ORIGINAL ARTICLE

The many, atypical presentations of musculoskeletal hepatocellular carcinoma (HCC) metastases

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Received 17 June 2014; accepted 23 August 2014
Available online 20 September 2014

KEYWORDS
HCC; Odd; Expansile; Skeletal; Metastatic

Abstract Purpose: To demonstrate many uncommon, non-classical clinical presentations of HCC that have been gathered from an endemic region in the Nile Basin.

Patients and methods: We will highlight cases of high quality MDCT performed for various clinical symptoms not classically associated with advanced or metastatic HCC and the role of image-guided biopsy in diagnoses. These include: (a) gradual progressive weakness of lower limbs; (b) Retrosternal pain not responding to medications; (c) severe right hip pain; (d) progressive cheek swelling. These symptoms further corresponded to musculoskeletal abnormalities, not typically associated with HCC, including: (a) lumbar spinal cord compression by expansile vertebral body lesion; (b) direct invasion of chest wall; (c) large expansile metastasis of right acetabulum; (d) expansible rib lesions with rib destruction; (e) painful cheek swelling.

Results: In numerous patients with a range of non-specific musculoskeletal complaints and various clinical presentations, the final diagnosis was HCC. The clinical presentation was dependent on uncommon skeletal deposits which were often expansile with the local effect of compression as underlying cause for the odd presentation. The important role of MDCT and Histopathological assessment in making correct diagnosis will be stressed.

Conclusion: HCC can often grow silently and may present late with odd non-classic clinical presentation.

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide (1). Major etiologic factors associated with HCC include infection with hepatitis C (HCV) and hepatitis B (HBV) viruses, excess alcohol intake and aflatoxin B1 exposure (2,3). HCC, with and without HCV infection, represents a major health problem in Egypt, where the two
pathological conditions are integrated in most cases (4). In Egypt, the incidence of HCC is increasing according to the National Cancer Institute records; the incidence of liver cancer is 21.9 and 4.5 per 1,000,000 per year in males and females respectively.

HCC causes about 1 million deaths each year worldwide. Patients usually present at an advanced stage when the growth is intractable as there are no early presenting symptoms and because of its great propensity for intra-biliary and intravascular invasion even when the tumor is small (5).

Metastasis from HCC occurs by hematogenous and lymphatic routes. Extra hepatic hematogenous metastasis indicates poor prognosis, it occurs in approximately 37% of patients. Common sites of metastatic spread include the lungs, intra-abdominal organs, bones, adrenals, lymph nodes, peritoneum and, rarely, skeletal muscle. Together spread of disease to the bones and muscle accounts for approximately 16% of all metastases. Metastasis to the skeletal muscles is extremely rare (6–8), especially chest wall muscles, gluteus muscle and anterior abdominal wall muscles.

Bone metastases from HCC are common and the incidence may range from 1 to 20% (9). Less frequently, bone metastases may be the first symptom of HCC. Bone metastases, isolated or multiple, from unknown primary HCC are exceptional and only a few case reports have been documented (9–12).

The aim of this study is to highlight and demonstrate many uncommon, non-classical clinical presentations of HCC that have been gathered from an endemic region in the Nile Basin.

2. Patients and methods

2.1. Patients

This study was approved by the ethics committee of our institution during the period between 2009 and 2013. It included 45 patients collected and selected retrospectively from about three hundred patients who came to the outpatient CT suite and interventional radiology unit in the El Minia University Hospital (referral hospital in upper Egypt), presented with a variety of clinical symptoms not classically associated with advanced or metastatic HCC. Patient age ranged from 33-80 years, 32 were males and 13 females. Three groups of patients were imaged for these clinical symptoms, the first group (a) Patients not known to be clinically or laboratory diagnosed as HCV or HBV positive and their first diagnosis by imaging was metastatic HCC. Second group; (b) Patients clinically and laboratory diagnosed as chronic liver disease (CLD), and their presentation was the metastatic complications of HCC. Third group; (c) patients clinically diagnosed as HCC, some of these patients were under various lines of percutaneous minimally invasive therapies (TACE and RF ablation). Skeletal metastatic manifestations were diagnosed during follow up as disease progression by imaging follow up.

Various clinical manifestations draw our attention to these skeletal metastasis included: (a) gradual progressive weakness of both lower limbs; (b) retrosternal pain not responding to medications and painful chest wall swellings; (c) severe hip and sciatic pain; and (d) progressive cheek swelling. These symptoms further corresponded to musculoskeletal abnormalities, not typically associated with HCC, including: (a) lumbar spinal cord compression by an expansile vertebral body lesions; (b) direct invasion of the chest wall; (c) a large expansile metastasis of the acetabulum and iliac bones; (d) expansible rib lesions with underlying rib destruction, and (e) painful cheek swelling.

High quality MDCT for the skeletal lesions was performed for all patients with the previous clinical symptoms that were not classically associated with advanced or metastatic HCC. Image-guided biopsy was performed for all patients from the metastatic lesions to confirm the diagnosis of HCC, to decide if we are going to perform ultrasound and multiphasic contrast MDCT imaging studies for patient’s liver searching for primary hepatic lesions.

2.2. Procedures

– Skeletal imaging using monophasic continuous scan after IV contrast material injection
– Multiphasic MDCT imaging of the liver was performed in hepatic arterial phase (HAP), portal vein inflow phase, and portal venous phase (PVP).
– CT, US guided tissue biopsy and histopathological assessment were the corner stone in our study to confirm the correct diagnosis of metastatic HCC in various parts of the skeleton and accordingly, we proceeded to further steps in the diagnosis of HCC, more skeletal survey to search for more skeletal lesions. Image guided biopsy was done for the patients of the first group and most of the patients of second group.

2.2.1. CT guided biopsy technique

Patients lie in a proper position according to the lesion location on the CT scanner couch. For the lesions in the spine, patients were in a prone position and the back was dripped well by disinfectant (Betadine) for at least 5 min. The lesion of interest was imaged to localize the target area for biopsy, and then skin mark was put to start the procedure by infiltration of local anesthetic agent starting from the skin deeply to the level of the periosteum to reduce pain. Co axial system was introduced to deliver the cutting needle to the region of interest. This co axial system was introduced using a CT fluoroscopy monitor in the CT suite (Bright Speed 16; GE Medical Systems). In cases of lesions with eroded bony cortex, introduction of the semi-automatic biopsy needle was done through co axial system to perform biopsy directly. At least two tissue cores were taken from the center and the periphery of the lesion to guarantee the presence of enough malignant tissue in the sample. In cases with intact bony cortex semiautomatic needle was not able to puncture the cortex and manual drilling by using bone biopsy set was used to take a full thickness core involving the cortex and the lytic portion of the lesion. (Bone biopsy needles were supplied by the same manufactures of the semiautomatic biopsy needle).

The biopsies are performed by using a 16-gauge core biopsy needle (Disposable semiautomatic biopsy instrument with variable throw, GMT GT50, German Medical technology (Beijing) Co., Ltd.). All NCBs were performed in a similar fashion using ultrasound or CT guidance to determine the needle position within the lesion. NCBs were collected into formalin, processed, sectioned, stained with hematoxylin and eosin and mounted using a DPX mounting medium. Representative sections were photographed under bright field optics using an Olympus light microscope.
**Table 1** Acquisition parameters of a 16-detector MDCT scanner (Bright Speed 16; GE Medical Systems).

<table>
<thead>
<tr>
<th>Phase</th>
<th>Thick speed</th>
<th>Interval mm</th>
<th>FOV</th>
<th>kV</th>
<th>mA</th>
<th>Total exposure time</th>
<th>Start preparation</th>
<th>Scan type</th>
<th>Beam collimation(mm)</th>
<th>Detector configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial</td>
<td>5</td>
<td>16</td>
<td>1.375:1</td>
<td>27.5</td>
<td>5</td>
<td>Large</td>
<td>120</td>
<td>7.9</td>
<td>25 s</td>
<td>Helical full</td>
</tr>
<tr>
<td>Portal</td>
<td>5</td>
<td>16</td>
<td>1.375:1</td>
<td>27.5</td>
<td>5</td>
<td>Large</td>
<td>120</td>
<td>13.7</td>
<td>65 s</td>
<td>Helical full</td>
</tr>
<tr>
<td>Delayed</td>
<td>5</td>
<td>16</td>
<td>1.375:1</td>
<td>27.5</td>
<td>5</td>
<td>Large</td>
<td>120</td>
<td>7.9</td>
<td>3 min</td>
<td>Helical full</td>
</tr>
</tbody>
</table>

**Fig. 1** Patient from the first group, presented with progressive lower limb weakness. (A,B) MDCT sagittal and coronal images of the lumbar spine showing solitary expanding lytic bony lesion involving the posterior portion of the vertebral body of the 5th lumbar vertebra with epidural component compressing the thecal sac. The pedicles are spared. (C) Axial CT image showing multiple enhanced lesions in the arterial phase of contrast enhancement. (D) Hematoxylin and eosin-staining of a representative moderately differentiated hepatocellular carcinoma sections showing groups of hepatocytes forming a thickened trabecular pattern lined by endothelial cells. The hepatocytes have increased nuclear/cytoplasmic (N:C) ratio and occasional prominent nucleoli.
2.3. Liver imaging

2.3.1. Imaging and image processing techniques

2.3.1.1. Imaging acquisition. CT studies were performed using a 16-detector MDCT scanner (Bright Speed 16; GE Medical Systems). The liver was scanned with a single breath-hold of 20-25 s. Contrast material was injected with a power injector (Medrad, Stellant) through an 18- or 20-gauge catheter into the antecubital vein. The injection rate was 3 mL/s. A total of 80-120 mL of nonionic contrast material was used. A timing bolus tracking technique was employed. The acquisition parameters were summarized in Table 1.

2.3.1.2. Image reconstruction. For image reconstruction, the axial source images with a 5 mm slice were transferred to an Advantage Workstation (AW) Volume Share 2 (GE Healthcare). Multiplanar reformatted images (MPR) images were obtained in the coronal and sagittal planes with a section thickness of 5 mm (Table 1).

3. Results

In the selected group of patients with a wide range of non-specific musculoskeletal complaints and various clinical presentations, the final diagnosis was HCC. The clinical presentation was dependent on uncommon skeletal deposits which were most often expansile with the local effect of compression as the underlying cause for the odd presentation (see Figs. 1–7).

First group of patients was surprisingly diagnosed as skeletal metastasis from HCC while they were not previously diagnosed as chronic liver disease or HCC patients. This group included 11 patients, 7 patients were complaining of lower limb related manifestations ranged from unrelieved sciatic pain to various degrees of lower limb weakness, imaging revealed expansile lytic bony lesions involving the vertebral bodies extending and compressing the adjacent bony lumbar canal and neural exit foramen, associated with a large soft tissue component extending to the para spinal

Fig. 2 Patient from the second group, presented with retro sternal pain not responding to medications, (A,B,C) MDCT axial and sagittal images of the upper abdomen and the lower chest showing left lobe hepatic lesions with direct extension to the retro sternal region which is seen inseparable from the posterior portion of the lower chest wall (sternum). (D) Hematoxylin and eosin-staining of a representative moderately differentiated hepatocellular carcinoma sections showing groups of hepatocytes forming a thickened trabecular pattern lined by endothelial cells. The hepatocytes have increased nuclear/cytoplasmic (N:C) ratio and occasional prominent nucleoli.
muscles. Two patients were complaining of painful chest wall swelling involving and destructing the ribs with sizable soft tissue component, one patient complained of headache associated with painful skull swelling and the referring neurosurgeon asked for CT brain with bone window for the skull, the lesion found as a soft expanding lytic bony lesion destructing the underlying skull bone with involvement of the dural coverings and small intra cranial extension. Two patients in this group were persistently complaining of hip joint pain and the referring orthopedic surgeon asked for scanning pelvis and hip joints for osteoarthritis, the result was destructive, expansile lytic bony lesions at the acetabular roof extending to the joint space (Table 2). Diagnosis in this group was suspected clinically and confirmed by high quality MDCT images, biopsy was crucial as a final confirming diagnostic tool to proceed to a further step to scan the liver searching for HCC diagnosis which was odd.

Second group; patients were previously diagnosed as chronic liver disease (CLD) either HCV or HBV positive carriers, they were on follow up schedule and medical treatment, the indications for CT scanning was either the site of complain or the rising level of alpha fetoprotein in their serum. This group included 15 patients (Table 2), seven patients were diagnosed as spinal deposits with various degrees of compression on the thecal sac, spinal cord, and neural exit foramina as well as para vertebral soft tissue component. Three patients were complaining of painful rib swellings, one patient of unexplained retro sternal pain not responding to medications, scanning the abdomen and the lower chest revealed left hepatic lobe hepatoma directly invading the lower part of the anterior chest wall. Three patients presented with skull vault and facial swellings. One patient presented with painful left iliac bone swelling extending to the adjacent ischio-rectal fossa (Table 2). Diagnosis in this group was relatively easier as the previous medical background made clinical suspicious directed toward the presence of CLD and its complications, metastatic HCC was the diagnosis both radiologically and pathologically.

Fig. 3 Patient from the second group, presented with unexplained right hip joint pain, (A,B) MDCT coronal images of the pelvis showing destructive lytic bony lesion involving the roof of the right acetabula reaching the articular surface of the right hip joint space. (D) Axial CT image of the liver showing left lobe hepatic lesion. (D) Hematoxylin and eosin-staining of a representative moderately differentiated hepatocellular carcinoma sections showing groups of hepatocytes forming a thickened trabecular pattern lined by endothelial cells. The hepatocytes have increased nuclear/cytoplasmic (N:C) ratio and occasional prominent nucleoli.
Third group; Patients already diagnosed as liver cirrhosis complicated by HCC on top, they were either on follow up or under treatment. In these 19 patients MDCT imaging revealed lytic bony lesions in different regions in the skeleton related to their site of complain. 12 out of 19 patients underwent MDCT scanning for the liver to assess treatment outcome after minimally invasive therapies (TACE and RF ablation), lytic spinal and pelvic lesions were encountered as disease progression after TACE and or RF ablation in the form of distant skeletal metastasis of the same characters described in the first group. Two patients had painful expanding rib swelling, two developed disfiguring skull swellings one showed ulcerated overlying skin, the oncologist referred them as a part of metastatic work up. Two patients suffered from pelvic pain, the imaging results revealed acetabular and iliac lesions destructing bones (Table 2). Diagnosis in this group was much easier as the patients were already known to be HCC under follow up schedule or under treatment, distant metastasis was considered a disease progression or treatment failure and biopsy was not done in this group.

Twenty-nine patients had single metastatic lesions, while 16 patients had multiple lesions at different parts of the skeleton. The number and distribution of bone metastasis and their site of preference were summarized in (Table 3).

4. Discussion

HCV, HBV and the resulting chronic liver disease are the most distressing health problems in Egypt in the recent decades, HCC is the terminal complication of CLD in most patients. Lack of medical care, health insurance, poverty and low socioeconomic standard add a heavy burden for the problem, making the patient to seek medical advice very late in the disease course, always after the appearance of complications.

Few data in the literatures are available about skeletal metastasis of HCC that make this kind of odd presentation.
of our patients surprising as a first presentation. Patients in the first group of the study presented by the complications without previous knowledge of being chronic liver patients and most of them were HBV positive carriers.

The frequency and distribution of bony metastases from HCC in this study were peculiar, especially in the first group that included 11 patients, in whom the first symptoms were bony metastases from unknown primary, HCC. Eleven patients is a considerable number compared to the published data by Qureshi (13) who reported that bony metastases as a first presentation of unknown HCC is rare and exceptional and only reported in very few case reports. Moreover the addition of image guided biopsy and microscopic confirmation add more strength in proving the odd skeletal metastases in 26 patients (1st and 2nd groups) from undiagnosed HCC in one clinical study in a four year time interval compared with the study by Kim (14) which included 53 patients over 10 years, our hospital is a referral hospital that made the time interval of our study groups of patients shorter compared with the others.

The characteristic MDCT imaging features of nearly all the detected skeletal metastases were large, destructive, osteolytic lesions with expansile soft tissue formation that exert compression of the underlying structure resulting in specific clinical presentations that correspond to the presenting clinical complaints of each patient, as progressive lower limb weakness due to spinal compression and resistant retrosternal pain due to direct sternal invasion from left hepatic lobe lesion. Some studies with a limited number of patients have described the characteristics of bone metastasis from HCC, such as soft tissue formation (15-19). Kim (14) confirmed the characteristic finding of soft tissue formation at a bone metastasis from a primary hepatocellular carcinoma.

Most of the metastatic bony lesions were single, they were encountered in 29 (64.4%) out of 45 patients, while 16 patients had multiple metastatic lesions. This nearly match study done...
by Kim (14) who reported that 37 patients had a single metastatic site, while 16 patients had multiple lesions. HCC in its odd presentation found to have special preference to the skeleton, the most common was the axial skeleton (71%), vertebrae and skull in 26 and 6 patients respectively. Dissemination of hepatocellular carcinoma cells to the vertebra was explained by Fukutomi (20), who reported that spread occurs through the portal vein-vertebral vein plexuses due to the presence of early vascular invasion mainly portal thrombus and/or portal hypertension. HCC metastatic lesions were either solitary or multiple with no specific order of frequency or explanation of either. These results conceded with that of Kim (14), Fukutomi (20), and Sneag (21), however the order of frequency and distribution of lesions in our result was in contradiction to their studies, a finding that may intensify the possibility of own specific distribution pattern of skeletal metastases from HCC in Egypt.

The second common site of metastases is the chest wall, it was found in 8 patients, and majority of them (6 out of 8 patients) were included in the 1st and 2nd groups, this was in contrary to the study of Qureshi (13) and Hyun (22) who postulated that bone metastases localized to the chest wall from unknown primary hepatocellular carcinoma are scarcely reported as anecdotal case reports in the literature.

Metastasis to the skull frequently occurs in patients with lung, breast and prostate cancer. However Hsieh (23) and Chan (24) had addressed that skull metastases from HCC have been rarely reported. In our results, skull was the third common site of bone metastases and it was detected in 6 patients, the lesions were osteolytic for both the outer and inner tables of the skull having extra and intra cranial components.

Pelvic bone was the least common site of skeletal metastases, it was found in only 5 patients in contrary to previous studies which reported that pelvic bones including the hip joints was the 2nd most common site of bony metastases from HCC (14,20,25).

HCC skeletal metastases in this study seem to exhibit unusual non classical clinical presentation associated with HCC resulting mostly from deposits in the axial skeleton with secondary compression effect.

Fig. 6 Patient from the third group, presented with painful cheek swelling. (A,B) MDCT axial and coronal images showing large expanding lytic bony lesion involving the left portion of the zygoma encroaching upon the left maxillary air sinus. (C) Axial CT image during the arterial phase of contrast enhancement showing sizable enhanced left lobe lesion. (D) Hematoxylin and eosin-staining of a representative metastatic hepatocellular carcinoma section shows sheets and small groups of hepatocytes with marked polymorphism and hyperchromatism. The malignant cells are surrounded by desmoplastic reaction.
5. Conclusion

HCC is a very common terminal complication of chronic liver disease, it can often grow silently and may present late with an odd non-classic clinical presentation which was not known before. Egyptian HCC looks to have unusual presentations by its tendency to have more aggressive behavior and preference to skeletal metastasis, mostly due to early vascular invasion. Underlying genetic abnormality should be stressed in the future researches, international multicenter studies from different endemic countries in the world should be carried out to figure out these odd non classical presentations.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Showing various clinical groups of patients and the distribution of skeletal lesions at different regions of the bony skeleton.</th>
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<tbody>
<tr>
<td>Spine</td>
<td>Chest wall</td>
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<tr>
<td>First group (11 patients)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>5 lumbar spine</td>
</tr>
<tr>
<td>Second group (15 patients)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>6 lumbar spine</td>
</tr>
<tr>
<td>Third group (19 patients)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>11 Lumbar spine</td>
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</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Showing number of lesions, single or multiple and which is the site of preference by each lesion.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single lesions</td>
<td>%</td>
</tr>
<tr>
<td>First group (11 patients)</td>
<td>8 patients</td>
</tr>
<tr>
<td>Second group (15 patients)</td>
<td>10 patients</td>
</tr>
<tr>
<td>Third group (19 patients)</td>
<td>11 patients</td>
</tr>
</tbody>
</table>

Fig. 7 Patient from the third group, underwent TACE for right hepatic lobe lesion 6 month follow up images revealed metastatic lesions, (A) MDCT coronal image showing dense lipidol particles in the lesion, bilateral supra renal metastatic deposits more evident at the left side as well as lytic bony lesion seen at the 4th lumbar vertebra. (B,C) axial CT images showing expanding lytic bony lesions involving the vertebral body of the 4th lumbar vertebral and the left iliac bone. (D) Hematoxylin and eosin-staining of a representative metastatic hepatocellular carcinoma section shows sheets and small groups of hepatocytes with marked polymorphism and hyperchromatism. The malignant cells are surrounded by desmoplastic reaction.
Conflict of interest

The authors declare no conflict of interest.

References