ORIGINAL ARTICLE

Skeletal metastatic distribution of HCC on ^{99m}Tc-MDP bone scan with a unique feature of Soft tissue component

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the 5th leading cancer which metastasizes to bones in 3%–20% cases. The routes of metastasis from HCC include hematogenous, lymphatic, or direct invasion/dissemination/ seedlings into the surrounding cavities. The ^{99m}Tc-methylene diphosphonate (MDP) bone scintigraphy is a sensitive imaging technique for early detection of skeletal metastasis.

Methods: Bone scans of 220 patients with HCC from 1st January 2012 to 31st December 2017, referred to Nuclear medicine department for evaluation of skeletal metastasis, were analyzed. About 70% presented with backache followed by rib cage pains (25%).

Results: Out of total 220 patients, 40 patients (18%) had skeletal metastasis on ^{99m}Tc-MDP bone scans, with solitary to multiple metastasis ratio was 1:9. Vertebrae were the most common site of metastasis (27/40 patients, 67%). Most striking characteristic of bone metastasis of HCC was the presence of soft tissue element in vertebral metastasis. This soft tissue element is responsible for compression symptoms in these patients. These soft tissue components were poorly outlined on routine planner bone scans due to poor^{99m}Tc-MDP uptake but were better diagnosed with Single Photon Emission Tomography / Computed Tomography.-

Conclusion: Skeletal metastatic distribution of HCC follows an unusual pattern on ^{99m}Tc-MDP bone scan with a unique feature of soft tissue component, especially in larger lesions involving spine. During radiotherapy planning, these soft tissue lesions must be included in the field of irradiation to improve post radiotherapy outcome and may play a vital role in determining progression or regression of the disease.

Keywords: Hepatocellular carcinoma (HCC), Bone metastasis, Soft tissue component, ^{99m}Tc-methylene diphosphonate (MDP) bone scintigraphy, ^{99m}Tc-MDP SPECT/CT.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the commonest primary liver tumors and the 5th leading cancer in the world. The incidence of HCC is even higher in the developing countries due to high prevalence of hepatitis C and Hepatitis B infections, with male-to-female ratio of approximately 2:4 [1,2]. The prevalence of hepatitis "C" is higher than hepatitis B (4.8 % *vs.* 2.5%). This high prevalence of hepatitis "C" infection in developing world is responsible for continuous rise in incidence of HCC [3]. The population of Pakistan is more about 220 million and 7.6 % of them are suffering from hepatitis [4]. In Past metastasis from HCC were seen rarely but trend has changed recently. Incidence of skeletal metastasis of HCC is increasing with increase in life expectancy and now accounts for 3%–20% of all HCC patients [5]. The ^{99m}Tc-methylene diphosphonate (MDP) bone scintigraphy (BS) is a sensitive imaging technique for the early detection of skeletal metastasis [6]. Skeletal metastases from HCC follow an unusual pattern and may accompany a soft tissue element (unique feature) as reported with computed tomography (CT) scan and magnetic resonance imaging (MRI) scans [7]. In the current study, we analyzed patients with HCC using ^{99m}Tc MDP bone scan with SPECT/CT to assess metastatic sites, pattern of distribution in skeleton, and accompanying soft tissue element.

MATERIAL AND METHODS

From 1st January 2012 to 31st December 2017, data of all patients with HCC referred to Nuclear Medicine Department for the evaluation of skeletal metastasis was analyzed. Total of 220 HCC patients (145 Males, 75 Females), referred to Nuclear Medicine Department for bone scanning were included in the study. All these patients were biochemically and radiologically proven cases of HCC based on high serum Alpha Fetoprotein (AFP) levels and radiological findings of ultrasound/multi-phasic CT scans. The age of patients ranged from 39 years to 74 years (Mean 56.5 ± 6). ^{99m}Tc-MDP bone scans of all patients were performed with Siemens single

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head E-cam and Infinia dual head gamma cameras equipped with low energy high-resolution collimators at 140 KeV peak with 20% energy window, to look for skeletal metastatic lesions. Bone scans of 40 patients showed skeletal metastasis. These 40 patients with skeletal metastasis were evaluated for the sites of metastatic involvement. Additional Single Photon Emission coupled with four slice low dose CT Hybrid imaging (SPECT/CT) was performed in 15 patients for further assessment of larger lesions in the spine.

RESULTS

From 1st January 2012 to 31st December 2017, 220 patients were referred for bone scan. In 90% patients, the prevailing symptom of presentation was bone pain. Out of which, 70% presented with backache followed by pains in the rib cage (25%) (Table 1). Out of 220 patients, 40 patients (18%) had skeletal metastasis on ^{99m}Tc-MDP bone scans.

Thirty were males and 10 were female with ratio of 3:1. Most patients with skeletal metastasis were having lesions at multiple sites. Solitary-to-multiple metastasis ratio was 1:9. Spine was the most common site of skeletal metastasis. Its involvement was in 67.5 % (27/40 patients), followed by the rib cage in 35 % (14/40 patients). Pelvic bones includes the hip joints in 17.5% (7/40 patients), upper limbs in 10% (4/40 patients), skull and sternum/clavicle each in 7.5% (3/40 patients), lower limbs 4% (1/40 patients), and scapula also in 4% (1/40 patients) (Table 2).

In skeletal metastatic lesions, vertebrae were the most common site of bone destruction (27/40 patients, 67%) with associated soft tissue component in larger spinal lesions. These soft tissue lesions were poorly outlined on routine bone scan due to poor ^{99m}Tc-MDP uptake. Due to poor ^{99m}Tc-MDP uptake, alone bone scan was unable to detect and characterize this soft tissue component associated with larger metastatic bone lesions in the spine (Figure 1). Additional Single Photon Emission Tomography / Computed Tomography (SPECT/CT) Hybrid imaging clearly showed bone destruction with associated soft tissue formation in the larger spinal lesions (Figure 2).

Table 1. Different parameters of patients included in the study.

Total number of patients (*N*1)	220
Number of patients with bone metastasis (*N*2)	40
Age (Mean)	55 years
Male: Females ratio	3:1
Hepatitis (C:B)	7:1
AFP Levels (Mean)	956
Bone pains in patients with metastasis (Yes:No)	9:1
Mets (Single:Multiple)	1:9

Table 2. Distribution of skeletal metastasis from HCC according to sites of involvement.

Sites of lesions (Bone metastasis)	Number of patients with metastasis (40)
Skull/Facial bones	3
Vertebrae, sacrum, Coccyx	27
Sternum/clavicle	3
Rib cage	14
Pelvic bone	7
Upper limbs	4
Lower limbs	1
Scapula	1

DISCUSSION

The incidence of viral hepatitis is high in developing countries. Hepatic parenchymal disease due to Hepatitis "C" Virus (HCV) and Hepatitis "B" Virus is common. Late presentation and delayed management of these patients due to poor socioeconomic status leads to multiple complications. A considerable proportion of these patients develop HCC as a fatal complication [8].

Metastatic lesions from HCC have been reported in almost every part of the body. The routes of metastasis from HCC include hematogenous, lymphatic, or direct invasion/dissemination/seedlings into the surrounding cavities. Hematogenous spread is the most common mode of spread. Lungs involvement via pulmonary capillary network is the most common site of distant lesions followed by adrenals, bones, and brain [9,10]. Lymphatic spread with involvement of regional and distal groups of lymph nodes is also seen. It is very important to differentiate these metastatic lymph nodes from benign enlarged lymph nodes seen in cirrhotic patients. Dissemination of tumor cells to peritoneum can be through direct extension by larger tumors invading the capsule or by seedlings implanted into the peritoneum via ascitic fluid [11].

In HCC, incidence of skeletal metastasis is rising (18% in our study) with unpredictable patterns of skeletal metastatic distribution on ^{99m}Tc-MDP BS [5]. Pain is often the principal symptom of presentation in patients with skeletal metastasis [12]. Most of our patients (25 out of 40 patients) complained of backache, while few (4 out of 40 patients) presented with pain in the rib cage.

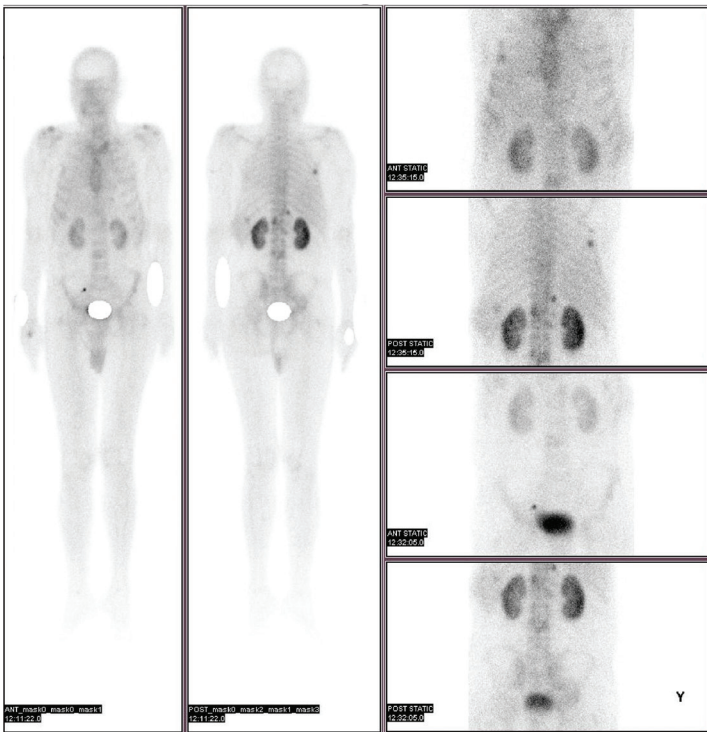

Figure 1. ^{99m}Tc-MDP bone scintigraphy of a patient with HCC showing multiple skeletal metastatic lesions.

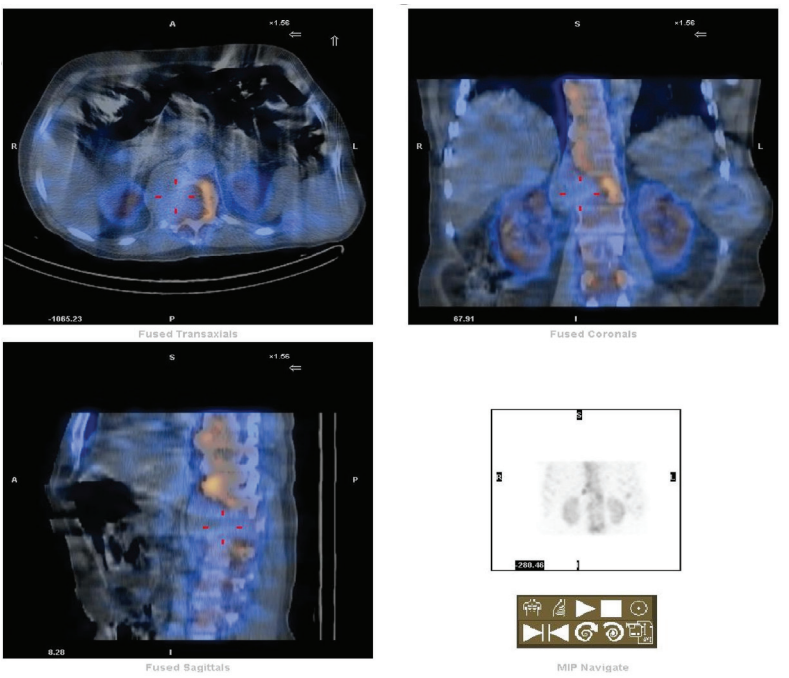

Figure 2. ^{99m}Tc-MDP SPECT/CT of patient with HCC showing soft tissue formation at the site of vertebral metastatic lesion as seen as para-vertebral soft tissue mass.

Most striking characteristic of bone metastasis of HCC was the presence of soft tissue element, especially in larger vertebral metastasis. This soft tissue element is under-diagnosed on simple bone scan alone as they appear as cold spots (Photon deficient), and therefore require additional CT scan/MRI scan for diagnosis, where they appear as soft tissue paravertebral masses [5]. This soft tissue element is responsible for compression symptoms and its localization is important for radiotherapy as a treatment [7]. Radionuclide (^{99m}Tc-MDP) planer BS usually underestimates the extent of these lesions as most of these metastatic lesions in the spine are osteolytic (Figure 1). Additional ^{99m}Tc-MDP SPECT/CT hybrid imaging clearly outlined these osteolytic lesions with high incidence of expansile soft tissue component seen (Figure 2). These lesions show infiltrative tendency to adjoining muscles and fatty tissues causing symptoms, i.e., pain, the most common one. They may exhibit compression symptoms, especially at vital sites like spinal cord, leading to pain, numbness, and limbs weakness. This is of utmost importance when it comes to treatment planning, i.e., irradiation of metastatic lesions. During radiotherapy planning, these soft tissue lesions must be included in the field of irradiation to improve post radiotherapy outcome. Pain can be the only presenting symptom in cases of direct invasion of ribs/sternum [5].

The ratio of single to multiple skeletal metastatic lesions was 1:9. This was contradictory to studies done by Mostafa et al. and Kim et al., who stated that most of the patients presented with single skeletal metastatic lesions [7]. This may be due to variable factors like different population, low health facilities, high incidence of chronic HCV, and different genotypes in our country.

Skeletal metastatic lesions from HCC showed unpredictable distribution. The central axial skeleton was the most common site of skeletal metastatic involvement, i.e., 75% (30/40 patients) in our study, which was contradictory to findings of Kuhlman et al. [13]. Rib cage was the most common site of metastatic involvement from HCC in that study. This may be due to regional variability. Out of 30 patients with axial skeleton involvement, 27 patients (90%) showed vertebral lesion, while 3 patients (10%)

showed lesions in the skull. Metastatic spread from HCC to vertebra had been attributed to hematogenous dissemination of tumor cells through portal vein-vertebral vein plexuses after portal vein thrombosis by vascular invasion by HCC [5]. In our study, the second most common site of metastatic involvement was rib cage, i.e., (14/40, 35%). Our finding was contradictory to findings by Qureshi et al. [14], and Hyun et al. [15], who reported metastatic lesions in rib cage as anecdotal cases in literature. The third commonest site of metastatic involvement was pelvic bones (7/40 patients, 17.5%) which can also be explained via spread through portal vein-vertebral vein plexuses. This was contradictory to the findings by Mostafa et al. who stated pelvic bones to be the most un-common site of skeletal metastasis in patients with HCC. Few studies have reported pelvic bones as the second most common site of metastatic involvement from HCC [8]. Upper limbs were involved in 4/40 patients (10%) followed by skull and sternum/clavicle each in 3/40 patients (7.5%). In our study, lower limbs & scapula both were the least common site of metastatic involvement, i.e., 1/40 patients (4%).

CONCLUSION

HCC has high propensity for bone metastasis with unpredictable patterns and high regional variability. The presence of soft tissue element with larger vertebral bone metastatic lesions is a unique feature of HCC that may be responsible for symptoms like pain, numbness and weakness of lower limbs. During radiotherapy planning, these soft tissue lesions must be considered, to be included in the field of irradiation to improve post radiotherapy outcome. Soft tissue element is better diagnosed with ^{99m}Tc-MDP SPECT/ CT than ^{99m}Tc-MDP planner bone scan. Diagnosis of soft tissue element is also important in determination of progression or regression of the disease.

List of Abbreviations

BS	Bone scan
CT	Computed Tomography
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
MDP	Methylene diphosphonate
MRI	Magnetic Resonance Imaging
SPECT	Single Photon Emission Computed Tomography

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Ethical approval

Ethical approval was sought from Ethics Review committee, PINUM Cancer Hospital, Ref No. PINUM/EC/03-19 dated 6-8-2019.

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