

# Unusual Metastases as Initial Presentation of Hepatocellular Carcinoma (HCC). A Case Series

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## ABSTRACT

**Objective:** To highlight the importance of unusual clinical presentation of HCC and to keep this diagnosis in your differentials.

**Methods:** This is a retrospective case series done in Liaquat national hospital. Data were retrieved from September 2014 till October 2019.

**Results:** Data of total 184 patients were reviewed. Four patients were found to have unusual initial presentation of HCC. All four patients were male. Age ranged between 48 to 80 years. All four patients presented with bony metastases. Involved areas were iliac bone, lumbar vertebrae, skull and maxilla. Three patients were HCV reactive. Only one patient was found to have multicentric hepatoma. Three patients were referred for palliative radiation. One patient lost to follow-up and one patient was started on sorafenib and he is responding well.

**Conclusion:** Unusual initial presentation of HCC is not common. This diagnosis should be kept in mind in patients presenting with skeletal metastases with unknown primary. Further studies are needed to understand this phenomenon and underlying mechanism.

**Keywords:** Hepatocellular carcinoma, Unusual presentation, Case series.

## INTRODUCTION

Liver cancer is the most rapidly increasing cancer in both men and women, with incidence rates more than tripling since 1980. From 2006 to 2015, the rate increased by about 3% per year. The death rate for liver cancer has more than doubled, from 2.8 (per 100,000) in 1980 to 6.7 in 2016. Over last four decades, the 5 years' survival rate has increased from 3% to 18% [1].

HCC is 5<sup>th</sup> most common cancer among men and second leading cause of cancer-related death in the world with highest case fatality rate. Among women, HCC is the 7<sup>th</sup> commonest cancer and 6<sup>th</sup> leading cause of cancer-related death [2]. Metastasis is a major cause for HCC related death, with some cases presenting with metastatic carcinoma before primary liver tumor is found.

Bone metastases from HCC, in particular, result in extremely poor patient prognosis, with a median survival of only 1 to 2 months [3]. Because of their rarity, there is no optimal treatment strategy for these patients and their outcome is poor.

This case series and literature review may be valuable for physicians to update their knowledge for daily practice. Enhanced recognition, early diagnosis, and appropriate management of atypical metastasis may help improve the overall outcomes of HCC.

## MATERIAL AND METHODS

We retrospectively reviewed record of all patients presented in Liaquat National Hospital (LNH) with diagnoses of HCC. Data from September 2014 till October 2019 were reviewed. We included all patients older than 18 years with initial presentation other than hepatobiliary complaints, with extra hepatic pathological diagnoses of HCC. Patients with concurrent malignancy, with diagnoses on liver biopsy or on treatment for HCC were excluded.

Medical, radiological and pathological records were reviewed to collect patients' Data.

## RESULTS

From September 2014 to October 2019, 184 Patients presenting with diagnoses of HCC were included. Four patients had unusual initial presentation. These four cases are summarized in (Table 1).

Details of these four cases are following:

### CASE 1

48 years old man known case of Hep C, presented in July 2018 with right iliac fossa pain for 5 months. Pain was gradual in onset moderate in intensity and radiating to right thigh. On examination a hard and fixed mass was palpable in the right iliac fossa measuring about 8 X 5 cm in size. Mass was mildly tender.

His work up showed mildly increased liver enzymes and raised alpha fetoprotein of 1102.3 IU/ml. His CT scan abdomen (**Fig. 1**) showed large soft tissue mass,

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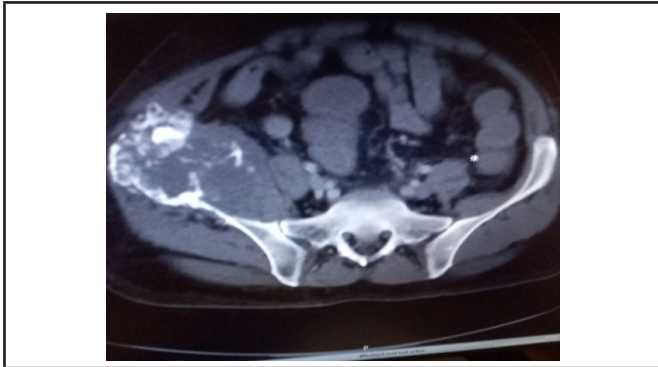
involving right psoas and right iliacus muscle causing destruction of the right iliac bone. Left lobe of liver showed a lesion with arterial enhancement and wash out in delayed phase, suggestive of hepatocellular carcinoma (**Fig. 2**).

Image guided biopsy of iliac mass suggestive of infiltrating carcinoma with hepatocellular differentiation (**Figs. 3A&B**).

Patient was advised for palliative radiation and started on Sorafenib 800 mg /day.

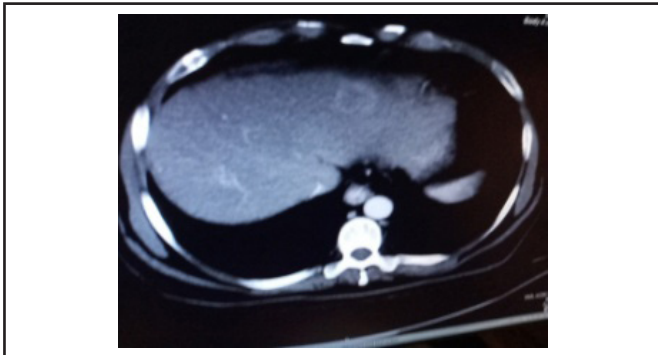
Follow-up scan done on 3<sup>rd</sup> April 2019 showed disease regression.

#### CT Scan Abdomen:



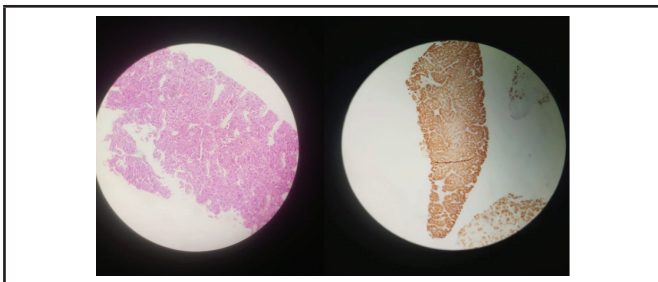
**Fig. (1):** Large soft tissue mass, involving right psoas and right iliacus muscle causing destruction of the right iliac bone.

#### CT Scan of Liver:



**Fig. (2):** In segment II of left lobe showing a lesion with arterial enhancement and wash out in delayed phase.

#### Trucut Biopsy of Right Iliac Fossa Mass (20/6/2018):



**Fig. (3): A** (right): H&E: Linear core of tissue exhibiting cells arranged in trabeculae separated by empty spaces. Cells are poly gonal with abundant eosinophilic cytoplasm and small round nuclei. **B** (Left): Hep Par 1 is diffusely positive in tumor cells.

Currently he is on sorafenib and advised to repeat scan and follow in oncology clinic.

#### CASE 2

80-year-old man is a known case of chronic liver disease (CLD) secondary to HCV. He presented in emergency room with complain of lower back pain for one week. Pain was sudden in onset severe in intensity and did not get relieve by analgesics. Pain was radiating to left leg till toes. On neurological examination his GCS was normal. Cranial nerves were intact. He had left foot drop, power in planter flexion and dorsi flexion was 0/5, power was 4/5 in the rest of involving muscle group and reflexes were diminished all over. His MRI lumbo-sacral spine (**Fig. 4**) showed an abnormal intensity area over body and right lamina of L2 vertebrae. It was associated with epidural component causing severe stenosis of spinal canal with bilateral nerve root impingement.

#### MRI Lumbosacral Spine:

He was operated on 16<sup>th</sup> March 2019 for right sided L1- L3 pedicle screw fixation and tumor debulking at the level of L2. Complete laminectomy of L2 and exit foraminotomy were done.

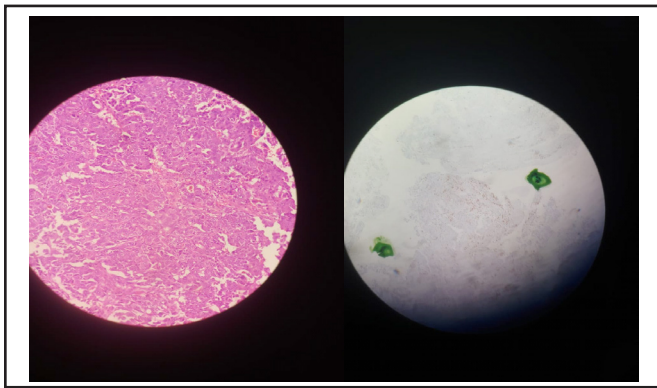
#### Histopathology:



**Fig. (4):** An abnormal intensity area involving body, right pedicle and lamina of L2 vertebrae associated with epidural component causing severe stenosis of spinal canal with bilateral nerve root impingement.

Histopathology showed fragments of neoplastic lesion arranged in the form of clusters separated by thin fibrous septae. Neoplastic cells are moderate to markedly pleomorphic having vesicular nuclei, clumped chromatin and abundant eosinophilic granular cytoplasm. Some cells showed cytoplasmic PAS positivity. Frequent mitosis was seen. Focally brown pigment was also noted (**Fig. 5A**).

Immunohistochemical studies were performed by DAKO envision method. CK AE1/AE3 (+++ve), CK 7 and 20 (-ve), Hep Par I focal +ve (**Fig. 5B**). Pathology was concluded as metastatic carcinoma with hepatoid differentiation with possibility of hepatocellular carcinoma (HCC).



**Fig. (5): A** (right) H&E: Neoplastic lesion arranged in the form of clusters separated by thin fibrous septae. **B** (left) Hep Par 1 is focal positive in tumor cells.

His CT chest and abdomen was done with contrast on 15<sup>th</sup> march to look for primary site. It showed Liver with irregular margins. No arterialized lesion was seen in liver. Few enlarged mesenteric metastatic lymph nodes were also noted.

His alpha feto protein was also checked, which was raised, 537 IU/ml (<5.8).

As his CT scan was negative for any lesion in liver, his PET scan was advised to look for any other site of involvement.

His FDG PET scan was done on 17<sup>th</sup> April 2019, which showed a hyper metabolic focus in segment V (SUV max 5.1). Hypermetabolic mesenteric deposit was seen lateral to right ureter. Another focus was seen in left subtrochanteric region consistent with bony metastasis.

Patient was referred for spinal radiation.

### CASE 3

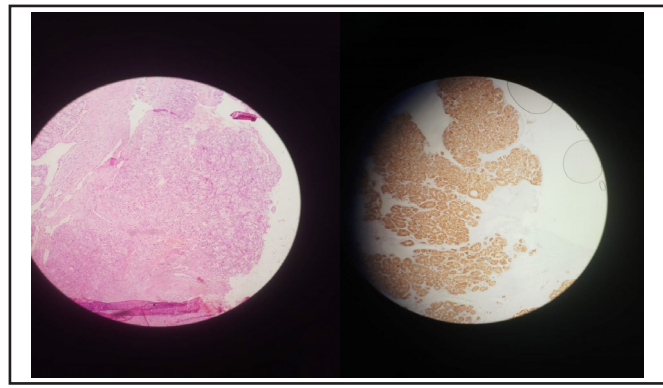
55-year-old man known case of hypertension, presented to outpatient clinic with scalp swelling for 6 months. According to history patient developed gradually progressive scalp swelling after head trauma 6 months ago. With initial suspicion of abscess, swelling was excised in some periphery hospital. But as it persisted, he came to neurosurgery clinic in LNH.

His CT brain done in October 2018, showed no significant lesion.

Excisional biopsy of this lesion was done on 7<sup>th</sup> Jan 2019. It showed a neoplastic lesion with large areas of necrosis and hemorrhage. Tumor showed trabecular and sinusoidal pattern of cells with moderate nuclear atypia vesicular nuclei and prominent nucleoli (**Fig. 6A**).

#### Histopathology:

Immunohistochemical studies were performed by DAKO envision method. CK AE1/AE3 (+++ve), CK 7 and CK 20 (-ve), CD 10 (positive), Hep Par I (+ve) (**Fig. 6B**).



**Fig. (6): A** (right): Showed multiple fragments of glial tissue, with a neoplastic lesion with large areas of necrosis and hemorrhage. Tumor showed trabecular and sinusoidal pattern of cells with moderate nuclear atypia vesicular nuclei and prominent nucleoli. Cytoplasm is pale eosinophilic. **B** (left): Hep Par 1 is positive in tumor cells.

Pathology concluded as metastatic hepatocellular carcinoma (HCC).

CT scan showed normal liver with single lesion in left adrenal gland. Bone scan (7/2/19) showed multiple lytic lesions in spine.

He was advised for palliative radiation to scalp lesion as having headache. He was given denosumab for his bony disease. He was planned to start on sorafenib. Then he lost to follow up.

### CASE 4

A 60 years old male having diabetes mellitus, hypertension, asthma and hepatitis was admitted with complain of right gum ulcerative lesion for 3 months and oral bleed for 2 months. Its size gradually increased over time. It was associated with loosening of teeth and difficulty in movement of tongue, weight loss and change of voice. He was addicted to betel nut. Before presenting in our hospital he received blood transfusion in peripheral hospital for bleeding from alveolar lesion. He was treated for hepatitis a month earlier. Ct scan done outside LNH on 2<sup>nd</sup> October 2018 revealed neoplastic oral cavity lesion posterior to maxilla on right side of midline. Histopathology done outside LNH on 11<sup>th</sup> September 2018 showed severe acute and chronic inflammation with ulceration and exuberant granulation tissue formation along with few clusters of atypical cell. Immunohistochemistry was largely unhelpful.

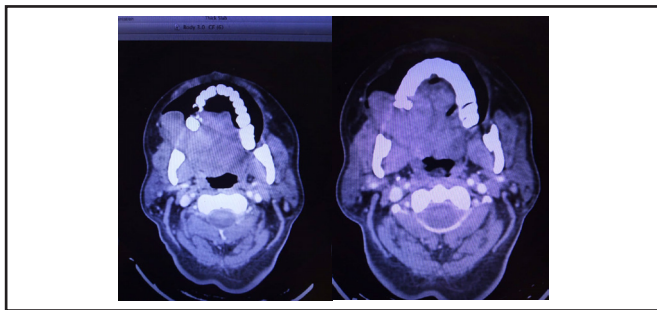
On examination he appeared pale with huge exophytic growth on right upper alveolus, behind right canine causing bulge over right cheek, pushing buccal mucosa medially and involving almost whole of palate (**Fig. 7**). Posterior extent was not visible. Anterior facial pillar was normal. Oropharynx, tongue, lower alveolus appeared normal. Left side of oral cavity and rest of systemic examination were normal. His CT scan Neck and chest showed a well-defined heterogeneously enhancing mass involving superior alveolus causing its erosion and destruction with extension into right maxillary antrum, causing erosion of walls of maxillary sinuses and hard palate (**Fig. 8**).



**Fig. (7):** Exophytic growth on right upper alveolus.

**CT Neck and Chest:**

Included section of upper abdomen showed altered texture of liver with irregular margin. Caudate lobe was also enlarged. Heterogeneously enhancing lesion was seen in segment VI and VII of right lobe of liver demonstrating washout on delayed images representing multicenter hepatomas in post cirrhotic liver.

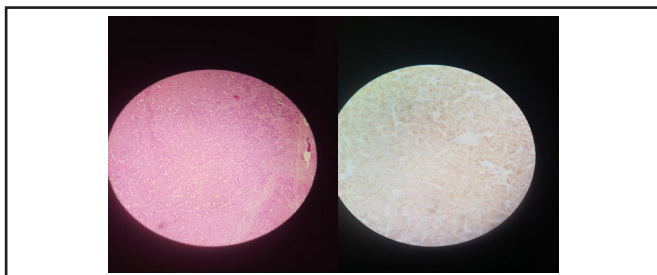


**Fig. (8):** Revealing a well-defined lobulated heterogeneously enhancing neoplastic mass involving superior alveolus causing its erosion and destruction with extension into right maxillary antrum, causing erosion of walls of maxillary sinuses and hard palate. It measured 5.4x 3.6 x 7.3 cm. Lesion was abutting tongue, soft palate, with mild intra nasal extension. Few lymph nodes were seen in neck at level I, II and III bilaterally.

Biopsy showed neoplastic lesion but due to crush artifact further characterization was not possible.

Then his right total maxillectomy was done and intra-operatively showed tumor was present in upper alveolus involving the right maxillary sinus through its lateral wall. Anterior, posterior and medial wall of maxillary sinus were not involved. Right orbit was also spared. Surgical histopathology specimen showed epithelial neoplasm. It's morphological and immunohistochemical features are suggestive of hepatocellular carcinoma (**Figs. 9A&B**).

Patient opted for best supportive care.



**Fig. (9):** **A** (right): H&E showed infiltrating malignant neoplasm. **B** (left): Hep Par 1 is positive in tumor cells.

**Table 1:** Characteristics of patients.

-	Case #1	Case # 2	Case # 3	Case #4
Age	48	80	55	60
Gender	male	male	male	male
Presenting Symptoms	Right iliac fossa pain	Lower back-ache	Scalp swelling	Right upper alveolus growth
H/o CLD	yes	yes	no	no
H/o antiviral treatment	yes	no	no	yes
HBsAg	Non-reactive	Non-reactive	Non-reactive	non-reactive
Ant HCV	Reactive	Reactive	Non-reactive	Reactive
Alpha fetoprotein	1102	537	5.2	not available
CT Liver	Fatty liver	CLD changes	normal	Multi-centrichepato-
Biopsy site	Right iliac fossa mass	Spinal SOL at L2	Scalp lesion	maxilla
Histopathology	infiltrating carcinoma with hepatocellular differentiation	Metastatic carcinoma with hepatoid differentiation	Metastatic carcinoma likely HCC	Metastatic carcinoma likely HCC
Hep par 1	positive	Focal positive	positive	positive
Treatment	Palliative radiation followed by sorafenib	Palliative radiation	Palliative radiation with bisphosphonate	best supportive care
Outcome	Responding to sorafenib	Plan to start sorafenib	Lost to follow	expired

**DISCUSSION**

It is estimated that hepatitis C is the most common cause of HCC in Pakistan [4]. Majority of patients with extrahepatic HCC foci had either intrahepatic stage IVA tumor or an intrahepatic stage III tumor at the occurrence of metastases. Patients with more advanced HCC (TNM classification, intrahepatic tumor stage, vessel invasion) at the first diagnosis of HCC developed extrahepatic metastases more. It can metastasize *via* the hepatic or portal veins to the lymph node, bones and lungs [5].

Hepatocellular carcinoma (HCC) are diagnosed either during routine screening or when symptomatic because of their size or location [6]. Screening has the highest impact with early detection and potential for cure. Ultrasound (US) and serum alpha fetoprotein (AFP) are used for screening purpose. Although US has sensitivity and specificity of >90% in detecting HCC, its efficiency is compromised in liver cirrhosis. National comprehensive cancer network has recommended 6 monthly US for screening in cirrhotic patients [7].

On CT, HCC generally appears as a focal nodule with early enhancement on the arterial phase with rapid washout of contrast on the portal venous phase of a three-phase contrast scan. MRI of HCC generally demonstrates high signal intensity on T2 imaging. Role of PET scan in HCC is also emerging now. Sensitivity of PET in detecting early lesion is low, but can be useful in metastatic setting [8].

Hepatocellular carcinoma (HCC) is the 4<sup>th</sup> most common cause of cancer-related mortality worldwide. >80% of HCC cases occur in countries with low socioeconomic status [9]. Worldwide the main risk factors for HCC are chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), aflatoxin-contaminated foodstuffs, heavy alcohol intake, obesity, smoking, and type 2 diabetes.

The American Cancer Society states the overall 5-years survival rate for all stages of liver cancer is 18% [10]. Patients often succumb to HCC within a year of diagnosis, and the survival is only few months if left untreated [11]. Metastases from HCC have extremely poor prognosis. Extrahepatic metastases are common with most common sites being lungs, intra-abdominal lymph nodes, bones, and adrenals. Bone metastases from HCC are infrequent, with a reported incidence ranging from 3 to 20% with extremely poor prognosis. Spinal metastases from HCC are extremely rare, with a frequency ranging from 0.2% to 2.2% and are associated with significant morbidity and mortality [3] with a median survival of only 1 to 2 months. Moreover, metastases to the bones of the head and neck regions are extremely rare. Initial presentation of unsuspected HCC as a bone metastasis is rarely reported [12-17]. There is enough literature to suggest that HCC should always be considered in the differential diagnoses in patients presenting with bone metastasis, with a few reports suggesting that this could be the first manifestation of HCC.

Monteserin L *et al.* [18] presented case series of three patients with skeletal lesion involving iliac bone, femoral neck and lumbar vertebrae. Two of these cases were similar to our first two cases, and also were managed on similar way.

Ruiz-Morales JM [12] presented two cases: one had lesions in vertebrae, iliac bone and sacrum, like our two cases, whereas second case had lesions at cervical vertebrae and shoulder. Similarly Hwang SW *et al.* [13] presented a case, with cervical vertebral involvement and iliac mass, managed with surgery, radiation and sorafenib.

Subasinghe D *et al.* [14], Goto T *et al.* [19] Guo X *et al.* [20], and Shim YS *et al.* [21] presented few cases with scalp swelling, very similar to our third case. Surprisingly one patient was also having history of head injury similar to our third case.

Lei Q *et al.* [22], Misra SR, [23], Alrumaih RA *et al.* [24], Custódio M *et al.* [25], Adnot J *et al.* [26], Xue LJ *et al.* [27], and Rai S [28] presented a case of zygomatic bone lesion, very similar to our fourth case.

The characteristics of bone metastases in hepatocellular carcinoma (HCC) have not been fully understood in literature, presumably because of rarity of condition. Bony metastases from HCC are often characterized by soft-tissue expansion with an abundant vascular component [29].

Due to rarity of condition, optimal treatment strategies are not well established. Early diagnosis is important for further therapy and improved survival. No systemic therapy has improved survival in patients with advanced hepatocellular carcinoma. Sorafenib (tyrosine kinase inhibitor) is a small molecule that inhibits tumor-cell proliferation and tumor angiogenesis and increases the rate of apoptosis. It shows benefit of 3 months in progression free survival [30].

When bone metastases are documented, a prompt multidisciplinary review with the application of radiation, operative, or combined modality management dictated by the clinical scenario should ensue. In the absence of a formal clinical trial in HCC, the available evidence indicates that bisphosphonate therapy is reasonable in patients with intact hepatic function and bone lesions. The observation that sorafenib reduces the risk of skeletal related events (SREs) is consistent with its documented antitumor activity [31]. Future expectation is with emerging targeted therapies for HCC, including immune checkpoint inhibitors [32].

Because of worsening effect on survival, an screening and treatment approach should be defined for bone metastases in patients with HCC. To date, there are no standard guidelines for HCC-related skeletal disease.

From a clinician point of view, our case series support the observation that SREs increase morbidity that worsen the quality of life and increase the economic burden. Importantly, metastases to the spine have been associated with a decrease in overall survival in patients with HCC [33]. There are several limitations to our study, as being single-center and retrospective, with small sample size.

There is need of multicenter, prospective study to establish guidelines for standard of care in patients with skeletal metastases as initial presentation.

#### ACKNOWLEDGEMENT

None.

#### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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