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CASE REPORT

Gallbladder Cancer: Complete Resection after Second Line Treatment in Stage IV Disease

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Introduction

Gallbladder carcinoma is rare, with an incidence of 1.6–2.0/100,000 in Western Europe; however, it is the most common cancer of the biliary tract accounting for 80–95% of these cancers [1–3]. It is far more common in central Europe, Chile, India, Korea, and Japan. The incidence increases with age and it is more common in women.

There are well-known risk factors, namely cholelithiasis (leading to a chronic inflammatory reaction in the gallbladder) [4–6], porcelain gallbladder, gallbladder polyps (solitary, greater than 1 cm), primary sclerosing cholangitis, chronic typhoid infection, congenital malformations, and obesity [2–5]. The interest of prophylactic cholecystectomy is being discussed.

Most cases have a silent evolution and are commonly diagnosed with local and vascular invasion, lymph node metastasis, and distant metastasis. It is, therefore, a disease with poor prognosis, with a mortality rate very close to the incidence rate. The overall mean survival is 6 months, and the 5-year survival rates are only 5–10% [7].

The only potentially curative treatment is surgery, namely in early stage disease, and open surgery should be performed in order to avoid seeding.

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Case Report

A 67-year-old woman was admitted in the emergency department with right abdominal pain, intense nausea, and history of spontaneous weight loss—which had started around 2–3 months before. She had no history of vomiting, and she had normal gastro-intestinal transit.

She had history of diabetes, hypertension, and dyslipidemia, all controlled with medication. She had no history of previous gastro-intestinal illnesses, namely she had no history of gallstones. She was nonsmoker and had no history of alcohol consumption.

She had no known history of any familial diseases.

She was taking omeprazole 20 mg once a day, losartan 50 mg once a day, metformin 500 mg thrice a day, and simvastatin 10 mg once a day.

On the clinical observation, she had guarding in the abdomen to palpation, and a 4 cm mass was identified in the epigastric region; the vesicular Murphy's sign was negative. She had an ECOG performance status of 1.

An abdominal echography was performed and revealed an abdominal mass with extrinsic hepatic compression, a mass in the gallbladder as well as a nodule in the hepatic parenchyma. An abdominal CT scan was then requested and a multinodular conglomerate with 8 × 15 cm in the pericefalo-pancreatic region, retroperitoneal adenopathies, and a nodular lesion with 4.5 cm in the inferior portion of the transition between the IV and V hepatic segments (gallbladder bed) were identified along with the 4 cm mass in the fundus of the gallbladder (Fig. 1). The radiological diagnosis was of a malignant lesion in the gallbladder with hepatic and lymph node metastases. The CEA was elevated—654 ng/mL (normal < 5 ng/mL), and Ca 19.9 was normal (< 2.0 UI/mL).

A microbiopsy of an epigastric lymph node (the most easily accessible lesion) showed a poorly differentiated adenocarcinoma.

The disease was staged as a cT3N2M1 (IVB) gallbladder cancer.

After multidisciplinary discussion with the departments of surgery, oncology, and radiotherapy, the decision was taken to initiate palliative chemotherapy treatment. The scheme chosen was capecitabine (650 mg/m^2 twice daily from D1-D14) plus gemcitabine (1000 mg/m^2 at D1 and D8), every 21 days. The response evaluation, after 3 cycles of treatment, showed disease progression (Fig. 1), the patient symptoms became worse with pain becoming more difficult to control and CEA remained elevated (617 ng/mL). The patient was started on second-line chemotherapy with the GEMOX scheme (gemcitabine 1000 mg/m^2 on D1 and oxaliplatin 100 mg/m^2 on D2, every 14 days).

The CT scan after 3 cycles showed partial response with a decrease of 50% in size of target lesions, there was also a clinical and analytical response (CEA decrease to 71 ng/mL). After 12 cycles of GEMOX, the abdominal CT scan showed a decrease of the hepatic lesion to 1.6 cm, the gallbladder mass to 0.9 cm, and all the adenopathies were smaller than 2 cm (Fig. 1). CEA decreased further to 8 ng/mL.

The chemotherapy was stopped, and at 11 months after stopping the treatment, the patient remained asymptomatic and the disease was stable; it was decided to re-discuss the situation with the surgery department.

An excision of the gallbladder, regional lymph nodes, and V and IVB hepatic segments was then performed. The histological study of the material confirmed the gallbladder adenocarcinoma with wide areas of mucous production and invasion of the muscularis própria (ypT2), with perineural invasion (Fig. 2a and b). The adenopathies and the hepatic parenchyma had extensive areas of necrosis, interpreted as the positive result of chemotherapy (Fig. 2c).

After surgery, the CEA became normal, and the patient remained asymptomatic.

At the last evaluation, she was asymptomatic. The analytical and imaging studies showed no evidence of disease recurrence, 3 years after surgery, and 5 years after the diagnosis.

Discussion

As in most cases of gallbladder cancer, this patient was diagnosed with advanced disease, and after appropriate imaging evaluation, the disease was found to have already spread to retroperitoneal lymph nodes and the liver; the multidisciplinary team agreed that the disease was unresectable.

The options for patients such as this one can be treatment with fluoropyrimidine-based or gemcitabine-based chemotherapy, endorsement in a clinical trial, receive a scheme of fluoropyrimidine chemoradiation, or receive best supportive care.

At the time of this diagnosis, the benefit of gemcitabine and cisplatin doublet had not yet been established [8, 9], so it was decided to start palliative treatment with capecitabine plus gemcitabine. This scheme has been mentioned in a couple of studies with good results.[10–13]

In 2005, Jae Young et al. [10] and J.J. Knox et al. [11, 12] have published two phase II trials supporting the use of capecitabine combined with gemcitabine (CapGem) in the treatment of advanced biliary tract cancers.

The benefit of a second-line treatment over best supportive care has not been defined; however, in order to try to achieve better control of symptoms, it was decided in this particular case—as the patient was fit, ECOG 1, and was developing opioid dependent pain—to try another chemotherapy scheme also approved in this setting—gemcitabine plus oxaliplatin scheme (GEMOX).

In 2007, Eckel et al. [7] reviewed the published data in order to define the best chemotherapy scheme according to the literature, and they have concluded, mainly based on phase

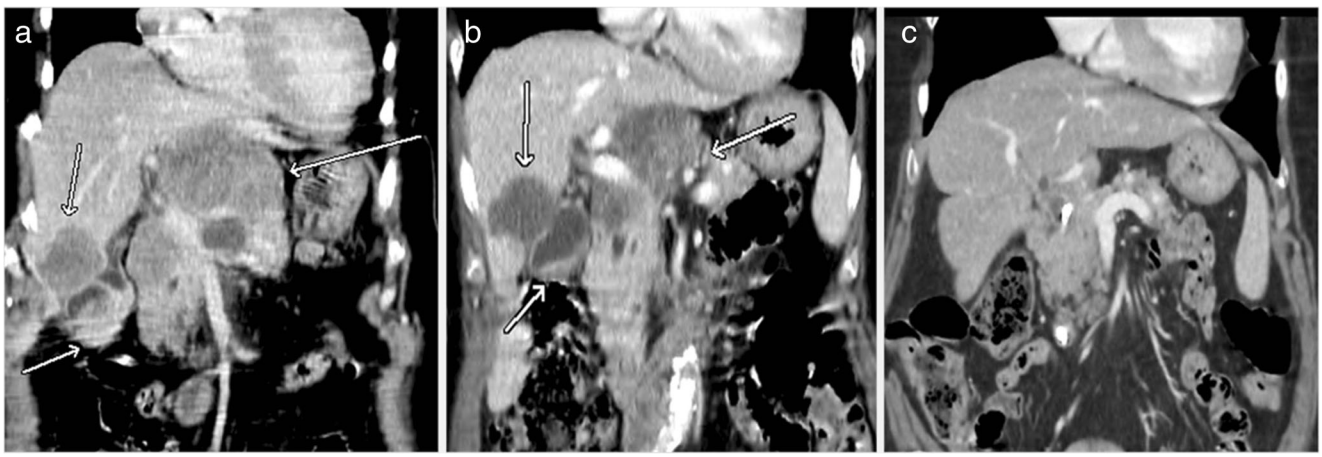

Fig. 1 Comparative images of the CT scan. **a**—At diagnosis; **b**—After 1st-line treatment with capecitabine/gemcitabine; the arrows point the multinodular conglomerate in the pericefalo-pancreatic region, the hepatic nodule, and the mass in the fundus of the gallbladder. **c**—Disappearance of the lesions after 2nd-line treatment with gemcitabine/oxaliplatin

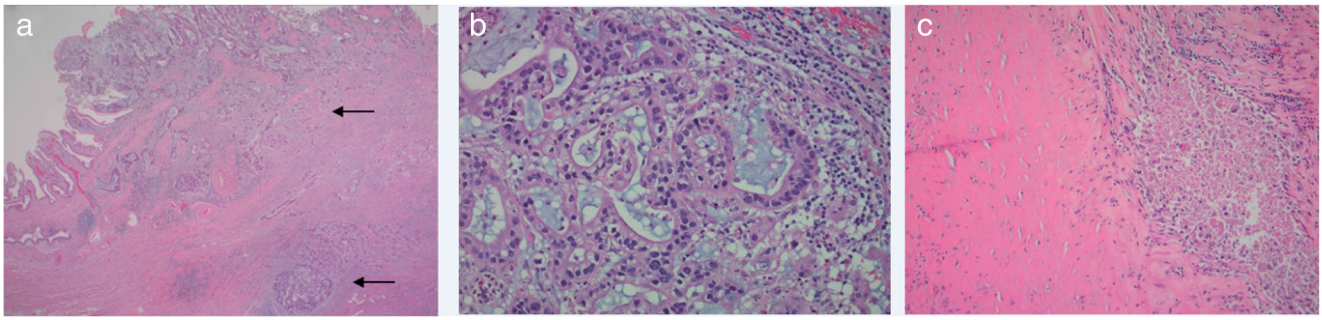

Fig. 2 Adenocarcinoma of the gallbladder. **a**—Extensive invasion of the muscular layer and perimuscular connective tissue (H&E, 20×); **b**—Infiltrative well-formed glands, with atypical columnar cells with mucin production (H&E, 200×). **c**—Liver tissue with extensive fibrotic and necrotic areas, with no viable tumor cells (H&E, 100×)

II trials that the scheme which allowed the best response rate and tumor control rate was gemcitabine combined with platinum. This conclusion was supported by ABC-02 trial—a phase III trial [8], 2010, which compared the treatment of gemcitabine with the doublet of gemcitabine and cisplatin in patients with advanced biliary tract cancer. In this trial, the authors noticed a 3.6 months increase in survival of patients treated with the doublet.

In order to have better tolerance, and because of the easier administration, most patients in clinical practice are treated with gemcitabine and oxaliplatin, as our patient was. Fiteni et al. [14] published a systematic review of the literature available in 2014, comparing these two schemes. The aim of this study was to determine the differences in terms of effectiveness in clinical outcomes between the use of cisplatin or oxaliplatin. In this article, a small survival advantage was observed in patients treated with cisplatin, although these patients experienced a higher incidence of side effects, which not influence the quality of life analysis. The authors, however, stated that the results of the study ought to be interpreted cautiously and that further confirmatory prospective randomized trials are needed taking into account an evaluation of quality of life.

In our case, the patient had a really good response to the second-line treatment, which enabled the discussion of surgery—which is potentially the only known curative option in the treatment of gallbladder cancer. After careful observation and discussion of the CT scan images, the disease was deemed resectable and surgery was successfully carried out.

Although this procedure was not standard—palliative chemotherapy allowed resectability. The pathological study confirmed the diagnosis and the response to the treatment.

In the literature, there is some information on the role of the surgery in stage IV disease, mainly in the Asian population. In 2007, Nishio et al. [15] reviewed retrospectively the records of 166 patients with stage IV disease who underwent surgery and described that patients with paraaortic lymph node metastasis or isolated liver metastasis survived longer than those with other distant metastasis or unresectable advanced cancer. Kang et al. 2012 [16], have also done a retrospective revision of 94 patients with stage IV disease who underwent surgery. They described a survival benefit of the surgery whenever it was possible to achieve complete resection in patients with hepatic metastatic nodules near the gallbladder bed or those with limited numbers of peritoneal implantations. In this study, the authors identified three independent prognostic factors: the preoperative serum CEA levels, the surgery with curative intent, and adjuvant chemotherapy. They suggested that surgery with systemic chemotherapy might be beneficial in carefully selected stage IVB disease.

The role of neoadjuvant chemotherapy has been discussed mostly in locally advanced disease. Creasy et al. [17] have recently published a retrospective study of 74 patients with locally advanced disease, treated in the Memorial Sloan Kettering Cancer Center in New York. In 30% of the patients, an attempted resection was done and in 14% this was definitive, allowing a median overall survival for this group of patients of 51 months (versus 11 months for the whole cohort). In stage IV disease, there are only small series of patients or case reports, with varied schemes of chemotherapy, showing some benefit—so prospective studies concerning this issue are needed.

Conclusion

This case report shows the importance of the individualized evaluation of patients. Although it is essential to follow the guidelines and standard procedures, in very particular situations the multidisciplinary approach, and continuous collaboration among different specialties allows optimal decision making in order to give the best treatment option for each patient. In this particular situation, there was a clear benefit from chemotherapy and from surgery. Prospective trials in order to identify the group of patient that might benefit more from this approach should be done.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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