrine tumours (NET) derive from neuroectodermal cells dispersed throughout a lot of anatomical sites. The digestive accounts about fifty-four percent but they also in respiratory, genital and head and neck district. In the United States the incidence of carcinoid tumours is 6.25 cases per 100,000 per year [1,2]. Maggard et al. demonstrate that incidence rates for carcinoid tumours have changed. The most common gastrointestinal site is not the appendix (as is often quoted), but the small intestine, followed in frequency by the rectum. The severity of pathology and survival rates differ between individual anatomical sites [1]. The rate of proliferation expresses by the number of mitoses per 10 high power microscopic fields and the percentage of tumour cells immunostained for Ki-67 antigen was introduced as the World Health Organization grading system of NET and correlates with prognosis. Using that scores NET are classified into three types: well-differentiated tumours of low grade malignancy with an indolent development and a good prognosis; moderately differentiated or intermediate grade neoplasms and poorly differentiated or high grade epithelial neoplasms that carry a poor prognosis. NET has typically slow growth and becomes clinically evident only at an advanced stage [9–11]. Primary liver neuroendocrine tumours have uncertain pathogenesis. They may originate from neuroendocrine cells present in the intrahepatic bile ducts [7,8]. However, primary hepatic NET is very rare and the first case was documented by Edmondson in 1958 [12]. In a range of presentation which goes from 3 to 83 years old we can describe a middle age of presentation of about 49–50 years old. Female are quite more affected by this pathology than males (58% of cases). This tumour, initially occurs without symptoms or with an unspecific abdominal pain. Other

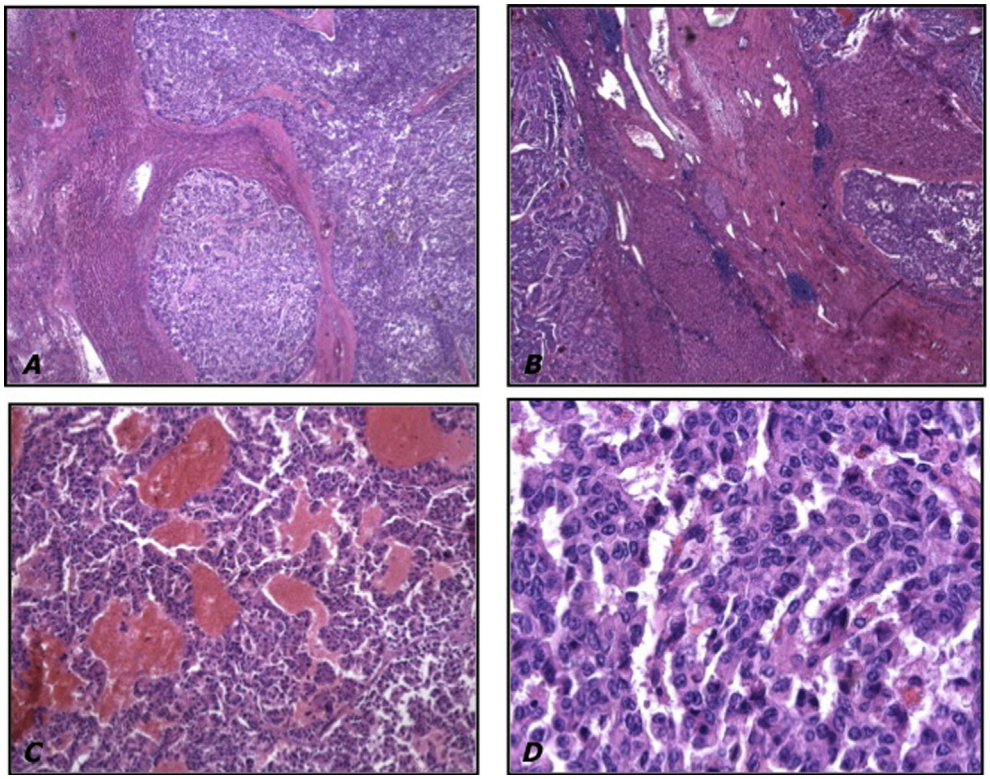

Fig. 1. Histochemical features of lesion: very vascularized neoplastic mass organized in trabeculae, consisting of cells with eosinophilic cytoplasm, atypical nuclear aspect and low mitotic index. Haematoxylin & Eosin staining. Original magnification ×4 (A); ×10 (B); ×20 (C); ×40 (D).

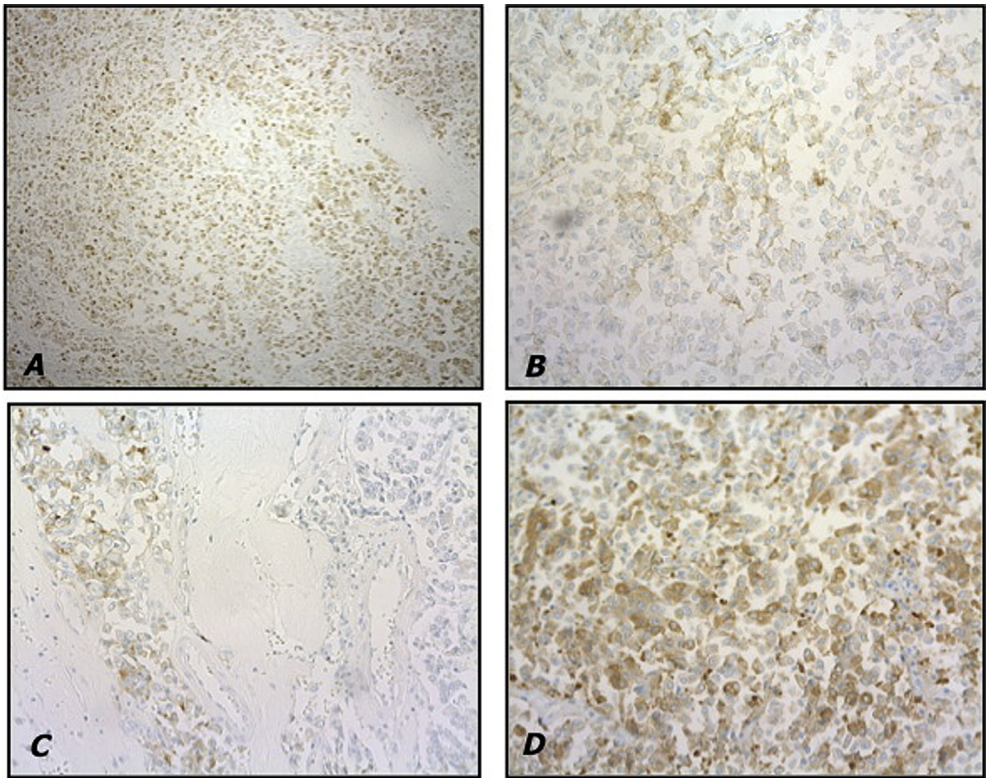

Fig. 2. Immunohistochemical findings using ABC/HRP method. Immunostaining for PAN cytocheratine (A); original magnification ×4. Immunostaining for CD 56 (B); original magnification ×10. Immunopositivity for Chromogranin (C); original magnification ×10. Immunopositivity for synaptophysin (D); original magnification ×20.

symptoms might be liver failure, haematemesis, flushing, or diarrhoea. Few patients showed Cushing and Zollinger–Ellison syndromes. The most frequently secreted hormones were gastrin (7/69 = 10.1%) and Chromogranin A. Most primary hepatic NETs are non-secreting although few researches actually described the secretion in the systemic circulation of several neuromediators like serotonin, histamine, bradykinin, gastrin, vasoactive intestinal peptide (VIP), insulin, glucagon, or prostaglandins [7,8]. Neovascularization plays an important role in development of all hepatic solid tumours. In hepatic neoplasms, neovascularization status is correlated with disease progression and patient prognosis. Endothelial progenitor cells (EPCs) have been proved to be the main source of adult neovascularization [13]. It has been confirmed that neovascularization is vital to further multiplication, metastasis, and recurrence in malignant tumours [14–16]. Differential diagnosis between primary hepatic NET and secondary localization should be established by number of masses and their size. A single large centrally situated tumour is suggestive of a primary tumour whereas neuroendocrine liver metastases present typically as multiple diffuse liver masses. Diagnostics procedure have as objective to detect the primary origin of the tumour and its neuroendocrine nature. The techniques that we might use are computerized tomography, magnetic resonance, CT or MR enteroclysis, somatostatin scintigraphy, octreotide scan, PET scan, gastroscopy, colonoscopy, endoscopic ultrasound of the pancreas, bronchoscopy, video capsule endoscopy or balloon enteroscopy, and operative exploration [17]. Hepatocellular carcinoma and cholangiocarcinoma may present areas of neuroendocrine differentiation [18,19]. Surgery should be the first-line therapy for patients with liver neuroendocrine tumour. Norton demonstrates that in primary and metastatic hepatic neuroendocrine tumour aggressive surgical approach can be performed safely. It results in excellent long-term survival and amelioration of symptoms [20]. However recurrences, mainly in the liver, remain high [21]. More recently liver transplantation (LT) has been proposed in selected patients that were not amenable to partial liver resection [22]. Liver metastases from neuroendocrine tumour (NET) can be treated by transarterial embolization (TAE) or transarterial chemoembolization (TACE) [23,24]. The interventional protocols for the management of liver metastases from neuroendocrine tumours are actually well described. For oligonodular liver metastatic deposits, local resection and/or LT is recommended, while in multinodular diseases with higher tumour load, TACE or TAE is recommended. New strategies for advanced neuroendocrine tumours in the era of targeted therapy are actually proposed. Several pathways and angiogenesis as important targets for NETs new molecular therapies [25]. In NETs, there is no hint of a remodelling of the Ca^{2+} toolkit, that has been observed in other malignancies, including renal cellular carcinoma [26–28], and prostate cancer [29], myelofibrosis [30], and has been put forward as alternative target for selective molecular therapies [16]. In conclusion primary hepatic carcinoid tumours are not frequent and their primary nature can only be diagnosed after thorough investigations and long-term follow-up. Aggressive surgical approach could be performed because long-term survival and cure can be expected. In selected

Table 1
Immunohistochemical results.

Marker	Score
PAN cytocheratine	+++
Synaptophysin	+++
CD 56	++
Chromogranin	+
Hep Par1	+
Cytocheratine 7	−
Cytocheratine 20	−

patients not amenable to partial liver resection liver transplantation can be considered. Some new therapeutic strategies are actually proposed.

Ethical Approval

Ethical approval was requested and obtained from the "Azienda Ospedaliera Cardarelli" ethical committee.

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Author contribution

Aldo Rocca: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also partecipated substantially in the drafting and editing of the manuscript.

Fulvio Calise: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Giuseppina Marino: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Stefania Montagnani: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Bruno Amato: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Germano Guerra: Partecipated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also partecipated substantially in the drafting and editing of the manuscript.

Conflicts of interest

All Authors have no conflict of interests.

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