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Rare Signet Ring Cell Carcinoma of The Gallbladder: A Case Report

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List of Abbreviations:

SRCC: Signet Ring Cell Carcinoma**;** CT: Computed Tomography**;** 5-FU: 5-Fluorouracil**;** PTGBD: Percutaneous Transhepatic Gallbladder Drainage**;** GB: Gallbladder**;** PET: Positron Emission Tomography**;** LN: Lymph Nodes**;** MUC-1: Mucin**;** CDX-2: Caudal-Type Homeobox 2**;** SMAD-4: SMAD Family Member 4**;** MARS1: Methionyl-tRNA Synthetase 1

1. Abstract

Signet ring cell carcinoma (SRCC) is a very rare form of gallbladder (GB) cancer. SRCC is highly invasive and aggressive and mainly exhibits nonspecific symptoms of benign GB lesions; therefore, this cancer is generally diagnosed at an advanced stage. Because it is a rare disease, there are no standard treatment guidelines. Herein, we report a patient with SRCC of GB diagnosed and treated in our hospital. An 80-year-old woman visited the hospital for laparoscopic cholecystectomy for suspected gallstone causing chronic cholecystitis. A routine computed tomography scan revealed a malignancy in the GB and the patient underwent a radical laparoscopic

Epidemiology, risk factor, diagnosis and treatment cholecystectomy. On biopsy, she was diagnosed with SRCC of GB with regional lymph node metastasis, which led to postoperative adjuvant 5-fluorouracil chemotherapy. She is currently being followed up without recurrence.

2. Introduction

Signet ring cell carcinoma (SRCC) is an extremely rare and highly aggressive type of cancer that accounts for a small fraction of all gallbladder (GB) malignancies. SRCC is known for its typical pathological appearance, which shows a signet ring shape in tumor cells due to the displacement of the nucleus to the periphery by intracytoplasmic mucin [1]. The most common GB malignancy is adenocarcinoma, which accounts for approximately 90% of all GB cancers. There are known risk factors for GB malignancies including gallstones, GB polyps, and abnormal pancreaticobiliary duct junctions. Little is known about SRCC of the GB because of its rare occurrence. A previous study showed that SRCC of the GB accounts for only 1.7% of GB adenocarcinomas, [wang] and consequently, there are no standard treatment guidelines. SRCC is typically known for its poor prognosis in gastric cancer where it is most commonly found1. Although SRCC of the GB also has a very poor 5-year overall survival rate of 7.2% 2, studies regarding its prognosis remain limited. Therefore, we herein present the unique case of an 80-year-old woman with SRCC of the GB who survived after receiving extensive surgery and 5-fluorouracil (5-FU) postoperative chemotherapy.

3. Case Report

The patient was an 80-year-old woman who presented to our hospital. Approximately a month before visiting the hospital, she was diagnosed with acute cholecystitis at a local hospital due to GB stone, and was treated with percutaneous transhepatic gallbladder drainage (PTGBD). There was no unusual family history. As the patient had to undergo cholecystectomy after PTGBD, she was preoperatively assessed as part of the laparoscopic cholecystectomy plan, with the suspicion of chronic cholecystitis caused by a gallstone. The laboratory results showed that the hemoglobin count was slightly low at 11.2 g/dL whereas the platelet count was high at

587000/μL. Liver enzymes including aspartate transaminase, alanine transaminase, and alkaline phosphatase were all within normal levels. Abdominal and pelvic computed tomography (CT) showed subacute calculous cholecystitis, suggesting coexisting GB stones with luminal distention, wall thickening, bile sludge, and pericholecystic infiltration. However, a 3-cm irregularly shaped papillary mass was also seen on the fundus of the GB on CT, consistent with GB cancer. In addition, CT showed an enlarged 1.3^{cm} pericholecystic lymph node (LN), consistent with metastasis (Figure 1). Therefore, screening and treatment for a benign lesion in GB was changed to screening and treatment for cancer in GB. In addition, a tumor marker test was performed, which showed normal carcinoembryonic antigen (CEA), while CA19-9 was 35.8 U/mL, indicating elevated levels within the normal range. Magnetic resonance imaging and positron emission tomography (PET) showed that the extent of the gallbladder cancer lesions was limited to the gallbladder and nearby LNs. Laparoscopic radical cholecystectomy was performed as a surgical treatment for GB cancer to resect the GB, part of the liver, cystic duct, and LN near the GB. During surgery, frozen section biopsy revealed a negative cystic duct resection margin and a negative pericolic cystic LN. Following surgery, pathological analysis revealed an 8.1 x 4.5 x 1.0 cm3 poorly differentiated adenocarcinoma (comprising 80% signet ring cell carcinoma and 20% biliary adenocarcinoma). The tumor infiltrated the perimuscular connective tissue on the peritoneal side (pT2) and metastasis to one of the regional LNs was confirmed (pN1). There was no distant metastasis to other organs (M0); therefore, the TNM staging was pT2N1M0 (stage IIIB). The entire resection margin was negative. Lymphovascular and perineural invasion was present and tumor infiltrating lymphocytes were <10%. Immunohistochemical staining showed that the mucins (MUC)-1 and MUC-2 were locally positive, MUC-5 was positive, MUC-6 was negative, caudal-type homeobox 2 (CDX-2) was locally positive, and p53 showed a wild-type pattern with increased expression in the tumor cell. S100P was focally positive in tumor cells, SMAD family member 4 (SMAD4) expression was decreased in tumor cells and methionyl-tRNA synthetase 1 (MARS1) was strongly positive with (3+/3). Following surgery, additional treatment was required because the regional node was positive. Chemotherapy was performed with 5-FU, because it is covered by insurance in Korea; 5-FU CTx 1000 mg injection 1550 mg (1 time/day) was given for 6 cycles every 3 weeks [2022.10.22~2023.02.18]. After the final chemotherapy session, the patient underwent a CT scan of abdomen and pelvis to assess her response to chemotherapy. No recurrent tumors or metastases were found and the patient is living without any health problems.

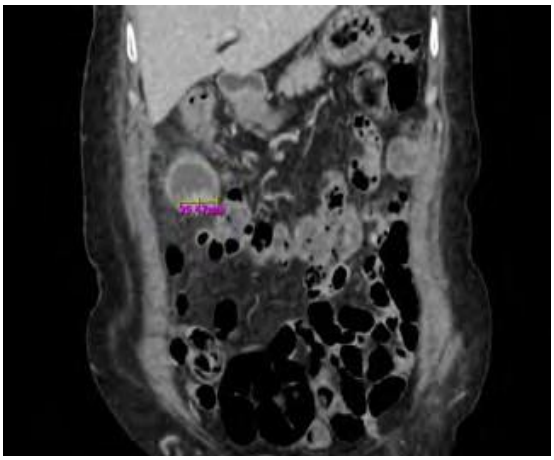

Figure 1: Abdominal CT imaging (pre-operation)

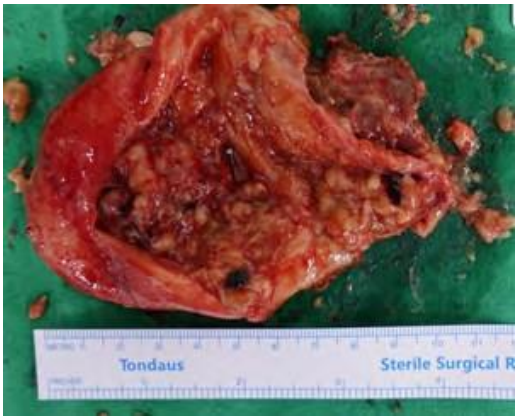

Figure 2: Gross findings of resected gallbladder

4. Discussion

GB cancers are often asymptomatic in the early stages. They may present with nonspecific symptoms such as right upper quadrant abdominal pain, nausea, jaundice, or malaise, often leading to the diagnosis of cholecystitis. This is the reason gallbladder cancer is diagnosed at a relatively advanced stage compared to other cancers. Our patient had a medical history of acute cholecystitis that led to PTGBD approximately 1 month prior to admission. When she visited our hospital for the first time, sustained PTGBD was observed; consequently, the plan was to perform only a cholecystectomy. However, routine CT checkup before cholecystectomy suggested the strong possibility of GB malignancy with probable metastatic LN involvement, which was later found to be advanced SRCC of the GB. Likewise, SRCC may be detected at a more advanced stage because it has more aggressive and invasive properties than typical adenocarcinoma, although both may become symptomatic at a similar time frame.

Currently, there is no consensus on adjuvant chemotherapy for SRCC of the GB. However, there are several options for postoperative chemotherapy of GB cancer, including capecitabine, gemcitabine, cisplatin, and 5-FU. The phase III BILCAP trial suggests capecitabine monotherapy as the primary recommendation for adjuvant therapy [3]. A case report from Japan mentioned the use of

gemcitabine and S-1 for stage IIIA gallbladder SRCC [4]. Another patient in India was given 5-FU for adjuvant therapy of stage 2B gallbladder SRCC, but died of liver failure 3 months after radical cholecystectomy. The patient was given 5-FU instead of cisplatin because he had nephrotoxicity, which also indicates that the physician primarily considered cisplatin for the regimen. This patient received 5-FU for adjuvant chemotherapy. Due to insurance coverage issues in Korea, 5-FU is generally considered an adjuvant regimen for GB cancer. The patient received 6 cycles of 5-FU chemotherapy, and the follow-up CT showed no distant metastasis or recurrence of the tumor. Since SRCC of the GB is extremely rare and the time of diagnosis of SRCC varies significantly among patients, it is difficult to compare the efficacy of each treatment option and patient survival. Treatment can vary widely from the extent of surgery to specific adjuvant regimen, but surgery combined with adjuvant chemotherapy had a better overall survival rate than surgery alone2. Therefore, we cannot confirm the superiority of one regimen over others without precise statistical analysis using a significant number of cases of SRCC of the GB. There are several risk factors for GB cancer that are characterized by chronic inflammation in the GB. As SRCC of the GB is included in GB cancer, it is necessary to consider this while assessing patient history and examination because known risk factors may affect the development of SRCC of the GB. Known risk factors for GB cancer include gallstones, porcelain GB, GB polyps, primary sclerosing cholangitis, Salmonella infection, Helicobacter infection, congenital biliary cysts, and abnormal pancreaticobiliary duct junction. Other factors include drugs that induce biliary carcinogenesis (methyldopa, oral contraceptives/menopausal hormone therapy, and isoniazid), carcinogen exposure, obesity, and elevated blood sugar. In particular, gallstones should be monitored closely as they are one of the strongest risk factors for GB cancer. Studies have reported that 70–90% of patients with GB cancer have gallstones [5-7]. Before being diagnosed with SRCC, our patient was also found to have gallstones. However, studies on how the aforementioned risk factors relate to SRCC of the GB are lacking, and further research needs to be conducted.

The SRCC of GB adenocarcinoma has been identified as a negative prognostic factor in GB adenocarcinoma owing to its lower differentiation and extremely aggressive properties. Studies by Wang et al. [2], have shown that gallbladder SRCC is significantly unfavorable in T stage, LN metastasis, distant metastasis, American Joint Committee on Cancer (AJCC) stage and histologic grade. In particular, regarding poor differentiation rate, it was 29.4% in non-SRCC, while 71.4% in SRCC; hence, it was demonstrated that SRCC has a very high rate of poor differentiation [2]. The patient in our case also had SRCC of GB, which was identified as an advanced cancer with AJCC stage IIIB. The degree of infiltration was up to the muscle, with regional LN metastasis. In addition, there was both perineural and lymphovascular invasion with a poorly differentiated type. Based on the histologic characteristics, the prognosis was considered poor. >90% of SRCCs in humans originate from the stomach, breast, and colon. Therefore, when a patient presents with SRCC in the GB, it is important to distinguish metastasis from other sites. Immunohistochemical staining along with complete clinical history is utilized for differentiation. According to Chu, breast SRCC is characterized by the co-expression of MUC1 and ER. Gastric cancer usually shows a heterogeneous CDX2 staining pattern, and colonic SRCC shows homogeneous CDX2 nuclear positivity, diffuse cytoplasmic MUC2, and MUC5AC positivity [8]. In this case, we performed immunohistochemical staining using MUC-1, MUC-2, MUC-5, MUC-6, CDX2, p53, S100P, SMAD4, and MARS 1. The staining pattern was different from that of gastric, colon, and breast SRCC. We also confirmed that there were no cancerous findings in other areas using PET CT, and diagnosed SRCC of GB adenocarcinoma.

Reference

1. Pernot S, Voron T, Perkins G, Lagorce-Pages C, Berger A, Taieb J. Signet-ring cell carcinoma of the stomach: Impact on prognosis and specific therapeutic challenge. World J Gastroenterol. 2015; 21(40): 11428-38.
2. Wang S. Clinicopathological characteristics and prognosis of signet ring cell carcinoma of the gallbladder. BMC Gastroenterol. 2021; 21(1): 248.
3. Primrose JN, Fox RP, Palmer DH, Malik HZ, Prasad R, Mirza D. BILCAP study group. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncol. 2019; 20(5): 663-673.
4. Masatsugu Hiraki, Hiroyuki Yakushiji, Kazuyoshi Hashiguchi, Sadami Harada, Naohiko Kohya, Keita Kai. Gallbladder carcinoma with a large monolocular cystic cancerous component. Oncol Lett. 2010; 1(6): 995-998.
5. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer. 2006; 118(7): 1591-602.
6. Zatonski WA. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. J Natl Cancer Inst. 1997; 89(15): 1132-8.
7. Hsing AW, Gao YT, Han TQ. Gallstones and the risk of biliary tract cancer: a population-based study in China. Br J Cancer. 2007; 97(11): 1577-82.
8. Chu PG. Immunohistochemical characterization of signet-ring cell carcinomas of the stomach, breast, and colon. Am J Clin Pathol. 2004; 121(6): 884-92.