Primary Squamous Cell Carcinoma of the Liver: Case Report and Review of Literature

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Abstract
Primary squamous cell carcinoma (SCC) of the liver is a rare cancer type. The overall survival of this cancer is short despite treatment and prognosis are poor. To our knowledge, there are around 30 cases of primary SCC of the liver described in the literature. Primary SCC of the liver is thought to be associated with a wide variety of hepatic conditions such as hepatic cyst, hepatolithiasis, or hepatic teratoma. We present the case of a 33-year-old male patient diagnosed with primary keratinizing SCC of liver associated with a hepatic cyst.

Introduction
Squamous cell carcinoma (SCC) usually arises from the malignant transformation of squamous cells in organs aligned with squamous epithelium such as skin, distal esophagus, urinary tract, lungs, cervix, and rectum [1]. In the liver, the overwhelming majority of SCCs are metastatic in nature from primary sites such as lung, thyroid, or gastrointestinal tract [1]. Primary SCC of the liver is an extremely rare entity with only 32 cases reported in the English literature from the 1970s till now [2].
Previous studies have shown an association between primary SCC of the liver and male sex [3], hepatic cysts, chronic cholecystitis, hepatolithiasis, or hepatic teratoma [1]. Pathogenesis is still yet to be elucidated, but one of the supported mechanisms includes chronic inflammation/irritation of the bile duct or congenital cysts, which promotes secondary squamous metaplasia and transformation [1]. Prognosis of this rare, aggressive cancer is very poor, as previous studies have shown an overall survival of less than 12 months [1].

Considering the extremely low prevalence of this cancer, we report the case of a primary keratinizing SCC of the liver associated with a hepatic cyst in a 33-year-old male patient presenting to the American University of Beirut Medical Center.

**Case Presentation**

We present the case of a 33-year-old male, occasional hubble-bubble smoker with no history of alcohol consumption, presented to our institution in July 2021 with fever, painless jaundice, and 15 kg unintentional weight in 2 months. Three months prior to presentation, the patient started experiencing jaundice and fatigue; he sought medical advice at another hospital where a CT scan of the abdomen showed a 6.2 × 6.3 cm cystic lesion in right liver at the porta hepatitis with another hypodense 10 × 9 cm lesion with irregular round cystic images and density of fluid (Fig. 1a). He underwent a laparoscopic cholecystectomy and percutaneous biliary drainage and common bile duct stent placement with relief of symptoms. A biopsy of the liver lesion was done and was initially reported as metastatic keratinized well-differentiated epidermoid carcinoma.

Upon presentation, physical examination revealed no specific findings. He did not have any palpable lymph nodes on the head, neck, and inguinal area. There were no suspicious skin

![Fig. 1.](image-url) **Fig. 1.** **a** A computed tomography scan of the abdomen revealing an 11.3 × 14.5 × 11.7 cm lobulated rim enhancing heterogeneous hepatic lesion with central necrosis and an air-fluid level and multiple pockets of gas. **b** Positron emission tomography CT scan showing large hepatic fluid collection and peripheral FDG uptake with mildly FDG avid small periportal lymph node and small epicardial lymph node. No other FDG avid disease is seen.
lesions. Breath sounds were clear, digital rectal examination was negative, and no perirectal mass or lesion was seen.

The patient reported continuous fever at home for which he received oral antibiotics but with no improvement. On presentation, the patient had elevated alkaline phosphatase (232 IU/L) and elevated gamma-glutamyl transferase (183 IU/L), and the rest of hepatic function panel was normal. C-reactive protein was elevated 238 mg/L. Complete blood count showed leukocytosis with neutrophilia (WBC 143,000/mm³, segmented neutrophils 70%), anemia (hemoglobin 9.7 g/dL), and thrombocytosis (platelets 6,140,003/mm³). Hepatitis viral markers were negative, and CA 19-9 and alpha-fetoprotein were within normal ranges. A CT scan of the abdomen and pelvis with IV contrast showed a large centrally necrotic heterogeneous mass with air fluid levels and pockets of gas, centered in the right hepatic lobe (occupying segments VIII, IV, and VII), in addition to a mild central, right, and left intrahepatic biliary ductal dilatation, most significant in the latter. The patient was started on IV antibiotics and underwent CT-guided drainage of the hepatic abscess, which subsequently grew *Citrobacter freundii*, *Enterobacter cloacae*, and *Enterococcus faecalis*.

Flexible fiberoptic laryngoscopy showed no evidence of primary head and neck malignancy. Rereading of the biopsy mentioned above showed keratotic dysplastic squamous epithelium. PET scan showed a large hepatic fluid collection with air fluid level/pockets of gas and peripheral FDG uptake, mildly FDG avid small periportal lymph node, and small epicardial lymph node, and no other FDG avid disease was seen (Fig. 1b).

Exploratory laparoscopy was done, which showed an exophytic mass originating from the liver; biopsy taken revealed the presence of keratinizing SCC; and immunohistochemical assay for PD-L1 expression (22C3 DAKO) was done, which showed that the CPS was <1, i.e., negative. Since no primary origin could be found in other suspected organs of the body despite extensive evaluation, the tumor was considered to be a primary SCC of the liver.

CT scan of the abdomen was repeated after completion of his antibiotic course and showed a mild interval increase in size in the large lobulated rim enhancing heterogeneous hepatic mass encroaching on the left portal vein and compressing/invading the left hepatic duct causing secondary mild-to-moderate left-sided intrahepatic biliary ductal dilatation.

Foundation studies were done, and biomarkers showed a stable microsatellite status and a tumor mutational burden – 8 Muts/Mband tumors. These factors would predict a poorer response to anti PD-1 immune checkpoint inhibitors, including approved therapies nivolumab and pembrolizumab compared to patients with microsatellite instability or high tumor mutational burden.

Genomic findings showed MYC amplification, which has been reported in SCCs in numerous studies, with incidences ranging widely from 26% of head and neck SCC to 100% of invasive laryngeal SCC cases, CASP8 R68*, DIS3 amplification, and PMS2 rearrangement all of which led to a defect in apoptosis, thus promoting cancer formation [4]. Other detected TP53 E286Q mutation has been observed in up to 95% of cutaneous SCC, 83% of esophageal SCC, 73% of head and neck SCC, 67% of lung SCC, and 8.3% of cervical SCC. Expression of p53 has been observed in HNSCC and has been correlated with a high recurrence rate [5].

Given the local invasiveness of the disease, surgical treatment was not an option. The patient was started on palliative chemotherapy with cisplatin and 5-FU with no checkpoint inhibitor since PDL-1 was negative.

**Discussion**

Primary SCC of the liver is an extremely rare entity with only 32 cases reported in the English literature from the 1970s till today [2]. The pathogenesis of the disease is still unknown; however, one proposed mechanism is that continuous irritation due to chronic inflammation...
of the biliary duct epithelium and/or congenital liver cysts can cause squamous metaplasia with malignant transformation. This is supported by the data that report the possible association of primary SCC with preexisting/concomitant diseases such as liver cysts and hepatolithiasis (majority of cases) [2]. Few cases also reported the possible association with hepatic teratoma [6]. Our patient was found to have keratinizing SCC of the liver after presenting with a large liver cyst on presentation.

Clinical presentation is usually nonspecific. The most common presentation is blunt abdominal pain/discomfort, jaundice, unintentional weight loss, and a palpable abdominal mass with tenderness of the right upper quadrant [1]. Our patient presented with fever and painless jaundice and a history of cholecystectomy 3 months prior to presentation as well as 15 kg weight loss in 2 months.

There is currently no specific serum marker for primary SCC of the liver unlike hepatocellular carcinoma [1]. Most patients present with elevated AST, ALT, and bilirubin as explained by the proposed chronic inflammation in bile ducts or liver cyst and invasion of the tumors [2]. However, patients can still present with normal liver enzymes [1]. In our case, the patient had normal AST and ALT with normal bilirubin and slightly elevated alkaline phosphatase and γ-GT. AFP and CA 19-9 levels were normal.

Regarding diagnosis, primary SCC remains a diagnosis of exclusion as metastatic SCC remains the most probable disease in the setting of the liver [7]. For this reason, it is necessary to exclude primary origins of the disease such as skin, head, and neck and lungs [2]. This was done in our case where PET CT scan and laryngoscopy did not show any primary origins for the patient’s SCC.

For imaging, CT is the most important imaging modality for preoperative investigation [2]. Findings in most cases include slightly low-density mass, and enhanced imaging showed uneven or mild enhancement or marginal enhancement during the arterial phase. There is also enhancement of the portal and delayed phases, and some patients also had intrahepatic bile duct stones, intrahepatic bile duct dilatation, and hepatic cysts [8]. Some patients show no clear liver mass by CT scan but only liver cyst or hepatolithiasis preoperatively, which complicates the diagnosis [2]. On CT, our patient showed a cystic lesion in the right liver at the porta hepatis another hypodense cystic lesion with irregular round cystic images and density of fluids.

Liver biopsy remains the confirmatory test for the diagnosis. Immune-histochemical staining done is usually positive for CK5/6, p63, and p40 as reported in previous studies [1]. Positive CK19 would confirm the bile ductular ontogeny of tumor cells and positive CK7, 8, 14, or 5/6 would indicate keratinized squamous epithelial origin [2]. Some tumors were reported to have PDL-1 positivity [1]. This is to be contrasted to hepatocellular carcinoma where IHC would show positivity for arginase 1 gpc3 hepatocytes and AFP and cholangiocellular carcinoma that is positive for CK19 and CK8 [1]. Our patient’s biopsy confirmed the diagnosis and IHC showed negative PDL-1 with strong and diffusely positive p16 immunostaining.

Foundation One CDx was done to identify any specific molecular alterations in the patient’s cancer, to match them with relevant targeted therapies, and also to test the microsatellite instability and tumor mutational burden to see how much the patient might benefit from immunotherapy [9], but it failed to demonstrate any clinical benefit in the setting of our patient.

There has not been an established treatment protocol for the disease, but data from previous cases showed a better prognosis for radical surgery as compared to palliative treatment with a median survival of 17 months versus 5 months [2]. Although most studies demonstrate the poor prognosis of this disease even after surgical resection, it remains the most recommended modality instead of drainage or partial resection [2]. To date, only 2 cases have been reported.
with remission of the disease: one with chemotherapy and surgery and the other with surgery alone [6, 10]. If surgery cannot be done or is not indicated, systemic intrahepatoarterial chemotherapy might be useful in patients with agents such as cisplatin and 5-FU [1]. In addition, transcatheter arterial chemoembolization and radiation can be offered as adjuvant for surgery or in inoperable patients [2]. In addition, it is also demonstrated that although the prognosis of the disease is poor overall, people presenting with liver cysts have a poorer prognosis than those with bile duct stones [2]. Surgical intervention was not an option in our case given the local invasiveness of the disease, and he was started on palliative chemotherapy using cisplatin and 5-FU.

**Conclusion**

In summary, primary liver SCC remains a very rare entity. Primary SCC of the liver is thought to be associated with a wide variety of hepatic conditions. Clinical presentation is usually nonspecific, and no specific serum marker is yet developed. There has not been an established treatment protocol for the disease; however, therapeutic options range from surgery to palliative care depending on the case.

**Statement of Ethics**

This is a case report involving one subject only, and according to the Institutional Review Board (IRB) at our institution, the need for approval was waived by the IRB at the American University of Beirut Medical Center (IRB-AUB). Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

**Conflict of Interest Statement**

The authors declare that they have no conflict of interest.

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**Author Contributions**

Conceptualization: Hazem Assi. Writing: Omar Fakhreddine, Yasser Fadlallah, Jawad Turfa, Mona Ali Hassan, and Nathalie Chamseddine. Review and editing: Omar Fakhreddine, Yasser Fadlallah, Jawad Turfa, Mona Ali Hassan, and Nathalie Chamseddine. Supervision: Hazem Assi.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.
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