



A Pure Primary Large Cell Neuroendocrine Carcinoma of the Gallbladder: A Case Report and Review of Literature

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Abstract

Pure Large Neuro Endocrine Carcinoma (LCNEC) of the gallbladder is so rare that until now only 10 cases have been described. Herein we aimed to report a new case treated in the Salah Azaiez National Cancer Institute in Tunisia. We also reviewed the clinical features of all cases reported so far. We reported the case of 67 years old men that had pure locally advanced LCNEC of the gallbladder, with posterior metastatic lymphadenopathy. He underwent a cholecystectomy followed by 6 cycles of Cisplatin and Etoposide chemotherapy, 3 cycles of gemcitabine and Capecitabine chemotherapy and a third line of metronomic Cyclophosphamide.

Keywords: Gallbladder; Neuroendocrine carcinoma; Large cells; CRP; CT

Introduction

Primary Neuro Endocrine Neoplasm (NEN) of the gallbladder is an exceedingly rare malignancy that accounts for 0.5% of biliary tract neuroendocrine tumor and 2.1% of all gallbladder cancers [1]. This entity doesn't have pathognomonic clinical or radiological features, therefore patients are mostly diagnosed after surgery or incidentally after a cholecystectomy. Surgical management represents the cornerstone of their treatment. However, standard therapeutic management remains undefined due to the scarcity of such localization.

Case Presentation

A 67-year-old man without past medical history presented in the surgical department with intermittent right-upper quadrant abdominal pain. Physical examination showed neither fever nor jaundice. The results of routine blood tests were normal, except a high level of CRP (C Reactive Protein). The abdominal ultrasonography revealed an irregular thickened gallbladder wall with multiple gallstones and an endoluminal hyperechoic nodular lesion, without any evidence of biliary tree dilatation. Abdominal CT scan and MRI showed a neoplastic lesion in the gallbladder invading the segment V of the liver. The lesion measured 40 mm × 46 mm × 70 mm. It was associated with a large posterior lymphadenopathy in contact with the inferior vena cava. No evidence of ascites was noticed. The patient was scheduled for surgery. Perioperative exploration revealed a morphologically altered gallbladder, with a thickened wall and a lesion strongly adherent to the liver surface. The tumor was locally advanced therefore surgery was incomplete and the lesion wasn't entirely sampled. The patient underwent only a cholecystectomy. Pathological examination showed a whitish gallbladder measuring 60 mm × 40 mm × 30 mm. The tumor invaded the entire vesicular wall (Figure 1). Resection margins were positive. Histological findings revealed a rosette formation, entirely composed of undifferentiated large cells. An extended necrosis (Figure 2), a high nuclear pleomorphism and a high mitotic rate (22 mitotic figures/2mm²) was observed. Immuno histochemistry revealed intense staining of Chromogranin, Synaptophysin and CD56. Only focal expression of pan-cytokeratin was present. Ki-67 index ranges between 40% to 90% (Figure 3a, 3b). Histological and immuno histochemistry findings supported the diagnosis of large cell neuroendocrine carcinoma of the gallbladder. The post-operative course was uneventful and the patient was referred to the oncology department. After this incidental discovery of a LCNEC, the patient underwent a total body Computed Tomography (CT) scan. This showed a persistent residual mass, but no other distant metastasis. Chromogranin A and Neuron Specific Enolase (NSE) blood levels were high, with a value of 266 ng/ml (normal range: 27-94) and 32.6 ng/ml (normal <16.3), respectively. Since the performance status of the patient was well preserved, the decision of

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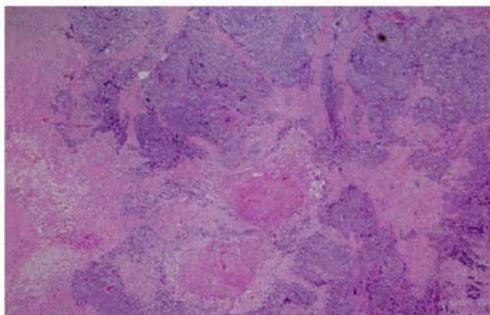


Figure 1: Low magnification showing a necrotic tumor invading the entire wall of the gallbladder (HE).

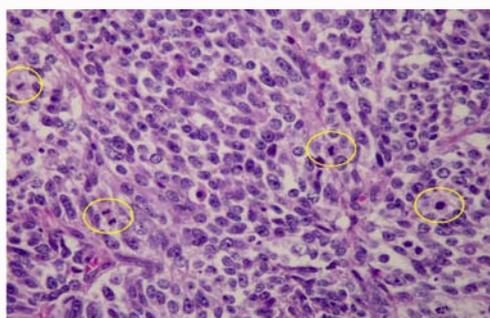


Figure 2: High magnification (x400) showing large cells and many mitosis (Hematoxylin-eosin).

the multidisciplinary meeting was to make a systemic chemotherapy regime similar to that used in the treatment of patients with non-small cell lung carcinomas, based on Cisplatin and Etoposide. The tumor responded well after four cycles of chemotherapy. CT scan showed a reduction of about 47% of the residual tumor. The patient was scheduled for local radiotherapy after two more cycles. Unfortunately, after the sixth cycle of chemotherapy, CT scan showed a local progression, so the patient was switched to second line chemotherapy of Gemcitabine and Capecitabine according to the decision of the multidisciplinary meeting. After 3 cycles of CT, the patient presented a radiological progression while keeping good general conditions. Therefore, the multidisciplinary consultation meeting opted for metronomic chemotherapy based on Cyclophosphamide which is currently underway.

Discussion

The WHO classification 2010 highlights 3 main classes of neuroendocrine neoplasm's: Grade 1 and 2 neuroendocrine tumors and grade 3 Neuroendocrine Carcinoma (NEC) that are

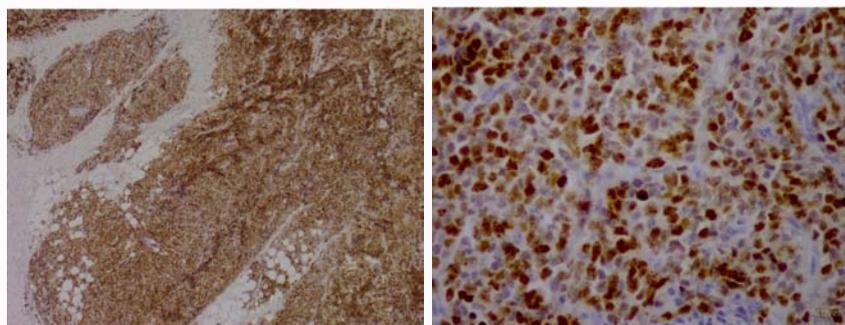
divided into Large Cell Neuroendocrine Carcinoma (LCNEC), Small Cell Neuroendocrine Carcinoma (SCC) and Mixed Adeno Neuroendocrine Carcinoma (MANEC) and are by definition poorly differentiated [2]. LCNEC is the least common histological subtype of NEC of the gallbladder and when present it is most often associated with another histological type. Pure LCNEC of the gallbladder is so rare that until now only a few cases have been described in literature [3] (Table 1). According to our knowledge, our report is the twelfth case reported so far. The origin remains controversial since the gallbladder does not normally contain neuroendocrine cells. However, given the presence of neuroendocrine cells in acute cholecystitis, some support the theory of a malignant transformation following intestinal or gastric metaplasia secondary to chronic inflammation. Others think that a transformation of multipotent stem cells present in the gall bladder is at the origin of the disease [4].

LCNEC is high grade neuroendocrine tumor characterized by neuroendocrine histological growth pattern that includes organoid, nesting, palisading and rosette-like structures. It's distinguished by increased mitotic activity (>10 mitoses/2mm) and extended necrosis. Large polygonal shaped cells with low nuclear cytoplasmic ratio, coarse vesicular chromatin and conspicuous nucleoli are common. Immuno histochemistry shows a strong cytoplasmic staining for neuroendocrine markers (Chromogranin A and Synaptophysin) [5].

NEC can be secretory causing symptoms such as flash syndrome, diarrhea hyperglycemia or non-secretory. The LCNEC described are most the time non secretory. The major signs reported are body weight loss, jaundice, abdominal pain or discomfort leading sometimes to a clinical picture mimicking an acute cholecystitis [6].

Radiological findings are not specific and may suggest other hepatobiliary tract tumors such as cholangiocarcinoma or hepatocellular carcinoma. The most common presentation is that of a focal or diffuse thickening of the wall of the gallbladder associated with an intra luminal polypoid mass. In most of the cases, the tumor is locally advanced with a focal invasion of the liver. The most encountered metastases are regional and distant lymph nodes, as well as liver metastases. Some cases of bones metastases and peritoneal carcinosis have been described [7].

Treatment: Most non metastatic LCNECs are locally advanced with local liver invasion. In these cases the most appropriate treatment seems to be a cholecystectomy with radical gallbladder bed clearance, liver segmentectomy followed by adjuvant Cisplatin and Etoposide CT. For metastatic cases of neuroendocrine carcinoma, the first line Etoposide and Cisplatin based chemotherapy is the standard of care. However, gallbladder location seems to have very poor prognosis. Multimodal treatment combining gallbladder surgery,



Figures 3a, 3b: Immunohistochemistry showing a high nuclear Ki-67 index.

Table 1: Clinical features of 11 pure large cell neuroendocrine carcinomas of gallbladder.

Authors	Age/ Sex	Clinical presentation	Size	Extension	Management	Outcomes
Papotti et al. [3]	M, 65	Symptomatic cholelithiasis	2.5 cm	Initially located	Cholecystectomy Recurrence : partial liver resection + CT	PFS: 4 months: Local + metastatic (Liver) recurrence OS: 18 months
Jun et al. [5]	F, 67	dull epigastric pain with palpable epigastric mass abdominal discomfort and jaundice	Huge, lobulated mass	Invasion of the liver segment 4 + one metastasis of liver segment 6	cholecystectomy	PFS: 12 months
Jun et al. [5]	M, 55	abdominal discomfort and jaundice		Coeliac aortocaval and paraaortic lymph nodes	CT (1 cycle)	PFS and OS: 1 months
Iype et al. [10]	F, 58	History suggestive of gallstones	2 cm x 2 cm	Coeliac and hepatic artery lymph nodes	Cholecystectomy followed 2 months later by radical gallbladder bed clearance, liver segment 4B/5 excision common bile duct excision, and lymphadenectomy up to coeliac nodes +adjuvant Cisplatin and Etoposide CT Hepatic biopsy + Intra-arterial CT + Pre-operative 3D-RT	PFS and OS: 18 months
Shimono et al. [8]	F, 64	Severe pain in right upper abdomen	11.5 cm x 10.5 cm	Large mass occupying middle and anterior segments of liver	Right tri segment ectomy Post-operative Cisplatin and Etoposide CT Partial cerebellectomy γ-knife irradiation	PFS: 35 months OS: 69 months
Lin et al. [9]	F, 65	Cushing's syndrome	Large mass	Initially located Recurrence : Liver metastases	Cholecystectomy and wedge-shaped liver resection Recurrence : Arterial embolization	PFS: 2 months
Okuyama et al. [11]	M, 64	abdominal fullness	25 mm	Cervical, axillary and left infraclavicular lymph nodes and small liver metastases Recurrence :Lymph nodes, liver and bone metastases Recurrence :Lymph nodes, liver and bone metastases	4 cycles: Cisplatin (60 mg/m ²) and Docetaxel (60 mg/m ²) followed by 3 cycles of carboplatin (120 mg/m ²) and Docetaxel (60 mg/m ²)	OS: 22 months
Buscemi et al. [12]	F, 76	4 month history of intermittent right-upper quadrant abdominal pain	1.8 cm	Liver metastases	Cholecystectomy followed by 2 cycles Cisplatin and Etoposide CT and 1 cycle Carboplatin and Etoposide CT+ Somatostatin analogs	OS: 5 months (died from acute myocardial infarction)
Kamboj et al. [13]	F, 50	NR	NR	Liver, Omentum, Adrenal Gland metastases	Cholecystectomy followed by 6 cycles of Gemzar Carboplatin CT	PFS and OS: 3 months
Kamboj et al. [13]	M, 61	NR	NR	Abdominal lymph nodes and mesenteric deposits	Cholecystectomy	PFS and OS: 2 months
Peters et al. [14]	M, 67	Intermittent right-upper quadrant abdominal pain	40 mm x 46 mm x 70 mm	Locally advanced (invading the segment V of the liver) with metastatic lymph nodes	Cholecystectomy followed by 6 cycles of Cisplatin and Etoposide CT Second line of Gemcitabine and Capecitabine CT	PFS: 6 months OS: 12 months

local treatment of metastases and systemic treatment seems to be appropriate. Shimono et al. [8] reported in 2009 a case of LCNEC gallbladder with liver metastases. A multimodal treatment associating intra-arterial CT, a preoperative 3D-RT, a right tri segment ectomy with a Cisplatin and Etoposide postoperative CT. After cerebellar progression, partial cerebellectomy with γ knife irradiation was performed. This multimodal treatment led to an encouraging 69-month overall survival. In case report of Lin et al. [9] treatment of hepatic progression by arterial embolization followed by systemic CT led to a 22 months overall survival.

Conclusion

Pure LCNEC of the gallbladder is exceedingly rare. Only 10 cases had been described in the literature until now. It has non-specific clinical or radiological signs. This entity seems to have a very poor prognosis. Because of its scarcity, treatment remains not clear. Nevertheless given its high malignancy, a multimodal management seems to be most appropriate.

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