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Review

"Pure" large cell neuroendocrine carcinoma of the gallbladder. Report of a case and review of the literature

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ABSTRACT

Primary Neuroendocrine Tumours (NETs) of the gallbladder are rare. Among all NETs of the gallbladder, large cell neuroendocrine carcinoma (LCNEC) is exceedingly rare. In most of the cases LCNECs are combined with other histological components. We reviewed clinical presentation and management of all patients with "pure" LCNEC from published literature since the first case was published in 2000, as well as one patient from our experience. Only 7 cases of "pure" LCNEC has been described in the last 15 years, our case is the eighth. The diagnosis of gallbladder NETs is rarely made preoperatively since the presentation generally consists of non-specific symptoms including upper abdominal pain, discomfort, jaundice, weight loss. The majority of patients are identified incidentally at the time of cholecystectomy for cholelithiasis. It is not possible to differentiate preoperatively between gallbladder adenocarcinoma and gallbladder neuroendocrine carcinoma (NEC) with imaging techniques. The only curative therapeutic modality for LCNECs is a complete en bloc surgical resection, including regional lymph node clearances and hepatic lobectomy, but only in patients without multiple metastasis. LCNECs benefit from an aggressive surgical resection in combination with chemotherapy, if resectability is possible. If the tumour is non-resectable, the primary management is therefore medical and not surgical. All patients with LCNEC presented a poor prognosis with a median survival of 10 months after the initial diagnosis. Only in five patients (62.5%) a wide surgical excision was performed, while in the other cases the tumour was non-resectable or multiple liver metastases were present at diagnosis.

1. Introduction

Primary Neuroendocrine Tumours (NETs) of the gallbladder are particularly rare, accounting for 0.5% of all NETs and 2.1% of all gallbladder cancers. They are more frequent in females (68%) and the age at presentation ranges from 25 to 85 years peaking in ages 75–79 years [1]. It seems plausible that the neuroendocrine cell origin for gallbladder NENs is either an undifferentiated stem cell or a mucosal neuroendocrine cell in the background of chronic inflammatory induced intestinal or/and gastric metaplasia leading to malignant transformation [2]. The current WHO classification divides neuroendocrine neoplasms of the gallbladder into the categories of neuroendocrine tumour (NET G1 and G2), small cell neuroendocrine carcinoma (SCNEC), large cell neuroendocrine carcinoma (LCNEC), mixed adenoneuroendocrine carcinoma (MANEC), goblet cell carcinoid and tubular carcinoid [3]. Among all NETs of the gallbladder, LCNECs are exceedingly rare [2], the first case reported in 2000 [4]. In most of the cases LCNECs are combined with other histological components, including adeno-, adenosquamous and mucinous carcinoma [5] To the best of our knowledge the case we report is the eighth case of a pure form of primary gallbladder LCNEC (GB-LCNEC), incidentally found at cholecystectomy in a 76-year-old woman. We also performed the review of all the cases of pure GB-LCNEC, as shown in Table 1.

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Table 1
Clinical features of 8 pure large cell neuroendocrine carcinomas of gallbladder: CHO, cholecystectomy; Chemo, chemotherapy; Chemo NS, chemotherapy administered, but drugs not specified; CisP, cisplatin; CarP, carboplatin; ETP, etoposide; CAV, cyclophosphamide adriamycin vincristine; CY,; DTX, docetaxel; LR, liver resection; LN, lymphnodes; 3D-RT, three-dimensional radiation therapy; CBD, common bile duct; LY, lymphadenectomy; FNA, fine needle aspiration; mths, months; wks, weeks; yrs, years; pt, patient.

Author [ref.]	Sex, age	Clinical presentation	Tumour location	Tumour size	Management	Metastasis	Outcome, follow-up (months)
Papotti et al. [4] 2000	M, 65	Symptomatic cholelithiasis	Fundus	2.5 cm	CHO, Chemo NS, Partial LR	Liver 4 mths after CHO	Dead, 14
Jun et al. [6] 2006	F, 67	Epigastric pain	Eccentric wall thickening with invasion of liver segment 4	Huge lobulated mass	Biopsy on gallbladder and liver mass Unresectable tumour Chemo NS	Liver segment 6 at diagnosis	Dead, 10
Jun et al. [6] 2006	M, 55	Abdominal discomfort and jaundice of 4 wks' duration	Extensive wall thickening with necrosis and a gallstone	Not reported	Biopsy on celiac lymphnode Unresectable tumour Chemo NS	Multiple LN (along the hepato-duodenal ligament, celiac axis, superior mesenteric artery, aorto-caval, para-aortic) at diagnosis	Dead, 1
Iype et al. [7] 2009	F, 58	18-month history suggestive of gallstones	Not specified	2 cm	CHO followed 2 mths later by radical gallbladder bed clearance, liver segment 4B/5 excision, CBD excision, and LY up to coeliac nodes Chemo (CisP, ETP)	Regional LN	Alive and well 16 mths after initial operation
Shimono et al. [8] 2009	F, 64	Severe pain in right upper abdomen	Large mass occupying middle and anterior segments of liver	11.5 × 10.5 cm	Intra-arterial Chemo Pre-operative 3D-RT Right Trisegmentectomy Post- operative Chemo (CisP, ETP) Partial cerebellectomy γ-knife irradiation	Liver, brain	Dead, 69 mths after initial diagnosis 3 yrs without recurrence since the last γ-knife irradiation
Lin et al. [5] 2010	F, 65	Cushing's syndrome	Body	Large ACTH producing mass	CHO + wedge shaped LR Chemo refused by the pt	Liver 2 mths after surgery	Dead, 2
Okuyama et al. [9] 2013	M, 64	Abdominal fullness	Fundus	2.5 cm	Biopsy on axillary LN and FNA of gallbladder Chemo (CisP,DTX,CarP)	Liver and multiple LN at diagnosis; LN, liver, bones 22 mths after Chemo	Dead, 22
Current report, 2015	F, 76	Abdominal pain with clinical history of cholelithiasis	Fundus	1.8 × 1.5 cm	CHO, Chemo (CisP, ETP, CarP)	Regional LN and liver at diagnosis	Dead, 5

2. Clinical scenario

A 76-year-old Caucasian woman, non smoker, was admitted to hospital in March 2011 with a 4 month history of intermittent right-upper quadrant abdominal pain. As regards the past history, the patient had undergone appendectomy 40 years previously and had a history of acute myocardial infarction and hypertension pharmacologically treated. There was no significant family medical history and her general physical examination was normal. There were no abnormal laboratory findings. The abdominal ultrasonography revealed an irregular thickened gallbladder wall and a 1.8 cm gallstone, with no evidence of biliary tree dilation, of pathological findings of the liver and ascites. The patient was scheduled for a laparoscopic cholecystectomy. During the operation the gallbladder appeared morphologically altered with a thickened wall and strongly adherent to the liver bed. We proceeded to conversion to complete cholecystectomy. The post-operative course was uneventful and the patient was discharged on the fifth post-operative day.

At pathological examination the tumour presented as a 1.8 cm whitish ulcerated mass in the fundus of the gallbladder. The lesion was entirely sampled. Microscopically the tumour displayed an insular growth pattern, often with rosette formation, entirely composed of large cells characterized by hyperchromatic nuclei with prominent nucleoli and a variable amount of cytoplasm. A high mitotic rate (>20 mitotic figures/10 HPF) was noted. Lymphovascular and perineural invasion were identified. Foci of intestinal metaplasia were observed in the peritumoral mucosa. The tumour invaded the wall of the gallbladder as far as the serosa. A metastatic 1.2 cm lymphnode in the fundus was detected. Tumour cells were diffusely positive for pan-cytocheratin, chromogranin A and synaptophysin. Ki-67 immunostain showed a 50% proliferative rate (Figs. 1–3). The histological and immunohistochemical findings were consistent with a pure form of GB-LGNEC.

After the incidental discovery of a LCNEC the patient underwent a total body computed tomography (CT) scan. This showed several metastatic lesions in the liver in all the segments except segment I and segment II, with a maximum diameter of 5 cm, multiple metastatic lymphnodes with a maximum diameter of 2.9 cm and mild ascites. Chromogranin A (CgA) blood levels were elevated with a value of 1823 ng/ml (normal range < 99 ng/ml), while neuron specific enolase (NSE) blood level was normal. The bone scan was negative. The 111In-pentetreotide scintigraphy (Octreoscan) showed the presence of a single hepatic lesion in segment IV.

According to guidelines [7], the patient started a first line chemotherapy with cisplatin and etoposide and completed a total of two cycles. Because of kidney function impairment, cisplatin was substituted by carboplatin at the third cycle. The main toxicity reported was a grade 4 neutropenia, well treated with granulocyte colony stimulating factor. Somatostatin analogs were administered in addition to chemotherapy, even if the patient did not present carcinoid syndrome. Ten days after the last cycle of chemotherapy, five months after the initial diagnosis she was admitted to another

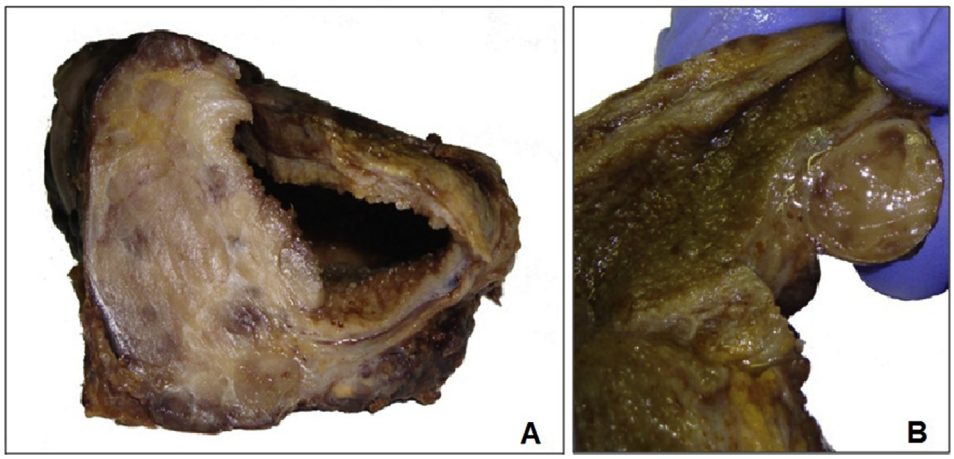

Fig. 1. Macroscopic view of the tumour mass (A) and of the metastatic lymphnode (B) in the fundus of the gallbladder.

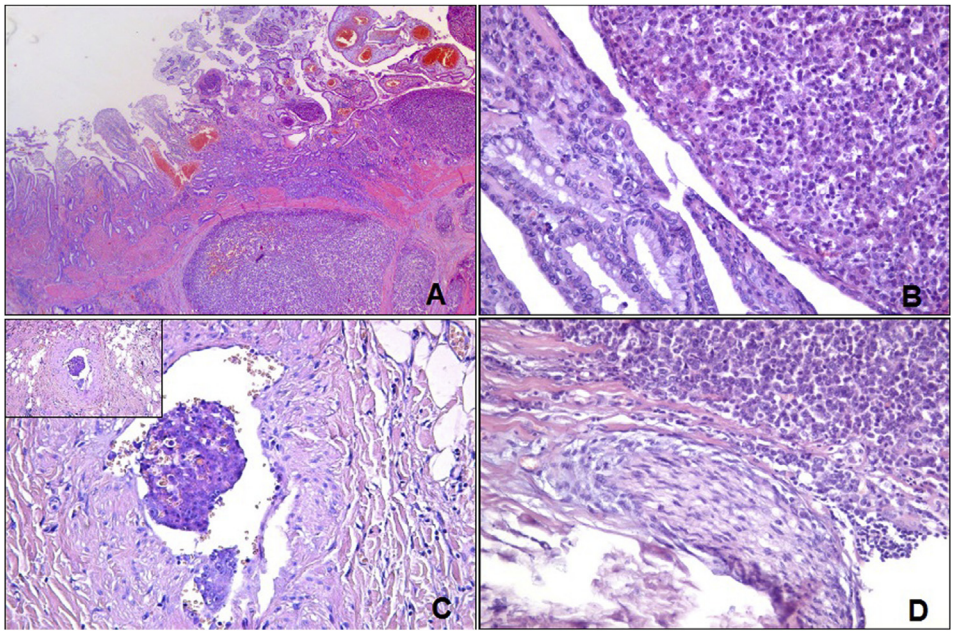

Fig. 2. Large cells arranged in an insular growth pattern deeply infiltrating the wall (A) Foci of intestinal metaplasia in the peritumoral mucosa (B). Evidence of vascular invasion (C). Evidence of perineural invasion (D) (H&E, original magnifications ×2.5, ×40, ×40 and ×40 respectively).

hospital complaining of abdominal pain. An acute myocardial infarction was diagnosed from which she died.

3. Discussion

The current WHO classification divides neuroendocrine neoplasms of the gallbladder into the categories of NET (G1, G2), SCNEC, LCNEC, MANEC, goblet cell carcinoid and tubular carcinoid [3].

Primary NETs of the gallbladder are particularly rare. In the Surveillance, Epidemiology and End Results (SEER) Program registry, only 278 cases have been reported between 1973 and 2005, and represent 0.5% of all NETs, and 2.1% of all gallbladder cancers [1]. According to the SEER registries the incidence of gallbladder NETs (all subgroups) in the US is 0.2–0.3/100.000 [10]. In a retrospective analysis of 25 gallbladder NETs, the age at presentation ranged from 26 to 79 years and 68% were women [11].

Primary GB-SCNEC is rare, with only 74 cases reported until 2011 [12,13]. Pure GB-LCNECs are exceedingly rare and to the best of our knowledge only 7 cases have been described in literature (Table 1). Ours represents the eighth pure case of GB-LCNEC reported. Liu et al. reported a series of 17 cases of LCNEC: 6 cases were pure LGNECs, 11 cases were combined with other histological components, including adeno-, adenosquamous and mucinous carcinoma. Cases with mixed histological components were classified as MANEC according to WHO 2010 [14] GB-LCNEC was first reported by Papotti et al., in 2000 [4]. It consists of polygonal shaped cells that are about three times larger than small-cell type, grows in an organoid pattern, exhibits rosetta-like areas and has large patches of necrosis. Immunohistochemical staining shows strong cytoplasmatic staining for neuroendocrine markers (chromogranine A and synaptophysin) [6].

It is now accepted that neuroendocrine cells derive from local multipotent gastrointestinal stem cells, rather than by migration from the neural crest as initially proposed [15]. Neuroendocrine cells are not present in normal gallbladder mucosa, while

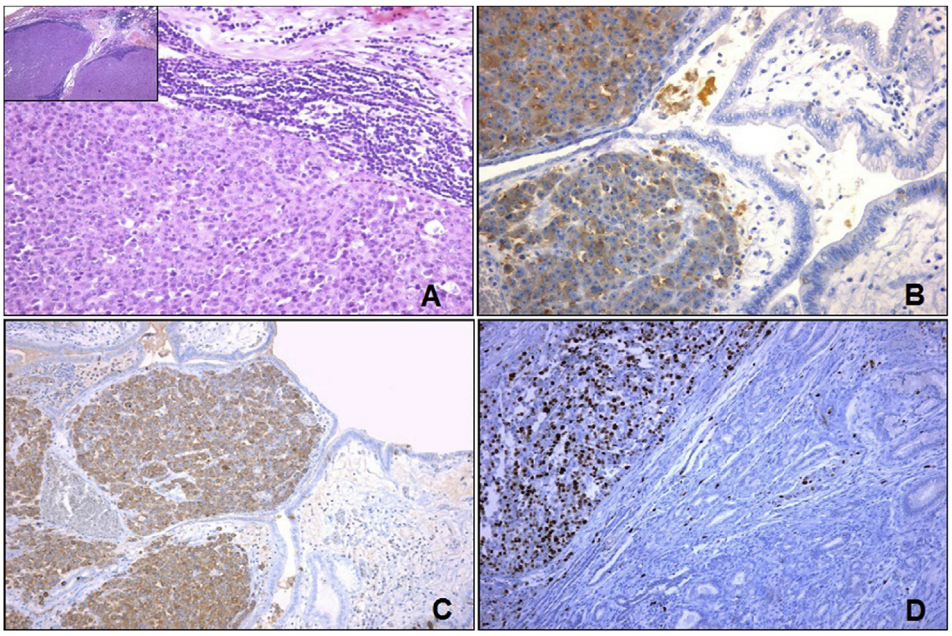

Fig. 3. Massive lymphnode metastasis (A) (H&E, original magnification ×10). Immunostains for chromogranin A (B) and synaptophysin (C) show diffuse cytoplasmatic positivity (immunoperoxidase, ×25 and 5× respectively). Immunostain for Ki-67 (D) shows a high proliferative rate (immunoperoxidase, x10).

gallbladder mucosa undergoing intestinal or/and gastric metaplasia, secondary to chronic inflammation due to cholelithiasis, expresses a variety of different neuroendocrine cells [16]. It seems plausible that the cell origin for gallbladder NETs may have two sources: an undifferentiated stem cell or else a mucosal neuroendocrine cell in the setting of chronic inflammatory induced gallbladder epithelial metaplasia leading to malignant transformation [2].

According to most previously reported cases of GB-LCNEC, the clinical symptoms and radiological findings of our patient were non-specific (Table 1). Upper abdominal pain and abdominal discomfort were the most common symptoms (6/8, 75%). Three patients (3/8, 37.5%) presented with a clinical history of symptomatic cholecystitis and ultrasonographic demonstration of gallstones [4,7]. As reported, the diagnosis of gallbladder NETs is rarely made preoperatively since the presentation generally consists of non-specific symptoms including upper abdominal pain, discomfort, jaundice, weight loss. The majority of patients are identified incidentally at the time of cholecystectomy for cholelithiasis [2].

It is not possible to differentiate preoperatively between gallbladder adenocarcinoma and gallbladder neuroendocrine carcinoma (NEC) with imaging techniques. The sensitivity of ultrasonography in the identification of gallbladder cancer is low accounting for 44% [17]. In our case, the abdominal ultrasonography revealed an irregular thickened gallbladder wall and a 1.8 cm gallstone, without the suspicion of a neoplasm.

Radiological findings of NEC have been described as a mass replacing the gallbladder, focal or diffuse wall thickening, with or without direct hepatic invasion, liver and lymph node metastasis [2]. If a gallbladder tumour presents along with a large hepatic mass and/or extensive lymphadenopathy at diagnosis, a NEC should be considered. However, other neoplasms such as hepatocellular carcinoma, cholangiocarcinoma, hepatic metastasis involving the gallbladder, gallbladder adenocarcinoma may have a similar pattern. Moreover, Jun et al. reported no significant difference in the CT findings of SCNEC and LCNEC of the gallbladder [6].

The only curative therapeutic modality for GB-NECs is a complete en bloc surgical resection, including regional lymph node clearances and hepatic lobectomy, but only in patients without multiple metastasis [18]. No rational surgical strategy currently exists for GB-NETs for different reasons: the rarity of the disease, the lack of predictive prognostic factors and the limited understanding of the biology of this tumour [2]. However, as shown in Table 1, most of the patients had multiple metastases or direct hepatic invasion with huge tumours at diagnosis, making them unsuitable for surgical treatment.

The role of radiotherapy and chemotherapy in the management of these tumours is unclear since in general NETs are insensitive to traditional radiotherapy [19]. It seems to be that GB-NECs benefit from an aggressive surgical resection in combination with chemotherapy, if resectability is possible [20]. If the tumour is non-resectable, the primary management is therefore medical and not surgical [2].

The chemotherapeutic agents recommended as the first-line treatment are cisplatin or carboplatin and etoposide, representing one of the standard regimens employed for the small cell lung cancer [21]. In our case as the treatment with cisplatin was not tolerated, cisplatin was replaced by carboplatin at the third cycle. Iwasa et al. showed that the first-line chemotherapy with cisplatin and etoposide for hepatobiliary poorly differentiated neuroendocrine carcinoma had only marginal antitumour activity and relatively severe toxicity compared with previous studies on extrapulmonary poorly differentiated neuroendocrine carcinoma treated with the same regimen [21,22].

Shimono et al. reported one case of GB-LCNEC with a survival of 69 months after the initial diagnosis due to the application of a multimodal treatment, including pre-operative intra-arterial chemotherapy and three-dimensional radiation therapy, right trisegmentectomy, post-operative systemic chemotherapy and γ-knife irradiation for brain metastases [8]. This result proves that radiation therapy is a useful modality for neoadjuvant and adjuvant therapy in achieving local control.

Unfortunately, excluding the case of Shimono, all patients with GB-LCNEC presented a poor prognosis with a median survival of 10 months after the initial diagnosis, as shown in Table 1. Only in five patients (62.5%) a wide surgical excision was performed, while in

the other cases the tumour was non-resectable or multiple liver metastases were present at diagnosis. Iype et al. reviewed 29 cases of poorly differentiated GB-NECs, including 4 GB-LCNEC, and concluded that the large-cell subtype presents a worse prognosis than the small cell variety and chemotherapy is more effective for SCNEC [7].

In conclusion, GB-LCNEC is extremely rare, only a few pure cases, without combination of other histological components, are reported in literature. An increased awareness and understanding of the biological background of this tumour is required. Given the lack of data, the best strategy appears to be an aggressive surgical management, comparable to the management of the more common gallbladder adenocarcinomas. Unfortunately, tumour recurrence is the typical outcome and the overall survival of GB-LCNEC remains discouraging.

Ethical approval

Ethical approval was not necessary.

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Author contribution

Salvatore Buscemi: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Corrado Rispoli: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Loredana Iannone: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Serena Testa: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Giovanni Antonio Della Corte: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

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

Attilio Ignazio Lo Monte: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Conflicts of interest

All Authors have no conflict of interests.

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