

## Pure Gallbladder Squamous Cell Carcinoma with Metastasis to the Liver: An Incidental Finding

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### Abstract

Squamous cell carcinoma of the gallbladder is a rare malignancy that represents 1-2% of gallbladder cancer diagnoses. Given its vague clinical manifestations, it is often diagnosed at an advanced stage. Treatment is challenging given the rarity and aggressiveness of this cancer and the lack of literature supporting treatment options. Surgical resection, if possible, is the primary first-line treatment in addition to chemotherapy both as adjuvant therapy and palliative care. This case report presents a 77 year-old African-American male with vague gastrointestinal complaints. Computed tomography revealed small bowel obstruction and lesions suspicious for malignancy in the gallbladder and liver. The patient was taken to the operating room for lysis of bowel adhesions and subsequent gallbladder and liver biopsies revealed squamous cell carcinoma of the gallbladder with metastasis to the liver. This case report shows that squamous cell carcinoma of the gallbladder could be considered for the differential of any biliary system pathology given that early intervention is critical for improving the prognosis.

### Introduction

Squamous cell carcinoma (SCC) is a very rare primary malignancy of the gallbladder and carries a poor prognosis. Ninety-eight percent of gallbladder cancer cases are adenocarcinoma and are locally invasive whereas the remaining 1-2% of gallbladder cancer cases have squamoid features. There are also two subtypes of squamous cell carcinoma of the gallbladder, namely, pure squamous cell carcinoma and adenosquamous carcinoma. The significance of this difference lies in the prognosis. Roa *et al.* (2011) demonstrated that adenosquamous carcinoma had a higher incidence and a worse prognosis than adenocarcinoma and that pure SCC had the worst prognosis due to its aggressive nature.<sup>1</sup> Metastasis is uncommon with pure SCC of the gallbladder. When metastasis does occur, it is often via direct extension, hematogenous spread, lymphatic metastasis, or portal tract spread.

SCC of the gallbladder is difficult to diagnose early due to its non-specific presentation. Demographically, it is more likely found in women, specifically in Caucasians.<sup>2</sup> Its incidence increases with age and it is often diagnosed at an advantaged stage. Diagnosis is often incidental as is with all cases of gallbladder cancer. Cases typically present similarly to cholecystitis and diagnosis is commonly made during cholecystectomy. First-line treatment consists of surgical resection of the gallbladder along with partial liver resection and possible removal of the biliary tract.<sup>3</sup> Chemotherapy and radiation often follow surgical treatment. Standard chemotherapy options would be gemcitabine with oxaliplatin, fluorouracil with leucovorin, and gemcitabine with cisplatin.<sup>4</sup> Given that SCC is more aggressive than adenocarcinoma, SCC carries a worse prognosis.

### **Case Report**

A 77 year-old African-American male presented to the emergency department complaining of abdominal pain that had persisted for one week associated with bilious vomiting and obstipation. He had been given lactulose by his primary care physician with no improvement in symptoms. The patient had denied weight loss or anorexia. He smoked cigarettes for 20 years but quit smoking 20 years ago and denied current alcohol use. He had no significant family history of cancer. His surgical history was significant for a previous appendectomy.

Upon physical examination, the patient exhibited no signs of jaundice. Palpation of the abdomen revealed it to be soft and non-distended with diffuse tenderness. Labs revealed total bilirubin of 0.6 mg/dL, alkaline phosphatase of 184 U/L, and albumin level of 2.6 g/dL.

Computed tomography (CT) scan of the abdomen revealed a high-grade small bowel obstruction as well as a liver lesion and gallbladder thickening. There was a 4.3 x 3.7 cm right hepatic dome lesion found in addition to a 3.1 x 2.9 cm lesion in the left hepatic lobe. Gallbladder wall thickening measuring 2.0 cm and retroperitoneal lymphadenopathy was also evident. The findings were indicative of gallbladder carcinoma with invasion of the adjacent hepatic parenchyma.

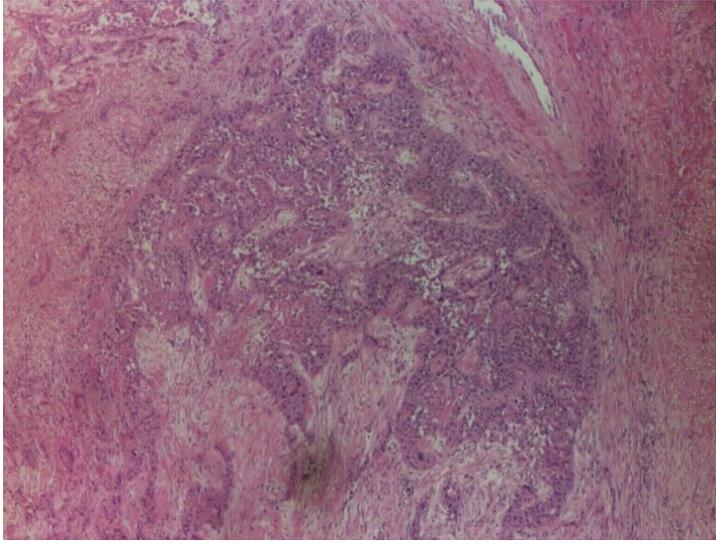
The patient was taken to the operating room for an exploratory laparotomy as management for small bowel obstruction. During the operation, the patient was found to have extensive adhesions of the small bowel to the anterior abdominal wall with a dense adhesion in the right lower abdomen – constituting a point of fixation.

Gross examination of the gallbladder revealed a large tumor on the fundus. Palpable adenopathy was observed in the portal area as well as the triangle of Calot. Visualization of the liver revealed obvious signs of metastasis in the dome of the liver as well as the area adjacent to the gallbladder. However, there was no evidence of distant metastasis in the lower abdomen. Two specimens from the liver and gallbladder were biopsied given the strong suspicion of malignancy.

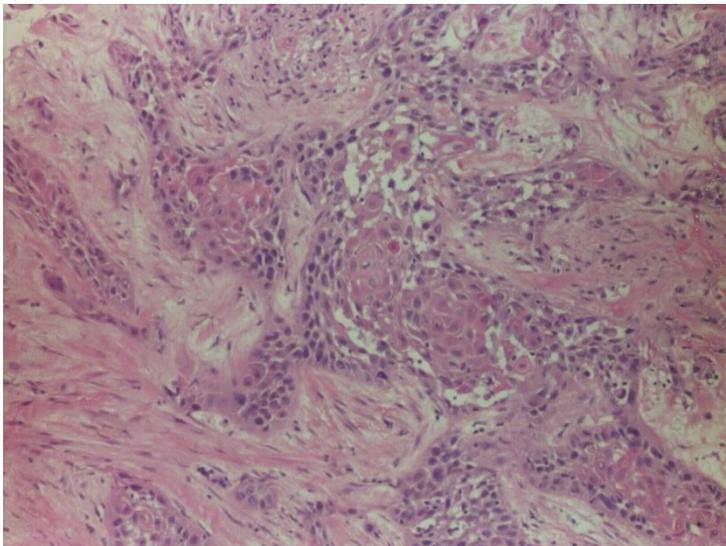
Frozen section of the liver revealed fibrocollagenous tissue with diffuse infiltration of dysplastic cells with glandular and squamoid features. Immunohistochemistry revealed the poorly

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differentiated cells to be positive for p63, CK 5/6, and CK19, which is consistent with a squamous cell phenotype. The malignancy was negative for TAG72, CA 19-9, CDX-2, CK20, PSA, PSAP, Hep Par1, and TTF-1 markers. CA 19-9 was less than 31.5 U/mL, alpha-fetoprotein (AFP) was 2.5 ng/mL, and antimitochondrial antibodies (AMA) were positive. Carcinoembryonic antigen (CEA) was within normal limits. The patient was referred for follow-up with oncology to be managed in a palliative setting.

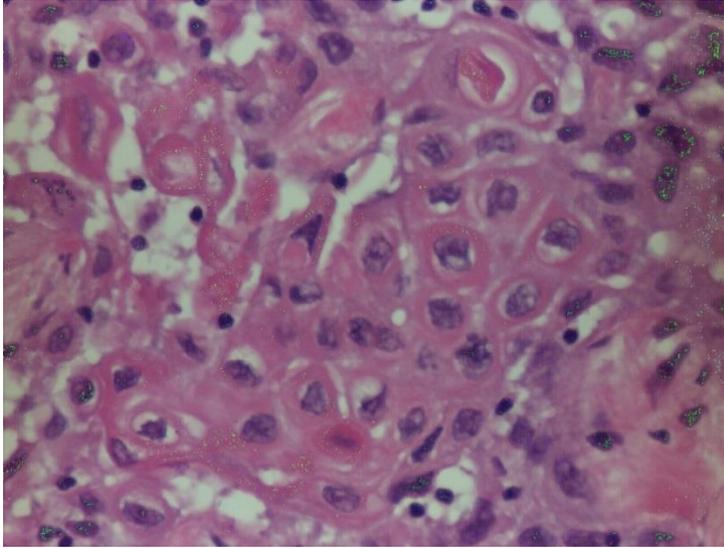


**Figure 1:** Liver biopsy – normal liver parenchyma is not identified.

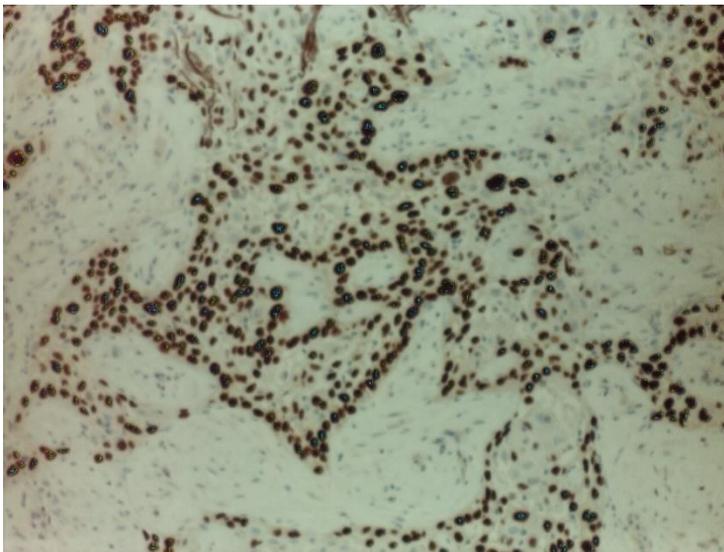


**Figure 2:** Squamous cell differentiation evident. Bile ducts also evident.

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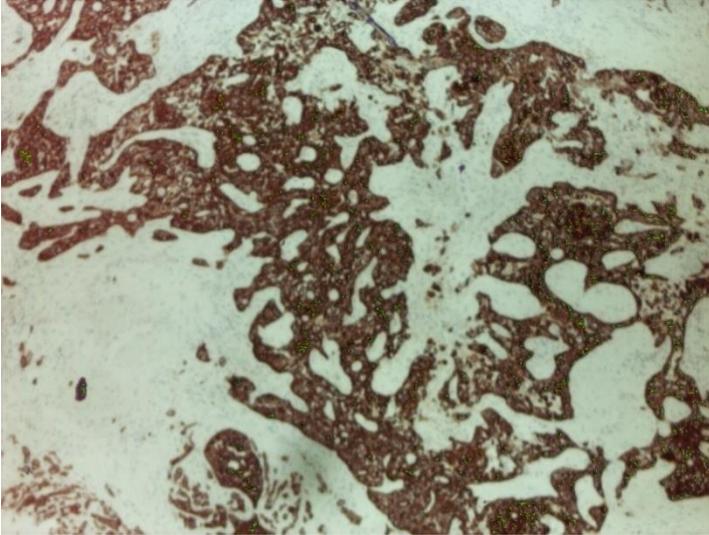


**Figure 3:** No evidence of glandular features.  
Intercalated discs visualized.

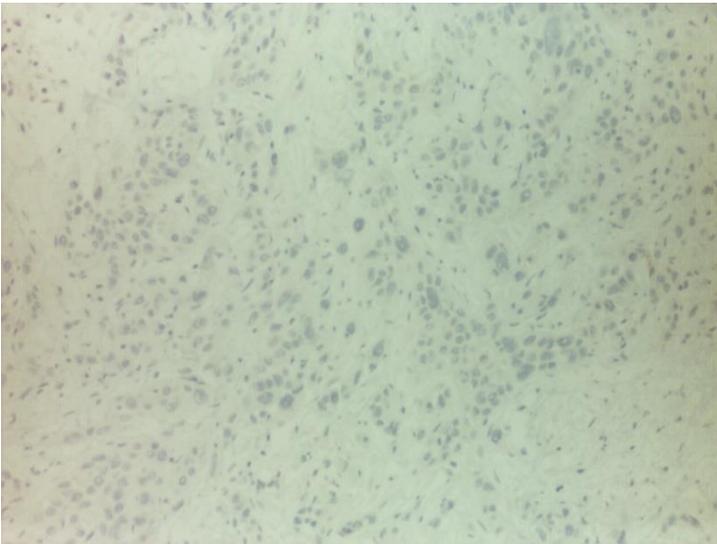


**Figure 4:** p63 IHC staining shows poorly differentiated squamous cell carcinoma.

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**Figure 5:** CK 5/6 IHC positive stain consistent with squamous cell immunophenotype



**Figure 6:** Positive MOC31 IHC stain confirms carcinoma and likely excludes hepatocellular primary origin

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## Discussion

In the study conducted by Roa *et al.*, of 606 invasive gallbladder carcinoma cases, 41 had identifiable squamous differentiation with the average patient aged 65 years old.<sup>1</sup> All except three had tumors in an advanced grade at the time of diagnosis. SCC of the gallbladder is believed to develop by two separate mechanisms: 1) malignant transformation of metaplastic squamous epithelium, or 2) squamoid metaplasia of an existing adenocarcinoma.

Clinically, SCC of the gallbladder carries vague clinical manifestations that often resembles that of cholecystitis. The patient discussed in our case report had no constitutional signs of malignancy such as unexplained weight loss. His initial presentation to a clinician may have simply suggested small bowel obstruction. This makes early diagnosis challenging given the lack of specific clinical manifestations. Treatment aims are either curative or palliative. Surgical resection is dependent on the presence of local invasion. Cholecystectomy is considered sufficient for early-stage disease whereas partial hepatic & biliary resection is advised in the presence of local invasion. Most patients are not good surgical candidates due to the presence of poor prognostic factors such as metastasis. Long-term prognosis is dependent on various factors such as peritoneal dissemination and metastasis. A repeat CT scan of the patient taken 3 months after resection revealed enlarging hepatic metastatic disease. The largest mass at the dome of the liver occupying segments 7 and 8 measured 7.4 x 5.6 cm, while it previously measured 4.1 x 3.6. There was an additional lesion within the left lobe of the liver and lower right lobe regional to the gallbladder fossa, both of which increased in size. Furthermore, new adrenal gland thickening and pulmonary nodules at the lung bases were noted, which were suspicious for metastatic disease.

In a retrospective review, R. Kanthin *et al.* demonstrated that while patients with adenosquamous/squamous cell carcinoma of the gallbladder had an overall worse prognosis than those with conventional adenosquamous gallbladder cancer, those patients achieved similar disease-free survival rates with R0 resection.<sup>5</sup> However, this result is not achievable if the SCC of the gallbladder is diagnosed at an advanced stage, rendering curative resection likely impossible.<sup>6</sup> If the patient is not an optimal surgical candidate, palliative chemotherapy is recommended; specifically with gemcitabine with oxaliplatin or fluorouracil with leucovorin.<sup>4</sup> In terms of length of survival, Roa *et al.* reported that these patients had a median survival of 5 months.<sup>1</sup> Anecdotally, there exist cases of survival beyond 5 years, particularly in the cases of early diagnosis.<sup>7</sup>

## Conclusion

SCC of the gallbladder is a particularly rare and aggressive form of gallbladder cancer. It presents with vague symptoms and is usually diagnosed post-operatively at an advanced stage, thus resection is often ineffective, and the prognosis is poor. Gallbladder malignancy, including SCC of the gallbladder, should be considered for the differential for biliary system pathology in an elderly patient with vague symptoms. Early diagnosis would improve the prognosis and patient outcome.

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## Acknowledgements

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## Author's Contributions

Khashayar Farzam & Victor Tin contributed equally to develop the case report.

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