Case Report

Squamous cell carcinoma of the gallbladder: a rare case with diagnostic and therapeutic challenges

Abstract

Background: Gallbladder carcinoma is a common biliary tract malignancy, with adenocarcinoma being the most common subtype. Squamous cell carcinoma (SCC) of the gallbladder is rare (2-3%) and its management is poorly understood.

Case presentation: We report a rare case of SCC of the gallbladder. A 50-year-old man with no medical history presented with fever, right hypochondrial pain, and general decline over the past month. Physical examination, revealed tenderness in the right upper quadrant. No palpable mass was detected on the abdominal examination. Laboratory tests revealed anemia, elevated white blood cell count, high C-Reactive Protein, and cholestasis. Abdominal CT scan identified a large mass (10 cm) involving the gallbladder and infiltrating liver segments IV and V, with additional nodular lesions throughout the liver. Histopathological examination confirmed the diagnosis of SCC. The liver biopsy of a hepatic metastasis revealed nests, trabeculae, and dyskeratotic cell clusters. Immunohistochemistry showed intense nuclear positivity for anti-p40 and moderate positivity for anti-cytokeratin 7, while anti-cytokeratin 20 was negative. In our patient, there is no squamous cell carcinoma at another site. The diagnosis of SCC of the gallbladder with hepatic metastasis was hence confirmed. As the tumor was unresectable, palliative chemotherapy with Gemcitabine-Cisplatin was recommended but was not administered due to the patient's rapid deterioration.

Conclusions: SCC of the gallbladder is a rare and aggressive tumor with poor prognosis. Its management includes surgical resection in localized cases and palliative chemotherapy for unresectable tumors. Further research is needed to enhance understanding and treatment of this rare malignancy.

Keywords: squamous cell carcinoma, gallbladder, chemotherapy

Volume 17 Issue 2 - 2026

H Elloumi,[1,2] E Slama,[1,2] M Mabrouk,[3] S Ben Hamida,[1,2] I Ganzoui,[4] I Cheikh[1,2]

[1]Faculty of Medicine of Tunis, University of Tunis El Manar, 1007 Tunis, Tunisia
[2]Departement of Gastroenterology, Habib BOUGATFA Hospital, Bizerte, 7000, Tunisia
[3]Departement of Oncology, Habib Bougatfa Hospital, Bizerte, 7000, Tunisia
[4]Departement of Radiology, Habib Bougatfa Hospital, Bizerte, 7000, Tunisia

Correspondence: E Slama, Faculty of Medicine of Tunis, University of Tunis El Manar, 1007 Tunis, Tunisia, Tel +216 50 140 246

Received: February 07, 2026 | **Published:** May 15, 2026

Introduction

Gallbladder carcinoma (GBC) is a prevalent malignancy within the biliary tract with adenocarcinoma being the predominant histological subtype, representing 80-95% of cases. In contrast, squamous cell carcinoma (SCC) represents a rare variant comprising only 2-3% of all GBC cases.[1–5]

Due to its rarity, there is limited understanding of SCC of the gallbladder. We report a case of pure SCC of the gallbladder and a comprehensive review of its etiopathogenesis, epidemiology, diagnosis, management and prognosis.

Case presentation

We present the case of a 50-year-old man with no significant medical history who presented with fever, right hypochondrial pain, and a general decline in health over the preceding month. Physical examination revealed tenderness upon palpation of the right upper quadrant. No masses were palpable.

Laboratory tests showed a hemoglobin level of 10.6 g/dL, a hematocrit of 32.7%, a biological inflammatory syndrome with a white blood cell count of 17.8 $\times 10^3/mm^3$ and a CRP level of 135 mg/L, and cholestasis, with γ-GGT elevated to 213 IU/L (normal range 10–71) and ALP to 197 IU/L (normal range 40–130). Bilirubin was 3 µmol/L. AST was 23 IU/L (normal range 10–40), and ALT was 25 IU/L (normal range 5–44).

An abdominal computed tomography scan revealed a large enhancing solid mass with a necrotic center involving the gallbladder and infiltrating segments IV and V of the liver, measuring approximately 10 cm in its largest dimension (Figure 1A), associated with multiple nodular lesions throughout all hepatic segments (Figure 1B). These lesions, ranging from 1 to 3 cm in diameter, exhibited irregular margins and a central hypodensity indicative of necrosis. Due to their multifocal distribution and association with the primary tumor, the liver lesions were considered metastatic.

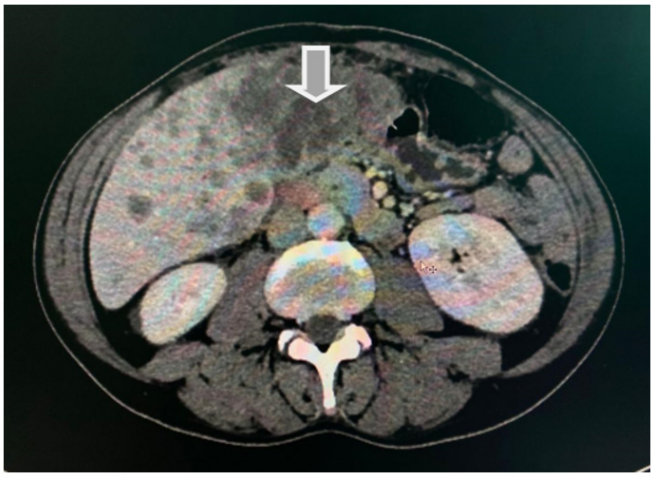

Figure 1A Non-contrast phase CT scan.

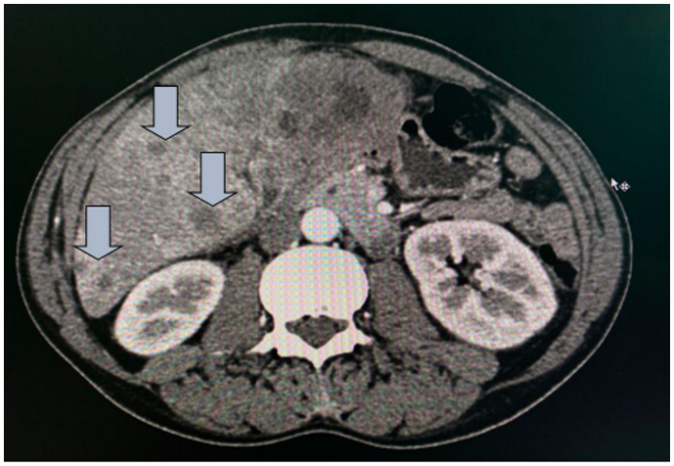

Figure 1 (A,B) CT scan figures: a tissue mass involving the gallbladder and infiltrating segments IV and V of the liver (Green Arrow), associated with secondary nodular lesions throughout all hepatic segments (Blue Arrows).

Figure 1B portal phase CT scan.

A biopsy of the metastatic liver tissue demonstrated, in the hematoxylin and eosin (H&E)-stained section, a malignant epithelial neoplasm composed of nests and sheets of atypical squamous cells. The tumor cells exhibited high nuclear-to-cytoplasmic ratios, pleomorphic and hyperchromatic nuclei, and prominent nucleoli. Frequent mitotic figures were identified, including atypical forms, reflecting high proliferative activity. Areas of keratinization and intercellular bridges were evident, supporting squamous differentiation. The overall architecture was disorganized, with invasion into the surrounding stroma (Figure 2A).

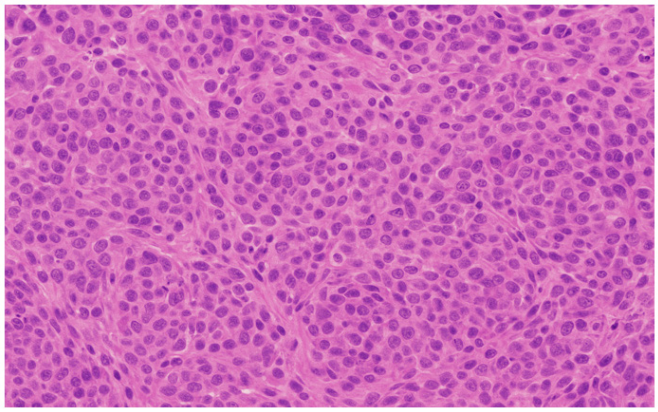

Figure 2A H&E staining showing nests, trabeculae, and dyskeratotic cell clusters with intercellular bridges, consistent with SCC (400x magnification).

Immunohistochemical analysis revealed intense and diffuse nuclear positivity for anti-p40 antibodies (Figure 2B) and moderate cytoplasmic and membranous positivity for anti-cytokeratin 5/6 antibodies (Figure 2C), with negative staining for CAM5.2 (Figure 2D). These features are diagnostic of squamous cell carcinoma.

Further investigations were conducted to exclude SCC of other origins before confirming a primary biliary source: a thoracic CT ruled out a pulmonary neoplasm, upper endoscopy and colonoscopy were normal, and an abdomino-pelvic CT ruled out lesions of the pancreas, bladder, or urinary tract.

The final diagnosis of SCC of the gallbladder with hepatic metastasis was inferred from the metastatic liver biopsy findings, supported by imaging and the absence of other primary sites. However, the lack of direct sampling from the primary gallbladder lesion limits definitive confirmation of its histological composition. This raises the possibility that an adenosquamous carcinoma with a predominant squamous component cannot be entirely excluded, though the immunohistochemical profile and clinical presentation align with reported cases of gallbladder SCC.

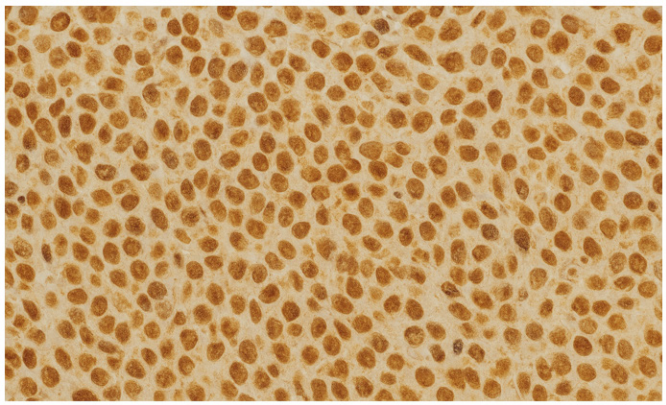

Figure 2B Intense nuclear positivity for p40, confirming squamous differentiation (400x).

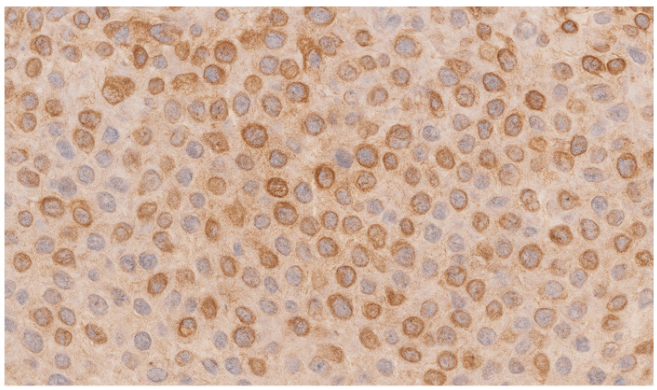

Figure 2C Positive CK5/6 staining, supporting SCC diagnosis (400x).

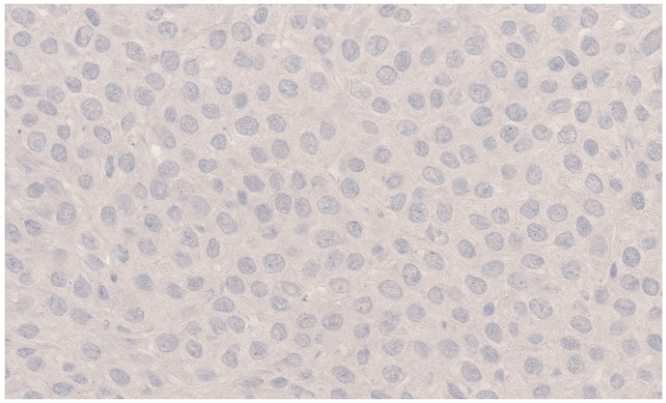

Figure 2D Negative CAM5.2 staining, ruling out adenocarcinoma (400x).

Figure 2 (A–D) Histopathological and immunohistochemical findings of pure squamous cell carcinoma of the gallbladder (liver metastasis biopsy). (A) H&E staining showing nests, trabeculae, and dyskeratotic cell clusters with intercellular bridges, consistent with SCC (400x magnification). (B) Intense nuclear positivity for p40, confirming squamous differentiation (400x). (C) Positive CK5/6 staining, supporting SCC diagnosis (400x). (D) Negative CAM5.2 staining, ruling out adenocarcinoma (400x).

Citation: Elloumi H, Slama E, Mabrouk M, et al. Squamous cell carcinoma of the gallbladder: a rare case with diagnostic and therapeutic challenges. *Gastroenterol Hepatol Open Access*. 2026;17(2):37–40. DOI: 10.15406/ghoa.2026.17.00633

Palliative chemotherapy with Gemcitabine–Cisplatin was recommended; however, due to a significant deterioration in the patient's overall health, chemotherapy was not administered. Unfortunately, the patient succumbed within three months of the initial diagnosis. No autopsy was performed due to family preferences and logistical constraints, limiting further histopathological evaluation of the primary lesion.

Discussion

Gallbladder carcinoma is a common biliary tract cancer. It is one of the most aggressive malignancies of the gastrointestinal tract. Gallbladder carcinoma includes several subtypes, including adenocarcinomas, adenosquamous carcinomas, and squamous cell carcinomas. SCC has a very low incidence rate and is responsible for only 2–3% of gallbladder malignancies.[1–5]

The pathogenesis of SCC of the gallbladder remains elusive. Several hypotheses have been suggested. One of these hypotheses is malignant transformation of ectopic squamous epithelium.[3] Malignant transformation of metaplastic squamous epithelium has also been evoked. This process describes the progression from metaplasia to dysplasia and ultimately carcinoma. Chronic irritation from gallstones can induce the differentiation of glandular cells into squamous cells within the gallbladder. Subsequently, these squamous metaplastic cells may undergo malignant transformation, leading to tumor formation.[2,3] The third hypothesis is squamous metaplasia in adenocarcinoma. In this context, squamous elements of a mixed adenosquamous carcinoma of the gallbladder exhibit excessive proliferation. Over time, these squamous cell components may completely replace the adenocarcinoma elements, culminating in the development of a squamous cell carcinoma.[3]

Recent studies have implicated CD109, a glycosylphosphatidylinositol-anchored glycoprotein, in the pathogenesis of SCC across various organs, including the gallbladder. Elevated CD109 expression, observed in recent studies,[6,7] inhibits transforming growth factor-β (TGF-β) signaling, promoting tumor progression by reducing apoptosis and increasing genomic instability.[7,8] This molecular insight, relevant to our case's aggressive behavior, warrants further investigation as a therapeutic target.

In terms of clinical presentation, clinical signs remain non-specific and appear at an advanced stage of the disease. Pain in the right hypochondrial region is the most significant symptom and occurs in 66% of patients. The detection of a palpable mass in the right upper quadrant is not specific but could be a crucial clue indicating the presence of malignancy. However, it may be clinically misdiagnosed as an abscess of the gallbladder.[1,3,8] In this case, the absence of a palpable mass and the rapid progression to hepatic metastasis highlight the challenge of early detection.

Abdominal ultrasonography is the initial test for diagnosis, as it is noninvasive and cost-effective. However, it cannot be used for tumor staging, and visualization of lymph nodes, intraperitoneal disease, and distant metastases is limited.[9]

Computed tomography remains the preferred examination for tumor diagnosis and staging. Its sensitivity and specificity for diagnosis are as high as 99% and 76%, respectively.[9]

Magnetic resonance imaging (MRI), including cholangiopancreatography, is not commonly used in the diagnostic process for gallbladder carcinoma.[10] It is sensitive in detecting obstructive jaundice, liver invasion, and hepatic and lymph nodal metastasis. Reported sensitivity rates for direct hepatic invasion and lymph node involvement on MRI can be as high as 100% and 92%, respectively.[10]

In patients with biliary obstruction without extraductal metastasis, ERCP-guided biopsies and EUS-guided fine needle aspiration or biopsy (FNA or FNB) may be options to obtain tissue samples [14]. ERCP is, however, not commonly used solely as a diagnostic procedure but mainly for the treatment of biliary obstruction.[11]

Histopathological examination is the only test that can confirm the diagnosis. It may be supported by immunohistochemical studies.

The immunohistochemical staining pattern is not entirely specific and is usually similar to that of bile duct and pancreatic carcinomas. A positive CK5/6 stain provides strong evidence for squamous differentiation, whereas a positive CK8/18 provides strong evidence for adenocarcinoma. Other cytokeratins, such as CK7, CK17, and CK19, and tumor-associated epithelial markers including CA19-9 and CEA are variable and non-specific.[12]

The curative treatment for SCC does not differ from that for other carcinomas and depends on the extent of local and regional spread. Studies have shown that surgical resection has been considered the cornerstone of treatment for many years, and complete resection is associated with increased survival.[1–3,5] Currently, cholecystectomy, hepatectomy, and lymphadenectomy constitute the gold standard. Resection of involved organs as part of a radical operation is justified in cases of localized lesions without metastasis or peritoneal dissemination.[1–3]

After surgical resection, most physicians recommend adjuvant chemotherapy with 5-fluorouracil. However, the benefits of the most effective adjuvant therapy or concurrent chemoradiotherapy remain debated.[1–4] A retrospective study conducted at the Mayo Clinic, in which most patients underwent extended oncologic resection, showed statistically significant survival benefits with adjuvant chemoradiotherapy. The median overall survival for patients receiving adjuvant chemoradiotherapy was 4.8 years, compared to 4.2 years for those who underwent surgery alone.[13] Based on these findings, it is reasonable to recommend adjuvant therapy for patients with stage II or higher gallbladder cancer following surgical resection. Chemotherapy options include gemcitabine, fluoropyrimidines, or gemcitabine-based combination therapies.[13]

As for unresectable cancers, the combination of gemcitabine and cisplatin is considered the standard palliative treatment.[9] with a median overall survival of 11.7 months[9] and a median progression-free survival of 8.0 months.[14]

No screening is currently recommended.[7] Performing a preventive cholecystectomy, as with gallbladder adenocarcinomas, for high-risk patients (those with stones larger than 3 cm, polyps >1 cm, pancreaticobiliary reflux, porcelain gallbladder, segmental adenomyomatosis, or xanthogranulomatous cholecystitis) remains the most effective preventive measure.[7]

Due to its rapid progression, most patients with gallbladder SCC present at an advanced stage with a poor prognosis, and the 5-year survival rate is around 1% despite surgical interventions. These tumors are typically invasive, often penetrating the entire gallbladder wall. Compared to gallbladder adenocarcinomas, the squamous component of GBCs proliferates at a higher rate than the glandular component. However, lymph node metastasis is less common compared to gallbladder adenocarcinomas. Their aggressive behavior is linked to a tendency for direct extension and early invasion into the liver and adjacent organs such as the stomach, duodenum, and

Citation: Elloumi H, Slama E, Mabrouk M, et al. Squamous cell carcinoma of the gallbladder: a rare case with diagnostic and therapeutic challenges. *Gastroenterol Hepatol Open Access*. 2026;17(2):37–40. DOI: 10.15406/ghoa.2026.17.00633

transverse colon.[1–5] This case's rapid progression to hepatic metastasis within three months aligns with this aggressive profile, reinforcing the urgency for molecular research into markers like CD109.[15]

Conclusion

The diagnosis of SCC of the gallbladder in this case was complicated by the reliance on a metastatic liver biopsy, highlighting the challenge of confirming the primary lesion's histology without direct sampling. The patient's aggressive clinical course, culminating in death within three months, underscores the poor prognosis of unresectable SCC. Further research into molecular markers, such as CD109, may offer targeted therapeutic options, addressing the current limitations in managing this rare malignancy.

Acknowledgments

None.

Conflicts of interest

The author declares that there are no conflicts of interest.

Funding

None.

References

1. Jin S, Zhang L, Wei YF, et al. Pure squamous cell carcinoma of the gallbladder locally invading the liver and abdominal cavity: A case report and review of the literature. *World J Clin Cases*. 2019 Dec 6;7(23):4163–4171.
2. Rekik W, Ben Fadhel C, Boufarou, et al. Primary squamous cell carcinoma of gallbladder. *Journal de Chirurgie Viscérale*. 2011;148(2):169–172.
3. Khan N, Afro N, Haider N, et al. A case of pure endophytic squamous cell carcinoma of the gallbladder: a rare entity with aggressive behaviour. *Turk Patoloji Derg*. 2012;28(2):181–183.
4. Hellara O, Njim L, Melki, et al. Carcinome épidermoïde pur primitif de la vésicule biliaire : à propos d'un cas. *Journal Africain d'Hépato-Gastroentérologie*. 2012;6(3):213–216.
5. Zhu C, Sun L, Wei Y, et al. Characteristics and survival prognosis of patients with pure squamous cell carcinoma of the gallbladder. *ANZ J Surg*. 2021;91(3):E91–E97.
6. Qi R, Dong F, Liu Q, et al. CD109 and squamous cell carcinoma. *J Transl Med*. 2018;16(1):88.
7. Ferdousi S, Khan SA. Primary squamous cell carcinoma of gall bladder: a case report. *Ibrahim Medical College Journal*. 2016;8(2):61–63.
8. Junior MAR, Favaro ML, Santin S, et al. Giant squamous cell carcinoma of the gallbladder: a case report. *World J Clin Cases*. 2019;7(18):2787–2793.
9. You MS, Ryu JK, Choi YH, et al. Therapeutic outcomes and prognostic factors in unresectable gallbladder cancer treated with gemcitabine plus cisplatin. *BMC Cancer*. 2019;19(10).
10. Niknejad M, Walizai T, Hacking C. *Gallbladder carcinoma*. Reference article, Radiopaedia.org, 2024.
11. Vogel A, Bridgewater J, Edeline J, et al. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(2):127–140.
12. Damiris K, Seltzer ES, Galan M, et al. A discussion of immunohistochemistry in diagnosing a rare case of adenosquamous carcinoma of the gallbladder. *J Case Rep Images Pathol*. 2021;7(1)20–23.
13. Gold DG, Miller RC, Haddock MG, et al. Adjuvant therapy for gallbladder carcinoma: the Mayo Clinic Experience. *Int J Radiat Oncol Biol Phys*. 2009;75(1):150–155.
14. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362(14):1273–1281.
15. Tan Z, Zhuofan D, Jianping G. Risk factors for the onset of gallbladder cancer: a review. *Int Surg J*. 2021;8(6):1951–1958.