Here we present a unique case report of development of mixed glandular-neuroendocrine cancer four years after complete resection of advanced adenocarcinoma of the gallbladder in a 72-year-old woman. Primary treatment consisted of extended cholecystectomy with wedge resection of the gallbladder bed including more than 2 cm of normal liver and dissection of the regional lymph nodes. Recurrent tumour was treated by extended right hemihepatectomy and adjuvant chemotherapy.

This case is the first description of mixed glandular-neuroendocrine cancer of the gallbladder and represents the long-term follow-up of a surviving patient with this stage of the disease. The authors discuss possible explanations of such a phenomenon and emphasize the need for evaluation of neuroendocrine differentiation in gallbladder carcinomas, which can be misdiagnosed, as it may be related to better prognosis, and may indicate the necessity of adjuvant chemotherapy application.

Key words: gallbladder, mixed tumour, neuroendocrine carcinoma, adenocarcinomas.

Mixed glandular-neuroendocrine cancer of the gallbladder. Report of a case

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Introduction

Presence of both exocrine and endocrine cells in adenocarcinomas of the gallbladder has been well recognized [1]. However, mixed glandular-neuroendocrine cell carcinomas of the gallbladder, which according to the WHO classification (2000) belong to neuroendocrine tumours (NET), are very rare [2]. So far, only a few cases of these gastrointestinal tumours have been described worldwide, and most of them were referred to as adenocarcinoma with carcinoid component. Composite adenocarcinoma with a non-secretory, highly malignant variant of neuroendocrine tumours such as neuroendocrine cell carcinoma is even more uncommon.

The influence of neuroendocrine differentiation in carcinomas of the gallbladder on prognosis and survival of patients is still unknown. According to previous studies, mixed cancers of the extrahepatic biliary tract may be associated with much poorer prognosis than that of other gallbladder carcinomas, irrespective of stage of the disease [3]. Earlier investigations also revealed that the behaviour of mixed glandular-neuroendocrine gastrointestinal tumours is determined mainly by the adenocarcinomatous element, regardless of the presence of endocrine cells [4]. In contrast, recent clinicopathological studies indicate that glandular/neuroendocrine malignant tumours of the gastrointestinal tract have a better prognosis than common carcinoma [5]. However, due to the small number of reported cases, the results of all these studies are still not representative. Nevertheless, from a clinical point of view, morphological subtyping of composite exocrine-endocrine cancer of the gallbladder seems to have fundamental implications for the selection of treatment modality, because anticancer activity of subsequent chemotherapy regimens in these tumours has been proven, in contrast to pure adenocarcinoma of the gallbladder, which is resistant to cytostatic treatment [6]. Thus, because of the wider range of novel treatment modalities, the reasonable conclusion is that for patients with mixed exocrine-endocrine tumours life expectancy may be prolonged. Nevertheless, the prognosis of malignant gallbladder tumours still remains very poor, and when they are diagnosed at a late stage, the tumours are usually fatal.

To our knowledge, this is the first case report of recurrence of mixed glandular-neuroendocrine cancer following macroscopically complete resection of advanced adenocarcinoma of the gallbladder. This case is the first description of coincidence of these tumours and represents one of the longest follow-ups of a surviving patient with this stage of the disease. Additionally, the authors discuss possible histogenetic and technical explanations of such a coincidence. Moreover, the authors emphasize the need for evaluation of neuroendocrine differentiation in gallbladder carcinomas, which can be misdiagnosed, as it may be related to better prognosis, and may indicate the necessity of adjuvant chemotherapy application.
Case presentation

A 72-year-old woman was admitted to the hospital on April 2004 with the presumptive diagnosis of cholecystolithiasis. The patient was qualified to undergo laparoscopic cholecystectomy. Intraoperatively, after initiation of pneumoperitoneum and insertion of four trocars through the abdominal wall, the presence of a tumour in the fundus of the gallbladder infiltrating neighbouring hepatic tissue was confirmed. Other organs were intact macroscopically. The decision of conversion from laparoscopic to open surgery was made. Extended cholecystectomy with wedge resection of the gallbladder bed including more than 2 cm of normal liver and dissection of the regional lymph nodes were performed. Histological examination of the resected specimen revealed adenocarcinoma of the gallbladder 5 × 3 cm in size (fig. 1). The patient has been followed up without any adjuvant treatment and after 53 months recurrence was confirmed during computed tomography examination. CT scans revealed a 38 × 34 × 41 mm hypodense focal non-circumscribed, faintly enhanced lesion suspected to be a malignant neoplasm within the right lobe and hilum of the enlarged liver. Spleen, pancreas, kidneys and adrenal glands were without focal lesions. Additionally, abdominal lymph nodes were not enlarged. The patient complained of right upper abdominal quadrant intermittent colic pain, nausea and epigastric fullness of one month duration. On physical examination no signs of somatic disease were found. On this basis, the patient was qualified for surgical treatment and underwent extended right hemihepatectomy. Postoperative recovery was not complicated.

Macroscopically part of the liver 15 × 10 × 7 cm in size with a solitary solid tumour of 4.5 cm in maximum diameter was confirmed. Routine haematoxylin/eosin stained sections from a formalin-fixed, paraffin-embedded surgical resection specimen were examined. Histologically, this tumour was composed of both adenocarcinoma and endocrine cell carcinoma (fig. 2). The two elements were randomly distributed, but also with apparent separation between them in many areas. The adenocarcinoma was a moderately differentiated tumour. In addition the endocrine carcinoma consisted of mainly cuneiform nests of medium-sized amphiphilic cells (fig. 3). The tumour was locally extended to the adjacent liver tissue (fig. 4), although no features of incision line infiltration were found. The Ki-67 index was assessed by avidin biotin conjugate (ABC) technique. The proliferation index evaluated by this method

Fig. 1. Adenocarcinoma of the gallbladder, HE (300×)

Fig. 2. Recurrent composite glandular-endocrine cell carcinoma of the gallbladder, HE (120×)

Fig. 3. Cuneiform nests of the neuroendocrine cancer, HE (200×)

Fig. 4. Mixed tumour of the gallbladder infiltrating normal liver parenchyma, HE (300×)
was 30%. In further immunohistochemical staining synapto
tophysin was locally strongly positive (fig. 5) but chromo-
granin staining was negative. Thus, on the basis of these
observations, the diagnosis of mixed glandular-neuroen-
docrine cancer of the gallbladder was established. The cell
population contained approximately equal amounts of both
tumour components.

Discussion

Because the natural history of malignant gallbladder
tumours is greatly asymptomatic in early stages, they are
not diagnosed until the cancer has spread and infiltrates
adjacent organs, which is related to the poor survival rate.
The overall survival is significantly prolonged in incidental
diagnosis of early stage gallbladder cancer. Local recurrences
following potentially curative resection of gallbladder can-
cer are most common, being the main pattern of treatment
failure. The overall median postoperative time to disease
recurrence is less than one year [7]. Most commonly locore-
gional recurrences of gallbladder cancer occur concomitantly
with distant metastases. Isolated local disease is rather
rare. The prognosis among patients with recurrent gall-
bladder cancer is very poor and overall survival does not
exceed 2 years. In our case the patient survived 4 years with-
out any recurrence of the disease, which is one of the
longest periods for this stage of the cancer. Moreover, histopathological examination of the recurrent tumour
revealed a different histotype.

In consideration of such long patient survival, the rea-
sonable question to ask is whether the primary resected
gallbladder tumour was adenocarcinoma or mixed endocrine/exocrine cancer. The authors did not establish
a definite diagnosis of composite tumour during repeated
examination of primary gallbladder tissue with negative
immunohistochemical staining of synaptophysin. Thus, the
previous diagnosis of gallbladder carcinoma was confirmed.
However, the final histopathological examination of these
tumours may not be accurate for multiple reasons [8]. Neu-
roendocrine tumours are relatively rare neoplasms and therefore many histopathologists may not be experienced
in their diagnosis. Furthermore, during routine histopatho-
logical investigation only part of the tumour is precisely
examined. Thus, there is still a possibility that some per-
centage of mixed glandular/neuroendocrine carcinomas
may be misdiagnosed as one of the invasive components
of these tumours, which may hypothetically have taken
place in the described case.

Unfortunately, establishment of a diagnosis of pure gall-
bladder adenocarcinoma in cases of mixed malignant
tumours has not been implicated with any other treatment
modalities, in contrast to neuroendocrine cell carcinoma,
which is proved to be more susceptible to chemotherapy.
Complete resection of the tumour with clear surgical mar-
gins remains the main possibility to achieve satisfactory
survival in neuroendocrine cancers, although objective
response rates to chemotherapy may reach 30-40%, which
indeed may be associated with survival prolongation, if it
is applied in an adjuvant regimen. Moreover, chemothera-
py may be applicable among patients with low-grade recur-
rent neuroendocrine cancers or primary dissemination.

Still, histopathology of mixed neuroendocrine tumours
is not clear. On the basis of immunohistochemical stainings
of gastrointestinal cancer cells it was proved that almost
40% of examined adenocarcinomas were positive for chro-
mogranin and polypeptide hormones, which are character-
istic for neuroendocrine tumours [9]. Some investigators
suggest the possibility of coincidence of adenocarcinoma
and neuroendocrine cancers in gastrointestinal malignan-
cies [10-13]. In our case the two elements appear rather sep-
arated, indicating the presence of two independent tumours
of different histotype.

Histogenesis of such tumours, as our case described,
may be controversial. One of the possible histogenetic
explanations of development of glandular/neuroendocrine
carcinomas is synchronous or metachronous neoplastic
differentiation of two different cell types [14-16]. So far
this concept has been discouraged and the hypothesis of
bidirectional neoplastic differentiation of multipotential
stem cells has been promoted, because it is more likely to
occur. However, in our patient the composite tumour
developed secondary to the resection of primary pure ade-
nocarcinoma of the gallbladder, which may be an argu-
ment in favour of the previous hypothesis. Indeed, such
a concomitance has to be associated with accumulation
of genetic alterations, which predispose to development
of synchronous or metachronous double tumours, and fur-
ther molecular studies are necessary to elucidate these
controversies.

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