BONE METASTASIS AS FIRST PRESENTATION OF HEPATOCELLULAR CARCINOMA

R.C. Bries, MD; C.R. Que-Ignacio, MD; J.T. Tullas, MD; R.F. Tan, MD; L.B. Gatchalian, MD; M.A.V. Chu, MD; S. Preza, MD; F.L. Domingo, Jr, MD

Section of Gastroenterology, Department of Internal Medicine

East Avenue Medical Center, East Avenue, Diliman, Quezon City, Philippines

Significance: Hepatocellular carcinoma usually metastasizes intraphepatically and extrahepatic metastasis are only seen in late stages and in 40-78% of patients with the most common site being the lungs, abdominal lymph nodes and the bone. This paper presents a case of a hepatocellular carcinoma in a 66-year-old old female who initially presented with bone pains.

Clinical Presentation: A 66-year-old, Filipino woman with no known comorbidities came in due to a 3 month history of right gluteal pain not relieved by medications. There were no other accompanying symptoms. Physical examination was unremarkable except for presence of right gluteal pain.

Management: Whole abdominal CT scan was done which revealed a fairly defined heterogeneously enhancing, lobulated mass in the right liver which had hyperemia on the arterial phase with delayed washed out. Liver biopsy done also revealed presence of well-differentiated hepatoceullular carcinoma and alpha-fetoprotein was also elevated. Patient was then started on Lenvatinib and referred to oncology for radiotherapy to address the bone metastasis.

Recommendation: Hepatocellular carcinoma presenting with bone metastasis is usually rare and very aggressive. Due to it being rare, optimal treatment strategies are not yet defined. Treatment usually includes a combination of chemotherapy with multikinase inhibitor and radiotherapy. In high prevalence countries like the Philippines, it is best to screen patients for hepatitis B to know patients who are at risk to develop hepatocellular carcinoma.

Keywords: hepatocellular carcinoma, bone metastasis, HCCA

BONE METASTASIS AS FIRST PRESENTATION OF HEPATOCELLULAR CARCINOMA

R.R. Bries, MD; C.R. Que-Ignacio, MD; J.E. Tullas, MD; R.I. Tan, MD; L.B. Gatchalian, MD; M.A.V. Chu, MD; S. Preza, MD; F.L. Domingo, Jr, MD

Section of Gastroenterology, Department of Internal Medicine

East Avenue Medical Center, East Avenue, Diliman, Quezon City, Philippines

Introduction

Hepatocellular carcinoma is the 5th most common cancer worldwide and 3rd leading cause of cancer deaths with a 5 year mortality rate of only 10% in late stages.[11] It is then prudent to diagnose it early. It usually presents with non-specific gastrointestinal symptoms like commonly abdominal pain, weight loss, generalized weakness and jaundice and screening is usually recommended in patients with cirrhosis and carriers of hepatitis B and hepatitis C. Hepatocellular carcinoma usually metastasizes intraphepatically and extrahepatic metastasis are only seen in late stages and in 40-78% of patients with the most common site being the lungs, abdominal lymph nodes and the bone.[1] This paper presents a case of a hepatocellular carcinoma in a 66-year-old old female who initially presented with bone pains.

Case presentation

Patient is a 66 year old female who was admitted due to right gluteal pain. History started 3 months prior to admission, patient started to complain of right gluteal pain, graded 5/10 in severity, pricking in character with accompanying numbness but was able to do activities of daily living. After 2 month (May 2019), there was still persistence of right gluteal pain. 1 month prior to admission, there was now increase severity of right gluteal pain now graded 10/10. Patient sought consult at a tertiary hospital in San Juan where patient was admitted for pain control with Paracetamol and Tramadol. Magnetic Resonance Imaging of the was done which revealed presence of osseous metastasis at the S1 to S2 with spinal stenosis as well as incidental finding of liver cyst. Patient was referred to orthopedic surgery service where patient was advised spinal surgery which they refused and decided to go home to rest. 1 week PTA, there was still presence of severe right gluteal pain not relieved by pain medications and is no longer able to lie flat/sit flat. Patient now prefers to stand up. Patient decided to sought second opinion with a rheumatologist which diagnosed patient to have spinal stenosis secondary to bone metastasis and was advised admission at our institution. Hence, was admitted.

Upon admission, patient was started on dexamethasone, morphine as well as pregabalin. Whole abdominal CT scan with triple contrast was requested which revealed a fairly defined, heterogeneously enhancing, lobulated mass in the right lobe measuring 12.1 x 8.9 x 12.0 cm (LxWxAP) and patient was then referred to our service for liver biopsy and co- management of liver mass. Upon referral to our service, we requested for hepatitis profile, alpha fetoprotein as well as triphasic scan of the liver. A liver biopsy was done which revealed well-differentiated hepatocellular carcinoma. Triphasic scan of the liver also revealed presence of hyperemia on the arterial phase with delayed wash out (Figure 1). AFP was also elevated (>1000.00) and hepatitis revealed presence of previous hepatitis infection with reactive anti-Hbc total. Patient was then diagnosed to have Hepatotcellular carcinoma BCLC B with possible bone metastasis, Liver Cirrhosis Child Pugh A secondary to past hepatitis B infection. Patient was then started on Linvatinib and was referred to oncologist who plans to start radiotherapy for the bone metastasis

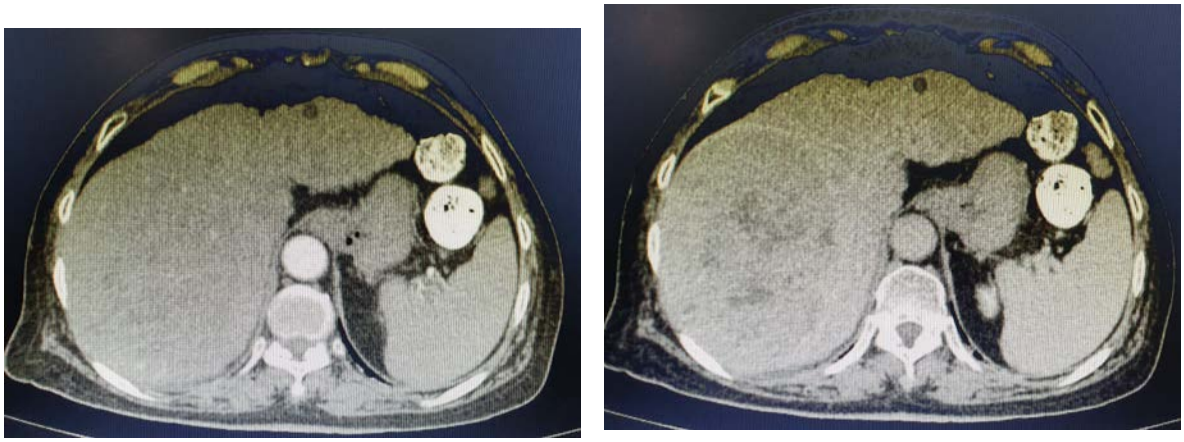

Figure1. Whole Abdominal CT scan with triphasic scan of the liver. CT scan noted presence of liver mass with presence of hyperemia on the arterial phase with delayed wash out

Discussion

The bone is one of the most common metastatic sites of cancers and presence of which usually connotes late stage cancer. In patients with bone metastasis, most frequently encountered primary cancers are prostate, breast, kidney, lung and thyroid and if none are seen, one must investigate other uncommon primary sites of bone metastasis.[2]

Hepatocellular carcinoma is the most common type of primary liver cancer. It is usually seen in patients with cirrhosis. Other risk factors included are those patients with chronic Hepatitis B and C, chronic alcohol consumption and non-alcoholic fatty liver disease. The incidence of hepatocellular

carcinoma in the world varies such that countries in Asia like China and Taiwan have more than 15 cases per 100,000 populations per year.[3]

Hepatocellular carcinoma usually metastasizes intrahepatically and that extrahepatic manifestations of hepatocellular carcinoma are uncommon and bone metastasis as initial presentation is very seldom. In a study done by Kim et. al., bone metastasis in hepatocellular carcinoma has an incidence ranging from 3-20%.[4] In hepatocellular carcinoma, most common bone involvement are the lumbar are (24%), followed by pelvic area (21%) and thoracic area (21%). In our patient, the bone metastasis was initially seen in the pelvic area.[4]

Bone metastasis is usually seen other cancer types most commonly in breast, prostate and lung. Bone metastasis in hepatocellular carcinoma occur due to the haematogenous spread of cancer cells which is due to the hypervascularity usually associated with this malignancy, which may facilitate this hematogenous spread. Therefore, hepatocellular cancer cells could invade the hepatic vein and disseminate through the pulmonary and systemic circulation. On the other hand, they may also tend to invade the portal vein, which results in portal thrombus that leads to dissemination to the vertebrae through the portal vein and/or vertebral venous plexuses route, as well as through systemic circulation. Also bone metastasis in hepatocellular carcinoma is usually the osteolytic type leading to bone destruction and fractures.[5]

In patients with hepatocellular carcinoma presenting with bone metastasis, optimal treatment strategies are not well defined because of its low incidence. According to a study done by Ruchi et. al, patients with bone metastases should be considered for chemotherapy or a bone-directed therapy, specifically local radiation, for localized disease.[6]

Systemic chemotherapy for hepatocellular carcinoma has been considered only in patients with advanced disease due to multiple effective loco-regional therapies that are in use for patients with unresectable disease confined to the liver.[7] However, overall response rate of cytotoxic chemotherapy like the most commonly used regimen (cis-dia- mminedichloroplatinum (CDDP) monotherapy) is quite low, and no combination regimen has been shown to have an increase in overall survival rate.

Sorafenib, a multikinase inhibitor, has been considered as an effective treatment for patients with advanced hepatocellular carcinoma with baseline ECOG PS (0–2) and Child–Pugh class A liver function just like in our patient. Lenvatinib which is the one used in our patient is also a multikinase inhibitor and was show to be non-inferior to sorafenib in overall survival in advanced hepatocellular carcinoma.[8]

Our goal in treating bone metastasis is for palliation of symptoms. Radiation therapy has previously been shown to provide effective palliation for skeletal lesions. A study by Seong et al. investigated the effectiveness of palliative radiation therapy for bone metastases from hepatocellular carcinoma. In that study, 51 patients received radiation therapy for a total of 77 metastatic bone lesions.[9] The median dose given was 30 Gy, with pain relief resulting in 56 (73%) lesions. Median survival from occurrence of bone metastasis was 5 months, with a 1-year survival of 15%. Another study now done by Choi showed the effectiveness of palliation for spinal metastases in patients with hepatocellular carcinoma. In that study, 192 patients receiving radiation therapy for spinal metastases from Hepatocellular Carcinoma were evaluated. Pain response was evaluated using the Brief Pain Inventory at the start of treatment, 2 weeks, and 3 months following the start of treatment. 41 (21.4%) had a complete pain response, and 151 (78.6%) were found to have a partial pain response.[10]

Conclusion

Hepatocellular carcinoma presenting initially bone metastasis is usually rare and very aggressive. Due to its low incidence rate, optimal treatment strategies are not yet defined. Also, the most commonly involved bone are the lumbar, thoracic vertebra and the pelvis. Treatment regimens for these patients usually involved a mixed of chemotherapy with a multikinase inhibitor which may improve median survival rate despite being a metastatic hepatocellular carcinoma. The use of radiation is not to improve the survival of the patient but it is used only for pain control. This case suggests that like in our country who still has a high prevalence of hepatitis B it is best to screen patients so that we can know patients who are at risked for developing hepatocellular carcinoma.

Bibliography

1. S. Katyal, MD, et. al (2000) **Extrahepatic Metastases of Hepatocellular Carcinoma.** *Radiology* Sept 2000 p. 698-703
2. A. Schmid-Alliana, et. al. (2018) **Understanding the Progression of Bone Metastases to Identify Novel Therapeutic Targets.** *Int J Mol Sci.* 2018 Jan; 19(1): 148.
3. D. Janevska, et. al. (2015) **Hepatocellular Carcinoma: Risk Factors, Diagnosis and Treatment.** *Open Access Maced J. Med Sci* 2015 Dec 15:3 (4); 732-736
4. Sangwong Kim, et. al. (2007) **Bone Metastasis from Primary Hepatocellular Carcinoma: Characteristics of Soft Tissue Formation.** *Cancer Res Treat.* 2007 Sep; 39(3): 104–108.
5. Marie Fukutomi, et. al. (2001). **Increased Incidence of bone metastases in hepatocellular carcinoma.** European Journal of Gastroenterology & Hepatology 2001, 13:1083±1088
6. Bhatia Ruchi, et. al. (2017) **Hepatocellular Carcinoma with Bone Metastases: Incidence,**

Prognostic Significance, and Management—Single-Center Experience. *J Gastrointestinal Canc* 11 Sept 2017

7. D. Germano and B. Daniele (2014) **Systemic therapy of hepatocellular carcinoma: Current status and future perspectives. *World Journal of Gastroenterology.*** 2014 Mar 28; 20(12): 3087–3099.
8. Masatoshi Kudo, et. al. (2018**) Lenvatinib versus Sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomized phase 3 non-inferiority trial**. *The Lancet.* Volume 391, Issue 10126, March 24, 2018, p 1163-1173
9. Seong J, Koom WS, Park HC. (2017) **Radiotherapy for painful bone metastasis from hepatocellular carcinoma.** Liver Int. 2005;25:261–265.
10. Chihwan Choi and Jinsil Seong (2015) **Predictive Factors of Palliative Radiotherapy Response and Survival in Patients with Spinal Metastases from Hepatocellular Carcinoma.** *Gut and Liver*, Vol. 9, No. 1, January 2015, pp. 94-102
11. John W. D. McDonald, et. al. (2019) **Evidence-Based Gastroenterology and Hepatology**. 4th ed. p 693