Hepatocellular Carcinoma in Situs Inversus Totalis: A case report and literature review

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ABSTRACT

Introduction: Situs inversus Totalis (SIT) is a rare congenital condition that occurs in less than 1% of the population. Hepatocellular carcinoma of fibrolamellar type is a rare variant of hepatocellular carcinoma comprising less than 1% of all liver cancer. Case Report: We report a case of Hepatocellular Carcinoma (HCC) of fibrolamellar type with Situs Inversus Totalis (SIT) that was treated by hepatectomy. A 49-year-old female with diagnosis of SIT was found to have a heterogeneous mass on her “left” lobe of her liver (medial aspect). Tumor feature on MRI was consistent with HCC of the Fibrolamellar type. She underwent an ultimately successful “left” hepatectomy with resection of segment II, III, IV and partially I. Final pathology confirmed fibrolamellar HCC. Conclusion: FLHCC and SIT are both exceedingly rare. Surgical resection of FLHCC in our patient with SIT was technically challenging.

Keywords: Fibrolamellar, Hepatocellular carcinoma, Situs inversus totalis

INTRODUCTION

Situs inversus Totalis (SIT) is a rare congenital condition characterized by mirror-image orientation of visceral organs relative to midline in both thorax and abdomen [1]. It is estimated to occur in less than 0.1% of the population. These patients have inverted but proper anatomy compared to incomplete situs inversus in which one or a group of organs are displaced.

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide especially in East Asia. It is overwhelmingly related to chronic liver diseases, particularly hepatitis B and hepatitis C infection. Excessive alcohol consumption, hepto-toxins and non-alcoholic fatty liver diseases are also significant risk factors. Fibrolamellar Hepatocellular Carcinoma (FLHCC), a variant of HCC, is an extremely rare disease, comprising less than 1% of all primary liver cancers. Unlike HCC, it has no association with hepatitis B or C infections and there are no specific risk factors. In fact, this cancer usually occurs in patients with no parenchymal liver injury or cirrhosis. It is also more common in younger patients, with a median age of 27 years [2, 3].

We present a case report of patient with diagnosis of FLHCC in SIT, who underwent surgical resection.
She presented to the emergency room with vague left sided abdominal pain for several months, associated with poor appetite and weight loss. The pain was located in the LUQ radiating to left shoulder. Clinical examination revealed mildly tender LUQ with palpable epigastric mass. On CT scan (Figure 1 (A and B)), she found to have 9 x 10 x 9 cm heterogeneous mass in the “left” lobe of her liver (medial aspect). Subsequent hepatic protocol MRI with Eovist (Figure 2 (A and B)) showed a well-circumscribed tumor involving predominantly Couinaud segment II and III but extending to segments I and IV. It was likely causing “left” portal vein occlusion. Mass features on MRI were consistent with HCC of the Fibrolamellar type. The mass demonstrated centripetal T2 hyperintensity and central prominent vascularity and hypointense signal, consistent with scar. The lesion also demonstrated heterogeneous peripheral enhancement with delayed central enhancement. Delayed imaging demonstrated washout with markedly diminished localization of Eovist as compared to the remaining liver parenchyma.

Laboratories were notable for a normal Alpha-fetoprotein (AFP 1.8 ng/ml) and a negative viral panel for hepatitis. Other notable laboratory values include Total Bilirubin (1.2 mg/dL), INR (1.0), AST (45 units/L), ALT (22 units/L), Alkaline Phosphatase (171 units/L), Albumin (4.1 g/dL), Platelet count (196 x 10^9/mL). The overall clinical picture was consistent with hepatocellular cancer (HCC) without evidence of metastatic disease. The remainder of the liver appeared healthy and there were no other imaging findings for chronic liver disease or portal hypertension.

The patient was a good operative candidate and she was offered surgical resection. She underwent “left” hepatectomy with resection of segment II, III, IV, and caudate lobe. A left subcostal incision with midline extension was used for exposure. There were no signs of carcinomatosis. The patient was also found to have a replaced “right” hepatic artery coming off the Superior Mesenteric Artery (SMA). This was first diagnosed on CT imaging and later confirmed intra-operatively. The transection plane was demonstrated following liver demarcation after extrhepatic “left” hepatic artery and portal vein ligation. A combination of crush and clip technique as well as harmonic scalpel was used to divide the parenchyma along this plane with ultrasound and palpation added to help maintain at least a 1 cm gross margin around the tumor. During the procedure, a liver-hanging maneuver was also utilized to help define the principle plane and facilitate transection. Low central venous pressure (CVP) anesthesia and the Pringle maneuver was also used intermittently during parenchymal transection. After transection of the liver parenchyma, the middle and left hepatic veins were subsequently identified and divided extrhepatically with suture repair. The tumor was found to abut the inferior vena cava as well as a portion of the right hepatic vein, but no gross tumor was left behind. Lastly, a saline bile duct exploration was performed via a cholangiogram catheter and additional bile leaks were individually repaired. Operating time was 6 hours and 45 minutes. Operative blood loss was 1200 ml. It was a technically challenging but ultimately considered successful major liver resection.

The patient was discharged on post-operative day 7 after an unremarkable post-operative course. Final pathology confirmed fibrolamellar HCC. It was moderately differentiated with micro-vascular invasion with tumor abutting the vena cava. Fibrosis score was: F0. Tumor was confined to the liver; however, the parenchymal margin was focally involved with invasive carcinoma and thus considered a R1 resection. Two sampled portal lymph nodes (2/2) were identified to contain metastatic tumor. The tumor was pathologically staged as T3aN1Mx (stage IVA).

Following in patient discharge, the patient underwent adjuvant chemotherapy with Sorafenib. However, she was re-admitted to the hospital six months after her initial surgery for obstructive jaundice. She was found to have complete obstruction of her distal bile duct draining the “right” liver with an accumulation of biloma. Multiple attempts of ERCP (Endoscopic retrograde cholangiopancreatography) and PTC (percutaneous transephatic cholangiography) were unsuccessful. Ultimately, the decision was made for surgical exploration. During the exploration, the sectoral bile ducts draining the anterior right liver seemed to be sclerosed from chronic inflammation. After proper identification of anatomy with cholangiogram, a end-to-side Roux-en-Y hepaticojejunostomy was fashioned to proximal healthy bile duct. No obvious malignancy was appreciated during surgery. The procedure resolved her biliary obstruction and she was successfully discharged. Three months follow up imaging MRI showed no evidence of biliary obstruction and no evidence of recurrent disease.
One year after hepatectomy, the patient presented to the hospital for symptomatic anemia and development of a painful soft tissue lesion in the right shoulder. During workup, she was found to have a stomach lesion at the cardia and endoscopy biopsy was consistent with metastatic HCC. The soft tissue lesion in the right shoulder was percutaneously biopsied with pathology also consistent with metastatic HCC. Imaging also demonstrated new enlarged right axillary and retroperitoneal lymph nodes. Due to the constellation of findings consistent of advanced disease, she was offered palliative chemo-radiation therapy with a poor prognosis. Unfortunately, she was lost to follow up shortly after this, and presumably, she had returned to her home country.

**DISCUSSION**

Situs inversus Totalis (SIT) is a rare congenital condition and the exact cause is unknown. It is theorized to be associated with in-utero insult due to the frequent association between Situs Inversus (SI) and other congenital defects. Animal and familial genetic studies have indicated a possibility of autosomal or X-linked recessive mode of inheritance. It is possible that the both mechanisms contribute to the development of this condition. Several rare congenital malformations have been associated with SI, including polysplenia syndrome, asplenia or Ivemark’s syndrome, and Kartagener syndrome. Congenital heart disease is found in up to 60% of these patients. Vascular anomalies such as interrupted IVC and preduodenal portal vein have been reported as well. Aberrant hepatic arterial anatomy also has a higher frequency in these patients. These complex congenital and developmental abnormalities greatly increase the complexity and difficulty of surgical procedures.

Fibrolamellar Hepatocellular Carcinoma (FLHCC), a variant of HCC, is an extremely rare disease, comprising less than 1% of all primary liver cancers. Unlike HCC, it has no association with hepatitis B or C infections and there are no specific risk factors. These tumors secrete characteristic hormones such as neurotensin and characteristic proteins such as vitamin B12 binding protein. Thus, fibrolamellar tumors may be the primary neuroendocrine tumors of the liver. In fact, they behave like neuroendocrine tumors in that they are well circumscribed and most often separated from adjacent blood vessels. Therefore, they are more likely to be resectable than classic HCC. In addition, they are slow growing, and complete cytoreduction for multifocal disease can result in long-term survival. Surgical resection results in a 5-year survival rate of 30–50% [4, 5].

Fibrolamellar HCC demonstrates nodal metastasis in 30% to 70% of cases on presentation, which is higher than HCC. Thus, the lymph nodes in the porta hepatis, celiac region, and peripancreatic areas should be examined and, if suspected, either sampled or resected [5].

**Hepatic resection**

Although liver resection has become safer with recent advancement in surgical techniques and devices, total situs inversus poses a different dimension of challenges for the surgeons. The patient presented in the case report was also identified to have a replaced right hepatic artery off the SMA on pre-operative imaging. Intra-operative ultrasound was performed in the case and it was helpful to identify relevant anatomy. One author has proposed using inverse mode (left/right) on the ultrasound to make anatomy easier to understand [6]. A liver-hanging maneuver was utilized to create a channel between liver parenchyma and IVC with retraction provided by an umbilical tape. This technique facilitates an anterior approach of parenchymal transection [7], that is particularly useful for bulky tumors that limit rotation of the liver about the caval axis.

**Situs inversus totalis in liver transplantation**

Situs inversus was formerly considered a contraindication for Orthotopic Liver transplant (OLT) due to the technical difficulty. Situs inversus was also frequently associated with vascular and visceral abnormalities. Recently, however, several successful transplantations have been reported in children, especially in cases of situs inversus with biliary atresia using modified surgical techniques [8–13].

**Hepatocellular carcinoma in SIT from literature review**

HCC in patients with congenital SIT are rare. In the literature, there are only a few reported cases. In 2012, Patel. R [14] published a review of 13 such cases (12 previously published case reports or letters to editor in additional to his own case report). These cases include 10 published in Japan, one published in Taiwan, one published in China and one published in Indian, which was the author’s own case report. Additional literature search was expanded, however, there are no other reported cases until the current one. It is also the first reported case outside Asia. Finally, it is the first such case with a diagnosis of FLHCC, compounding the uniqueness of this patient.

She was beyond transplant criteria and otherwise an appropriate candidate for resection. Regional techniques such as chemo or radio-embolization may have provided benefit if she had not been thought operable. She did have a microscopic positive margin, which is a technical risk of the surgery especially with large tumor and aberrant anatomy. It is unclear whether preoperative embolization would have afforded some tumor shrinkage that would have made the operation technically easier. The patient did have nodal metastases and unfortunately developed relatively early recurrence. The summary of fourteen cases of HCC with SIT is described in Table 1 [15–20].
CONCLUSION

FLHCC and SIT are both exceedingly rare. Surgical resection of FLHCC in our patient with SIT was technically challenging. Despite initial success, the patient suffered from disease recurrence and metastasis.

REFERENCES

13. Patel RB, Gupta NR, Vasava NC, Khambholja JR, Chauhan S, Desai A. Situs inversus totalis (SIT)

Table 1: Summary of 14 cases of Hepatocellular Carcinoma (HCC) with Situs Inversus Totalis (SIT)

<table>
<thead>
<tr>
<th>Case</th>
<th>Year</th>
<th>Author</th>
<th>Country</th>
<th>Age/sex</th>
<th>Tumor location</th>
<th>Size (cm)</th>
<th>AFP</th>
<th>Viral markers</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1983</td>
<td>Kanematsu [15]</td>
<td>Japan</td>
<td>37/M</td>
<td>R lobe</td>
<td>Multi-focal</td>
<td>1400000</td>
<td>HbsAg+</td>
<td>R lobectomy</td>
</tr>
<tr>
<td>2</td>
<td>1983</td>
<td>Wada [16]</td>
<td>Japan</td>
<td>85/M</td>
<td>L lobe</td>
<td>10x8x7</td>
<td>200</td>
<td>-</td>
<td>Autopsy finding</td>
</tr>
<tr>
<td>3</td>
<td>1989</td>
<td>Kim [17]</td>
<td>Japan</td>
<td>66/F</td>
<td>R lobe</td>
<td>14x12</td>
<td>4000</td>
<td>HbsAg+</td>
<td>R lobectomy</td>
</tr>
<tr>
<td>4</td>
<td>1990</td>
<td>Kanchira</td>
<td>Japan</td>
<td>59/M</td>
<td>Seg. VIII</td>
<td>3</td>
<td>2388</td>
<td>Neg</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>1996</td>
<td>Kamiike [1]</td>
<td>Japan</td>
<td>69/F</td>
<td>Seg VII</td>
<td>3x2</td>
<td>291</td>
<td>-</td>
<td>Segmental resection</td>
</tr>
<tr>
<td>6</td>
<td>1996</td>
<td>Iwakura</td>
<td>Japan</td>
<td>63/F</td>
<td>Seg VI</td>
<td>1.5x1.3</td>
<td>N</td>
<td>HCV+</td>
<td>Segmental resection</td>
</tr>
<tr>
<td>7</td>
<td>1999</td>
<td>Seshimo</td>
<td>Japan</td>
<td>70/M</td>
<td>Seg II</td>
<td>2.3x2.3</td>
<td>160</td>
<td>HCV+</td>
<td>Segmental resection</td>
</tr>
<tr>
<td>8</td>
<td>2003</td>
<td>Cheng</td>
<td>Taiwan</td>
<td>43/M</td>
<td>Seg II, III, IV</td>
<td>10x9x7</td>
<td>27910</td>
<td>HbsAg+, HCV+</td>
<td>L lobectomy</td>
</tr>
<tr>
<td>9</td>
<td>2004</td>
<td>Kakinuma [18]</td>
<td>Japan</td>
<td>70/F</td>
<td>Seg. V, VI, VIII</td>
<td>2.5x2</td>
<td>N</td>
<td>HCV+</td>
<td>Segmental resection</td>
</tr>
<tr>
<td>10</td>
<td>2004</td>
<td>Niki [19]</td>
<td>Japan</td>
<td>66/M</td>
<td>Seg. II, V</td>
<td>3</td>
<td>N</td>
<td>Neg</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>2006</td>
<td>Swada</td>
<td>Japan</td>
<td>76/M</td>
<td>R lobe</td>
<td>T2</td>
<td>803</td>
<td>Neg</td>
<td>Segmental resection</td>
</tr>
<tr>
<td>12</td>
<td>2007</td>
<td>Li [20]</td>
<td>China</td>
<td>53/M</td>
<td>R lobe</td>
<td>10cm</td>
<td>49</td>
<td>Neg</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>2011</td>
<td>Patel [14]</td>
<td>India</td>
<td>49/F</td>
<td>Seg. VII, VIII</td>
<td>12x11x10</td>
<td>N</td>
<td>Neg</td>
<td>R lobectomy</td>
</tr>
<tr>
<td>14</td>
<td>2013</td>
<td>Present</td>
<td>USA</td>
<td>49/F</td>
<td>L lobe</td>
<td>9x10x9</td>
<td>N</td>
<td>Neg</td>
<td>L lobectomy</td>
</tr>
</tbody>
</table>

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Author Contributions
Kai Zhao – Substantial contribution to concept and design, Acquisition of data, Analysis and interpretation of data, Drafting of article, Revision of intellectual content, Final approval of version to be published

Philip Bao – Substantial contribution to concept and design, acquisition of data, Analysis and interpretation of data, Drafting of article, Revision of intellectual content, Final approval of version to be published

Guarantor of Submission
The corresponding author is the guarantor of submission.

Source of Support
None.

Consent Statement
Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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