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Simultaneous occurrence of metastasizing carcinoid tumour of the gallbladder and chromophobe renal cell carcinoma in a young man

L. Morelli[1], F. Piscioli[1], E. Cudazzo[2], F. Del Nonno[3], S. Licci[3]

(1) Department of Pathology, "S. Maria del Carmine" Hospital, Rovereto (TN), Italy ; (2) Department of Surgery, Hospital of Guastalla (RE), Italy ; (3) Department of Pathology, National Institute for Infectious Diseases "L. Spallanzani" IRCCS, Rome, Italy.

Abstract

Carcinoid tumour is an endocrine neoplasia described for the first time in 1888 and rarely observed in the extrahepatic bile ducts. Gallbladder carcinoid tumour was first reported by Joel in 1929.

An endoluminal gallbladder lesion, with a bizarre echogenicity, and a mass in the upper pole of the left kidney were found in a 27 year-old man. The patient underwent a cholecystectomy with partial hepatectomy and a polar renal resection. Histological examination revealed a typical gallbladder carcinoid tumour with regional lymph nodal metastasis and a renal cell carcinoma, with morphological and histochemical features of the chromophobe type. This is a distinctive, rare variant, often described in the literature in association with other neoplastic and non-neoplastic diseases.

To our knowledge, this is the first report of gallbladder carcinoid tumour with an unexpected aggressive behaviour in a very young patient, with concurrent renal cell carcinoma, chromophobe variant. (Acta gastroenterol. belg., **2007**, 70, **371-373**).

Introduction

The "carcinoid" term was used for the first time in 1888 by Lubarsch *et al.* who observed several ileal tumours with specific features in two patients at autopsy (1). Some years later, in 1906, Ciaccio *et al.* affirmed the endocrine origin of such tumours, and this was later successfully confirmed by Gosset and Masson in 1914 (2). The description of the so-called "carcinoid syndrome" (clinical systemic manifestations of the neuroendocrine properties of these tumours) was first noticed by Pernow and Waldenstrom in 1954, who observed a characteristic constellation of symptoms in a series of patients with intestinal carcinoids (3). In the last decades of the twentieth century many scientists elucidated the structural, functional and biochemical properties of the carcinoid tumours (CTs), and the analysis of patient data permitted to define the epidemiology and prognostic features of these neoplasms. The CTs can be summarized on the basis of the substances they secrete ; they are packed with neurosecretory granules containing hormones and biogenic amines and they can range from indolent, unrecognized entities to highly active, sometimes metastatic tumours.

They are typically classified on the base of their embryonic gut origin and are histologically classified as "typical" or "atypical", related to the degree of differentiation. "Typical" CT is by definition a tumour with neuroendocrine differentiation and classical histological architecture with trabecular, insular or ribbon-like cell clusters, with no or minimal cellular pleomorphism and sparse mitoses, whereas the term "atypical" refers to aggressive forms of poorly differentiated CT with increased mitotic activity and nuclear atypia (4).

Primary gallbladder CT (GCT) was first reported by Joel in 1929 (5) and 47 cases have been reported so far. The sex distribution of this lesion parallels that of gallbladder carcinoma with a marked female predominance, and the age of the reported cases ranges from 12 to 79 years. Endocrine tumours of the gallbladder and extrahepatic bile ducts include the CT (well differentiated endocrine tumour), the small cell carcinoma (poorly differentiated endocrine carcinoma) and the mixed endocrine-esocrine carcinoma. The CTs of the extrahepatic ducts are exceedingly rare (0,1-2% of all gastrointestinal CTs), with most reported cases occurring in the gallbladder (6).

The renal cell carcinoma (RCC), chromophobe cell type, was first reported by Thoenes *et al.* (7) ; it is a distinctive, rare variant (approximately 5% of all RCCs) that maybe in the past has been confused with other variants of RCC and oncocytoma, with which it is closely related and often associated. In 2003 Boor *et al.* described an unusual coincidence of multiple synchronous kidney tumours with a metachronous rectal adenocarcinoma (8). In the same year, Levine *et al.* reported a simultaneous occurrence of an appendiceal CT and RCC (9). This is, to our knowledge, the first report of simultaneous occurrence of chromophobe RCC and GCT.

Case report

In January 2004 a 27-year-old man presented to the attention of the surgeon after an abdominal ultrasonographic exam, performed for abdominal pain, showed an endoluminal gallbladder lesion, with a bizarre

Correspondence to : Dr. Stefano Licci, Department of Pathology, National Institute for Infectious Diseases "L. Spallanzani" IRCCS, Via Portuense, 292, 00149 Roma, Italy. E-mail : licci@inmi.it

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echogenicity, and a mass in the upper pole of the left kidney. He presented no other clinical symptoms, with neither manifestations of carcinoid syndrome nor detectable common serum tumour markers, including Ca 15.3, Ca 19.9 and TPA. His relatives had no medical history of von Hippel-Lindau disease (VHLD). A total body computerized tomography scan excluded other lesions in the lungs or at other sites of the gastrointestinal tract and pancreaticobiliary system. The patient underwent a cholecystectomy with partial hepatectomy and a polar renal resection. No other macroscopic lesions were observed in the abdomen during the operation. On gross examination, the gallbladder lesion was located in the fundus region, fragile, cauliflower-shaped and 3 cm in diameter. The microscopic examination revealed a neoplastic proliferation characterized by an insular and trabecular pattern of growth, cells with large, eosinophilic, granular cytoplasm, nuclei with no or mild atypia, and rare mitotic figures (Fig. 1a, 1b). No clear cells were observed. The neoplasia was extended to the lamina propria and the muscular tissue with no infiltration of the perivisceral serosa and no figures of perineural or vascular invasion. Intestinal metaplasia of the contiguous mucosa was observed. The gallbladder resection margin and the excised liver parenchyma were free from disease. A typical CT was suspected on the basis of the morphological features. The immunohistochemical study, performed on sections from the paraffin-embedded tissue with immunoperoxidase using the automatic Ventana staining system (Benchmark), showed positivity of the neoplastic cells for cytokeratin AE1/AE3, cytokeratin 7, CD56, synaptophysin and chromogranin A (Fig. 1c). The tumour displayed a coexpression of epithelial and neuroendocrine markers, as typically seen in CTs. TTF-1, the thyroid transcription factor-1 expressed in lung adenocarcinoma and CT, was negative, as well as cytokeratin 20 and CDX2, usually expressed in colon cancer, and inhibin. Ki67, an antigen related to the proliferative state of cycling cells, was expressed in 30% of the neoplastic cells, indicating a high proliferation rate and therefore a presumable higher aggressiveness of the tumour (10). Regional lymph nodal metastasis was observed. A conclusive diagnosis of typical GCT was made and, on the basis of the tumour local extension and lymph nodal involvement, a pT_2N_1 staging sec. UICC 2005 was assigned.

The nodular renal lesion was greyish, firm and 3.5 cm in diameter. The histological examination revealed a renal cell carcinoma, with morphological and histochemical (colloidal iron stain positivity) features of the chromophobe variant (Fig. 1d), with neither infiltration of the perirenal tissue nor invasion of the renal vena. The resection margin was free from disease. On the basis of the tumour size, a pT_1 staging sec. UICC 2005 was assigned.

The patient died 4 months after the surgical intervention from GCT peritoneal metastases radiologically detected.

Discussion

The detection and description of CT in unusual localizations, such as gallbladder, is subject of rare but interesting communications. Many papers are present in the world literature about this neoplasia, but none reported the association of this neoplasm with another tumour. Only Berner described in his articles the "synchronicity" of digestive carcinoids with other malignant tumours, but no primary endocrine tumour was localized in the gallbladder (11-12). The differential diagnosis for GCT principally includes poorly differentiated adenocarcinomas with numerous endocrine cells and small cell carcinomas. Since almost one third of gallbladder adenocarcinomas show a variable amount of endocrine cells, immunohistochemical reactions for chromogranin and synaptophysin in such lesions might lead to an erroneous diagnosis of CT (13). In adenocarcinomas the extensive gland formation and a more severe cytological atypia help in establishing the right diagnosis, together with only focal, scattered positivity for chromogranin and synaptophysin. Conversely, a diffuse and strong positivity in all tumour cells favours a diagnosis of CT. Small cell carcinoma may occasionally display a trabecular growth pattern with rosette formation, morphological features that may mimic a CT. However, the diffuse chromatin pattern, the high mitotic rate, the extensive tumour necrosis and only focal positivity for chromogranin and synaptophysin are the hallmarks for the right diagnosis. In our case the contiguous mucosa showed diffuse intestinal metaplasia. This finding supports the hypothesis that GCT arises from endocrine cells, which are normally absent in the mucosa lining epithelium of the gallbladder, but present in the metaplastic epithelium, often secondary to an inflammatory process. Moreover, in this case the aggressive evolution of GCT, in spite of the typical morphological aspect, contrasts with the literature data showing that 82.4% of GCTs remain localized, and that the 5-years overall survival is 60.8% ± 14.8% (14).

Furthermore, our patients did not have a familial history of VHLD, nor he showed any symptom or sign of this disease. This autosomal dominant genetic disorder is characterized by multiple clear cells neoplasms in various organs including kidney, central nervous system, adrenal gland, pancreas an epididymis. This disorder could explain the concurrence of the two different tumours, but in this case we did not find an explanation of the simultaneous presence of the two neoplastic diseases.

Inhibin, a gonadal hormone acting as a suppressor in the synthesis and secretion of pituitary follicle stimulating hormone, was previously studied in the GCTs by Sinkre *et al.* (15), Hoang *et al.* (16) and Konishi *et al.* (17), which obtained controversial results (positivity for Sinkre and Hoang, negativity for Konishi). Further studies are necessary to establish the true value of the expression of inhibin in CTs.

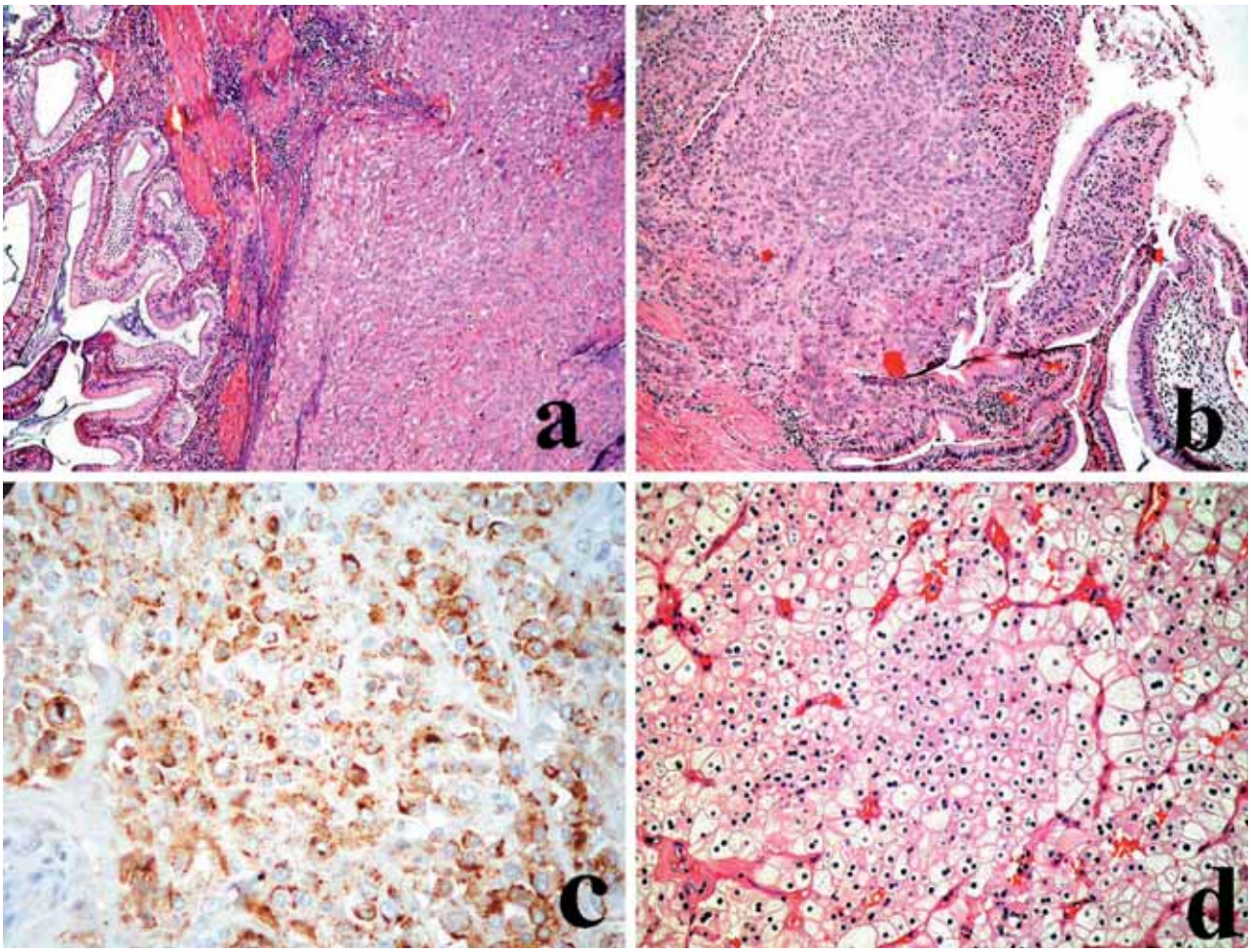

Fig. 1. — a) and b) Gallbladder carcinoid tumour (Hematoxylin & Eosin, 100×) ; c) Chromogranin A immunostain shows diffuse, granular positivity of neoplastic cells (200×) ; d) Renal neoplasia with morphologic features of renal cell carcinoma, chromophobe variant (Hematoxylin & Eosin, 200×).

According to the revision of the world literature provided by PubMed, this is the first report of typical GCT in a young patient with an unexpected aggressive behaviour and concurrent RCC, chromophobe variant.

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