A Case of Focal Small-cell Neuroendocrine Carcinoma in the Vicinity of the Extrahepatic Bile Duct, Adjacent to an Extensive Biliary Intraepithelial Neoplasm: A Diagnostic Challenge with Major Clinical Implications

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Abstract. *Gastroenteropancreatic neuroendocrine tumors are known for their aggressiveness. Diagnosis of various bile duct pathologies, like biliar intraepithelial neoplasm, mixed adenoneuroendocrine carcinomas or small cell carcinomas, is challenging. This case report focuses on a rare case of a focal primary minute small cell carcinoma in the vicinity of the extrahepatic bile duct, presenting itself next to an extensive biliar intraepithelial neoplasm. This finding led to adjuvant chemotherapy, followed by major surgery. Therapeutic approach was based on CT and MRI scans but most importantly on immunohistochemistry and histological evaluation. Initially CR seemed achievable, but metastases were to be found rapidly. The authors want to underline the fact that major clinical decisions are based on sometimes tiny specimens; as literature shows it is absolutely advisable to use markers to differentiate the dignity of investigated areas. The authors call for keeping collision of tumors in mind and adding KOC staining and using it in a routine manner examining biliary duct lesions.*

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) arise from the neuroendocrine cell system and present a complex biological behavior, as they differ not only in hormonal diversity but also metastatic behavior and consequently in their aggressiveness (1, 2). In 2010, the world health organization published a new classification for gastrointestinal neuroendocrine neoplasms (Tables I and II), pointing to morphological criteria and proliferative index (1, 2). In this classification the term 'mixed adenoneuroendocrine carcinoma' (MANEC) has been added (Table I) and describes tumors that are composed of both epithelial and neuroendocrine parts of at least 30% (3, 4). This tumor type, which has to be clearly differentiated from other entities, is staged into high-, intermediate- and low-grade malignancy (3-5).

Neuroendocrine carcinomas comprise of small cell carcinomas (Table II) among others, which are defined by a poor differentiation and a high metastatic potential (1, 2). Not only diagnosis but also prognostic information is based on tumor cell differentiation, on the mitotic count or the proliferative index, measured by Ki-67. Statistically, small cell carcinomas in organs other than the lung account for fewer than 5% of the entire group (6).

Another distinct pathological entity of the bile duct system are biliary intraepithelial neoplasms (BilINs). Diagnosis of BilIN is based on histopathological evaluation and defined as dysplastic epithelial change, whereby the differentiation between inflammation-induced reactive changes and true dysplasia clearly classified as BilIN changes the clinical impact (7-9). Based on morphological criteria, such as loss of cellular polarity or nuclear hyperchromasia, BilINs can be divided into low-, intermediate- and high-grade (BilIN1, BilIN2 and BilIN3, respectively) (7, 9). BilIN3 describes a carcinoma *in situ* (7, 10).

Diagnosis of bile duct pathologies *per se* may be a challenge as specimens are usually of small size due to the limited amount that can be taken by fine-needle aspiration or brush biopsy (2). For staging of GEP-NETs, positron-emission tomography (PET) is believed useful, especially in patients with locally-limited disease (2). The majority of gastrointestinal neuroendocrine carcinomas have metastasized

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Table I. *Classification of neuroendocrine neoplasms of the gastrointestinal system.*

Neuroendocrine tumor (NET)	G1	G2
Neuroendocrine carcinoma (NEC)	G3 large cell	G3 small cell
Mixed adenoneuroendocrine carcinoma (MANEC)	Low-grade, intermediate-grade, high-grade	

at the time of diagnosis (11). Prognosis depends on the classification at the time of diagnosis. Even for patients with localized disease, the long-term survival is poor (2, 12) and therefore therapeutic delays should be avoided. Evidence-based guidelines for definitive treatment of GEP-NETs are currently still lacking; however for metastasized tumors, first-line therapy with cisplatin and etoposide seems to be favorable (11, 12). For second-line therapy, clear recommendations are also still not available (11) For localized tumors, surgical intervention alone appears to be insufficient (2), hence several authors have called for neoadjuvant chemotherapy followed by definitive surgery if possible, most likely prolonging long-term survival (2).

We report a rare case of a minute focal small cell carcinoma in the vicinity of the extrahepatic bile duct, arising adjacent to an extensive BilIN.

Case Report

In August 2014, a 61-year-old male patient presented due to abdominal pain, icterus of sclera and skin, with nausea, as well as pruritus of the whole integument. Despite a history of curative prostatectomy in 2012 due to an acinar carcinoma [pT2c, N0 (0/5), Gleason score: 3+4=7], he was otherwise healthy and was not on any medication. Laboratory parameters revealed highly elevated liver enzyme levels (Table III), however, hepatitis parameters were found to be normal. Abdominal sonography revealed cholestasis, sludge within the common biliary trunk and a gritty gall bladder. Performing an endoscopic retrograde cholangio pancreaticography a malignant 1.5 cm-long stenosis was suspected within the common biliary duct, resulting in a dilated proximal common biliary duct. A stent was inserted into the *ductus hepatocholedochus* and liver enzymes decreased gradually (Table III), as did the icteric sclera and cutis. Cytology however showed many atypical cells but no malignant cells. Magnetic resonance cholangiopancreaticography again underlined a suspected tumor of the biliary duct. Furthermore carbohydrate antigen 19-9 (CA19-9) was found to be slightly elevated (41.1 U/ml; normal range=0.0-37.0 U/ml). A PET-computed tomography (CT) completed the preoperative staging, verifying significant pathological tracer uptake in the middle of the common biliary duct, highly suspicious of a tumor.

Transduodenal fine-needle aspiration was used to gain cells for histological evaluation. Immunohistochemistry was performed on Ventana autostainer (Ki67, S100p, TTF1) and Dako immunostainer (RNA oncogene K homology domain containing protein overexpressed in cancer=KOC, CEA mono, p53, Mesothelin).

Table II. *Grading of neuroendocrine neoplasms of the gastrointestinal system.*

Grade	Mitotic count	Ki67 index
1	<2 per 10 high-power fields	<2%
2	2-20 per 10 high-power fields	3%-20%
3	> 20 per 10 high-power fields	>20%

Ki67 (Ventana r.t.u.) ER: CC1 mild Detection: iViewDAB

S100p (Biocare) 1:100 ER: CC1 mild Detection: UltraView DAB

TTF1 (Ventana r.t.u.) ER: CC1 Std Detection:UltraView DAB

KOC (m-a-L523S, IMP3; Dako)1:100 HIER: Microwave Dako pH 9.0 Detection:DakoK5007 Chromogen DAB

CEAmono (Thermo Scientific) 1:4000, HIER: microwave natriumcitrate pH 6.0 DetectionK5007 Chromogen DAB

P53 (Clone DO-7, Dako) 1:100, HIER: watherbath ER pH 6.0, Detection: Dako K5001, Chromogen: AEC

Mesothelin (Novocastra) 1:50, HIER: microwave Dako pH 9.0, Detection Dako K5007, Chromogen DAB

Slides for Ventana were paraffinized, pre-treated and counterstained on the stainer.

Slides for Dako stainer were entparaffinized in Xylol, descending alcohol until TBS. This was performed in microwave or waterbath for 40 min at 98˚C followed by cooling down at room temperature for 20 min, rinsed in TBS and put into the stainer. For counterstaining, haemalaun was used, rinsed in hot tap water, followed by ascending alcohol and BA mounting with Entellan (Merck Millipore, Billerica, MA, USA) for IHC detected with DAB and those with AEC were mounted with Aquatex from water without alcohol treatment (Figures 1 and 2).

Using this tiny biopsy specimen a small-cell neuroendocrine carcinoma [G3, Ki67=90%, neural cell adhesion molecule (NCAM)-positive, thyroid transcription factor-1 (TTF-1) –negative] was diagnosed. The baseline CT with focus on the liver and biliary system confirmed a tissue mass with an extension of 2.7×2.1 cm at the middle of the *ductus hepatocholedochus* and suspected pathological lymph nodes at the retroperitoneal region (Figure 3 A and B).

Table III. *Liver parameters at the time of diagnosis and during therapeutic interventions.*

Liver parameter	Time point				
	First contact with patient	Day1 after implantation of stent	Four days after implantation ofstent	Prior to PCT	Normal range
Bilirubin, mg/dl	12.60	8.23	4.92	1.29	0.30-1.20
ASAT (GOT), U/l	184	56	81	29	10-50
ALAT (GPT), U/l	286	102	85	32	10-50
y-GT, U/l	934	523	361	91	10-71
AP, U/l	155	139	118	76	40-129
CHE, U/l	7221	6111	6662	n.a.	4260-12920

Based on an interdisciplinary Tumor Board consensus regarding the histological features and the high proliferative index, chemotherapy was initiated with the following treatment regimen: etoposide at 100 mg/m^2 body surface area (BSA), cisplatin at 25 mg/m^2 BSA over 3 consecutive days respectively. The patient received four cycles of chemotherapy in total. The subsequent CT showed clear response of the tumor, no lymph node metastases were detected and the previously described soft-tissue mass had regressed almost completely (Figure 3 C and D). Additionally, magnetic resonance imaging (MRI) confirmed the CT scan findings.

Surgery was subsequently performed without any complications, including resection of the choledochal duct, a biliodigestive anastomosis, cholecystectomy and lymphadenectomy. Histology showed no lymph node metastases nor any malignancy of the gall bladder. However, at several foci of the choledochal duct, low-grade as well as high-grade BilIN (BilN-1 and BilN-3, respectively) were observed (Figure 2). Furthermore, only tiny residual infiltrates of a poorly differentiated small cell neuroendocrine carcinoma (G3) were found in the vicinity of the extrahepatic bile ducts (Figure 1); surgical margins were free of tumor cells. The patient went to follow-up with an overall good performance score (Eastern Cooperative Oncology Group: 0). However, the next MRI staging 3 months later revealed several hepatic, lymph node and osseous metastases, and treating oncologists opted for further palliative therapy.

Discussion

We report a diagnostic challenging case of the collision of two rare entities – a focal small cell carcinoma in the vicinity of the extrahepatic bile duct and BilIN covering the epithelial surface over a great distance. Immunohistological analysis and consequent diagnosis had a major impact on the clinical proceedings.

Given the little amount of material that is gained by fine-needle biopsy, it should be mentioned that accurate diagnosis is challenging (9). A collision of pathologies, in this case BilINs and tumor cell aggregates, should always be kept in mind, no matter how tiny these might be. Furthermore, it is interesting to speculate as to whether one entity might have led to the origin of the other, or at least have been influenced by it. NETs, for example, are able to produce chromagranin A and synaptophysin, and growth factors or hormones, such as adrenocorticotropic hormone, somatostatin or GH-releasing factor, among others (1, 5). It is not impossible that these might lead to the origin of BilINs *per se*. Furthermore, the epithelium itself might also change due to neuroendocrine molecules produced by NETs. However, a collision of tumors must be clearly differentiated from MANECs, which are known quite often to evolve in the gastrointestinal tract (4). Several hypotheses exist regarding the pathogenesis of MANECs. One possibility is for example a bi-clonality of tumors, another is that a cell clone might be able to differentiate into both exocrine and neuroendocrine directions (3, 4). However, the pathogenesis does not seem to be fully elucidated and Gurzu *et al*. called for using the stem cell marker CD133 in MANECs for further investigations of histogenesis (3). Harada *et al*. investigated MANEC cases and stated that they seem not to be as rare as previously assumed (5). As the neuroendocrine part of MANECs of the biliary system has a major impact on the prognosis, in fact this part seems to be responsible for their aggressiveness, the importance of the correct diagnosis is clear (3, 5). MANECs seem to have distinct histological features, as the outer-part of the tumor is mostly adenocarcinoma, but the inner part consists of neuroendocrine components (5). Furthermore, MANECs express specific markers, such as chromagrin or synaptophysin, due to the neuroendocrine aspect, and other site-specific carcinoma markers (3).

Adenocarcinomas arising from the biliary tract are no longer rare, quite the contrary is the case, their incidence is on the rise (9, 10). Correct grading and classification is a challenge and based on the investigators' experience. Keira *et al*., who retrospectively analyzed samples of bile duct

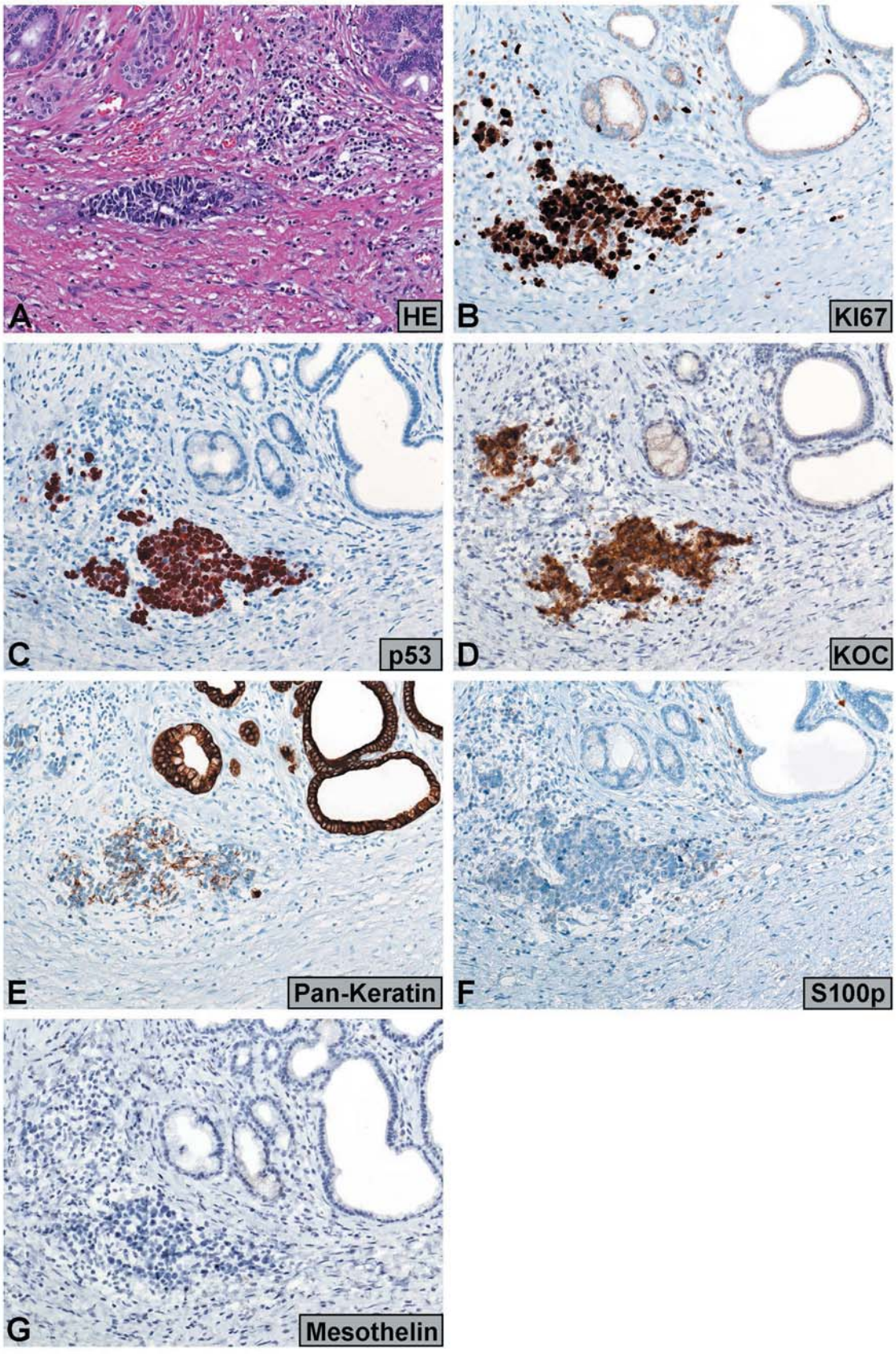

Figure 1

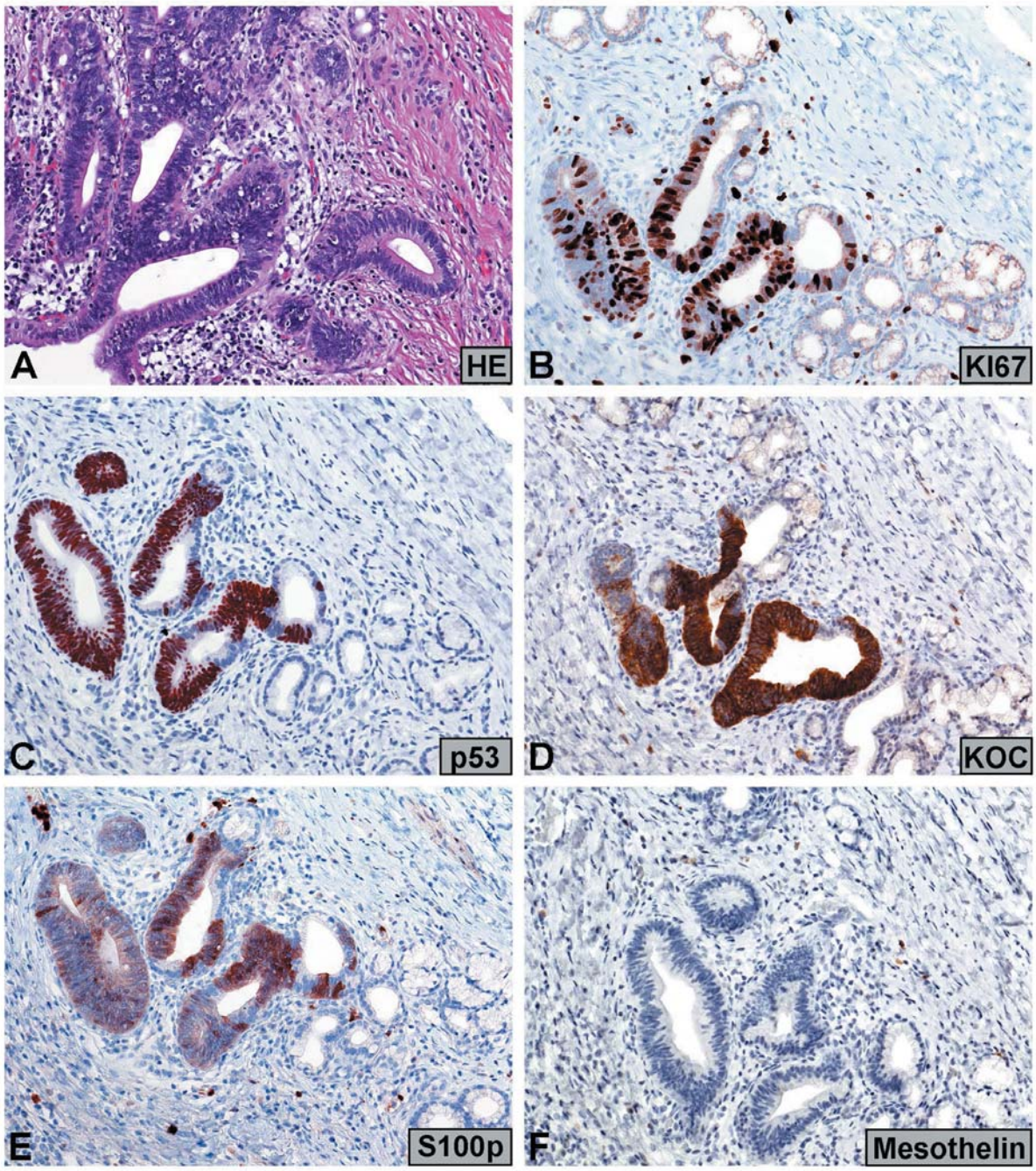

Figure 2

Figures 1 and 2. *The wall of the common bile duct and the cystic duct is fibrotic, slightly widened. Epithelium is configured as single-layered columnar to cubic-layered epithelium. Nuclei are predominantly located at the basal layer (low-grade BilIN, BilIN1). Several enlarged cells show stratification, and are hyperchromatic as well as irregular and presenting prominent nucleoli. The surrounding cytoplasm is basophilic (high-grade BilIN, BilIN3). BilIN3 is found only focally at the opening point of the ductus hepatocholedochus. Immunohistochemistry shows epithelial cells of the duct as being strongly positive for pan-keratin and keratin 7. The BilIN3 areas are strongly-positive for the markers KOC and S100P, whereas BilIN1 cells are only weakly-positive for S100P. The proliferative rate, determined with the proliferative marker Ki67 is high within BilIN3 areas and many epithelial cells are positive for p53, however, only weakly-positive for mesothelin. Within the extensive mass of BilINs, few neuroendocrine differentiated tumor cell aggregates are present, showing a cap-shaped reaction to pan-keratin. These tumor cells are negative for keratin 7 and highly positive for KOC and p53, with a very high proliferative rate (Ki67=95%). This carcinoma cell population is negative for mesothelin and S100P. Cancer cells positive for N-CAM, chromogranin, synaptophysin, TTF-1 or prostate-specific antigen are not detectable.*

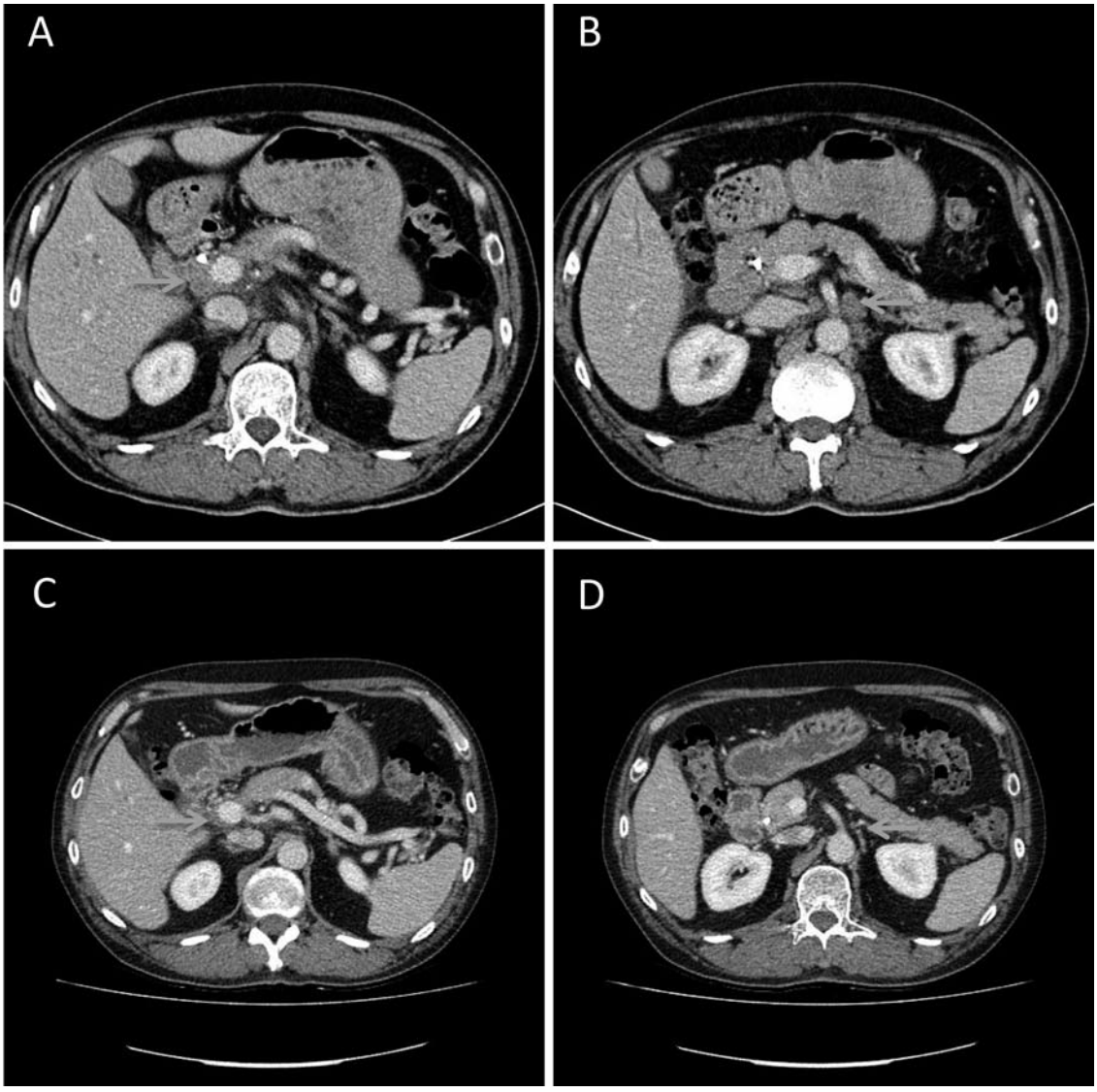

Figure 3. *Computed tomographic (CT) scan showing a soft-tissue mass posterior to the common bile duct and adjacent to the portal vein (arrow in A) and enlarged retroperitoneal lymph nodes (arrow in B). Follow-up CT scan after polychemotherapy showing distinct decrease of the soft-tissue mass (arrow in C) and regression of the lymph nodes (arrow in D).*

cancer and BilINs, underlined once more the importance of proper immunohistochemical analysis. They called for usage of claudin-18, maspin and p53 (9). As BilIN-3, the most dysplastic and morphologically altered type is believed to represent a pre-cancerous lesion (9, 10), the search for potential invasiveness is mandatory in order to possibly diagnose cancer. In a review in 2014, Matthaei *et al*. retrospectively examined histological samples of the biliary tree and the gallbladder (10). They considered whether BilINs may present the widening of a tumor, yet without invasiveness, as they found the presence and co-existence of BilIN more frequently in larger cancer formations (10). Nonetheless, in the same review, they noted that BilIN was found in about 50% of resection margins of biliary duct tumors (10).

In 1997 KOC was initially described as a marker of pancreatic cancer (13), but was found in several other entities during subsequent years (12, 14, 15). In the literature, KOC is also known as IMP3, L523S and IGFBP2 (12, 14). This member of the insulin-like growth factor messenger RNA-binding protein family is believed to be useful for indicating malignancy, and seems even to be typical of biological aggressiveness, being known for its potential to distinguish benign from malignant lesions (12, 14, 16). IGF-binding

proteins are of great interest in recent research; and IGF2 mRNA binding protein p62/IGF2BP2-2 is not only believed to be responsible for the development of steatosis, as well as important factor in lipid metabolism (17), but also possibly is a promoter of non-alcoholic fatty liver diseases and even hepatocellular carcinoma (18). In 2007, Simon *et al*. retrospectively evaluated KOC expression in extrapulmonary small cell carcinomas and found that at least 89% of the examined samples stained positively for KOC (12). Impressively, these authors described positivity of up to 100% in cancer of the gastrointestinal region, *i.e*. of the colorectum and stomach (12). Interestingly, in carcinoid tumors, they did not find any positivity for KOC (12). However, in a review by Findeis-Hosey and colleagues in 2007, KOC expression was mentioned in a lower number of carcinomas (up to 74%) of the gastrointestinal region, comprising of adenocarcinomas of the esophagus, stomach and colorectum (14). They, moreover, described positivity in the hepatobiliary system (hepatocellular carcinoma, cholangiocarcinoma, gallbladder carcinoma) in up to 87% (14). As mentioned earlier, KOC might be useful for differentiation of benign and malignant lesions, but as described by Findeis-Hosey *et al*. also for distinction of low- *versus* high-grade dysplasia (14), as KOC appears to be only sparsely expressed in low-grade lesions. This is quite congruent to the findings by Hart *et al*. (8) who evaluated KOC staining to sensitivity, as determined in biliary brush specimens. In our case, almost all tumor cells stained positively for KOC, with a strong staining intensity.

P53 is known to be up-regulated in possibly all, but especially in higher grades of atypia, whereas S100P is believed to be present only in BilIN2 or 3 or even carcinoma (7). As diagnosis of BilIN is challenging, Sato *et al*. suggested a diagnostic algorithm; however apart from S100P, these authors did not propose an additional marker. Riener *et al*., however, analyzed biopsies from the biliary duct and focused on KOC staining in low-grade *vs*. high-grade dysplasia and differentiation to invasiveness (tumor) (15). Up to 100% of cells were stained in high-grade dysplastic regions, whereas only weak or even no staining was found in those presenting low-grade dysplasia (15). Riener *et al*. suggested KOC as a potential marker for distinguishing bile duct carcinomas *vs*. high-grade *vs*. low-grade dysplasia in the extrahepatic biliary tract (15). This was also stated by Hart *et al*., who suggested an algorithm for biliary brushing specimens supported by usage of KOC (8). In a recent 10-year literature review, an immunostaining panel, including KOC, S1004A and cytology was also suggested by Burnett *et al*., who focused on testing for pancreatobiliary cancer (19). In a meta-analytical approach, a sensitivity of up to 75% in pancreatobiliary cancer using KOC and S100P was reported (19).

In our case, the finding of the focal primary small cell carcinoma next to an extensive BilIN led to neoadjuvant chemotherapy, followed by surgical resection of the choledochal duct, a biliodigestive anastomosis, cholecystectomy and lymphadenectomy. The therapeutic approach was based on CT and MRI scans but most importantly on histological evaluation and immunohistochemistry. One might argue that in our patient, the small cell carcinoma in the vicinity of the extraheptic bile duct might be a metastasis from a still unknown primary of the lung or the duodenum. However, PET-CT did not reveal any indication of pathological uptake in those regions. Immunohistochemical staining for TTF-1, which could indicate a primary tumor of the lung, was also negative. Therefore, from our point of view, a primary tumor of the lung or duodenum is unlikely.

We want to underline the fact that major clinical decisions are sometimes made based on tiny specimens. As literature shows, it is absolutely advisable to use markers to differentiate the nature of the investigated areas. In our opinion, it is mandatory to aim for the most accurate diagnosis possible, and a collision of tumors should always be kept in mind; furthermore, we call for the addition of KOC staining and its use in a routine manner when examining biliary duct lesions, especially in the case of small specimens; this may be a diagnostic challenge with major clinical implications.

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