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CASE REPORT

HEPATOCELLULAR CARCINOMA WITH NEUROENDOCRINE DIFFERENTIATION PRESENTING AS METASTATIC SOFT TISSUE LESION.

AUTHORS

1. Dr. Vinayak Kshirsagar, Professor of Surgery, Dr. D. Y. Patil Medical College and Hospital, Dr. D.Y. Patil Vidyapeeth, Pimpri, Pune, 411018.
Email: vinayakkshirsagar80@gmail.com
Mobile: 9850930621
2. Dr. Mahendra Bendre, Professor of Surgery, Dr. D. Y. Patil Medical College and Hospital, Dr. D.Y. Patil Vidyapeeth, Pimpri, Pune.
Email: mahendrabendredr@gmail.com
Mobile: 9561744365

3. **Corresponding Author-** Dr. Rishi Chowdhary Narra, Resident of Surgery, Dr. D. Y. Patil Medical College and Hospital, Dr. D.Y. Patil Vidyapeeth, Pimpri, Pune.
Email: rishichowdhari@gmail.com
Mobile: 9959004462

ABSTRACT

Hepatocellular carcinoma is a common subtype of primary liver malignancy, in addition to cells with hepatic differentiation. It can rarely contain additional cell populations such as neuroendocrine carcinoma (NEC) or cholangiocarcinoma. Mixed hepatocellular carcinoma – neuroendocrine carcinoma (HCC-NEC) are extremely rare tumours, constituting about 0.40% of all primary hepatic malignancies. Most of them are incidentally diagnosed after surgical resection of liver and have a very aggressive behaviour. Very few cases have been reported worldwide.

We hereby present a unique case of HCC–NEC in an elderly male, the patient presenting to us as a soft tissue mass in paraspinal region which revealed a metastatic lesion from a primary hepatic HCC–NEC tumour, only after undergoing investigations. Ours is probably the first case in literature where a primary HCC-NEC has presented as a metastatic soft tissue deposit. Inspite of multimodalities of treatment like surgical resection and chemotherapy, the prognosis in such cases remains extremely poor.

KEY WORDS

Hepatocellular carcinoma, neuroendocrine differentiation, paravertebral soft tissue tumour, metastatic lesion.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the primary malignant neoplasm of liver, composed of cells with hepatic differentiation. Rarely HCCs contain additional cell populations such as neuroendocrine carcinoma (NEC) or cholangiocarcinoma [2].

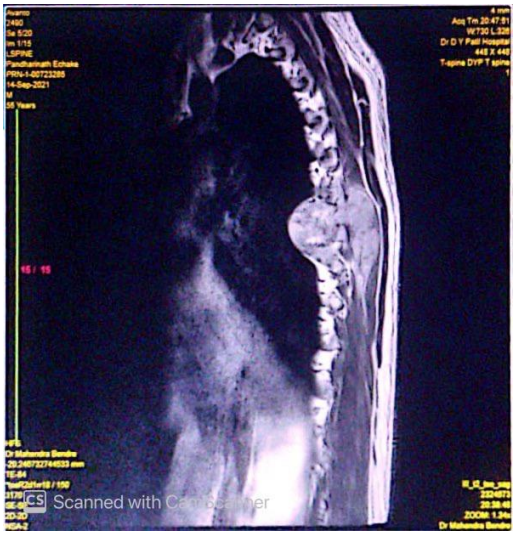
Mixed hepatocellular carcinoma – neuroendocrine carcinomas (HCC-NEC) are very rare, amounting to 0.40% of primary hepatic tumours, in analysis of 125 primary hepatic tumour samples by Nomura et al[9]. Most of these patients present with abdominal symptoms with localisation of liver lesion on radiographic examination like USG/CT. Presentation of such a patient with distant metastatic lesion is

ISSN 2515-8260 Volume 09, Issue 07, 2022

extremely rare. We hereby present a case of patient presenting with a soft tissue mass in paraspinal region, which is diagnosed later as metastatic lesion of a primary HCC-NEC tumour in liver, an exceedingly rare occurrence. Primary mixed NEC and HCC has a very aggressive course, having a behaviour similar to primary hepatic NEC, most of the patients of which die within 1 year with or without tumour resection[6].

CASE REPORT

A 55 year old male patient presented with swelling over right scapular region of 1 month duration. Patient was a chronic alcoholic and had lost significant weight over the last month, but did not give h/o any other major illness/jaundice/abdominal pain. Examination revealed enlarged left supraclavicular node. Local examination showed 5cm x 7cm diffuse firm swelling overlying right scapular and paravertebral region. Systemic examination including abdomen was normal. Routine investigations were normal except mild anemia and small soft tissue opacity in the paraspinal region overlying T6-T7 area in radiography.



MRI Thoracolumbar Spine

MRI of thoracolumbar spine revealed soft tissue lesion around T6-T7 paravertebral region with erosion of 6th and 7th ribs, along with erosion of transverse process of T6 vertebra, extending into corresponding neural foramina.

CT scan thorax and abdomen confirmed the extent of the lesion as above along with incidental finding of cirrhotic liver with solid-cystic mass lesions in segments V, VI, VII, VIII in right liver lobe. PET scan showed metabolically active lesions in right liver lobe and metabolically active left supraclavicular and retroperitoneal lymph nodes along with active expansile destructive lesion in right paravertebral area at T6-T8 vertebral level. USG guided biopsy of both paravertebral and liver lesions was suggestive of hepatocellular carcinoma with neuroendocrine differentiation.

Immunohistochemistry of the tissue was positive for synaptophysin and chromogranin. Pan-CK was positive for occasional cells while Ki67 positive in 60%. Tumour cells were diffusely positive for Hep-Par-1.

DISCUSSION

Hepatocellular carcinoma (HCC) is the commonest subtype of primary liver cancer (PLC), constituting about 70-85% of all cases[1] . Although HCC is primarily composed of cells with hepatic differentiation, it can contain additional population of cells such as neuroendocrine carcinoma (NEC), cholangiocarcinoma or sarcomatous components[2] . Mixed hepatocellular carcinoma-neuroendocrine

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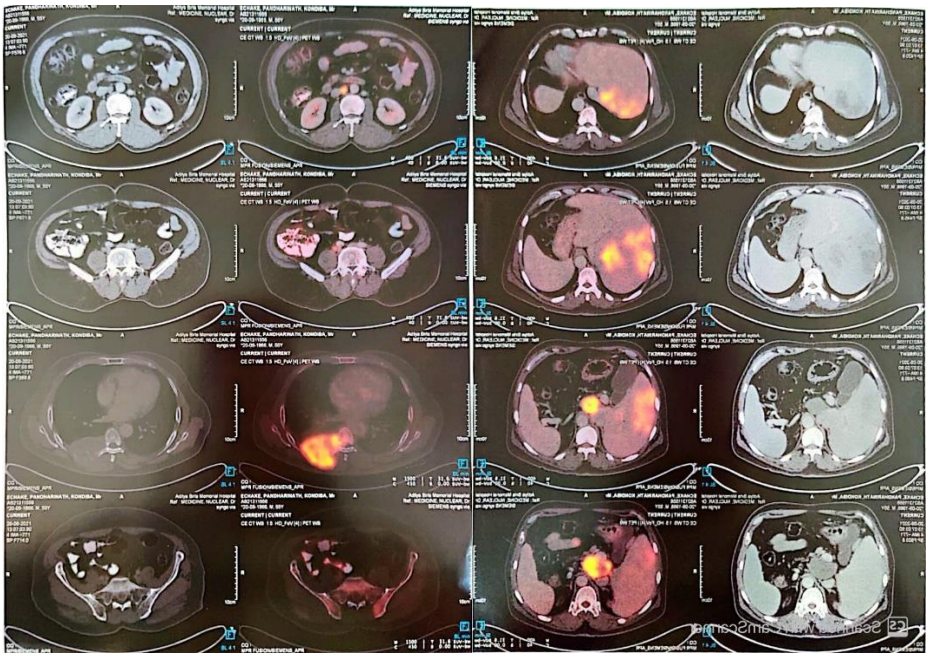
carcinomas (HCC-NEC) are extremely rare, accounting to 0.40% of all primary hepatic tumours , as reported by Nomura et al[9].

Primary HCC-NEC can present as a collision tumour where HCC and NEC components create distinctive tumours without any transitional zone, having an incidence of 0.1-1% of primary hepatic malignancies[7]. It can also present as a combined tumour where HCC and NEC components are in contact with each other, often having a transitional zone where both the components are admixed with each other[2], having incidence of 2-3% of all primary hepatic malignancies. Combined tumours are postulated to be arising from stem cells evolving into divergent differentiation and most frequently contain hepatocellular and cholangiocarcinoma elements[7] . They are also postulated to arise from neuroendocrine cells in intrahepatic bile duct epithelium[3] . About 20-40% of primary NEC-HCC have developed in non-cirrhotic livers, as is evidenced in many of the studies.



PET CT Images

Although patients with mixed HCC-NECs may present as abdominal mass, most of these cases were diagnosed incidentally after surgical resection of tumours[2] . In our case, the patient presented as a metastatic deposit simulating soft tissue paraspinal tumour, which is extremely rare and probably is the first case being reported in available literature so far. The primary hepatic tumour was only revealed incidentally after thoracoabdominal CT scan and PET scan were performed.

It is important to make a clear distinction between primary intrahepatic NEC and metastatic NEC from extrahepatic organs[3], as the former is extremely rare showing both HCC and NEC components in the same lesion, as also is evidenced in our case. Based on predominant histologic component, they may exhibit varying imaging features on CT and MRI. Gallium-68 Dotatate is widely used for detection of neuroendocrine tumours and their metastases, having higher sensitivity and specificity compared to octreotide scans[1].

Serum markers such as AFP and CA 19-9 are frequently raised in HCC and CC respectively. Increase in AFP-L3 has been shown to be specific for HCC, while elevations in AFP are also detected in metastatic neuroendocrine tumours to liver[1] . Serum chromogranin is also used as a marker for tumours with neuroendocrine differentiation[1] . Nomura et al[9] has also described an additional variant as ‘intermediate type’ where poorly differentiated cancer cells express markers for both HCC

ISSN 2515-8260 Volume 09, Issue 07, 2022

and NEC like co-expression of Hep-Par-1 (HCC marker) and Chromogranin (NEC marker). Immunohistochemistry was positive for synaptophysin and chromogranin in our case, while Ki67 was present in 60% of tissue samples. Tumour cells also were diffusely positive for Hep-Par-1.

No concrete data is available regarding behaviour, prognosis and management of mixed HCC-NEC tumours, as only a limited number (about 28 till date) have been reported[2] . About half of these cases succumbed within a year of the diagnosis and around 2/3rd of them had a recurrence in short follow up period[2] .

Various modalities of treatment are advocated with surgical resection, while liver transplant is not proving to be superior to minor or major hepatectomy. Other forms of treatment such as transarterial chemoembolisation, radioembolisation or chemotherapy are also employed in patients who are poor surgical candidates[1]. Cisplatin and etoposide were commonly used in combination to treat the recurrence. Although most of the patients with pure high grade neuroendocrine carcinomas succumb within few months after diagnosis, reports of same combined NEC-HCC cases showed longer survival without recurrence upto 28 months[4] . Our patient also underwent chemotherapy, consisting of cisplatin and etoposide, but unfortunately succumbed within 6 months.

Other miscellaneous presentations also have been reported in literature. A case of combined HCC-NEC with ectopic secretion of parathyroid hormone has been reported by Hyun Jung Kwon et al[5]. A fat containing combined HCC-NEC of liver has been documented by Atsuyuki Ikeda et al[8]. Incidence of symptomatic skeletal metastases of HCC-NEC is reported to be 1.5-7.3% by C. Rory Goodwin et al, and median occurrence of spinal metastases from time of diagnosis is 13 months along with 7 month survival[10].

CONCLUSION

Mixed hepatocellular carcinoma-neuroendocrine carcinomas (HCC-NEC) of liver are extremely rare tumours, accounting for 0.40% of all primary hepatic malignancies. Most of these tumours were diagnosed incidentally after surgical resection of liver and only few cases have been reported in literature till date. Ours is a unique case of asymptomatic mixed HCC-NEC involving liver, and the patient presenting with a soft tissue mass in paraspinal region, which turned out to be a metastatic deposit from the same. The behaviour of these tumours is very aggressive, and almost half of these cases succumb within a year of diagnosis, with a recurrence in almost of 2/3rd of these cases.

Any paravertebral mass in elderly patients should be viewed with suspicion and patient investigated thoroughly to rule out any metastatic deposits, especially from HCC-NEC hepatic neoplasm for an early diagnosis and management.

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