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Case Report

Incidental detection of intrahepatic cholangiocarcinoma in an explant liver: An unforeseen encounter

Soundarya Ravi[1], **Srinivas Bheemanathi Hanuman**[1]*, **Biju Pottakkat**[2]

[1]*Dept. of Pathology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India*
[2]*Dept. of Surgical Gastroenterology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India*

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ABSTRACT

Incidental intrahepatic cholangiocarcinoma (i-ICCA) is an uncommonly encountered malignancy in an explant liver. The presence of i-ICCA in an explant liver indicates poor prognosis and high chances of recurrence. Therefore, histopathological diagnosis of i-ICCA in an explant liver specimen is crucial for the patient. In this case report, we present a case of i-ICCA diagnosed in an explant liver showing features of alcoholic cirrhosis with a brief discussion on its salient features and relevant differential diagnoses.

1. Introduction

Intrahepatic cholangiocarcinoma (ICCA) is a type of primary liver malignancy arising from the biliary tract. ICCA is the second most common epithelial malignancy of liver after hepatocellular carcinoma (HCC).[1–3] Patients with HCC satisfying Milan criteria are generally taken up for liver transplant (LT). On the contrary, LT is contraindicated for ICCA patients due to poor outcome and high recurrence rates.[4] In spite of aggressive pretransplant workup, a very few cases of incidental ICCA (i-ICCA) have been detected in explant specimens. Therefore, precise diagnosis of i-ICCA in an explant liver by ruling out its differential diagnoses is of paramount importance due to vast differences in post-transplant management and prognosis. Herein we report a case of i-ICCA diagnosed in an explant liver in a patient with alcoholic cirrhosis.

2. Case Report

A 47 year old male presented with complaints of bilateral lower limb swelling and abdominal distention for one month along with 4 to 5 episodes of non-projectile vomiting. He did not have fever, hematemesis, haematochezia, chest pain, bony pain or breathlessness. He was an alcoholic for the past 30 years, reformed in the past 2 years and a known diabetic on treatment for 3 years. On examination he was moderately built with mild icterus and bilateral pitting pedal oedema. He also had abdominal distention due to moderate ascites and mild splenomegaly.

Laboratory tests of the patient are shown in Table 1. Viral markers like HIV, Hepatitis B Virus and Hepatitis C Virus were non-reactive. Hemogram of the patient revealed anemia and thrombocytopenia. Upper GI endoscopy revealed Grade 1 esophagal varices and mild portal hypertensive gastropathy.

Contrast enhanced computed tomography (CECT) of abdomen showed an ill-defined, arterially non-enhancing lesion measuring 3.5 cm in maximum dimension with an enhancing capsule located in segment 5 of liver. The background liver was grossly shrunken with atrophy-

* *Corresponding author*.
E-mail address: srinivas.bh08@gmail.com (S. B. Hanuman).

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Table 1: Laboratory tests of the patient with biological reference interval

S.No	Test Name	Test results	Biological reference interval
1	Total bilirubin	3.81 mg/dL	0.3 - 1.2 mg/dL
2	Direct bilirubin	1.63 mg/dL	0.03 - 0.18 mg/dL
3	Alanine transaminase (ALT)	85 U/L	0 - 50 IU/L
4	Aspartate transaminase (AST)	38 U/L	0 - 50 IU/L
5	Gamma glutamyl transferase (GGT)	186 U/L	0 - 30 IU/L
6	Alkaline phosphatase (ALP)	163 U/L	30 - 120 IU/L
7	Albumin	2.77 g/dL	3.4 - 4.8 g/dL
8	Hemoglobin	9.5 g/dL	14 – 18 g/dL
9	Platelet count	40 x 10^9 /L	150 – 450 x 10^9/L

hypertrophy complex. Intrahepatic biliary radicle dilation (IHBRD) was not noted. CECT Abdomen findings suggested a possibility of HCC arising in a background of chronic liver disease. Based on the history, clinical examination and radiological findings, the working diagnosis made by the clinicians was alcohol related chronic liver disease (Child Pugh C) with suspicion of HCC. As this lesion fulfilled Milan criteria, the patient underwent orthotopic living donor liver transplantation of the right liver.

We received the explant liver for further histopathological examination. Grossly the explant liver appeared shrunken with weight of 945 grams. Capsular surface of the liver as well as the cut surface showed numerous micro and macro-nodules of size ranging from 2 to 5 mm. In addition, the right lobe of the liver showed a nodule of diameter 2 cm just beneath the capsule. On cut surface, this nodule measured 4 cm in maximum dimension and appeared ill-defined, solid and grey-white to brown in colour with focal greenish friable areas. (Figure 1 a) The structures at the porta hepatis appeared unremarkable. No lymph nodes were submitted with the specimen.

Microscopic examination of the nodule revealed a tumour composed of tumour cells arranged predominantly as solid sheets, single infiltrating cells and focal glandular pattern surrounded by dense desmoplastic stroma. (Figure 1 b) These tumour cells exhibit moderate to marked nuclear atypia at places with central large ovoid vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm. Brisk mitotic activity was noted in the tumour. Large areas showed coagulative tumour necrosis. Focal areas showed bile pigment in the lumen of these malignant glands. (Figure 1 c) However, these cells did not show any eosinophilic globules or bile pigments. This tumour infiltrates into the hepatic parenchyma but does not infiltrate the visceral peritoneum. Lympho-vascular and perineural invasion was not seen.

Background liver showed architectural distortion. Hepatic parenchyma was divided into multiple varying sized complete nodules surrounded by dense bands of fibrosis. (Figure 1 d) The hepatocytes in these nodules exhibited regenerative nuclear atypia, intrahepatic cholestasis with patchy lobular neutrophilic infiltrates. There was porto-portal approximation with marked fibrosis and moderate lympho-plasmacytic infiltrate which was extending into the fibrous bands. Bile ductular proliferation was seen along these fibrous bands. Masson trichrome stain highlighted the fibrous bands separating the nodules. (Figure 2 a)

On immunohistochemistry (IHC), the tumour cells were positive for CK7 and CK19 and negative for HepPar1, Glypican-3, Arginase and CK20. (Figure 2 b, c and d) Based on gross findings, histomorphology and immunohistochemistry, a final diagnosis of incidental intrahepatic cholangiocarcinoma was made with background liver showing features of micro and macronodular cirrhosis secondary to alcohol related chronic liver disease. Following transplant, the patient's general condition improved with good recovery.

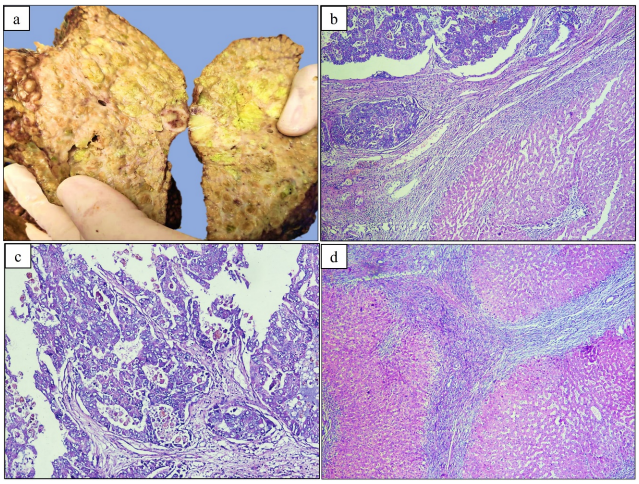

Figure 1: a): Cut surface of the liver explant specimen shows an ill-defined, solid, grey-white tumour with focal greenish friable areas. Adjacent liver shows micro and macro-nodules; **b)**: Microscopy shows tumour arranged in glandular pattern separated from adjacent liver by fibrous stroma. (100x; H&E); **c):** High power view of the tumour with intra-luminal bile pigment. (400x; H&E); **d):** Adjacent liver shows mixed micro and macro-nodular cirrhosis. (100x; H&E)

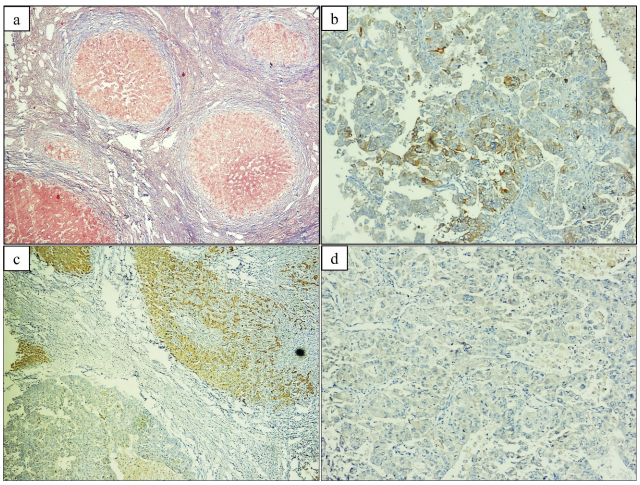

Figure 2: a): Bands of fibrosis are highlighted by Masson Trichrome stain. (100x; MT); **b):** Tumour cells express cytoplasmic positivity for CK7 and CK19 immunostains. (400x; IHC) **c)**: Tumour cells are negative for HepPar1 (Hepatocytes - internal control is positive) (100x; IHC) **d)**: Tumour cells are negative for CK20 (400x; IHC)

3. Discussion

"Incidental" intrahepatic cholangiocarcinoma (i-ICCA) is defined as detection of occult ICCA in patients undergoing LT for other indications. Despite the availability of state-of-the-art imaging modalities, incidental tumours are detected following transplant in explant specimens. The most common tumour to be detected incidentally in liver explants is HCC. The incidence of i-ICCA is quite rare and comprises only 0.7% of the liver explants.[5,6] Generally, biliary diseases affecting bile ducts such as primary sclerosing cholangitis (PSC) are important risk factors in development of cholangiocarcinoma (CCA).[1] However recent literature cites that even other non-biliary parenchymal liver diseases such as alcoholic liver disease can contribute to the development of ICCA as seen in our case.[7]

As per current protocols, LT is indicated only for perihilar CCA and not for ICCA. Surgical resection remains the mainstay of treatment for ICCA. Pretransplant detection of ICCA is in fact considered as a contraindication for LT. Many studies have revealed that the presence of incidentally detected ICCA in an explant liver had poor prognostic impact and tend to have high chances of recurrence.[8–10] Hence, it is important to diagnose ICCA in explant liver and differentiate it from its histological mimickers.

The close histopathological mimic of ICCA to be ruled out is intrahepatic metastasis from adenocarcinomas of pancreas and upper gastrointestinal tract. But the morphological and immunohistochemical characteristics (positivity for CK7 and CK19) are similar to that of ICCA and therefore poses diagnostic difficulty.[2] However, liver metastasis most often presents as multifocal lesions as opposed to our case where there was a solitary lesion. Furthermore, the occurrence of metastasis in a cirrhotic liver is quite rare.

As HCC is the most common malignancy that can arise in a background of cirrhosis, the possibility of HCC has to be ruled out in an explant liver.[11] It is worthwhile to remember that both HCC and ICCA possess similar risk factors and can arise in a background of non-biliary chronic liver disease.[1] In addition, ICCA can also be misdiagnosed as HCC on radiology in a small proportion of cases, when there is lack of typical radiological features as demonstrated in our case.[3] But the management and prognostic aspects vary between HCC and ICCA. In our case, the tumour had predominantly solid pattern with moderate to marked nuclear atypia and prominent nucleoli, which can be observed in moderately to poorly differentiated HCC as well. However, the presence of dense desmoplastic stroma surrounding the tumour and negativity for hepatocyte immunohistochemical markers (HepPar1, Glypican-3 and Arginase) and expression of CK7 and CK19 aided us in excluding the possibility of HCC.

Combined hepatocellular carcinoma – cholangiocarcinoma (cHCC-CC) is a very rare primary liver malignancy which can closely resemble ICCA both radiologically as well as morphologically.[2] This tumour contains areas of typical HCC and CCA which can be deeply intermingled or can be seen in separate areas of the same tumour. Diagnosis of cHCC-CC can be made based on histomorphological identification of both the components which should be confirmed by performing IHC markers of hepatocytic and cholangiocytic lineage highlighting the respective components.

Histopathological diagnosis of incidental tumour in an explant liver specimen is vital as such patients require long term follow up to look for recurrence. The occurrence of i-ICCA in a background of alcoholic cirrhosis radiologically mimicking HCC and the presence of solid pattern of the tumour with moderate degree of differentiation created diagnostic conundrum in our case. However, with the help of certain morphological soft pointers and judicious use of panel of lineage specific immunohistochemical markers, a precise diagnosis can be rendered.

4. Conclusion

Our case report focuses on the importance of identification of i-ICCA in an explant liver specimen. Explant liver specimens should be diligently sampled and submitted for histopathological examination to exclude the possibility of incidental tumours. Accurate diagnosis can be rendered by good histopathological approach and wise use of immunohistochemistry.

5. Source of Funding

None.

6. Conflict of Interest

None.

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Author biography

Soundarya Ravi, Senior Resident https://orcid.org/0000-0002-9370-5063

Srinivas Bheemanathi Hanuman, Professor https://orcid.org/0000-0002-9619-6719

Biju Pottakkat, Professor

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