Primary hepatic carcinoid: A case report and literature review

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Author contributions: Fenoglio LM and Severini S contributed equally to this work; Fenoglio LM, Severini S, Ferrigno D, Gollè G, Serraino C, Bracco C and Migliore E designed the research; Fenoglio LM, Severini S, Castagna E and Pomero F performed the research; Fenoglio LM, Severini S, David E and Salizzoni M analyzed the data; Fenoglio LM, Severini S and Ferrigno D wrote the paper.

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Received: January 15, 2009 Revised: April 10, 2009
Accepted: April 17, 2009
Published online: May 21, 2009

Abstract

Carcinoids are tumors derived from neuroendocrine cells and often produce functional peptide hormones. Approximately 54.5% arise in the gastrointestinal tract and frequently metastasize to the liver. Primary hepatic carcinoid tumors (PHCT) are extremely rare; only 95 cases have been reported. A 65-year-old man came to our attention due to occasional ultrasound findings in absence of clinical manifestations. His previous medical history, since 2003, included an echotomography of the dishomogeneous parenchymal area but no focal lesions. A computed tomography scan performed in 2005 showed an enhanced pseudonodular-like lesion of about 2 cm. Cholangio-magnetic resonance imaging identified the lesion as a possible cholangiocarcinoma. No positive findings were performed to exclude the presence of extrahepatic neoplasms. Diagnosis of PHCT was established. The patient underwent left hepatectomy, followed by hormone therapy with sandostatine LAR. Two months after surgery he had a lymph nodal relapse along the celiac trunk and caudate lobe, which was histologically confirmed. The postoperative clinical course was uneventful, with a negative follow-up for hematocchemical, clinical and radiological investigations at 18 mo post-surgery. Diagnosis of PHCT is based principally on the histopathological confirmation of a carcinoid tumor and the exclusion of a non-hepatic primary tumor. Surgical resection is the recommended primary treatment for PHCT. Recurrence rate and survival rate in patients treated with resection were 18% and 74%, respectively.

INTRODUCTION

Carcinoids are tumors of neuroendocrine origin, capable of producing functional peptide hormones. The literature has reported different classifications, mainly based on either anatomo-pathological and/or clinical criteria of neuroendocrine tumors of ubiquitous distribution. Several organs may be involved, such as the adrenal gland (pheochromocytoma), the thyroid (midollar carcinoma) and the lung, where microcytoma accounts
for 20%[1] while carcinoids represent 1%-2% of all pulmonary neoplasms in the typical variant (80%-90%) and atypical (10%-20%)[2,3].

About 54.5% of carcinoid tumors arise within the gastrointestinal system and frequently metastasize to the liver[4]. Primary hepatic carcinoid tumor (PHCT) is an extremely rare neoplasm affecting relatively young subjects with an average age of 45 years[5] and no gender predominance. Diagnosis of PHCT is mainly achieved through histological confirmation and exclusion of other sites of the disease[6].

Here, we report the case of an occasional finding of a hepatic lesion, which led to the diagnosis of PHCT after a complicated diagnostic process.

**CASE REPORT**

A 65-year-old man presented with hypertension, peripheral vascular disease, and statin treated dyslipidemia. His previous medical history, dating back to spring 2003, included an echotomography of the dishomogeneous parenchymal area with no focal lesions. A computed tomography (CT) scan showed no steatosis in the image area. In July 2005, a CT scan of the asymptomatic patient showed an enhanced a pseudonodular-like lesion of about 2 cm localized in hepatic segments Ⅱ-Ⅲ, with intra-hepatic biliary dilatation (Figure 1).

The patient was admitted to hospital for further clinical investigations. Blood chemical analyses showed no abnormalities, not even the presence of markers (CEA, CA 19-9, α FP). The laboratory results are shown in Table 1.

Due to the doubtful interpretations of the radiological findings, a magnetic resonance imaging (MRI) was carried out (Figure 2). The investigation revealed a pseudonodular mass of about 5 cm × 3 cm characterized by low signal intensity both on T1 and T1FS weighted images, as well as weak irregular high signal intensity on T2 and T2FS weighted images. Moreover, an intra-hepatic biliary dilatation was described at the source of the lesion, thus leading us to suspect a heteroplastic lesion similar to a cholangiocarcinoma.

The patient was therefore referred for an 18-fluorodeoxyglucose positron emission tomography (PET), which proved negative. This confirmed by histological examination of a biopsy sample from the lesion. The cytohistological and immunohistochemical picture proved to be consistent with a hepatic localization of a low-grade malignant neuroendocrine carcinoma (presence of anti-chromogranin and Ki 67 antibodies; positive for synaptophysin and S 100 protein) while serum markers were negative (CgA, NSE).

Octreotide scintigraphy using 111 In-pentetreotide (octreotide scan) confirmed the diagnosis as well as enhancing a marked hyperactivity near the lesion in the left hepatic lobe associated with adenopathy in the interaortocaval site (Figure 3A). The patient thus underwent further investigations to exclude metastases with extra hepatic lymph node involvement by endoscopic examinations of the gastroenteric tract (esophagus-gastro-duodenoscopy, colonoscopy, and capsular endoscopy) and analysis of the respiratory systems (bronchoscopy) which all proved negative.

The patient suffered no flushing, no abdominal pain, and no alvus alteration. Moreover, the patient only referred to some successive episodes of angioneurotic edema of the face in the previous 10 years, regardless of the disease in question. As a result, the patient underwent an uncomplicated left hepatic resection and appendectomy with an uneventful postoperative clinical course. Subsequently, octreotide therapy was
Table 1 Hematological values of the patient and normal range

| Variable          | Patient value | Normal value | Variable          | Patient value | Normal value |
|-------------------|---------------|--------------|-------------------|---------------|--------------|
| Erythrocytes      | 4.93 × 10^12 | 4.2-5.4      | Amylase           | 60 U/L        | 30-110       |
| Leucocytes        | 8.16 × 10^12 | 4-10         | Total proteins    | 8.3 g/dL      | 6.3-8.2      |
| Hemoglobin        | 14.9 g/dL    | 12-16        | Urea              | 79 mg/dL      | 10-50        |
| Platelets         | 2.22 × 10^12 | 150-400      | LDH               | 250 U/L       | 313-618      |
| Creatinine        | 1.1 mg/dL    | 0.7-1.2      | ISR               | 15 mm/s       | 1-30         |
| PT                | 95%          | 70%-100%     | CRP               | 3 mg/L        | up to 3      |
| Total bilirubin   | 1 mg/dL      | 0.2-1.3      | α FP              | 2.6 mg/mL     | up to 5      |
| GPT               | 22 U/L       | up to 40     | CA 19-9           | 7 mg/mL       | up to 37     |
| GGT               | 84 U/L       | 12-58        | NSE               | 8.7 mg/mL     | up to 14     |
| ALP               | 73 U/L       | 38-126       | CgA               | 72 mg/mL      | 20-98        |
| Albumin           | 4.8 g/L      | 35-52        | Anti HCV          | Negative      |              |
| Cholinesterase    | 7924 U/L     | 4650-12220   | HbsAg             | Negative      |              |
| Total cholesterol | 258 mg/dL    | 145-200      | Triglycerides     | 125 mg/dL     | 50-170       |

Results of left hepatectomy show an extended nodular mass measuring about 2.5 cm × 1.5 cm arranged on the back part of the caudate lobe, indicating a lymph node localization of disease.

administered subcutaneously via octreotide scan at 2 mo from resection which showed a dishomogeneous distribution of the radioactive drug in the liver site, without any focal images, which warranted further investigation (Figure 3B).

CT scan confirmed the presence of an extended nodular mass measuring about 2.5 cm × 1.5 cm on the back part of the caudate lobe, in close contact with the celiac tripod. The mass was attributable to lymph node recurrence of the disease (Figure 4). The patient showed no signs of evolutive chest disease or any other particular clinical signs.

After a strict clinical and instrumental follow-up period, jointly conducted by an oncologist and a surgeon, the patient’s clinical and radiological picture remained stable, as demonstrated by the octreotide therapy. The patient then underwent a surgical lymph node exeresis. The histological finding was compatible with the lymph node metastasis of the neuroendocrine tumor (Figure 5). The postoperative clinical course was uneventful, with a negative follow-up for hematological, clinical and radiological investigations at 18 mo post surgery.

DISCUSSION

Neuroendocrine tumors cover a wide range of neoplasms that originate in the neuroendocrine cells that spread throughout the body. Recent studies have suggested an increase in the incidence of these tumors over time\(^5\). In particular, Maggard et al\(^6\) reported a 6.3% increase in 1997 compared with 1973. This could be attributed to an enhanced classification of these tumors and better use of endoscopic techniques for screening purposes. In 1998, 90% of neuroendocrine tumors were reported to occur within the gastrointestinal tract, particularly at the level of the terminal ileum and appendix\(^8\). However, more recent studies have reported a less frequent gastroenteric involvement (54.2%) followed, in decreasing order, by the lung (30.2%), pancreas (2.3%), reproductive system, (1.2%), biliary tract (1.1%), and head and neck (0.4%). As far as the gastrointestinal tract is concerned, a slighter greater involvement of the appendix has been reported compared other sites, such as the small bowel (44.7%) followed by the rectum (19.6%), appendix (16.7%) colon (10.6%) and stomach (7.2%)\(^4\).

PHCTs are rare neuroendocrine tumors, representing 0.3% of all carcinoids, and were first described by Edmonson in 1958\(^9\). Recent studies reported a survey on 95 cases of PHCT\(^10\,11\). The liver is the most frequently involved organ due metastatic disease from extrahepatic neuroendocrine tumors, thus justifying the physician’s efforts in ruling out the presence of other diseases before confirming this organ as the primary nature of the tumor\(^1\).

Indeed both the clinical exclusion criteria and the histological confirmation represent a diagnostic means to approach this rare disease.

The clinical onset of neoplasms is often aspecific and related to mass effect on the liver and adjacent organs. Likely symptoms include pain, weight loss, palpable mass, while less common is the classic carcinoid syndrome (skin flushing, abdominal pain and episodes
of diarrhea) which are present in 5% of cases\cite{5} and more frequently found in tumors which metastasize to the liver.

The clinical course of PHCT is generally painless compared to other neuroendocrine neoplasms with a more malignant progression. The latter may be characterized by varying degrees of pleomorphism, greater mitotic activity, vascular invasion and necrosis\cite{15,17}. From the morphological point of view, in accordance with the literature, our patient presented well-differentiated PHCT with low-grade malignancy, minimum pleomorphism, low mitotic index and poor necrotic foci.

The first level diagnosis consisted of non-invasive imaging. A traditional ultrasound scan revealed a hypeeregenic mass containing multiple cystic lesions, while a CT scan confirmed a cystic pattern. Moreover, angiography might demonstrate multiple hypervascular and centrally located radiolucent areas\cite{16}. Classical PET with fluorodeoxyglucose did not prove to be advantageous in neuroendocrine tumor imaging\cite{17}. Thus, a serotonin precursor 11C-5 hydroxy tryptophan was developed as a tracer for PET-scanning, which can be concentrated within carcinoid tumors\cite{16}. Findings using this application are encouraging, allowing the identification of the primary tumor in 84% of cases\cite{15,17}. Primary carcinoid tumors and distant metastasis in patients affected by neuroendocrine tumors are better detected by osteooscan scintigraphy compared to the CT scan and the MRI\cite{16}.

The presence of somatostatin receptors within the tumoral cell is best suited for scintigraphy. There are five receptor subtypes (SSTR 1-5) each having different functional properties and binding specificity for the target tissue\cite{16}. Octreotide binds with high affinity to the somatostatin subtype 2 receptor (SSTR 2), which is widely expressed on the cell surface with neuroendocrine characteristics. Certain diagnosis is, however, achieved by fine needle aspiration or biopsy. Immunohistochemistry confirms neuroendocrine origin of PHCT by detecting the markers CgA, NSE, chromostatin, CEA and synaptophysin\cite{16}. Measurement of plasma CgA and repetition of the octreoscan scanning provide the basis for follow-up\cite{5}. Although PHCT appears to be a low malignancy tumor with slow progression, treatment effectiveness and prognosis are difficult to establish owing to its rarity and subsequent lack of prospective data\cite{5}. Surgical resection is the most commonly used therapy and it is considered the treatment of choice\cite{19} in about 85% of primary hepatic carcinoids\cite{20,21}. This procedure cannot be performed in the 10% of patients affected by metastatic hepatic carcinoid\cite{5,19}. For these cases, as well as for non operable tumors, therapy with radionuclides and the somatostatin analog 177Lu-DOTA-Tyr3-octreotate, are the most modern and promising, not only in terms of stabilization but also with regard to disease regression with minimal toxicity\cite{20,21}. Other therapeutic interventions have been tried for curative and palliative purposes, such as systemic chemotherapy, hepatic artery chemoembolization (only in cases of non resectable or recurrent disease), somatostatin hormone therapy or its analogs performed as a stand-alone therapy or as an adjunct to surgery\cite{5,19}. Hormone therapy is indicated in carcinoids causing functional symptoms, however, no evidence is available as to the control of disease progression. Moreover, this therapy might only exert cytostatic effects\cite{22-24}. Indeed, evidence does exist demonstrating that somatostatin analogs can inhibit tumour growth, at least for a certain period of time\cite{20,27}, but further studies are necessary to evaluate this effect.

Recent reports have demonstrated a favourable prognosis at 5 years in 74% of surgically treated cases with an 18% recurrence rate\cite{19}. Post-resection perihepatic lymph node involvement has been infrequently reported in the literature without hepatic involvement, similarly to bone and lung metastasis\cite{19,24}.

In 2001, Iwao et al\cite{18} analyzed 53 cases of PHCT reported in the English language literature. Accordingly, lymph node involvement occurs in 60% of cases. A case report of 2002\cite{29} confirmed a case of metachrone lymph node metastasis after a 5-year follow-up in one case of surgically treated PHCT.

The case reported here is unique due to its discovery by chance during an abdominal scan which the patient was undergoing for other reasons.

The extremely long evolution, and the absolute lack of pathognomonic symptoms of the disease, resulted in successful diagnosis following a complex process lasting two years. Moreover, the diagnostic course was characterized by the physician’s efforts to rule out
extrahepatic neoplasms with possible hepatic metastatic disease.

A diagnostic algorithm proposed by a study published in 2003 underlined the need for thorough research into neuroendocrine neoplasms of the small bowel (mid gut), large bowel (hind gut), bronchi (foregut) and pancreas (islet cell). In fact, a small sized lesion can metastasize extensively to liver tissues and might not be detected during a classic diagnostic approach.

In conclusion, a regular clinical and instrumental post-surgical review is essential for identifying possible tumor recurrence as well as detecting previously unrecognized primary extrahepatic lesions.

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