DOI: 10.7860/JCDR/2025/78146.22085

Case Report

Pathology Section

Undetected Hepatocellular Carcinoma Initially Manifesting as Pathologic Fracture of Femur: A Case Report

SAROJINI RAMAN[1], PRAJNA DAS[2], URMILA SENAPATI[3], BHABANI SHANKAR MAHAPATRA[4]

ABSTRACT

Hepatocellular Carcinoma (HCC) is the most common primary liver malignancy and its global incidence and mortality have shown an upward trend recently. According to GLOBOCAN 2020, it is the 4th most frequent cause of death worldwide. Despite advances in diagnostic and therapeutic modalities, many patients present at an advanced stage with a dismal prognosis. HCC often metastasises to the lungs, lymph nodes and abdominal organs. Bone metastasis is reported in only 5–7% of primary HCCs. The long bones, such as the femur, are rare sites for distant metastasis compared with the axial skeleton. HCC typically presents as a large space-occupying lytic lesion with systemic symptoms. Extrahepatic isolated bone metastasis without clinical signs or symptoms of liver injury as the sole initial manifestation in HCC is very uncommon. Present case is of primary HCC in a non cirrhotic liver metastasising to the femur in a patient with no known co-morbidities. This case highlights the fact that metastatic HCC should be included in the differential diagnosis in cases presenting with lytic bone lesions of unknown primary in older males, even in the absence of liver cirrhosis. Early radiological intervention and aggressive management policies should be adopted to extend survival.

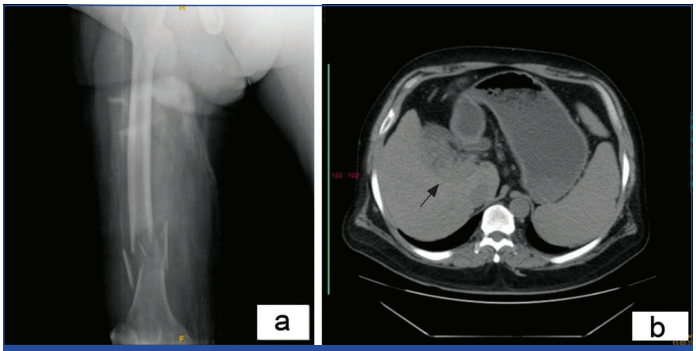
Keywords: Bone neoplasm, Liver cirrhosis, Radiological intervention

CASE REPORT

A 50-year-old male patient was admitted to the orthopaedics ward with complaints of difficulty walking for one month. He had no other significant history of injury or accident. Clinically, a fracture of the right distal femur was suspected. Routine investigations revealed anaemia, thrombocytopenia, and mildly raised liver enzymes [Table/Fig-1]. Magnetic Resonance Imaging (MRI) of the right thigh showed a compound fracture with a surrounding lytic lesion [Table/Fig-2a]. Computed Tomography (CT) of the thorax showed no significant abnormality. However, CT abdomen revealed the liver with multiple small hypodense and non enhancing conglomerated lesions, measuring 2.9×2.5 cm in total. These findings were suggestive of eosinophilic abscess, regenerative nodules, or carcinoma [Table/Fig-2b]. The Liver Function Tests (LFTs) were normal. The patient underwent Open Reduction and Internal Fixation (ORIF) with plating of the right distal femur. After surgery, the patient was stable. On examination, the right thigh had no visible swelling or deformity. Range of Motion (ROM) of the knee was 0°-130°. Dorsalis pedis pulse and toe movement were present; no Distal Neurovascular Deficit (DNVD) was noted. The final clinical diagnosis was fracture of the distal right femur with a lytic lesion. Biopsy from the lytic area was sent for histopathological study. Gross specimens consisted of multiple grayish-brown tissue fragments ranging from 0.1 cm in diameter to 0.5×0.3×0.2 cm. Histopathology revealed multiple bits of core biopsies comprising fibro-collagenous tissue, foci of lamellar bone infiltrated with tumour cells arranged in nests and cords surrounded by sinusoidal vessels. Tumour cells were polygonal with abundant eosinophilic granular cytoplasm, vesicular nuclei, and prominent nucleoli, with many showing intranuclear inclusions. Focally, greenish bile pigments were present within the cytoplasm of tumour cells [Table/Fig-3a,b]. The histopathological impression was metastatic carcinomatous deposits in bone, possibly from the liver. Immunohistochemistry (IHC) revealed Hep Par-1 and cytokeratin positivity in tumour cells [Table/Fig-3c,d].

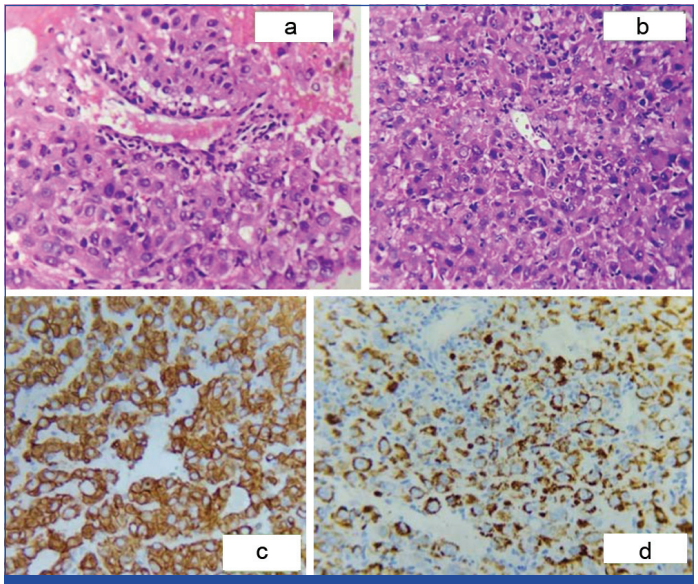
Investigations	Observed value	Reference value
Haemoglobin (gm/dL)	12.0	15±2
Total RBC Count (TRBC) (million/cmm)	6.04	5±0.5
Mean Corpuscular Volume (MCV) (fl)	69	92±9
Total Leukocyte Count (TLC) (/cmm)	13100	4000-10, 000
Differential Leukocyte Count (DLC)	N 78%, L 18%, M 03%, E 01%, B 00%	N (40-80%), L (20-40%), M (2-10%), E (1-6%), B (<1-2%)
Total Platelet Count (TPC) (/cmm)	90000	2.8±1.3
Serum Urea (mg/dL)	21.0	20-40
Serum Creatinine (mg/dL)	0.82	0.7-1.3
Serum uric acid (mg/dL)	8.00	3.5-7.2
Urine Bence Jones protein	Negative	-
SGPT (U/L)	29	7-56
SGOT (U/L)	43	8-45
Total bilirubin (mg/dL)	1.16	0.1-1.2
Direct bilirubin (mg/dL)	1.0	<0.3
GGT (U/L)	90	5-40
Alkaline Phosphatase (ALP) (IU/L)	98	30-130
Serum albumin (g/dL)	3.8	3.4-5.4
Serum globulin (g/dL)	2.4	2.0-3.5

[Table/Fig-1]: Laboratory investigations.
SGPT: Serum glutamic pyruvic transaminase; SGOT: Serum glutamic oxaloacetic transaminase; GGT: Gamma-glutamyl transferase



[Table/Fig-2]: a) Fracture femur with a lytic lesion at fracture site; b) CT abdomen and pelvis shows a small heterogeneous mass in liver with a thin pseudocapsule (marked by arrow) that was enhanced in arterial phase and displayed washed-out and mosaic patterns in portal venous and delayed phases, respectively.

Thus, the final confirmed diagnosis was hepatocellular carcinoma metastasis to the femur bone. After histopathologic diagnosis, further investigations showed serum Alpha-fetoprotein (AFP) level was low (20 IU/mL); Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) were negative. The patient was planned for systemic sorafenib, Radiofrequency Ablation (RFA), and follow-up.



[Table/Fig-3]: a) Tumour cells in nest pattern in core biopsy with haemorrhage, (H&E, 400x); b) Large pleomorphic tumour cells around sinusoidal vessels with intranuclear inclusions and cytoplasmic bile pigments, (H&E,100X); c,d) Strong Cytokeratin and Hep Par 1, IHC positivity in tumour cells.

DISCUSSION

Bone malignancies, whether primary or secondary, comprise 1.1% of all malignancies. Secondary bone malignancies outnumber primary bone tumours (<1%) [1]. Bone is the third most common site for metastasis of solid neoplasms after the lung and liver, and the incidence has recently shown a definite upward trend. Tumours with the greatest tendency for bone metastasis are breast and prostate, followed by lung, kidney, thyroid, and melanomas [2]. The incidence of bone metastasis from HCC has been reported to range from 25.5-38.5% [3]. The index case had no liver-related symptoms or signs at presentation with a pathologic fracture of the femur. Recent literature searches reveal similar cases of bone metastasis presenting as the initial manifestation of silent HCC in 19 cases reported by Sun CH et al., and Ruiz-Morales M et al., [4,5]. The sites of metastasis commonly described are the vertebrae, ribs, and skull, unlike present case. The femur as a site of metastasis has been described by Wang X et al., only. These authors also describe patients who were chronic carriers of viral hepatitis infections or had chronic liver disease like cirrhosis or chronic alcohol use, contrasting with index case [6,7]. Bone metastasis may be the first sign of relapse in patients with a treated cancer, and patients are rarely curable once bone is involved, implying a grave prognosis. Bone metastases present as osteolytic or osteoblastic lesions as they disturb the normal bone remodeling process. Clinically, patients present with severe bone pain, neurological deficits, palpable subcutaneous masses, pathological fractures, and dysregulated calcium and phosphorus metabolism leading to hypercalcaemia. These skeletal-related complications significantly increase morbidity and mortality in patients [8]. Pain is usually localised to the area over the metastatic tumour and worsens with activity. The pathophysiologic mechanisms underlying severe pain in these patients include tumour-induced osteolysis, local production of nerve growth factors and various cytokines, direct infiltration of nerves, and the presence of microfractures. Fractures are common in weight-bearing bones with structural damage to both cortical and trabecular bone, having detrimental effects on quality of life in such patients [9]. Malignant hypercalcaemia, induced by increased osteoclastic activity and enhanced renal tubular reabsorption of calcium due to parathyroid hormone–related peptide in the setting of volume depletion, can occur. Spinal cord compression presenting as paralysis, urinary retention, or incontinence poses a medical emergency requiring urgent treatment [10].

Bone is not the preferred site for metastasis of HCC. HCC usually spreads to the lungs, lymph nodes, and adrenal glands. However, it may be the first presenting symptom in about 5-7% of HCC cases, and these metastases are usually multiple [11]. When bone metastasis presents as a single focus, it can be treated with radiation therapy, chemoembolisation, or surgery. Thus, skeletal-related sequelae like bone pain can be relieved without the side-effects of continuous systemic analgesic therapy. It does not affect the prognosis of the primary neoplasm.

Bone metastases from the liver are typically osteolytic and form a hypervascular expansile mass. Metastasis occurs through the portal vein–vertebral venous plexuses when blood passes through these plexuses due to portal hypertension or portal thrombosis. This pathway also explains why there is more craniospinal and pelvic bone involvement [12]. A peculiarity of the index case was that the patient had no prior clinical symptoms of a primary hepatocellular malignancy. The liver enzymes were found to be abnormal only after histologic diagnosis. The overall size of the HCC was ≤3 cm, with no evidence of cirrhosis, which is usually seen in the background of HCC. Clinically, the case was initially misdiagnosed as inflammatory or benign.

Resectability of HCC, the interval between the diagnosis of primary HCC and bone metastases, the presence of multiple metastases, and liver function status are important prognostic factors that affect survival in such patients [13]. Management of metastatic bone tumours involves not only treatment of the primary neoplasm but also treatment of complications like bone pain and lysis. Therefore, osteoclast inhibitors such as bisphosphonates, denosumab, and radium-223 are used to reduce skeletal morbidity and improve survival [2].

CONCLUSION(S)

Although bone metastasis from HCC is uncommon, it should be considered in the differential diagnosis of secondary bone tumours of unknown origin. Extrahepatic HCC metastasis to bone carries a dismal prognosis, for which only systemic or supportive treatment is available. Proper diagnosis is essential for prompt initiation of local or systemic therapy and improved survival.

REFERENCES

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209-49.
[2] Macedo F, Ladeira K, Pinho F, Saraiva N, Bonito N, Pinto L, et al. Bone metastases: An overview. Oncol Rev. 2017;11(1):321.
[3] Kim S, Choi Y, Kwak DW, Lee HS1, Hur WJ, Hyun Baek YH, et al. Prognostic factors in hepatocellular carcinoma patients with bone metastases. Radiation Oncology Journal. 2019;37(3):207-14.
[4] Sun CH, Tsai MY, Huang WH, Liao CH. Solitary skull metastasis mimicking a meningioma with dural tail sign as the initial presentation of hepatocellular carcinoma: A case report and a brief review. Interdisciplinary Neurosurgery: Advanced Techniques and Case Management. 2021;25:101255.
[5] Ruiz-Morales JM, Dorantes-Heredia RD, Fredy Chable-Montero F, Manjarrez SV, Sánchez NM, Kuba DM. Bone metastases as the initial presentation of hepatocellular carcinoma. Two case reports and a literature review. Ann Hepatol. 2014;13(6):838-42.
[6] Wang X, Liu J. Hip joint and femur metastases as the first symptom of hepatocellular carcinoma detected by bone scintigraphy. Radiol Infect Dis. 2015;2:134-36.
[7] Ielasi L, Stefanini B, Piscaglia, Granito A, Tovoli F. A case of advanced hepatocellular carcinoma with bone metastases managed with tyrosine kinase inhibitors and aggressive palliative radiation therapy: Role of combination therapy for extending survival. Gastroenterol Insights. 2023;14:38-44. Available from: https://doi.org/10.3390/gastroent14010005.
[8] Monteserin L, Mesa A, Fernandez-Garcia MS, Gadanon-Garcia A, Rodriguez M, Varela M. Bone metastases as initial presentation of hepatocellular carcinoma. World J Hepatol. 2017;9(29):1158-65.

[9] Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006;12:6243s-6249s.
[10] Grill V, Ho P, Body JJ, Johanson N, Lee SC, Kukreja SC, et al. Parathyroid hormonerelatedprotein: Elevated levels in both humouralhypercalcaemia of malignancy and hypercalcaemia complicating metastatic breast cancer. J Clin Endocrinol Metab. 1991;73:1309-15.
[11] Tang ZY. Hepatocellular carcinoma-cause, treatment and metastasis. World J Gastroenterol. 2001;7:445-54.
[12] Ahmad Z, Nisa AU, Uddin Z, Azad NS. Unusual metastases of hepatocellular carcinoma (hcc) to bone and soft tissues of lower limb. J Coll Physicians Surg Pak. 2007;17(4):222-23.
[13] He J, Zeng ZC, Tang ZY, Fan J, Zhou J, Zeng MS, et al. Clinical features and prognostic factors in patients with bone metastases from hepatocellular carcinoma receiving external beam radiotherapy. Cancer. 2009;2710-20.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Pathology and Laboratory Medicine, AIIMS, Bhubaneswar, Odisha, India.
2. Associate Professor, Department of Pathology, KIMS, Bhubaneswar, Odisha, India.
3. Professor, Department of Pathology, KIMS, Bhubaneswar, Odisha, India.
4. Assistant Professor, Department of Orthopaedics, SCBMC, Cuttack, Odisha, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sarojini Raman,
Assistant Professor, Department of Pathology, AIIMS,
Bhubaneswar-751019, Odisha, India.
E-mail: sraman10371@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jan 20, 2025
- Manual Googling: May 01, 2025
- iThenticate Software: May 12, 2025 (6%)

ETYMOLOGY: Author Origin

EMENDATIONS: 5

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Jan 18, 2025**
Date of Peer Review: **Feb 07, 2025**
Date of Acceptance: **May 14, 2025**
Date of Publishing: **Dec 01, 2025**