Extra-pulmonary neuroendocrine carcinomas in the biliary system: Two case reports and a literature review

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Abstract

Primary biliary tract neuroendocrine tumors (NET) are extremely rare and only 237 cases have been published to date. Herein are described two patients with neuroendocrine carcinoma (NEC) of the biliary system, along with a literature review of this rare malignancy. The overall and disease-free survival tended to be shorter among patients with biliary NEC than biliary adenocarcinomas, probably because a definitive preoperative diagnosis and effective treatment options for advanced biliary NEC were unavailable. Therefore, a precise preoperative diagnosis and adjuvant and/or neoadjuvant therapy including chemoradiation leading to radical surgery appeared important to improve the prognosis of patients with biliary NEC.

Introduction

Neuroendocrine carcinoma (NEC) originates from endocrine cells of the systemic neuroendocrine system and arises mainly in the lungs, gastrointestinal tract and pancreas. Primary NEC of the biliary tract is extremely rare and distinctive with aggressive clinical behavior. Herein are described two patients with NEC of the biliary tract, along with a review of the literature with a discussion of the clinical presentation, pathological findings, and therapeutic management of this disease.

Case reports

Table 1 summarizes the findings the two cases.

Case 1

A 56-year-old previously healthy woman presented with abdominal discomfort in January 2006. Ultrasonography and contrast-enhanced computed tomography (CT) revealed a massive tumor in the gallbladder with gallstones and a large lymph node at the hepatoduodenal ligament (Figure 1). The tumor had directly spread to the liver. Subsequent staging CT of the chest and abdomen did not identify any metastatic lesions to the lungs or other abdominal organs. Histological examination of a needle biopsy of the invasive liver tumor revealed atypical cells with large, irregular nuclei with nuclear molding, inconspicuous nucleoli and scant cytoplasm (Figure 2A). Immunohistochemical staining of formalin-fixed, paraffin-embedded tissue sections revealed tumor cells with high mitotic activity (MIB-1: 70%) that were positive for synaptophysin and negative for chromogranin A (Figure 2B, C, D). These histological features and the immunophenotype were characteristic of NEC, and the clinical findings supported a diagnosis of primary NEC of the gallbladder. The estimated stage of the disease in this patient was cT4cN2cM0 sStage IVB.

Two cycles of combination chemotherapy with cisplatin (60 mg/m^2, day 1) and irinotecan (60 mg/m^2, days 1, 8, and 15; 4 weeks/cycle) decreased the size of the primary tumor on abdominal CT images (Figure 3). Further chemoradiotherapy was planned with the aim of surgical resection. Abdominal CT after one cycle of cisplatin (60 mg/m^2) and etoposide (100 mg/body) with radiation (54 Gy/30 fr) revealed further decreases in the size of the primary tumor and the disappearance of abnormal lymph nodes at the hepatoduodenal ligament. Extended radical cholecystectomy (modified Glenn operation) was performed.

Histopathology revealed mostly metamorphic NEC and well-differentiated adenocarcinoma (MIB-1: 10%) in the gallbladder. The invaded part of the gallbladder bed was replaced by scarring necrosis, fibrosis, and histiocytic assembly

(Figure 4). The stage of this tumor was pT3pN1 (#13)pM0 fStage III. Post-surgical adjuvant combination chemotherapy comprised 17 cycles of nedaplatin (60 mg/m^2 day 1) and irinotecan (60 mg/m^2 days 1, 8, and 15; 4 weeks/cycle). The patient has remained disease-free for 10 years since the initial diagnosis.

Case 2

A 73-year-old, previously healthy man presented with jaundice in December 2006. An enhanced tumor at the vater papillae and dilated intrahepatic bile duct was identified by CT (Figure 5). Subsequent staging CT images of the chest and abdomen did not identify any metastatic lesions on the lung or other abdominal organs. One lymph node was found between the celiac artery and left renal artery. Endoscopic retrograde cholangiopancreatography (ERCP) revealed stenosis, bending and tortuosity of the lower bile duct and a dilated upper bile duct (Figure 6). Histological examination of biopsy specimens of the vater papillae and endoscopic nasobiliary drainage (ENBD) revealed atypical cells with large, irregular nuclei with nuclear molding, inconspicuous nucleoli and scant cytoplasm (Figure 7). These features were characteristic of NEC, and the clinical findings supported a diagnosis of primary NEC of the vater papillae and the lower bile duct. The estimated stage of the disease in this patient was cT4cN3cM0 sStage IVB.

The patient was treated by pancreaticoduodenectomy in January 2007. An intraoperative pathological examination did not find metastasis in the lymph nodes around the aorta.

Histopathological assessment revealed that the tumor in the vater papillae and the lower bile duct consisted of neuroendocrine carcinoma (MIB-1: 90%) and no adenocarcinoma (Figure 8). This tumor was finally staged as pT4pN1(#13)pM0 fStage IVA.

Post-surgical chemotherapy comprised three cycles of cisplatin (60 mg/m^2 day 1) and irinotecan (60 mg/m^2 days 1, 8, and 15; 4 weeks/cycle). The patient has remained disease-free for 9 years since the initial diagnosis.

Discussion

NEC occurs mainly in the lungs and accounts for approximately 20% of all primary lung carcinomas.[1] Extra-pulmonary NEC represents 4% of all NEC and those in the biliary system are rare; extrahepatic bile duct and gallbladder reportedly account for only 0.41% of primary NEC sites.[2]

Davies reported neuroendocrine tumor (NET) of the distal bile duct and pancreatic duct in 1959.[3] However, they presented more peri-ampullary, than bile duct NET. Pilz reported the first case of biliary-tract NET in 1961.[4] An extensive search of PubMed

revealed that 237 reports have described biliary system NET and NEC since 1959 (Table 2).[3-74] Pathological assessment in the present review was classified according to the 2010 WHO classification.[75] The pathological features of mixed adeno-neuroendocrine carcinoma were similar to those of poorly-differentiated endocrine tumors. Therefore, mixed adeno-neuroendocrine carcinoma was classified as NEC for convenience.

Epidemiology

The mean age of the reported patients was about 57 (range, 6 to 78) years and 59.5% of them were female, indicating that NET and NEC in the biliary system tended to occur more frequently among women.

Location

The most common site of malignancy in the biliary system was the gallbladder (62.9%), followed by the common bile duct (20.7%), common hepatic duct (9.7%), cystic duct (5.4%), vater papillae (1.3%), and others.

Preoperative diagnosis

Only 17 (14.8%) patients were preoperatively diagnosed based on pathological cytological or biopsy findings and the accuracy was 47.0%. These rates were lower than those for other organs. This might be associated with technical difficulties with obtaining biopsies at the biliary system.

Pathology

The most common histopathological type of NET and NEC in the biliary system was poorly differentiated endocrine carcinoma (38.7%), followed by carcinoid (35.6%), mixed adeno neuroendocrine carcinoma (13.3%), and well-differentiated endocrine carcinoma (12.4%).

Metastasis

Metastasis was evident in 165 patients (69.6%) at the time of diagnosis. Chen et al. reported that NET progressed rapidly, with early liver invasion and lymphatic metastasis.[71] Therefore, most patients with biliary NET were diagnosed when the disease had already progressed.

Therapeutic management

Therapeutic options for primary biliary NEC are often limited due to the advanced nature of the disease at initial diagnosis. Surgical resection has been the best option for a cure to date. Ten (52.6%) of 19 patients with NEC in the present study were treated by radical resection and six (60.0%) of them were preoperatively diagnosed from cytological or biopsy findings with 83.3% accuracy.

Neoadjuvant chemotherapy was rarely administered to reduce the volume of the tumor and permit tumor resection. The median survival of three patients with

unresectable NEC who were treated with neoadjuvant chemotherapy and/or radiation and radical surgery in these reported cases was 3.9 years. These findings indicate that neoadjuvant chemotherapy and/or radiation might substantially benefit patients with initially unresectable biliary NEC.

Adjuvant therapies including radiation and chemotherapy conferred encouraging therapeutic effects upon patients with biliary NECs. Eleven (57.9%) of 19 patients with NEC in the present series underwent adjuvant therapy, with a median survival of 1.3 years. Chen et al. reported that the median survival duration after adjuvant radiation and chemotherapy following surgical resection was 12.7 months, compared with only 3 months for patients who were only surgically treated.[71] These findings indicate that adjuvant chemotherapy and radiation might substantially benefit patients with biliary NEC.

In conclusion, biliary NEC is a specific type of biliary carcinoma with a very low incidence. Overall and disease-free survival tended to be shorter for patients with biliary NEC than biliary adenocarcinomas, because of imprecise preoperative diagnostic methods and limited treatment options for advanced biliary NEC. Therefore, preoperative diagnosis should be clarified and adjuvant and/or neoadjuvant therapy including chemoradiation should be applied before radical surgery to improve the prognosis of patients with biliary NEC.

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Conflict of interest

The authors declare that they have no conflicts of interest concerning this article.

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Table 1. Summary of two cases.

	Case1	**Case2**
Location	Gallbladder	Vater papillae
Stage	IVb	IVa
Therapy	Neoadjuvant chemotherapy (CDDP+CPT-11 2 courses) →Chemortherapy and radiation (RT 54Gy/30Fr+CPT-11/VP16) →Extended radical cholecystectomy →Adjuvant chemotherapy (NED+CPT-11 17 courses)	Pancreatoduodenectomy →Adjuvant chemotherapy (CDDP+CPT-11 3 courses)
Pathology	Mixed adenoneuroendocrine carcinoma	Poorly differentiated neuroendocrine carcinoma
Survival	10 years	9 years
Recurrence	No	No

Table 2. Literature review of NET and NEC of the biliary system.

Authors	Year	Patients (n)	Mean Age	Gender	Location	Metastasis	Pathology	WHO 2010	Pre-operative diagnosis	Neo-adjuvant therapy	Operation	Adjuvant therapy	Survival	Rerer ence
Davis	1959	1	N/A	N/A	CBD (Periampullary)	Liver	Carcinoid	NET G1	N/A	N/A	N/A	N/A	No evidence of recurrence, 20 yrs	3
Pilz	1961	1	55	F	CBD	No	N/A	N/A	N/A	N/A	N/A	N/A	No evidence of recurrence, 18 mos	4
Little et al	1968	1	41	F	Hilar	No	N/A	N/A	N/A	N/A	N/A	N/A	Died, 3 weeks	5
Bergdahl	1976	13	N/A	N/A	GB: 10 pts Biliary tract: 3 pts	3Pts	Carcinoid	NET G1	N/A	N/A	N/A	N/A	Autopsy, 5 pts	6
Judge et al	1976	1	19	M	Hilar	Liver LN	Poorly differentiated carcinoma (Small cell)	NEC	N/A	N/A	No	N/A	Died, 6th hospital day, Autopsy	7
Gerloch et al	1979	1	32	M	CBD	No	Carcinoid	NET G1	N/A	N/A	N/A	N/A	N/A	8
Vitaux et al	1981	5	N/A	N/A	N/A	N/A	Carcinoid	NET G1	N/A	N/A	N/A	N/A	N/A	9
Abe et al	1983	1	64	M	CBD	Liver	Carcinoid	NET G1	N/A	N/A	N/A	N/A	Died, 10 mos	10
Goodman et al	1984	1	28	F	Cystic duct	LN	Somato-statinoma	NET G1	No	No	Cholecystectomy	Radiation	No evidence of recurrence, 9 mos	11
Jutte et al	1986	1	62	M	CHD	No	Carcinoid	NET G1	N/A	N/A	N/A	N/A	No evidence of recurrence, 24 mos	12
Nicolescu et al	1986	1	50	F	Cystic duct	No	Carcinoid	NET G1	N/A	N/A	N/A	N/A	N/A	13
Alexander et al	1986	1	64	F	CBD	No	Carcinoid	NET G1	N/A	N/A	Yes	N/A	No evidence of recurrence, 8 mos	14
Chittal et al	1989	1	46	F	Cystic duct	No	Carcinoid	NET G1	N/A	N/A	N/A	N/A	No evidence of recurrence, 3 yrs	15
Fujita et al	1989	1	55	F	CBD	No	Carcinoid	NET G1	N/A	N/A	N/A	N/A	No evidence of recurrence, 6 mos	16
Bickerstaff et al	1989	1	57	F	CBD	No	Carcinoid	NET G1	N/A	N/A	N/A	N/A	No evidence of recurrence, 6 mos	17
Brown et al	1990	1	35	F	Hilar	No	Carcinoid	NET G1	No	No	Yes	N/A	No evidence of recurrence, 7 days	18
Bumin et al	1990	1	38	F	CBD	No	Carcinoid	NET G1	No	No	Choledochotomy	N/A	N/A	19

Angeles-Angeles et al	1991	1	39	F	CBD	LN	Carcinoid	NET G1	No	No	Exploratory laparotomy	N/A	No evidence of recurrence, 42 mos	20
Barron-Rodriguez et al	1991	1	36	M	CBD	Liver	Carcinoid	NET G1	N/A	N/A	N/A	N/A	Died,4days	21
Rugge et al	1992	1	64	F	Cystic duct / CBD	No	Carcinoid	NET G1	No	No	Laparotomy	N/A	No evidence of recurrence, 12 mos	22
Gembala et al	1993	1	28	M	Hilar / RHD	Liver	Carcinoid	NET G1	N/A	N/A	N/A	N/A	N/A	23
Manduja no-Vera et al	1995	1	53	F	CBD	No	Gastrinoma	NET G1	No	No	Yes	N/A	No evidence of recurrence, 8 mos	24
Sankary et al	1996	1	47	F	Hilar	No	Carcinoid	NET G1	No	No	Trisegmentectomy	No	No evidence of recurrence, 4 yrs	25
Hao et al	1996	1	47	F	CBD	No	Carcinoid	NET G1	No	No	Liver transplantation	N/A	No evidence of recurrence, 5 mos	26
Kopelman et al	1996	1	44	M	CBD	Liver	Carcinoid	NET G1	No	No	Choledochoduodenostomy	Pancreatic oduodenostomy	No evidence of recurrence, 18 mos	27
Belli et al	1996	1	78	M	CBD	No	Carcinoid	NET G1	No	No	Bile duct resection	N/A	No evidence of recurrence, 15 mos	28
Nahas et al	1998	1	61	F	Hilar	N/A	Carcinoid	NET G1	No	No	Bile duct resection	N/A	No evidence of recurrence, 6 mos	29
Ross et al	1999	1	65	M	CBD	No	Carcinoid	NET G1	No	No	Pancreatic oduodenostomy	N/A	No evidence of recurrence, 19 mos	30
Hermina et al	1999	1	69	M	Gallbladder	LN	Carcinoid	NET G1	No	No	Cholecystectomy	N/A	N/A	31
Ronald et al	1999	2	52	F: 2 pts	Hilar	No	Carcinoid	NET G1	Cholangiocarcinoma	No	CBD excision	No	No evidence of recurrence, average 34 mos	32
Chen et al	2000	1	14	M	Hilar	N/A	Carcinoid	NET G1	No	No	Yes	N/A	N/A	33
Maritra et al	2000	7	50	F: all	EHBD	LN:2 pts	Carcinoid	NET G1	No	No	Segmental resection Pancreatic oduodenostomy	N/A	No evidence of recurrence, average 6.6 yrs	34
Juturi et al	2000	1	43	M	CBD	N/A	Carcinoid	NET G1	No	No	Pancreatic oduodenostomy	N/A	No evidence of recurrence, 3.5 yrs	35
Turrión et al	2002	1	51	F	Hilar	N/A	Carcinoid	NET G1	N/A	N/A	N/A	N/A	N/A	36
Pawlik et al	2003	1	59	M	Hilar	LN	Carcinoid	NET G1	Cholangiocarcinoma	No	CBD excision	No	N/A	37
Podnos et al	2003	2	46	F: 2 pts	CBD	N/A	Carcinoid	NET G1	No	No	Yes	N/A	N/A	38
Volpe et al	2003	1	19	M	CBD	N/A	Carcinoid	NET G1	N/A	N/A	N/A	N/A	N/A	39
Menezes et al	2004	1	30	M	CBD	LN	Carcinoid	NET G1	Cytology (Inconclusive)	No	CBD excision	N/A	No evidence of recurrence, 18 mos	40
Ligato et al	2005	1	33	F	Hilar	N/A	Carcinoid	NET G1	N/A	N/A	Yes	N/A	N/A	41
Hubert et al	2005	3	56	M: 2 pts	CBD	Liver: 1pt	Carcinoid	NET G1	Biopsy: 1 pt	No	Radical resection:2 pts	N/A	No evidence of recurrence, average 9yrs	42
Nesi et al	2006	1	30	M	CBD	No	Well-differenciated endocrine carcinoma	NET G2	No	No	Pancreatoduodenectomy	N/A	No evidence of recurrence, 7 yrs	43
Kim et al	2006	1	67	F	CBD	No	Well-differenciated endocrine carcinoma	NET G2	No	No	Pancreatoduodenectomy	N/A	N/A	44
Caglikulekci et al	2006	1	40	F	Hilar	N/A	Carcinoid	NET G1	No	No	CBD excision	N/A	N/A	45
Honda et al	2006	1	76	M	CBD	No	Well-differenciated endocrine carcinoma	NET G2	Cytology (Adonocarcinoma)	No	Pancreatoduodenectomy	N/A	Liver metastasis, Alive 10 mos	46
Todoroki et al	2007	1	73	M	CBD	No	Clear cell carcinoid	N/A	No	No	Pancreatoduodenectomy	N/A	No evidence of recurrence, 12 mos	47
Sethi et al	2007	1	51	M	CHD / Cystic duct	No	Well-differenciated endocrine carcinoma	NET G2	Cytology (Inconclusive)	No	CBD excision	N/A	No evidence of recurrence, 22 mos	48
Stavridi et al	2007	1	N/A	N/A	Cystic duct	N/A	Neuroendocrine tumour	N/A	No	No	Yes	N/A	N/A	49

Ferrone et al	2007	1	52	M	EHBD	No	Carcinoid	NET G1	No	No	Trisegmentectomy,CBD resection	N/A	N/A	50
Jiménez et al	2008	1	60	M	Hilar	N/A	Carcinoid	NET G1	N/A	N/A	N/A	N/A	N/A	51
Nafidi et al	2008	1	31	F	CBD	No	Well-differenciated endocrine carcinoma	NET G2	Biopsy (Negative)	No	CBD excision	N/A	N/A	52
Gusani et al	2008	1	N/A	N/A	CBD	N/A	Carcinoid	NET G1	N/A	N/A	Yes	N/A	No evidence of recurrence, 11 yrs	53
Schmitt et al	2008	1	N/A	N/A	Hilar	N/A	Carcinoid	NET G1	N/A	N/A	N/A	N/A	N/A	54
Constantini et al	2008	1	N/A	N/A	CHD	N/A	Adenocarcinoid	N/A	N/A	N/A	N/A	N/A	N/A	55
Felekouras et al	2009	1	60	F	Cystic duct	No	Well-differenciated endocrine carcinoma	NET G2	No	No	CBD and BD resection	N/A	No evidence of recurrence, 16 mos	56
Price et al	2009	3	N/A	N/A	CBD: 2 pts Hilar: 1 pt	N/A	Neuroendocrine	N/A	N/A	N/A	N/A	N/A	N/A	57
Tonnhofer et al	2009	1	6	F	CBD	LN	Neuroendocrine	N/A	N/A	N/A	Extended resection	N/A	No evidence of recurrence, 2 yrs	58
Elise et al	2009	1	71	M	CHD	No	Well-differenciated endocrine carcinoma	NET G2	Biopsy (Neuroendocrine carcinoma)	No	Extended left hepatectomy	N/A	Alive, 7mos	59
Zhan et al	2010	1	10	M	CBD	N/A	Carcinoid	NET G1	N/A	N/A	N/A	N/A	N/A	60
Squillaci et al	2010	2	61	M: 2 pts	CBD: 2 pts	N/A	Well-differenciated endocrine carcinoma	NET G2	N/A	N/A	N/A	N/A	No evidence of recurrence, average 50 mos	61
Tsalis et al	2010	1	77	M	Hilar	No	Neuroendocrine	N/A	No	No	Left hepatectomy CBD resection	N/A	N/A	62
Lee et al	2011	4	56	M: 3 pts	GB: 2 pts CBD: 1 pt Vater: 1 pt	N/A	Carcinoid	NET G1	Misdiagnosed	No	Yes	N/A	N/A	63
Athanasopoulos et al	2011	1	43	M	CBD	No	Carcinoid	NET G1	Biopsy (Inconclusive)	No	Pancreatoduodenectomy	No	No evidence of recurrence, 18 mos	64
Mezi et al	2011	1	51	M	Gallbladder	N/A	Neuroendocrine	N/A	No	No	Cholecystectomy	No	No evidence of recurrence, 45 mos	65
Kim et al	2011	1	48	F	Gallbladder	No	Mixed adenoneuroendocrine carcinoma	NEC	Biopsy (Small cell neuroendocrine carcinoma)	No	Hepatopancreaticoduodenectomy	Chemotherapy (6 courses)	No evidence of recurrence, 18 mos	66
Ajay et al	2012	1	69	F	Left hepatic duct	Liver	Neuroendocrine	N/A	Biopsy (Neuroendocrine)	Unresectable	Unresectable	Chemotherapy	Alive, 1 yr	67
Song et al	2012	1	55	F	Gallbladder	Liver LN	Mixed adenoneuroendocrine carcinoma	NEC	Biopsy (Small cell neuroendocrine carcinoma)	Yes (6 courses)	Cholecystectomy Hepatic wedge resection	Chemotherapy (3 courses)	No evidence of recurrence, 7 mos	68
Smith et al	2014	1	47	F	Gallbladder	LN	Small cell neuroendocrine carcinoma	NEC	Biopsy (Small cell neuroendocrine carcinoma)	Yes (6 months)	Radical cholecystectomy	N/A	No evidence of recurrence, 1 yr	69
Chen et al	2014	2	48	M: 2 pts	Gallbladder: 2 pts	Liver: 1pt LN:1 pt	Poorly differenciated endocrine carcinoma: 1pt Mixed adenoneuroendocrine carcinoma: 1pt	NEC: 2 pts	No	No	En bloc cholecystectomy:2pts	Chemotherapy: 2 pts	No evidence of recurrence, average 8 mos	70

Chen et al	2015	10	59	M: 3 pts	Gallbladder	LN:9 pts Liver: 2pts	Neuroendocrine carcinoma: 6pts Mixed adenoneuroendocrine carcinoma: 4pts	NEC: 10 pts	N/A	No	Radical resection:2 pts Palliative resection:8 pts	Chemotherapy: 2 pts Radiation: 2 pts	Median survival time: 3 mos	71
Fattach et al	2015	2	59	M: 1 pt	Gallbladder: 2 pts	LN:2 pts Liver: 1pt	Small cell neuroendocrine carcinoma: 1pt High grade neuroendocrine carcinoma: 1pt	NEC: 1 pt NET G2: 1 pt	Biopsy (High neuroendocrine carcinoma):1pt	No	Complex resection	Chemotherapy: 2 pts	N/A	72
Hosoda et al	2016	1	35	M	CBD	No	NET G2	NET G2	No	No	CBD resection	No	N/A	73
Adachi et al	2016	121	64	M: 42 pts	Gallbladder	LN:83pts Liver 66pts	Small cell neuroendocrine carcinoma: 82pts Mixed adenoneuroendocrine carvinoma: 22pts	NEC: 121 pts	N/A	N/A	Surgery:67 pts Chemotherapy:53pts	N/A	Median survival time: 8 mos	74
Our case 1		1	56	F	Gallbladder	LN	Mixed adenoneuroendocrine carcinoma	NEC	Biopsy (Neuroendocrine carcinoma)	Chemotherapy (2 courses) Radiation	Extended radical cholecystectomy	Chemotherapy (17 courses)	No evidence of recurrence, 10 yrs	
Our case 2		1	73	M	Vater papillae	LN	Poorly differentiated neuroendocrine carcinoma	NEC	Biopsy (Neuroendocrine carcinoma)	No	Pancreatoduodenectomy	Chemotherapy (3 courses)	No evidence of recurrence, 9 yrs	

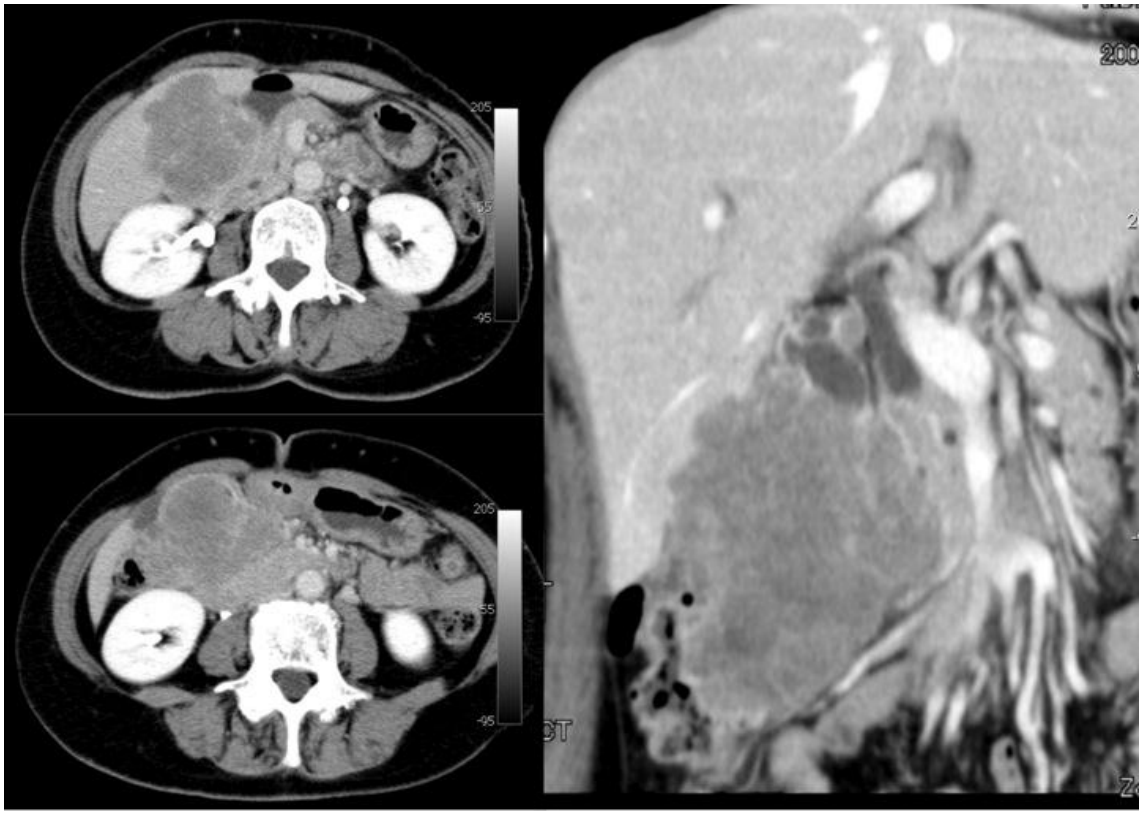

Figure 1: Massive tumor in gallbladder with gallstones and large lymph node at hepatoduodenal ligament.

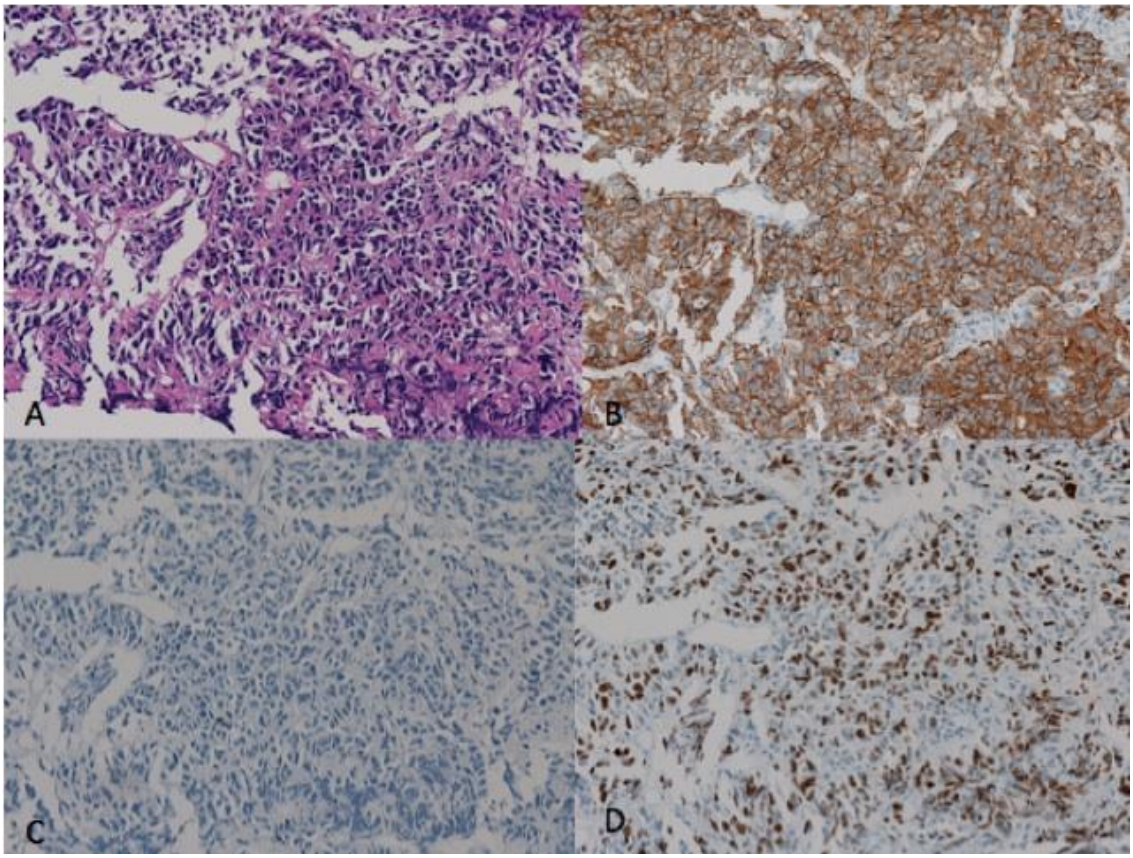

Fig. 2: Atypical tumor cells. A. Atypical cells have inconspicuous nucleoli, scant cytoplasm, and large, irregular nuclei with nuclear molding. B, C and D. Tumor cells with high mitotic activity (MIB-1: 70%) are positive for synaptophysin and negative for chromogranin A.

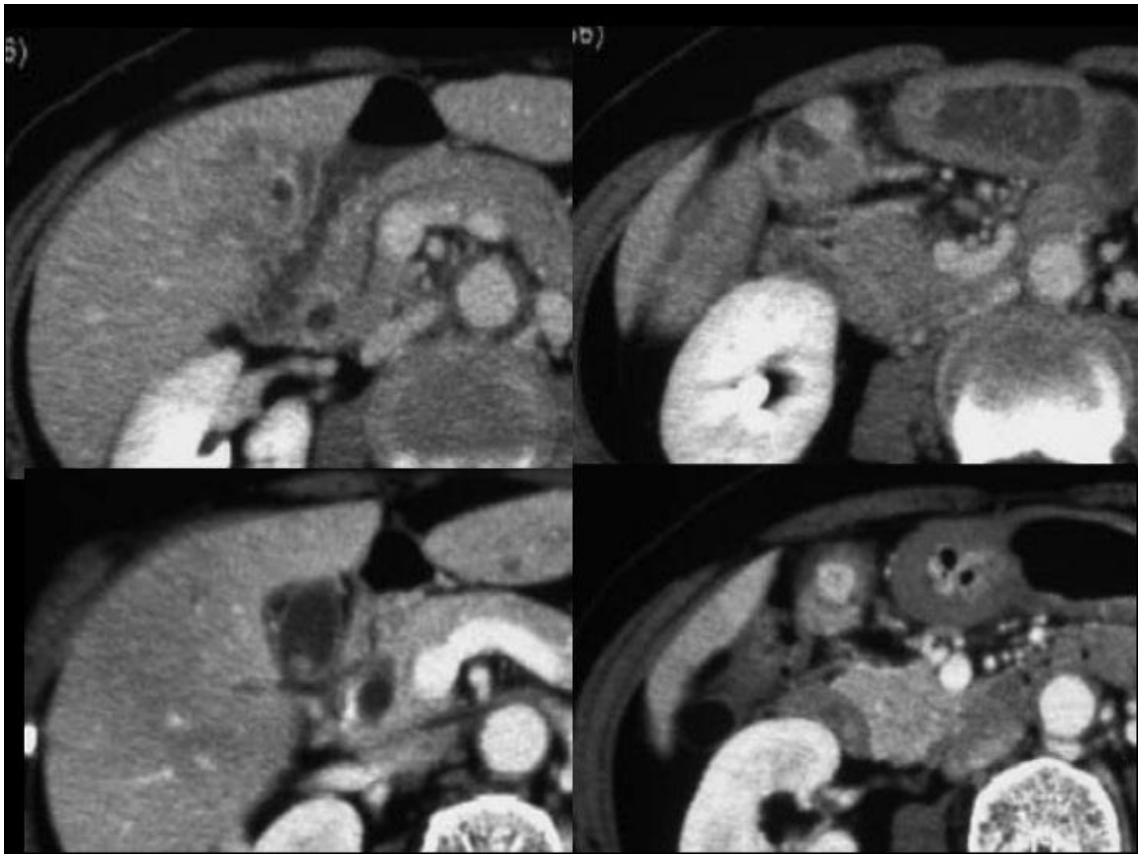

Fig. 3. Abdominal CT findings. Primary tumor is reduced after two cycles of combination chemotherapy.

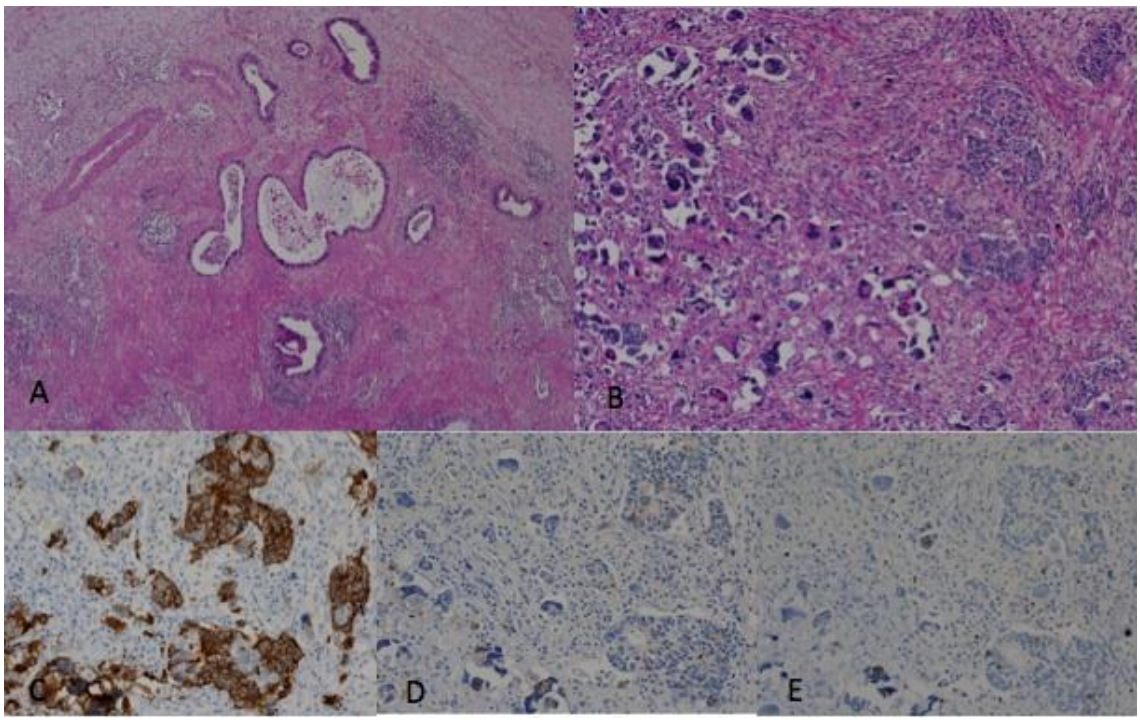

Fig. 4. Mostly metamorphic NEC and well differentiated adenocarcinoma (MIB-1: 10%). Invaded area of gallbladder bed is replaced with scarring necrosis, fibrosis and histiocytic assembly.

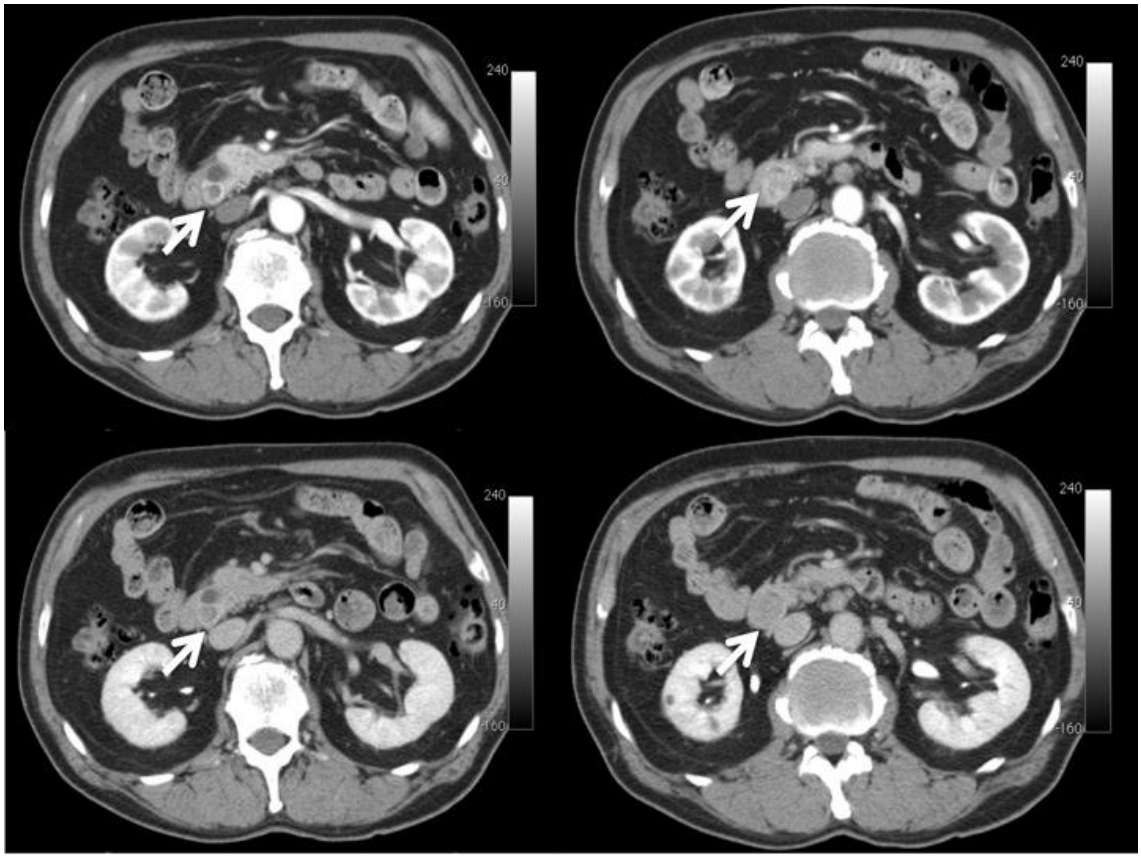

Fig. 5. Enhanced tumor at vater papillae and dilated intrahepatic bile duct.

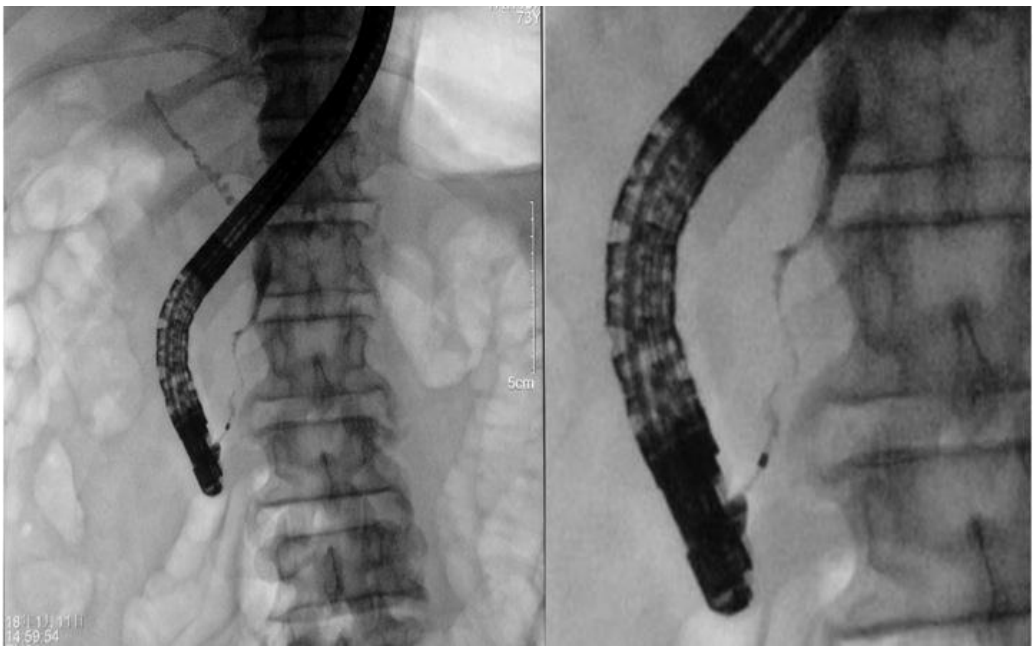

Fig. 6. Stenosis, bending and tortuosity of lower bile duct and dilated upper bile duct.

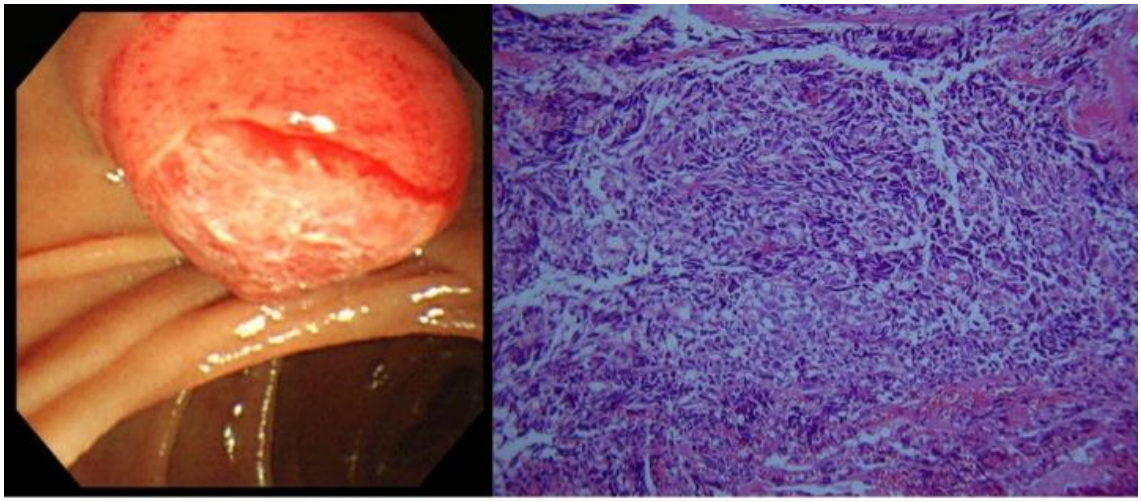

Fig. 7. Atypical cell with large, irregular nucleus with nuclear molding, inconspicuous nucleoli and scant cytoplasm.

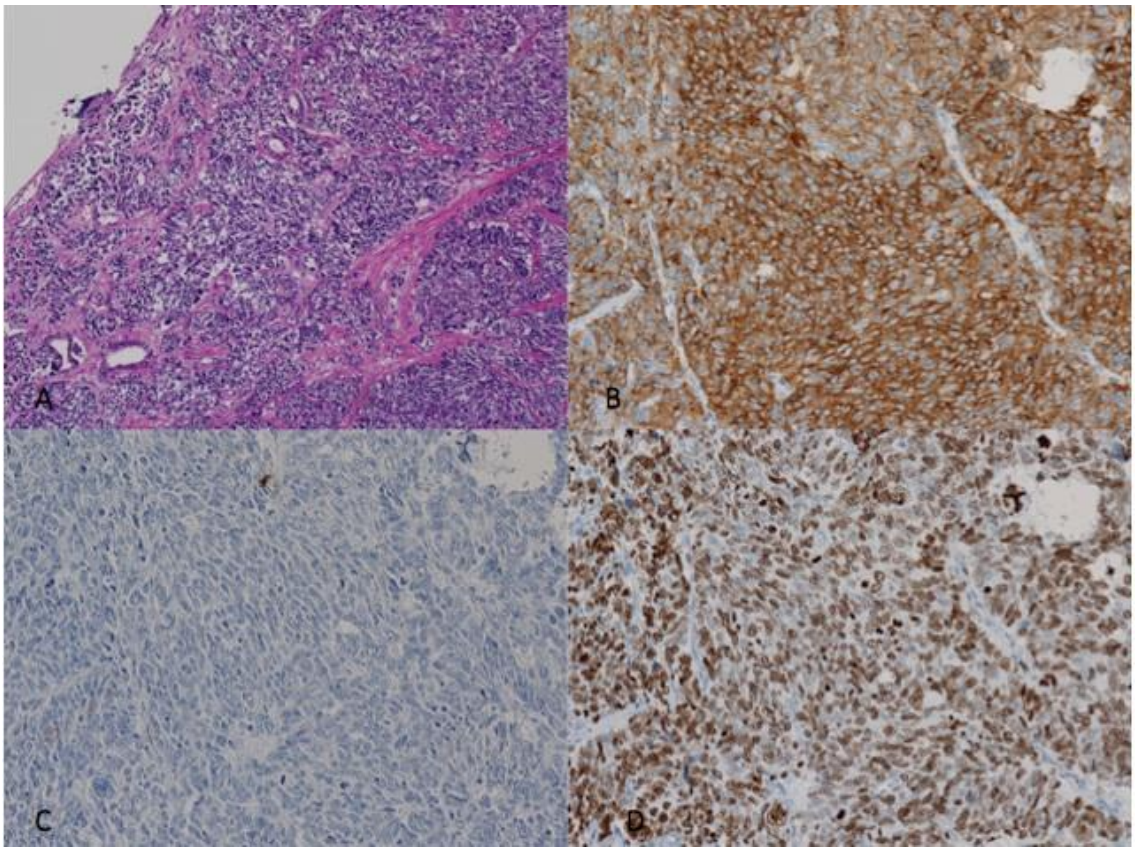

Fig. 8. Tumor in vater papillae and lower bile duct.
Tumor consists of neuroendocrine carcinoma (MIB-1: 90%) and adenocarcinoma is absent.