Colorectal Liver Metastasis, Primary Gallbladder Carcinoma and Myelofibrosis Present Simultaneously in a Liver Resection Specimen

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Abstract
Myelofibrosis and gallbladder carcinoma are both very rare diseases. This case report describes a patient with a history of myelofibrosis and colorectal carcinoma who was diagnosed with colorectal liver metastases. Surgery was performed to remove the metastases, and on site, the gallbladder was removed because of involvement in one of the liver lesions. After pathological examination, a primary gallbladder carcinoma and myelofibrosis were found in addition to the liver metastases. The combination of diseases was not likely to be interconnected but rather an unlucky course of events for the patient.

Introduction
This case report describes three different malignant diseases present in the same patient at the same time, with gallbladder carcinoma and myelofibrosis being very rare diseases and with no known interconnection between them.

Colorectal carcinoma is a well-known cause of malignancy in the Western world, and about half of the patients progress to liver metastases, which in 2 out of 3 patients is respon-
sible for death [1]. Colorectal carcinoma metastasizes hematogenously through the portal vein system to the liver. Metachronous colorectal liver metastases are mostly asymptomatic and found at follow-up, but unexplained weight loss, fever, fatigue and icterus can be the presenting symptoms. The only curative option is surgical resection. Over the past few years, great progress has been made in targeting unresectable colorectal liver metastases with chemotherapy to reduce their size, make them resectable and increase patient survival [1]. When colorectal liver metastases are radically resected, the 5-year survival for patients varies between 25–60% [2]. Synchronicity of the primary tumor and the liver metastases, the number of liver lesions and the interval between the primary tumor and the metastectomy are prognostic factors for survival. Even a repeated metastasectomy after initial resection can prolong survival in selected populations [3].

Gallbladder carcinoma is a much rarer disease that has a high variability in incidence worldwide, correlated to the prevalence of gallstones. The highest numbers are found in South America, India (21.5/100,000), Pakistan, Japan and Korea [4]. In the USA (1–2/100,000) and the Netherlands (0.88/100,000), the incidence is much lower. Because of these low incidence numbers, research is difficult to perform, and therefore the whole pathological mechanism is not yet fully understood. A well-known risk factor of gallbladder carcinoma is cholelithiasis, having a high prevalence in South America, probably causing the high numbers of gallbladder carcinoma in these areas [5, 6] in combination with genetic factors and lower access to cholecystectomy. Other risk factors are female gender (6:1), increasing age and Caucasian race [7]. Because gallbladder carcinoma is asymptomatic in most cases, it is mostly diagnosed as an incidental finding during cholecystectomy, on a CT scan or it is revealed in the pathological report after cholecystectomy. Surgical resection is the only curative option. The prognosis of gallbladder carcinoma is poor.

Myelofibrosis is a very rare disease, with an estimated incidence of 0.5–1.5/100,000 [8]. It is a malignant hematological myeloproliferative disease, mostly manifesting in the sixth decade of life. Megakaryocyte proliferation causes the production of factors that stimulate fibroblasts to make connective tissue. This causes repression of all other blood cells and stimulation of extramedullary hematopoiesis. The WHO criteria for diagnosis include megakaryocyte proliferation, JAK2V617F mutation, no evidence for any other myeloid disease, and can be accompanied by leukoerythroblastosis, increased LDH levels, anemia and splenomegaly [9]. Patients with myelofibrosis have a higher risk of complications after surgery because of the higher risks of infection and bleeding [10]. Stem cell transplantation is the only curative treatment available. Without successful stem cell transplantation, the prognosis is variable but poor, although the prognosis of patients with the JAK2V617F mutation has increased with the introduction of JAK2 inhibitors.

Case Presentation

A 67-year-old active male with a medical history of myelofibrosis, aortic valve stenosis, mitral valve insufficiency, deep venous thrombosis and terminal kidney failure was diagnosed with a sigmoid carcinoma. A laparoscopic sigmoid resection was performed without complications and with full recovery. The pathological report showed a pT3N1M0 sigmoid carcinoma, and the multidisciplinary surgical oncologic team advised that follow-up was the best subsequent treatment. Seven months after the initial surgery, the patient was referred to a multidisciplinary surgical oncologic team of a tertiary liver center.

He was referred because at follow-up, the ultrasound of the liver showed two hyperechoic lesions with a hypoechoic halo around them. This is known as the bulls-eye aspect and
made us suspect a malignant lesion (fig. 1a). Besides the liver lesions, some abnormalities of the gallbladder were found. In the fundus of the gallbladder, a polyp-shaped mass was detected. The gallbladder wall at this point was not distinguishable from the mass, and there was a second small thickening of the gallbladder wall in the body of the gallbladder (fig. 1b). The patient had no symptoms at the time of the abdominal ultrasonography.

A complementary MRI without contrast was performed and showed multiple abnormalities: two well-circumscribed lesions in segments 6/7 and 5 of the liver with a hypointense signal intensity on the T1-weighted image, a slight hyperintense signal intensity on the T2-weighted image and a slightly restricted diffusion in the edge of the lesions. These signal characteristics matched the characteristics of colorectal metastases (fig. 1c) [11]. The mass in the gallbladder was a thickening of the wall of the fundus, with a slight hyperintense signal on the T1-weighted image and a partly hyperintense partly isointense signal intensity on the T2-weighted image. There was a minimally restricted diffusion. These signal characteristics combined with the ultrasound made us suspect a gallbladder carcinoma, although this suspicion was not described in the initial radiology report (fig. 1d) [12, 13].

The multidisciplinary team decided that surgery was the best option. An elective operation was scheduled, and the surgeon performed a wedge resection of segments 5 and 7 of the liver, and a radiofrequency ablation was used to treat a lesion in segment 3. Although the suspicion of gallbladder carcinoma at the time of surgery was low, the surgeon decided to remove the gallbladder simultaneously because of invasion of the segment 5 liver lesion into the gallbladder. Finally, a lymph node at the pancreas head was removed. There were no complications during surgery.

The pathological report showed a partial liver resection in which two lesions were identified after dissection. One lesion was located in the liver and the other lesion was located in the wall of the gallbladder (fig. 2a). The intrahepatic lesion showed a similar histological morphology as the sigmoid carcinoma as well as expression of CK 20, confirming the colorectal origin of the lesion (fig. 2b). Histological examination of the lesion in the wall of the gallbladder showed a primary tumor of the gallbladder infiltrating the wall of the gallbladder. The tumor of the gallbladder showed expression of CK 7, supporting the histological outcome of primary adenocarcinoma of the gallbladder (fig. 2c). Furthermore, histological examination of the liver in the sinusoid spaces showed separate strongly enlarged tumor cells corresponding with the morphology of the preexisting diagnosed myelofibrosis (fig. 2d). In summary, there were three types of tumors present in the partial liver resection: metastases of the known sigmoid carcinoma, localization of the known myelofibrosis and an unexpected primary tumor of the gallbladder.

The postoperative phase was complicated by electrolyte disorders, wherefore extra dialysis was necessary, and gastroparesis, for which temporary parenteral nutrition was administrated. The first postoperative MRI of the abdomen after 2 weeks showed a normal postoperative situation except for a paralytic ileus. The ileus was resolved, and the patient recovered and was discharged from the hospital 2 weeks after the surgery. The multidisciplinary team decided that follow-up was the best adjuvant treatment for the patient.

**Discussion**

The patient described in this case report showed three different malignancies in the same liver specimen: the preexistent myelofibrosis, the recently diagnosed liver metastases and an unknown gallbladder carcinoma. An interconnection between these malignancies could have been possible.
Colorectal carcinoma is not known to be associated with gallbladder carcinoma or myelofibrosis. However, patients with familial adenomatous polyposis and an APC mutation tend to have a higher risk of extracolonic manifestations such as desmoid tumors, tumors of the gynecological organs and malignant tumors of the hepatobiliary system, although evidence is mainly based on case reports and is therefore not strong [14]. Hemminiki et al. [15] described a possible association of family members of patients with myelofibrosis and colorectal cancer in a Swedish cohort. However, the numbers in this study are very small and, as the authors suggest, could have been possibly influenced by chance. Therefore, this study has no strong evidence of an interconnection between myelofibrosis and colorectal cancer. Because patients with myelofibrosis can be treated with a big range of medication, including cytostatica, one can think that these medications could possibly increase the chance of developing another malignancy. The patient in this case, however, was not treated with drugs for myelofibrosis that could have contributed to the development of colorectal or gallbladder carcinoma.

**Conclusion**

Although marginal evidence of associations between colorectal carcinoma and gallbladder carcinoma and myelofibrosis was found, it is not likely that the three primary malignancies in this patient were inter connected with each other but were rather an unlucky course of events.

**Statement of Ethics**

The authors have no ethical conflicts to disclose. Informed consent was obtained from the presented patient.

**Disclosure Statement**

The authors have no conflicts of interest.

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Fig. 1. Radiological findings. a Ultrasound: buls-eye aspect of the liver lesion (red arrow). b Ultrasound: mass in the wall of the gallbladder (red arrow). c T1-weighted MRI: low signal of the liver lesion (left red arrow) and gallbladder mass (right red arrow). d T2-weighted MRI: high signal of the liver lesion (left red arrow) and a partly high, partly low signal of the gallbladder mass (right red arrow).
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Fig. 2. Pathological findings. a Macro photograph of the dissected liver resection demonstrating a lesion in the liver on the left and on the right another lesion in the wall of the gallbladder. b Immunohistological CK 20 stain, demonstrating that the tumor cells of the intrahepatic tumor are CK 20 positive, whereas the liver parenchyma is negative. Magnification ×200. c Immunohistological CK 7 stain demonstrating positive tumor cells in the wall of the gallbladder, supporting the histological outcome that the primary origin of the tumor is the gallbladder. Magnification ×50. d In the sinusoid spaces of the liver, separate strongly enlarged tumor cells are present, corresponding with the morphology of the preexisting myelofibrosis. Magnification ×200.