

Rare Coexisting Hepatocellular and Gallbladder Carcinomas: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: **Male, 64-year-old**
Final Diagnosis: **Hepatocellular carcinoma**
Symptoms: **Weight loss • fatigue • lack of appetite • fever**
Clinical Procedure: **—**
Specialty: **Surgery**

Objective: **Rare coexistence of disease or pathology**
Background: Multiple primary malignancies in a single patient are considered to be quite rare. However, due to the wider availability of advanced imaging methods and, more regular check-ups, they are becoming more common in clinical practice. To determine the diagnosis of multiple primary malignancies, each tumor must be completely separate and cannot be from metastasis of one or the other. Coexisting hepatocellular carcinoma and gallbladder carcinoma are extremely rare, with only a few case reports published. We believe that to determine the most effective therapeutic management, the results of as many cases as possible should be documented. Regardless of limited data, curative resection may be the most beneficial treatment option in terms of overall survival.
Case Report: We present the case of a 64-year-old man first diagnosed with hepatocellular carcinoma with possible infiltration of the gallbladder wall as appeared on a CT scan. However, the definitive histopathologic examination revealed the coexistence of hepatocellular carcinoma and gallbladder carcinoma. In this case report, we offer an insight into the entire diagnostic process, as well as the chosen surgical approach and adjuvant therapy. Moreover, we present our approach to preoperative biopsy, the decision-making process throughout the whole diagnostic and therapeutic course, and the achieved results.
Conclusions: In cases of double primary malignancies, the choice of therapeutic strategy depends on the type and stage of both malignancies, but procedures with curative intent are superior. We present the outcome and overall survival of the patient after the surgery and adjuvant chemotherapy for synchronous hepatocellular carcinoma and gallbladder carcinoma. Since the liver is the organ most commonly affected by metastatic dissemination of primary tumors, exclusion of metastatic disease is particularly important.

Keywords: **Carcinoma, Hepatocellular • Gallbladder Neoplasms • Surgical Oncology**

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Introduction

Synchronous malignancies are defined as the occurrence of a second malignant tumor at the same time or within 6 months after the discovery of the first malignancy [1]. Due to the wider availability of imaging methods and regular check-ups, the incidence of primary synchronous malignancies is becoming more frequent. Considering that the coexistence hepatocellular carcinoma and gallbladder carcinoma is extremely rare and only a few cases have been reported, the clinical data and information on outcome remain limited [2]. The clinical importance of this case report lies in the diagnostic challenge between hepatocellular carcinoma infiltrating the wall of the gallbladder and the coexistence of hepatocellular carcinoma and gallbladder carcinoma as separate entities. A resection for hepatocellular carcinoma is not followed by adjuvant chemotherapy, but gallbladder carcinoma requires adjuvant treatment after the resection to achieve better overall survival, which is why the therapy must be modified according to both entities. Due to its rarity and unavailability of a standardized treatment algorithm, we consider this case report to be a notable addition to the existing literature.

Case Report

Clinical presentation

A 64-year-old man was admitted to the Department of General, Visceral, and Transplant Surgery of the University Hospital in Martin (UHM). Prior to admission, he was hospitalized at the Department of Internal Medicine for a differential diagnosis of persistent fever, progressive weight loss (20 kg in 1 year in total), lack of appetite, and progressive fatigue syndrome. The described symptoms reportedly worsened a month before admission to the Department of Internal Medicine. Most of the initial laboratory parameters examined after admission were within the reference range, except anemia (Hb): 101g/l, hypoalbuminemia (Alb): 32.6 g/l and slightly elevated liver enzymes – aspartate aminotransferase (AST): 1.03 IU/l; alanine transferase (ALT): 1.90 IU/l; gamma-glutamyl transferase (GGT): 2.6 IU/l; and alkaline phosphatase (ALP): 3.96 IU/l. According to medical documentation, the patient had arterial hypertension, chronic ischemic heart disease, chronic gastritis of uncertain genesis, dyslipidemia, and type II diabetes on a diet without the need for oral antidiabetics or insulin. In the past, he underwent abdominal aorta aneurysm surgery and subsequent hernia surgery in the laparotomy scar. Preoperatively, his performance status was assessed as 0 according to the ECOG classification, as he was fully active, without physical activity restrictions.

Diagnostic Tests

Due to clinical symptoms of significant unintended weight loss, lack of appetite, and a progressive fatigue syndrome with elevated liver enzymes, we chose to perform a CT scan as the first step of a diagnostic process to exclude a malignancy. CT showed the presence of an extensive lesion in the right lobe of the liver with an intimate relationship to the gallbladder (Figure 1A-1C). The tumor size was 90×70 mm and it had characteristics of a malignant tumor: a hypodense character of the tumor compared to surrounding unaffected hepatic tissue on the arterial phase, irregular border of the tumor with infiltrating growth, and suspected infiltration of underlying anatomic structure. Based on the CT scans, we suspected a hepatocellular carcinoma infiltrating the wall of the gallbladder. To exclude a metastatic character of the lesion with a primary origin in the gastrointestinal tract, both gastroduodenoscopy and colonoscopy were performed, without any pathological findings. As a next step, we examined serology for viral hepatitis B and C, which was negative. Tumor markers assays showed an elevation of Ca 19-9 (236.33 U/ml), while AFP (2.03 ng/ml) and CEA (2.61 ng/ml) were within the reference range.

After completing the diagnostic process, CT scans were evaluated by a surgeon to consider the possibility of surgical removal. Partial resection of segments 5 and 6 with cholecystectomy “en-block” was required for complete removal of the tumor, in case of tumor infiltration of the gallbladder wall. Due to the lesion’s proximity to the gallbladder and lack of apparent radiological findings on imaging, it was impossible to precisely determine the origin of the lesion. Considering the progressive weight loss during the 1 year before the admission and lack of appetite, nutritional support with high-energy, high-protein sipping was indicated before the surgery. Despite preoperative biopsy being the diagnostic criterion standard, it was not indicated due to several reasons, and in cases of resectable disease, the definitive histopathological evaluation provides much more reliable information than biopsy, because missed, necrotic, or insufficient tissue may not be representative enough. Another reason not to perform the preoperative biopsy was the risk for implantation of peritoneal metastases, especially in the case of primary gallbladder adenocarcinoma with secondary infiltration of the liver, which would negatively affect the outcome. The surgery was performed within 3 weeks after the initial CT scans discovered the liver tumor.

Surgical Intervention

After entering the abdominal cavity by laparotomic approach and releasing the liver from its attachment ligaments, perioperative ultrasonography of a whole liver was done. Perioperative ultrasonography is used for the localization of the tumor, to mark resection borders, and to detect possible other lesions.

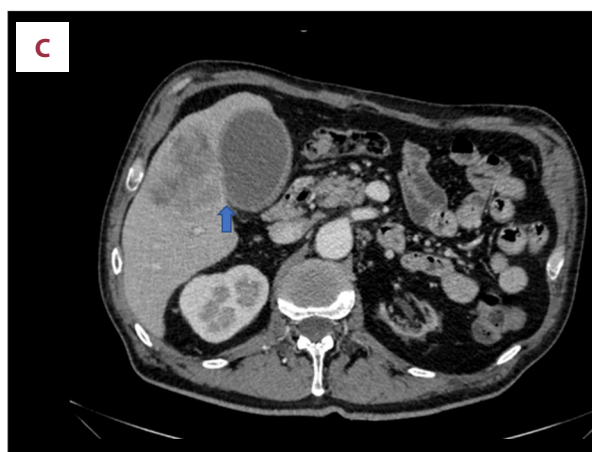
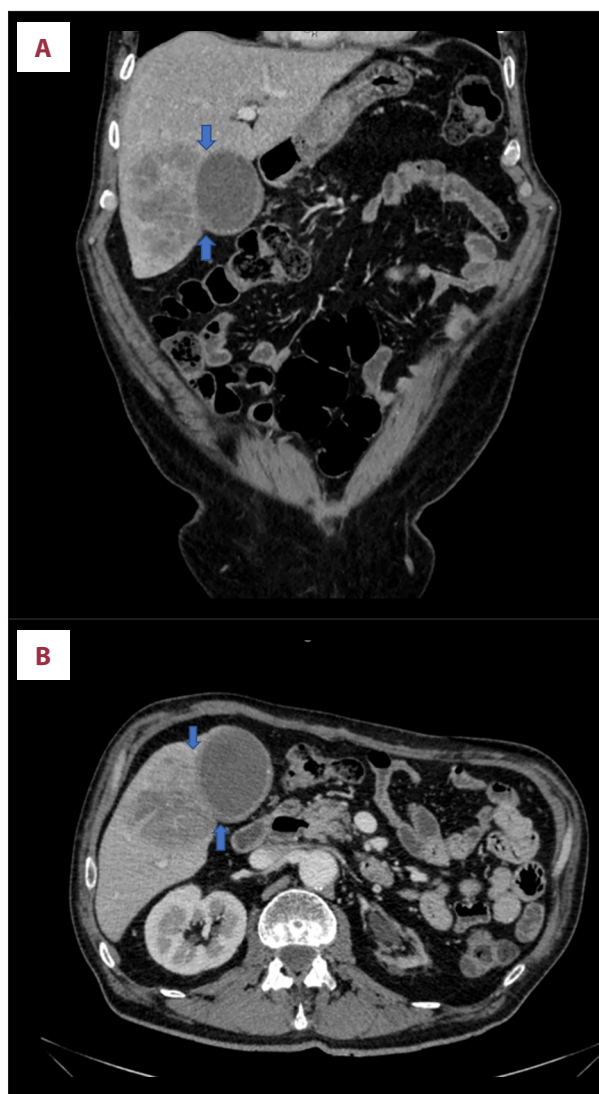


Figure 1. (A-C) Tumorous lesion within the right hepatic lobe with very intimate relationship to the gallbladder. The border between the hepatic tissue and the gallbladder wall had practically disappeared, as indicated by arrows.

loss. Apart from significant blood loss, the patient had stable vital signs throughout the operation, and vasopressor circulatory support was not required.

Postoperative Care

After the surgery, the patient was placed on an intensive care bed, where he was invasively monitored for 3 days. Due to the temporary liver dysfunction and the intermittent postoperative hypocoagulation, a hepatoprotective regimen and substitution of hypocoagulation by the fresh frozen plasma were necessary. Laboratory parameters were examined daily, with adequate correction. In addition, there were no other postoperative complications such as infection or biliary fistula, and the patient was discharged on the 6th postoperative day.

Histological Findings

The histopathologic examination showed the presence of dual malignancy. The first was the poorly differentiated inflammatory type of hepatocellular carcinoma in the field of chronic hepatitis /unknown before the operation, classified as pT-3NxMx with grade G4. The second malignancy discovered in the resected tissue was moderately differentiated adenocarcinoma of the gallbladder in the terrain of “the terminal stage porcelain gallbladder,” classified as pT2NxMx, with grade G2 (Figures 2-4). According to the definitive histopathologic examination, resection margins did not include any malignant cells, which means the R0 resection was successfully achieved. The hepatocellular carcinoma exhibited microvascular invasion and intrahepatic periportal spreading, which are considered to be negative prognostic factors. In addition to the close relationship with the gallbladder wall, the hepatocellular carcinoma

During the ultrasonography, the tumorous infiltration of the gallbladder was confirmed, which required the “en-block” resection of the liver tumor with the gallbladder to minimize the risk of implantation of peritoneal metastases. Due to enlargement of the gallbladder and the tension of its wall, we first punctured the gallbladder and drained the contents. A total of 1000 ml of purulent bile was evacuated, followed by the preparation of structures of the Calot triangle and their interruption. The resection line was outlined by electrocoagulation approximately 10 mm from the outer line of the tumor. A non-anatomical resection of S5-6 liver segments was performed using a harmonic scalpel and the Kelly technique. Perioperative blood loss was 1400 ml, replenished with 2 transfusion units of erythrocyte mass and 2 transfusion units of fresh frozen plasma during the operation. Perioperative hemostasis was achieved by argon plasma coagulation, hemostatic sutures, and metal clips. Regardless of the hemostatic methods, a low central venous pressure was required to minimize further blood

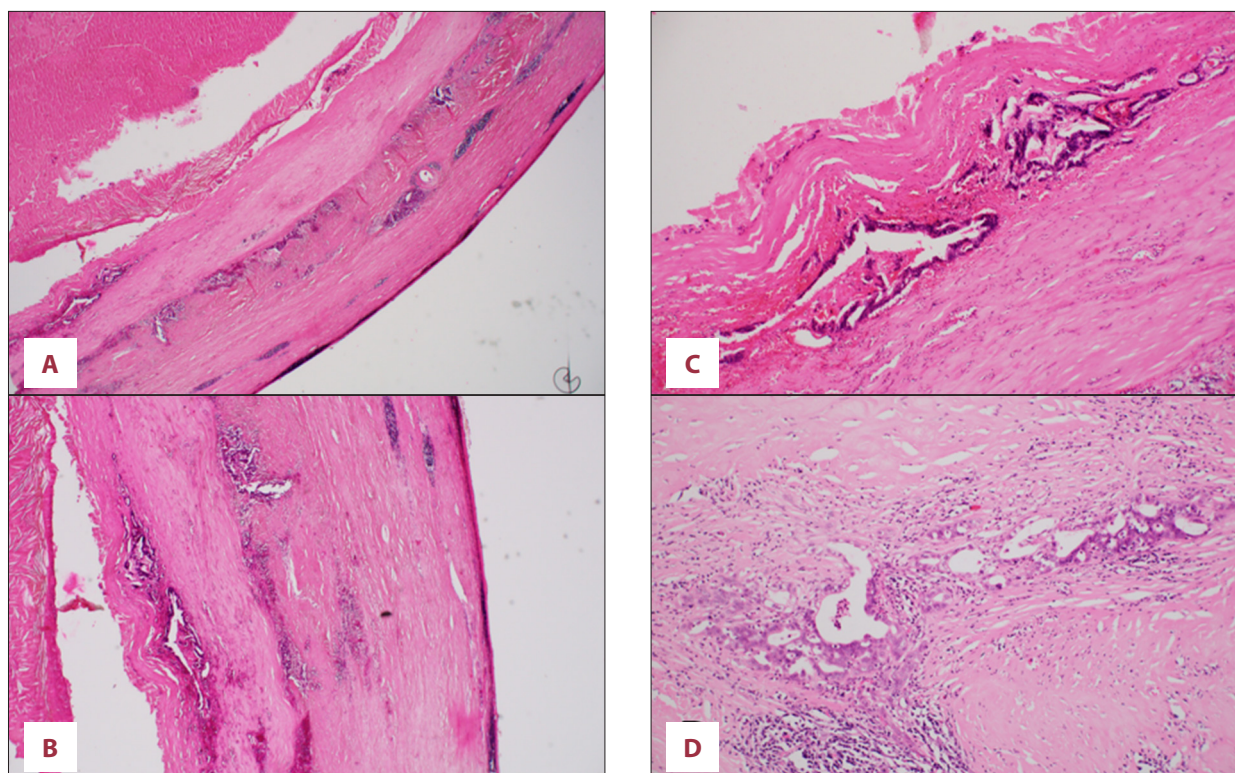


Figure 2. (A-D) Gallbladder carcinoma at various magnifications, with hematoxylin-eosin stain. Fibrohyaline thickened gallbladder wall without smooth muscle layer, typical for the terminal stage of chronic cholecystitis, the so-called “porcelain gallbladder.” The gallbladder cavity with remnants of cholelithiasis, with completely absent mucosa. Original magnification $\times 40$ (A). The gallbladder wall is infiltrated with irregular glandular formations. Original magnification $\times 100$. (B). Cubic and cylindrical cells with voluminous, pleomorphic, and dense nuclei, indicating adenocarcinoma of the gallbladder. Original magnification $\times 400$ (C) and $\times 200$ (D). (Archive of the Institute of Pathological Anatomy UHM).

and gallbladder wall were completely separate. In addition, a microvascular invasion was confirmed in the gallbladder carcinoma, and the whole thickness of the gallbladder wall was infiltrated, but the superficial serosa remained intact.

Follow-Up

Considering the histopathological findings, including the presence of a gallbladder adenocarcinoma, therapeutic management had to be modified. A hepatocellular carcinoma on its own does not require adjuvant chemotherapy, but the outcome of patients diagnosed with gallbladder carcinoma is dependent on adjuvant therapy. After the surgery, the patient received oxaliplatin in combination with gemcitabine. He came for the postoperative check-up 3 months after the resection with a control CT of the chest and abdomen, while still on chemotherapy, without direct signs of local recurrence or metastatic dissemination to the lungs. Nevertheless, lymphadenopathy of the hepatoduodenal ligament and arteria hepatica communis was visualized, so potential locoregional metastatic spread could not be ruled out. All examined tumor markers were negative: AFP was 3.4, Ca 19-9 was 19.9, and CEA was 0.7. Due to

unspecific regional lymphadenopathy, the PET/CT was considered to be more useful in evaluation of hypermetabolic viable malignant cells, but completion of chemotherapy was required.

PET/CT, performed 8 months after the resection and after the end of chemotherapy /6 cycles in total/, revealed the progression of lymphadenopathy in the portocaval region, and the retropancreatic, aortocaval, paraaortic, and right phrenic lymph nodes were massively affected. The liver remained without local recurrence. On the other hand, PET/CT revealed an accumulation of 18-FDG in the S8 segment of the left lungs, which was highly suspicious for metastatic dissemination. Since there has been progression of the malignancy, surgical treatment would not benefit the patient, as adequate radicality would not be reached. Due to the reasons mentioned above, palliative chemotherapy was indicated. The overall survival of the patient was 530 days after the operation. Data on the overall survival of patients after liver resection for coexisting hepatocellular carcinoma and gallbladder carcinoma are limited and few case reports have been published. Zhang (2018) reported a patient with similar synchronous primary malignancies who refused an adjuvant chemoradiotherapy, and the overall

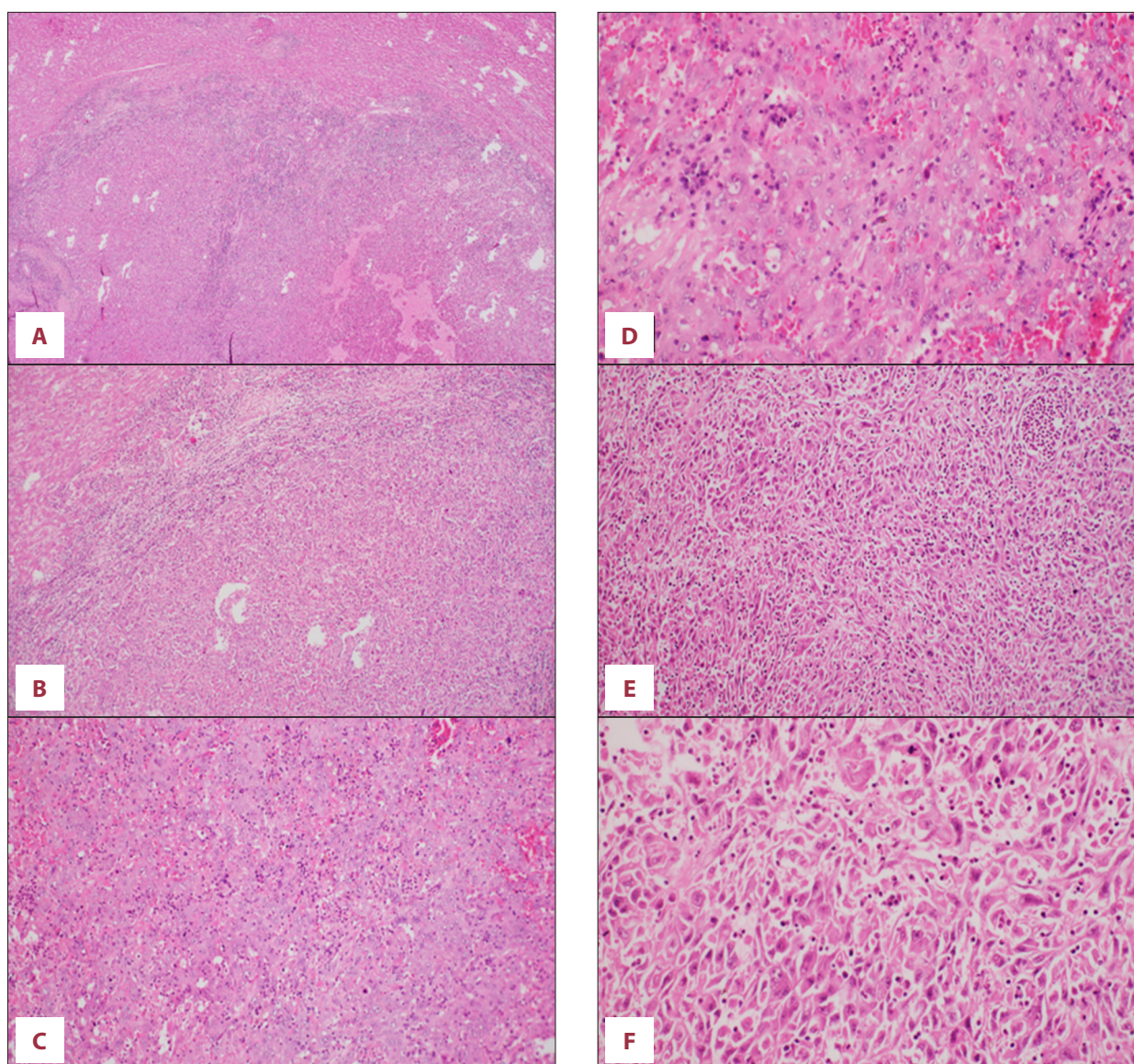


Figure 3. (A-F) Histopathological appearance of hepatocellular carcinoma, with hematoxylin-eosin stain. Expansive tumor with an absent capsule on the surface, with extensive inflammatory peripheral reaction (A). Irregular, polygonal cells with eosinophilic cytoplasm and voluminous vesicular nuclei with visualized nucleoli. Numerous multinucleated tumor cells and rich lymphoplasmacytic inflammation in the tumor with a high concentration of neutrophils, characteristic for the "inflammatory" type of HCC (B). Original magnifications (A – $\times 40$, B – $\times 100$). Uniform component of hepatocellular carcinoma (C – $\times 200$, D – $\times 400$). Pleomorphic component of hepatocellular carcinoma (E – $\times 200$, F – $\times 400$). (*Archive of the Institute of Pathological Anatomy UHM*).

survival was only 8 months after the surgery [2]. According to these findings, adjuvant chemotherapy could probably provide longer overall survival.

Discussion

The occurrence of multiple primary malignant tumors in a single patient is generally considered very rare and the overall rate

varies between 0.73% to 11.7% according to Demandante [3]. Moreover, the coexistence of hepatocellular carcinoma and gallbladder carcinoma is extremely rare; our search of the literature found only 4 case reports in the English language describing the synchronous occurrence of these primary malignancies [1,2,4-6]. Clinically, in rare cases like these, it is important to document every new case in detail to determine the most effective treatment approach according to the achieved outcome and overall survival.

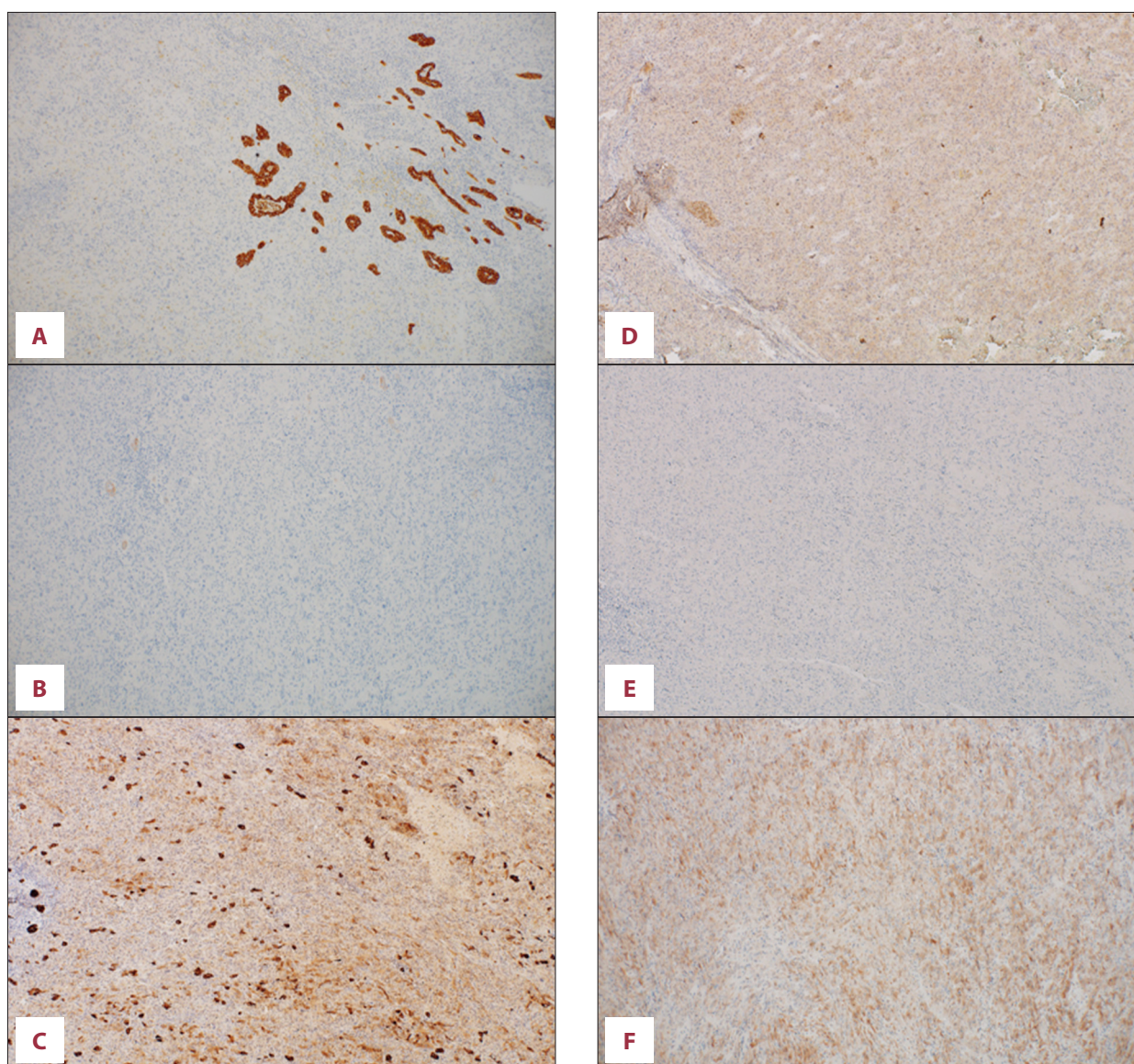


Figure 4. Results of immunohistochemical staining of hepatocellular carcinoma (A-F). Immunohistochemically, tumor cells are positive for CK7 (A), AE1/AE3 (C), and arginase1 (F). The tumor cells were negative for CK19 (B), glypican3 (E), and HepPar1 (D). Original magnification $\times 100$ (A-F). (Archive of the Institute of Pathological Anatomy UHM).

In terms of diagnostic criteria required for the diagnosis of multiple primary malignant tumors, all of them were proven during the definitive histopathologic examination in the presented case: (1) features of malignancy were present in the definitive histopathologic evaluation of each tumor, (2) none of tumorous lesions represented the metastasis of one or the other, and (3) each tumor was distinct and separate [2]. Besides the diagnostic criteria for multiple primary malignancies, we distinguish 4 main types of multiple primary malignancies: (1) multicentric, in which tumors have their origin in the same tissue/organ; (2) systemic, in which tumors arise from the same organ system; (3) tumor occurrence in paired organs, such as the breasts; and (4) the co-incidental occurrence of tumors in

unrelated organs [1]. The presented case is an example of systemic synchronous primary malignant tumors. Although the development of hepatocellular carcinoma and gallbladder carcinoma do not share the same molecular pathways, the entire hepatopancreatobiliary system shares a common embryonic origin, which is why the occurrence of multiple malignancies arising from different sites of the same system is not surprising, especially given the well-known risk factors [4].

In addition to the embryonic background, many other reported factors may interfere with carcinogenesis. In terms of hepatocellular carcinoma development, the most significant risk factors confirmed by many studies are cirrhosis of the liver and

chronic hepatitis caused by hepatitis B or hepatitis C infection. On the other hand, there is an increasing rate of HCC development in metabolic dysfunction-associated steatotic liver disease (MASLD) documented in developed countries [7]. In the presented case, the histopathologic examination revealed the development of HCC in the area of a chronic hepatitis uncertain genesis, but it was impossible to rule out autoimmune hepatitis. Unfortunately, for unknown reasons, our patient did not undergo proper diagnostic tests following the surgery. On the other hand, an adenocarcinoma of the gallbladder developed from the terminal stage “porcelain gallbladder,” which is widely accepted as a pre-cancerous condition. Regarding the development of gallbladder cancer according to the recent literature, the main risk factors are female sex, gallbladder stones (especially larger than 3 cm in diameter or multiple stones), obesity, and chronic infection with *Salmonella typhi* or *Helicobacter bilis* [8,9]. In reports of similar cases, the most common risk factors associated with the development of synchronous hepatocellular carcinoma and gallbladder carcinoma were gallbladder stones, chronic hepatitis B, and cirrhosis caused by alcohol abuse [1,2,4]. Zhang et al speculated that chronic irritation of the gallbladder affects surrounding liver tissue, leading to inflammation of liver tissue and possibly causing malignant transformation of hepatic progenitor cells [2].

It is necessary to perform a differential diagnosis of HCC because the liver is the most common organ with metastatic involvement [6,10]. Preoperatively, patients may be misdiagnosed with metastasis of gallbladder cancer or a primary malignant liver tumor infiltrating the gallbladder wall [11]. Therefore, the diagnostic criterion standard remains the histopathological examination of tumor tissue. In general, definitive histopathologic examination is considered much more reliable because tissue obtained by biopsy may not be sufficiently representative due to missed or insufficient samples [2]. In our patient, we decided not to perform a biopsy due to the definitive histopathologic examination after complete resection of the tumor and the high risk of peritoneal metastases implantation, which would negatively affect the outcome and overall prognosis. Moreover, from a surgical point of view, waiting for the result of a preoperative biopsy would allow possible progression of the disease and would not influence the therapeutic algorithm, regardless of the results. In 3 similar reported cases, preoperative biopsy was performed in 1 case, and surgical removal of the tumor was performed in 2 cases, followed by definitive histopathologic evaluation [1,2,4].

In cases of multiple coexisting malignancies, overall survival depends on the most malignant tumor [11]. Curative resection of the tumors, if possible, is the most effective intervention to prolong overall patient survival. Moreover, in patients with multiple malignancies, the treatment strategy should be chosen in conjunction with treatment for the second malignant

tumor [2]. In addition to the pathological type and stage of each tumor, the therapeutic approach also significantly depends on the patient's overall condition according to the ECOG classification [11]. While our patient's performance status was evaluated as 0 and the lesion was resectable, non-anatomic resection of the affected segments with synchronous “en-block” cholecystectomy as a part of the resection was indicated.

In terms of treatment modification in this particular case, the R0 resection of both tumors “en-block” was followed by adjuvant chemotherapy, which is not recommended for hepatocellular carcinoma, but it can reportedly improve overall survival of patients with gallbladder carcinoma. Clear proof of that is the overall survival of our patient, which was 17.4 months, which is comparable to the longest survival reported in the literature (17 months) [2]. However, the overall survival of patients with coexisting hepatocellular carcinoma and gallbladder carcinoma is much worse than the 5-year hepatocellular carcinoma survival rate, varying from 20% to 70%, depending on tumor stage [12]. Researching available data, in 2 cases patients underwent laparotomic cholecystectomy with resection of surrounding liver tissue infiltrated with the tumor. On the other hand, there was 1 reported patient with early-stage hepatocellular carcinoma who underwent RFA and standard cholecystectomy for gallbladder carcinoma. Adjuvant chemotherapy or radiotherapy following surgical resection in indicated cases was not administered due to the patient's refusal, so data on adjuvant therapy remain limited [1,2,4].

Conclusions

Due to its rarity and heterogeneity, the coexistence of multiple primary malignancies in a single patient is a complex issue with no standard therapeutic algorithm. The chosen therapeutic strategy strongly depends on the stage of both malignancies, but procedures with curative intent are superior, if possible. In the presented case report, we demonstrated the outcome and overall survival of the patient after the surgery and adjuvant chemotherapy targeted to gallbladder cancer. In comparison to similar cases, our patient has one of the longest overall survivals, and suggests the benefit of chemotherapy following the surgery. We consider preoperative biopsy to be an unnecessary step in the context of the resectable disease, since waiting for the results can postpone the surgery, and a definitive histopathological examination obtains much more reliable information. Since the liver is the organ most commonly affected by metastatic dissemination of primary tumors localized in other systems, exclusion of these is key. Since a primary tumor of the gastrointestinal tract associated with liver metastases is most common, preoperative gastroscopy and colonoscopy are required to exclude these malignancies.

Patient Consent

Every possible effort was made to contact the next of kin of the deceased patient to obtain consent, but was unsuccessful.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Kim JW, Han JW, Jung SY, et al. Synchronous double primary malignant tumor of the gallbladder and liver: A case report. *World J Surg Oncol*. 2011;3(9):84
2. Zhang ZG, Chen Y, Ji R, et al. Synchronous cancers of gallbladder carcinoma and combined hepatocellular cholangiocarcinoma: An unusual case and literature review. *BMC Cancer*. 2018;18(1):1046
3. Demandante CG, Troyer DA, Miles TP. Multiple primary malignant neoplasms: Case report and a comprehensive review of the literature. *Am J Clin Oncol*. 2003;26(1):79-83
4. Unver M, Ozturk S, Bozbiyik O, et al. Incidental early gallbladder carcinoma with hepatocellular carcinoma: A rare synchronous double primary malignant tumor. *Journal of Medical Cases*. 2014;5:561-63
5. Imada J, Hoshino H, Nishimura D, et al. Case report: multiple cancers: Hepatocellular carcinoma and adenocarcinomas of the common bile duct and the gall-bladder in a woman with primary biliary cirrhosis. *J Gastroenterol Hepatol*. 1996;11 (1):546-50
6. La Greca G, Barbagallo F, Rodolico M, et al. Hepatocarcinoma, gallstone disease and gallbladder carcinoma: A case report of a rare incidental association. *Chir Ital*. 2004;56(1):571-74
7. Ge XY, Sun MC, Wang TY, et al. Analysis of risk factors of hepatocellular carcinoma and establishment of a clinical prognosis model. *Front Oncol*. 2023;22(13):1067353
8. Dutta EK, Lewis MG, Albert S. Risk factors associated with gall bladder cancer in high incidence areas in India: a systematic review protocol. *BMJ Open*. 2022;12(3):e056849
9. Xu Y, Chen QN, Wang H, et al. Synchronous hepatocellular carcinoma and gallbladder adenocarcinoma with neuroendocrine differentiation: A case report and literature review. *BMC Surg*. 2020;20(1):246
10. Zeng QA, Qiu J, Zou R, et al. Clinical features and outcome of multiple primary malignancies involving hepatocellular carcinoma: A long-term follow-up study. *BMC Cancer*. 2012;12(1):148
11. Kim SH, Min JS, Hwang KC. Multiple primary malignant tumors. *J Korean Surg Soc*. 2022;1984:26:314-19
12. Calderon-Martinez E, Landazuri-Navas S, Vilchez E, et al. Prognostic scores and survival rates by etiology of hepatocellular carcinoma: A review. *J Clin Med Res*. 2023;15(4):200-7