



Primary Hepatic Neuroendocrine Tumor with Hepatocellular Carcinoma: A Rare Case Report

Basant Mahadevappa^{a++}, Rohith Muddasetty^{a#*}
and Vinu Sankar^{at}

^a HCG Hospital, KR Road, Bangalore-560027, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/95153>

Case Study

Received: 20/10/2022

Accepted: 27/12/2022

Published: 29/12/2022

ABSTRACT

Aim: Hepatocellular carcinoma is the most common primary liver malignancy followed by intrahepatic cholangiocarcinoma. The diagnosis of primary hepatic neuroendocrine tumor, a rare liver lesion, generally occurs during histological examination.

Case Report: A 48 year old male patient presented with a lesion in the segment 5/6 of liver clinically and imaging features suggestive of Hepatocellular carcinoma. He underwent resection of the lesion. Final histopathological analysis of the lesion showed combined Hepatocellular carcinoma and neuroendocrine tumor. DOTANAC scan was done postoperatively which confirmed primary hepatic neuroendocrine tumor by ruling out primary neuroendocrine tumor elsewhere. He is currently on adjuvant chemotherapy.

Discussion and Conclusion: Primary hepatic neuroendocrine tumor is a rare malignancy. It is mandatory to search for primary neuroendocrine tumors in rest of the gastrointestinal system

⁺⁺ Fellowship Consultant in HPB Surgery and Liver Transplantation;

[#] Junior Consultant in HPB Surgery and Liver Transplantation;

[†] Fellow in HPB Surgery and Liver Transplantation;

*Corresponding author: E-mail: rohith.m.setty@gmail.com;

before making the diagnosis. Combined Hepatocellular carcinoma and primary hepatic neuroendocrine tumor is a rare tumor which needs multidisciplinary team discussion to formulate treatment plan.

Keywords: Hepatocellular carcinoma; hepatic neuroendocrine tumor; Ki 67; Hep Par; CD 56; synaptophysin, Arginase.

1. INTRODUCTION

Primary hepatic neuroendocrine tumor (PHNET) is a rare tumor. It occurs in about 0.3% of all neuroendocrine tumors [1]. These tumors arise from neuroendocrine cells capable of producing functional peptides. Majority of these tumors occur in small bowel constituting about 44.7% of all the lesions [2]. PHNET must be histologically confirmed to be NETs for the diagnosis. Imaging studies are not specific for PHNET; most of them mimic hepatocellular carcinoma (HCC) or cholangiocarcinoma [3]. The definitive diagnosis is frequently made once the tumor has been removed and after confirming that there are no primary lesions elsewhere. Being a rare lesion, staging and treatment guidelines have not been formulated. However, surgical resection plays a crucial role [3]. Here we present a case of combined HCC and PHNET because of its rarity.

2. CASE PRESENTATION

A 48 year old male presented to us with a history of vague upper abdomen pain and loss of appetite for duration of 1 month. He was recently diagnosed to be a diabetic when evaluated as a part of routine health check. He was evaluated with ultrasound abdomen which showed a fatty liver with an irregular mixed echoic lesion in the right lobe of liver. We have evaluated him with routine blood investigations and imaging studies. His complete blood picture, renal and liver function tests were within normal limits. His tumor markers showed elevated Alfa fetoprotein (AFP) of 196ng/ml, Carcinoembryogenic antigen (CEA) and Carbohydrate antigen 19-9 (CA19-9) were within normal limits. Hepatitis viral markers were negative. Contrast enhanced CT of abdomen was suggestive of 10.7 x 6.1 cm partly exophytic mass lesion in segment 5/6 of liver with contrast enhancement features suggestive of hepatocellular carcinoma. There were multiple enlarged lymph nodes in the periportal area largest measuring 1.9*2.1cm. PET scan showed

an SUV of 4.0 in the liver lesion and 3.3 in the lymph nodes. Figs. 1 and 2 showing the pictures of CT abdomen and PET scan.

With a working diagnosis of hepatocellular carcinoma, we planned for diagnostic laparoscopy followed by resection of the tumor. On diagnostic laparoscopy, we found liver was non cirrhotic, no evidence of ascites or peritoneal metastasis. Large irregular mass arising from liver segment 5/6 was noted. We proceeded with laparotomy; greater omentum adherent to the liver mass was released. Lymph nodes in the periportal area were dissected. Fundus down cholecystectomy performed after ligating the cystic artery and duct. The lesion was resected with a 5cm margin from the tumor. Postoperative period was uneventful; patient was discharged on post-operative day 5. Figs. 3, 4 showing intraoperative picture and specimen images.

Histopathological examination of the lesion showed features suggestive of both hepatocellular carcinoma and large cell neuroendocrine carcinoma. The large lymph nodal mass also contained cells of large cell neuroendocrine cell carcinoma. Immunohistochemistry (IHC) markers were done to confirm the diagnosis using clone technique. Liver lesion contained 80% of the tissue suggestive of HCC which were positive for HepPar and Arginase; 20% of the tissue with large round cells positive for Synaptophysin and CD 56 suggestive of large cell NET. Tissue from lymph node was positive for Synaptophysin and CD 56. Figs. 5, 6 showing microscopic picture of the lesion and IHC.

Postoperatively, patient underwent DOTONAC scan which ruled out any other primary NET lesions (Fig. 7), confirming PHNET. He was started on adjuvant chemotherapy. Six months following resection, patient is under regular follow up with imaging studies and has not developed any recurrence or new lesions.



Fig. 1. CT abdomen pictures showing the lesion, Red arrow marking lymph nodes and blue arrow marking the liver lesion

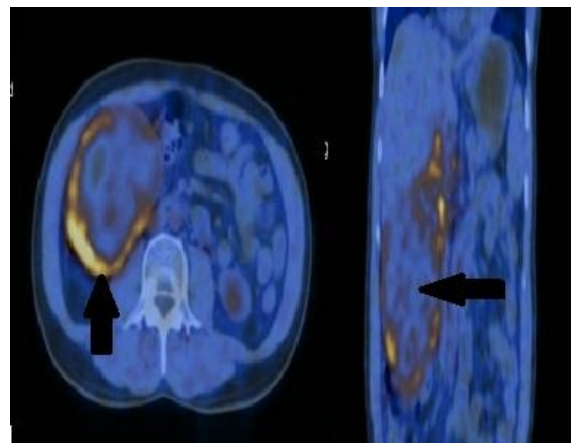


Fig. 2. PET scan images, Arrow showing the lesion in segment 5, 6 of liver with PET uptake

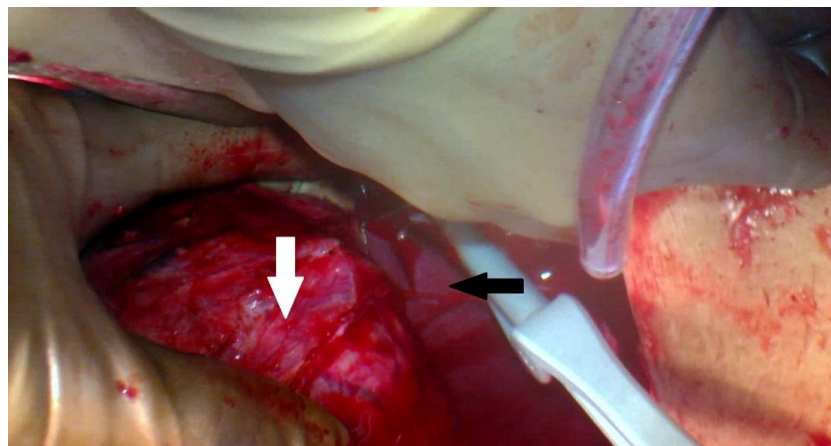


Fig. 3. Picture showing liver lesion, Black arrow- Liver surface, White arrow-lesion

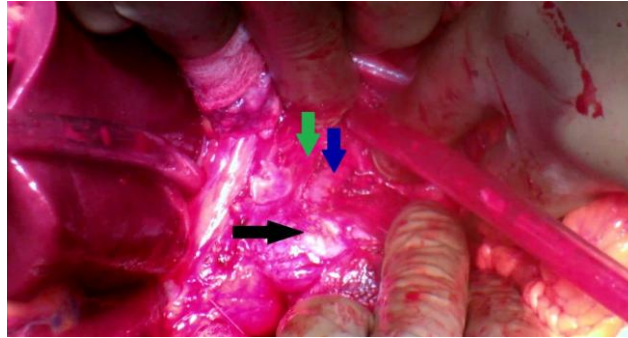


Fig. 4. Picture showing portocaval lymph nodes. Green arrow- bile duct, blue arrow portal vein, black arrow- lymph nodes

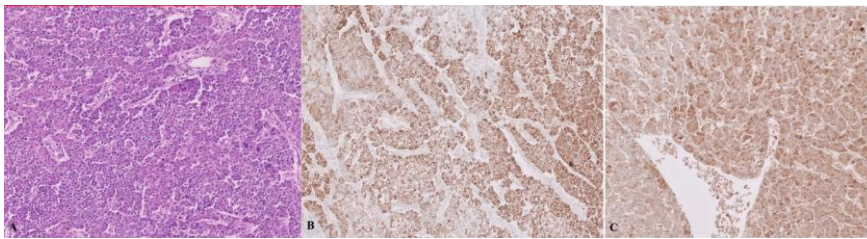


Fig. 5. Images of HCC. A- High power magnification showing neoplastic hepatocytes with high Nuclear: Cytoplasmic ratio arranged in trabecular pattern, B- HepPar staining, C- Arginase staining

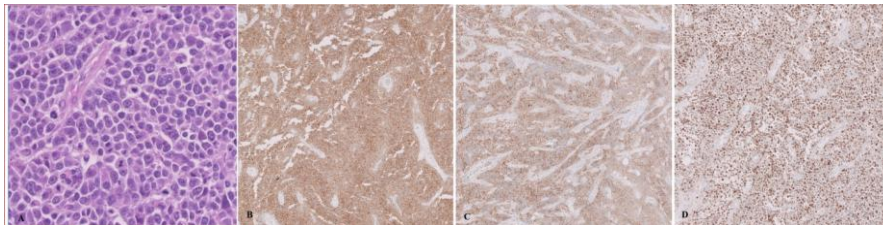


Fig. 6. Images of NEC. A- High power magnification image showing large round cells with scant cytoplasm and hyperchromatic nucleus, B- Synaptophysin staining, C- CD 56 staining, D- Ki 67 staining

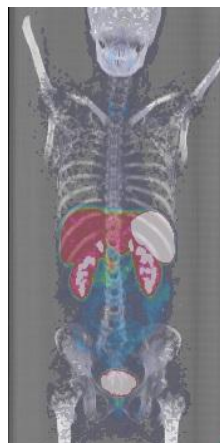


Fig. 7. Image of DOTONAC scan showing no active uptake of the tracer in the body confirming the lesion removed as PHNET

3. DISCUSSION

HCC of liver is the most common primary liver tumor. It constitutes 75% of all primary liver tumors [4]. Risk factors for HCC include chronic viral hepatitis B/C, aflatoxin and alcohol. Off late, HCC related to nonalcoholic hepatic steatosis and steatohepatitis from obesity, metabolic syndrome and diabetes are increasing [5]. The diagnosis of HCC is mainly by radiological study which shows classical arterial enhancement and washout with delayed capsular enhancement along with elevated tumor marker AFP [6]. Biopsy is not mandatory for a resectable lesion [7]. Treatment of HCC depends on various factors like performance status, anatomical location, residual liver quality and distant spread. Treatment options include resection, transplantation, ablation, trans arterial chemotherapy and radiotherapy [8].

Combined PHNET and HCC is an uncommon lesion described in the literature. Gyu HC et al have reported similar case in 2016 in a 72 year old male [9]. Jianwei Lan et al have described a similar case in an 39 year old male where the final diagnosis was made only after histopathological examination [10]. Mixed PHNET and HCC reported in literature are limited and few of them are as follows Barsky et al. [11], Artopoulos et al. [12], Vora et al [13] and Aboelenen et al. [14]. All these articles have stressed on the fact that preoperative clinical and radiological picture mimicking as HCC and diagnosis being done by histopathological and immunohistochemistry analysis. In our case we encountered similar picture of lesion appearing as HCC on imaging however large lymph nodes were a distinct finding. A diagnosis of PHNET was arrived after histopathological confirmation of NET in the liver and ruling out primary site outside the liver.

The treatment of such lesions are confusing, guidelines have not be performed due to the rarity of the lesion. Combination chemotherapy of Etoposide and Cisplatin is advised for neuroendocrine tumors. However, we have considered a multidisciplinary team discussion and arrived at a consensus to treat the patient with Cisplatin and Etoposide chemotherapy with Atezolizumab and Bevacizumab combination once in 3 weeks for three cycles and reevaluate with a DOTONAC scan.

4. CONCLUSION

PHNET with HCC is a rare tumor of liver. Diagnosis is made only on the final histopathological and immunohistochemistry marker evaluation. Evaluation to find out primary NET elsewhere is essential before further treatment. Multidisciplinary team discussion should be considered in treating these patients, owing to the rarity of the lesions, to formulate treatment plan.

CONSENT

Informed consent is obtained from the patient for publication of this article.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

ACKNOWLEDGEMENTS

We thank members of Department of Radiology and Pathology in our Institute for their support in preparing this article.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Caplin ME, Buscombe JR, Hilson AJ, Jones AL, Watkinson AF, Burroughs AK. Carcinoid tumour. *Lancet Lond Engl.* 1998;352(9130):799–805.
2. Maggard MA, O'Connell JB, Ko CY. Updated population-based review of carcinoid tumors. *Ann Surg.* 2004;240(1):117–22.
3. Kellock T, Tuong B, Harris AC, Yoshida E. Diagnostic Imaging of Primary Hepatic Neuroendocrine Tumors: A Case and Discussion of the Literature. *Case Rep Radiol.* 2014;2014:e156491.
4. Dasgupta P, Henshaw C, Youlden DR, Clark PJ, Aitken JF, Baade PD. Global Trends in Incidence Rates of Primary Adult Liver Cancers: A Systematic Review and Meta-Analysis. *Front Oncol.* 2020;10:171.

5. Petrick JL, McGlynn KA. The changing epidemiology of primary liver cancer. *Curr Epidemiol Rep.* 2019;6(2):104–11.
6. Gaillard F. Hepatocellular carcinoma | Radiology Reference Article | Radiopaedia.org [Internet]. Radiopaedia. [cited 2022 Nov 28]. Available:<https://radiopaedia.org/articles/hepatocellular-carcinoma>
7. Guidelines Detail [Internet]. NCCN. [cited 2022 Aug 19]. Available:<https://www.nccn.org/guidelines/guidelines-detail>
8. Vogel A, Martinelli E, Vogel A, Cervantes A, Chau I, Daniele B, et al. Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines. *Ann Oncol.* 2021;32(6):801–5.
9. Choi GH, Ann SY, Lee SI, Kim SB, Song IH. Collision tumor of hepatocellular carcinoma and neuroendocrine carcinoma involving the liver: Case report and review of the literature. *World J Gastroenterol.* 2016;22(41):9229–34.
10. Lan J, Guo D, Qin X, Chen B, Liu Q. Mixed Neuroendocrine Carcinoma and Hepatocellular Carcinoma: A Case Report and Literature Review. *Front Surg* [Internet]. 2021 [cited 2022 Nov 28];8. Available:<https://www.frontiersin.org/articles/10.3389/fsurg.2021.678853>
11. Barsky SH, Linnoila I, Triche TJ, Costa J. Hepatocellular carcinoma with carcinoid features. *Hum Pathol.* 1984;15(9):892–4.
12. Artopoulos JG, Destuni C. Primary mixed hepatocellular carcinoma with carcinoid characteristics. A case report. *Hepatogastroenterology.* 1994; 41(5):442–4.
13. Vora IM, Amarapurkar AD, Rege JD, Mathur SK. Neuroendocrine differentiation in hepatocellular carcinoma. *Indian J Gastroenterol Off J Indian Soc Gastroenterol.* 2000;19(1):37–8.
14. Aboelenen A, El-Hawary AK, Megahed N, Zalata KR, El-Salk EM, Fattah MA, et al. Right hepatectomy for combined primary neuroendocrine and hepatocellular carcinoma. A case report. *Int J Surg Case Rep.* 2014;5(1):26–9.

© 2022 Mahadevappa et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:

<https://www.sdiarticle5.com/review-history/95153>