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Case Report

Leukocytosis and a Rare Gallbladder Sarcomatoid Carcinoma: A Case Report

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Abstract

Gallbladder sarcomatoid carcinoma is a rare and aggressive malignancy, often presenting with abdominal symptoms. The tumor typically has high metastatic potential, even after surgical resection. The paraneoplastic leukemoid reaction is an uncommon manifestation of solid tumors. Here, we report a case of a female patient who presented with abdominal fullness, weight loss, and unexplained afebrile leukocytosis. She was diagnosed with gallbladder sarcomatoid carcinoma following surgery and experienced a rapid recurrence of leukocytosis upon tumor relapse. This report highlights the unique clinical presentation of the patient and also discusses the treatment approach and decision-making process involved in her management.

Keywords: Gallbladder, leukocytosis, paraneoplastic leukemoid reaction, sarcomatoid carcinoma

Introduction

Primary gallbladder cancers account for approximately 1.2% of all cancer diagnoses[1] and are predominantly adenocarcinomas. Sarcomatoid carcinoma is a rare subtype estimated to account for 1.7%–4.3% of gallbladder cancers.[2,3] To date, just over 100 cases have been reported in the English literature.[4] This tumor subtype is highly aggressive and is associated with a poorer prognosis compared to typical gallbladder adenocarcinoma.[2,3] Patients commonly present with advanced disease and symptoms such as abdominal pain, anorexia, weight loss, and jaundice. Imaging findings typically reveal a gallbladder mass with involvement of adjacent organs or lymph nodes, similar to those seen in gallbladder adenocarcinoma. Even after surgical resection, the rapid development of recurrence or metastatic tumors is common.[3-5]

Case Report

A 67-year-old woman with no significant medical history presented with intermittent epigastric fullness and vague

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abdominal pain for 2 months. She reported decreased appetite and a 4-kg weight loss during this period. A gallbladder mass was identified via abdominal ultrasound at a local clinic, prompting her referral to our hospital.

On physical examination, no specific abnormalities were noted. Laboratory findings revealed microcytic anemia (hemoglobin 9.4 g/dL), leukocytosis (white blood cell [WBC] count 17.52 × 10^3/μL, with 92% neutrophils), and hypoalbuminemia (albumin 3.04 g/dL). Her serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels were within normal limits. Ultrasound imaging showed a 6-cm mixed echogenic gallbladder mass without gallbladder wall thickening. Abdominal computed tomography (CT) revealed a heterogeneously enhancing gallbladder mass with focal wall dimpling [Figure 1], without evidence of hepatic lesions or lymphadenopathy. Magnetic resonance cholangiopancreatography confirmed that the tumor was confined to the gallbladder, with no invasion of adjacent organs or biliary tract dilation [Figure 2].

Partial parenteral nutrition was initiated to improve her general condition, and ampicillin/sulbactam was prescribed to address leukocytosis, as concurrent infection (e.g. cholecystitis) could not be excluded. The leukocyte alkaline phosphatase (LAP) score was 329.

She then underwent indocyanine green fluorescence-assisted laparoscopic surgery. The gallbladder appeared smooth externally, with minor omental adhesion corresponding to the dimpling observed on CT. No peritoneal seeding, ascites, or invasion of adjacent organs (colon, duodenum, or liver) was identified. A cholecystectomy was performed first, which revealed an intact outer gallbladder layer circumferentially [Figure 3]. Inside the gallbladder, a pedunculated intraluminal tumor arising from the mucosa on the peritoneal side was identified [Figure 4]. Intraoperative frozen section analysis revealed spindle cell malignancy and she subsequently underwent portal hepatis lymphadenectomy, although hepatic resection was not performed.

The patient recovered uneventfully postoperatively, and her WBC count returned to normal the following day (5.94 × 10^3/μL). She was discharged shortly thereafter. Pathological examination identified a 6.7 cm × 4.4 cm × 4.3 cm pedunculated tumor invading the perimuscular connective tissue layer. Microscopically, the tumor exhibited both malignant epithelial (<10%) and mesenchymal (>90%) components [Figure 5a]. The epithelial component was high-grade adenocarcinoma, while the mesenchymal component comprised spindle cells with marked nuclear pleomorphism and frequent mitoses. Surgical margins, including the cystic duct and circumferential gallbladder wall, were tumor-free. While the cystic duct lymph node contained metastatic carcinoma cells, the pericholedochal and hepatic artery lymph nodes were free of tumors. Immunohistochemical staining demonstrated strong cytokeratin (CK) positivity (AE1/AE3) in the epithelial components, with focal weak CK positivity

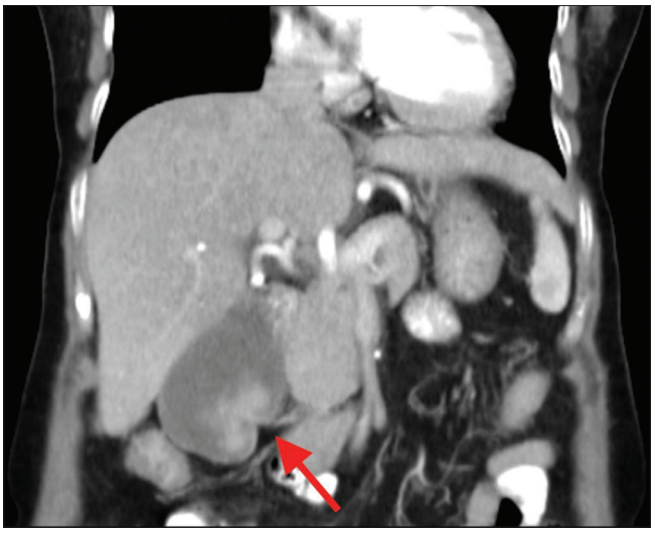

Figure 1: A gallbladder mass with heterogeneous enhancement was observed. The gallbladder wall exhibited focal dimpling (arrow), without evidence of generalized thickening

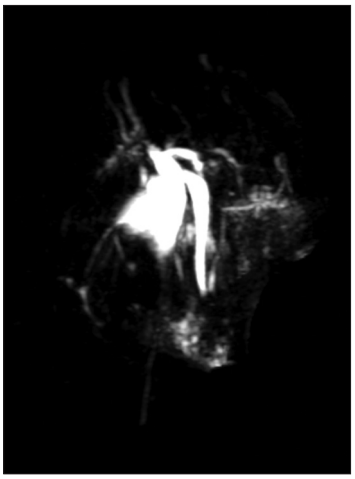

Figure 2: Magnetic resonance cholangiopancreatography showed no intrahepatic bile duct dilatation or compression of the common bile duct

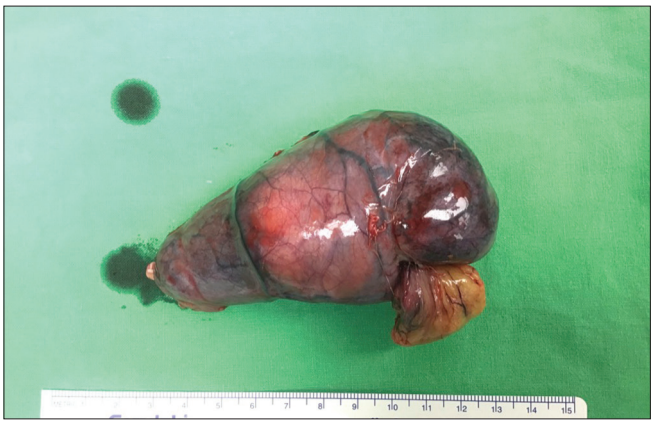

Figure 3: The serosal layer of the gallbladder exhibited a smooth surface on both the peritoneal and hepatic sides, with the exception of some omental adhesions on the peritoneal side

in spindle cells [Figure 5b]. The spindle cells were negative for desmin (D33), S100 (polyclonal), CD34 (QBEnd/10), and alpha-smooth muscle actin (1A4), consistent with a diagnosis of gallbladder sarcomatoid carcinoma.

The patient regained her appetite and gained 3 kg after returning home. Adjuvant concurrent chemoradiation therapy (CCRT) was initiated, comprising 5000 cGy in 25 fractions targeting the gallbladder fossa and liver hilum, combined with oral capecitabine (Xeloda) 500 mg twice daily.

Three months later, she experienced epigastric fullness and reduced bowel movements. Laboratory tests revealed rebound leukocytosis (WBC count 31.75 × 10^3/μL). CT of the chest and abdomen demonstrated a large right liver tumor and 2-cm nodule in the right upper lung [Figure 6], suggestive of metastatic disease. Her condition rapidly deteriorated, with symptoms including dyspnea, leg edema, significant appetite loss, and marked ascites. Due to poor performance status, she was unable to tolerate salvage chemotherapy with gemcitabine and cisplatin. Comfort care was provided, and she died less than six months after surgery.

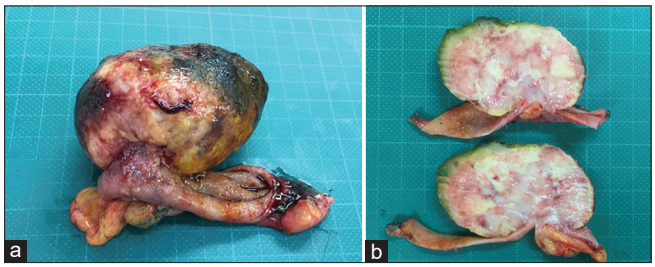

Figure 4: The tumor was a lobulated, well-defined mass entirely located within the gallbladder lumen (a). It had a pedunculated attachment originating from the gallbladder mucosa on the peritoneal side (b)

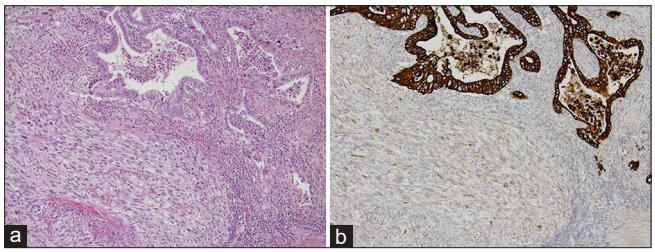

Figure 5: (a) Sarcomatoid carcinoma with admixture of malignant epithelial and spindle cell components (H and E, ×100). (b) The malignant epithelial component was strongly immunopositive for CK (AE1/AE3) diffusely, while the spindle cell component showed weak CK positivity focally (×100). H and E: Hematoxylin and eosin, CK: Cytokeratin

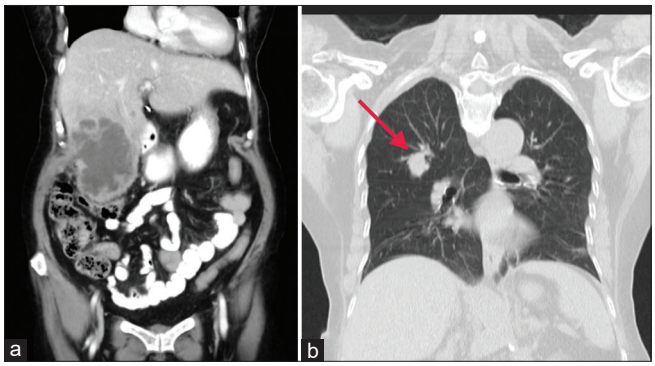

Figure 6: (a) A computed tomography scan of the chest and abdomen performed 4 months after surgery revealed a large hypo-enhancing hepatic mass in segment V. (b) An irregular 2-cm lung nodule was identified in the right upper lobe (arrow). Both findings were suggestive of recurrent tumors

Discussion

Sarcomatoid carcinoma (carcinosarcoma) can occur in the uterus, lungs, breast, and kidneys, but it has rarely been reported in the gallbladder. This tumor is composed of both epithelial (carcinomatous) and mesenchymal (sarcomatous) components, possibly due to gallbladder carcinoma de-differentiation, leading to higher malignancy.[5,6] Epithelial-mesenchymal transition (EMT), where epithelial cells gain mesenchymal traits, has been proposed as a mechanism of cancer progression. EMT enhances cell migration and invasion, potentially increasing recurrence risk.[2,7,8]

Patients with gallbladder sarcomatoid carcinoma are often diagnosed at an advanced stage, limiting the opportunity for curative surgery. Moreover, due to the highly malignant behavior and rapid recurrence or metastasis, treatment outcomes are typically poor. In the largest meta-analysis to date involving 68 cases, the median overall survival was only 5 months.[6] Surgical resection remains the primary hope for curing localized disease in eligible patients. However, significant heterogeneity exists regarding the indications for surgery and systemic treatment regimens.

In a Taiwanese study,[3] six (4.3%) sarcomatoid carcinoma cases were identified among 141 surgically resected gallbladder cancer patients over 18 years. The median survival of these six patients was 2.5 months, as tumors recurred shortly after curative resection. Even though three patients received fluorouracil-based chemotherapy postoperatively, none survived beyond 5 months. In another case series of seven patients published in 2020,[9] the authors reported that nearly all advanced-stage (III/IV) cases (five patients) developed disease progression or metastasis within 3 months postsurgery. Among them, only one stage IIIb patient underwent adjuvant chemotherapy (gemcitabine and capecitabine) combined with concurrent radiotherapy. Although this patient experienced disease recurrence, she achieved a progression-free survival of 12 months and an overall survival of 15 months, suggesting that adjuvant therapy may offer a survival benefit for patients with locally advanced disease.

Due to the rarity of gallbladder sarcomatoid carcinoma, standardized systemic treatment guidelines are lacking. Consequently, current practice is generally based on the principles established for conventional gallbladder cancer. In a randomized Phase III trial[10] of patients with resected

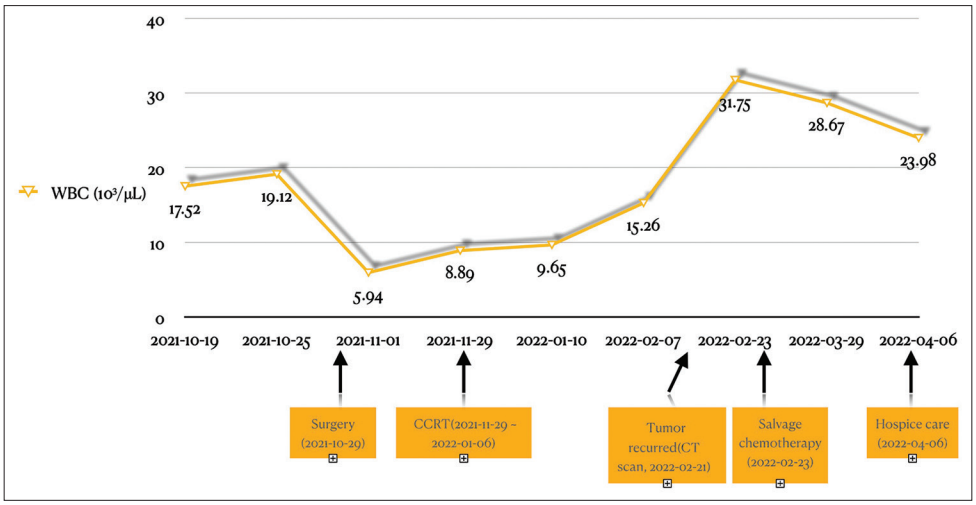

Figure 7: Changes in white blood cell count during the disease course

biliary tract cancers (18% of whom had gallbladder cancer), adjuvant capecitabine was shown to delay the time to tumor recurrence, leading to an increased median overall survival compared to observation alone (49.6 months vs. 36.1 months; adjusted hazard ratio 0.84, 95% confidence interval 0.67–1.06). Based on these findings, capecitabine is currently the first-line recommendation for the adjuvant treatment of biliary tract cancers in the NCCN guidelines.[11] The role of CCRT was also explored in a single-arm Phase II study in which patients with resected extrahepatic cholangiocarcinoma and gallbladder carcinoma were treated with adjuvant capecitabine plus gemcitabine, followed by capecitabine-based CCRT.[12] A median overall survival of 35 months, even in the R1 resection subgroup, suggests the potential efficacy of such treatment.

In our patient, the disease exhibited two unique features. The first of which was leukocytosis. Leukemoid reaction (LR) is characterized by persistent leukocytosis (WBC > 40,000/μL with dominant neutrophils) in the absence of hematologic malignancy.[13] Common causes include infection, severe hemorrhage, hemolysis, intoxication, or solid malignancies. Paraneoplastic LR (PLR) refers specifically to LR caused by cytokine-secreting solid tumors without bone marrow involvement. Granulocyte colony-stimulating factor is the most common cytokine responsible for leukocytosis in PLR. Unlike infection-related LR, PLR patients are often afebrile and clinically stable. The diagnosis of PLR is supported by a reduced WBC count following tumor burden reduction. The LAP score can also help differentiate PLR from chronic myeloid leukemia (CML), with a high LAP score favoring PLR and low score indicating CML.[13] Although the WBC count of our patient did not meet the PLR threshold, her leukocytosis, and WBC rebound upon tumor recurrence were consistent with PLR [Figure 7]. Initial leukocytosis also led to the consideration of cholecystitis as a differential diagnosis, despite the absence of right upper quadrant tenderness. Granger and Kontoyiannis[14] reported that PLR accounted for 10% of extreme leukocytosis cases in 758 non-hematologic cancer patients and that it was associated with a poor prognosis (78% of the patients died or were discharged to a hospice within 12 weeks). To our knowledge, our patient is the first reported case of gallbladder sarcomatoid carcinoma-related PLR.

The second feature was the tumor morphology. The mass had a well-defined border, was entirely within the gallbladder, and did not invade the liver. The interface between the gallbladder and liver was smooth, allowing detachment without disruption. Given the lack of gross liver involvement and the patient's poor nutritional status, adjacent hepatic segment resection was not performed, despite being a recommended procedure for T2 gallbladder adenocarcinoma.[15,16] While radical cholecystectomy with liver and lymph node resection has been shown to improve survival, tumor biology and stage rather than surgical extent often determine outcomes.[17]

In summary, gallbladder sarcomatoid carcinoma is a rare but highly aggressive disease. Unusual afebrile leukocytosis may be a distinctive feature, potentially linked to tumor-related PLR. While curative resection remains the cornerstone of treatment for eligible patients, further exploration of the pathogenesis of the disease and the development of novel therapeutic agents are essential to improve outcomes.

Declaration of patient consent

This study was performed in accordance with and conforming to the Declaration of Helsinki. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest
There are no conflicts of interest.

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