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CASE REPORT

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Cannonball Pulmonary Metastases as Initial Presentation of Hepatocellular Carcinoma: A Case Report and Literature Review

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Abstract

Background Hepatocellular carcinoma is a major public health problem, as is considered the fastest growing cause of cancer-related death. Cannonball metastases as an initial finding in hepatocellular carcinoma are considered a rare phenomenon.

Case Presentation A 59-year-old man presented to the outpatient clinic for subacute cough, asthenia, and involuntary weight loss. Chest X-ray showed multiple, round, bilateral pulmonary solid lesions. Contrast-enhanced computed tomography of the chest and abdomen revealed multiple bilateral, contrast-enhanced pulmonary nodules known as "cannonball" lesions and a heterogeneous lesion located in the right lobe of the liver with retroperitoneal lymphadenopathy. A biopsy was performed, and the histopathological result was compatible with metastatic poorly differentiated hepatocellular carcinoma. Due to the advanced stage of the disease, the patient received palliative care and expired two months later.

Conclusion Cannonball metastases in hepatocellular carcinoma are considered a rare finding and represents a poor prognosis. It is important to awaken the interest of clinicians in a timely diagnosis, as well as a possible suspicion of hepatocellular carcinoma in patients with this radiographic pattern.

Keywords Hepatocellular carcinoma, Metastases, Cannonball metastases, Pulmonary metastases, Case report

Background

Hepatocellular carcinoma (HCC) is the most common form of liver cancer and accounts for approximately 90% of cases worldwide. HCC represents a major public health problem, as it is considered the fastest growing cause of cancer-related death in the United States and if this trend continues, it is estimated to become the third leading cause of cancer-related death by 2030 [1].

There is a spectrum of clinical presentations depending on the stage of HCC. It is estimated that up to 50% of HCC cases, particularly in developing countries, may present incidentally with advanced stage HCC, identified on a cross-sectional imaging study performed for other reasons or after developing symptomatology such as malaise, loss of appetite, weight loss, abdominal pain, or worsening liver dysfunction, leading to an overall poor prognosis [1].

The presence of extrahepatic metastases, which occurs in 13.5-42% of cases, is considered a terminal stage of HCC. The most common extrahepatic metastatic sites are lung, followed by the lymph nodes, and bone. HCC metastases to the lungs are commonly described as single or multiple lesions [2]. However, cannonball metastases

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as an initial finding in HCC are considered a rare phenomenon and, to the best of our knowledge, few cases have been described in the literature.

Herein, we report the case of a rare, but clearly recognized case of widespread cannonball pulmonary metastases as initial presentation of HCC.

Case presentation

A 59-year-old man presented to the outpatient clinic for subacute cough, asthenia, loss of appetite, and involuntary weight loss of one month's duration. Relevant past medical history included obesity, metabolic dysfunction-associated steatotic liver disease as well as remission of type 2 diabetes after lifestyle modification by using a low-calorie diet and significant increase in physical activity. Physical examination revealed decreased breath sounds in the right lung. The rest of the physical examination was unremarkable, and the patient was vitally stable. Initial laboratory results demonstrated a white blood cell count of 11.5 (4.5-11) cell/dL, hemoglobin 15 (11.5-18) g/dL, platelet count 155 x 10^3/mm^3 (150-450), alanine aminotransferase 65 (20-60) UI/L, aspartate aminotransferase 68 (20-60) UI/L, albumin 3.1 (3.5-5.2) g/dL, lactate dehydrogenase 455 (180-310) UI/L, total bilirubin 0.90 mg/dL (0.0-1.2), direct bilirubin 0.35 mg/dL (0.0-0.3), indirect bilirubin 0.55 mg/dL (0.0-0.8), prothrombin time 13.1 seg (10-15), partial thromboplastin time 28.4 seg (20-35.5), INR 1.09 (0.8-1.2), glucose 135 (60-100) mg/dL, creatinine 1.1 (0.5-1.2) mg/dL, alpha-fetoprotein concentration 16.71 ng/mL (0.0-8.7). Serological panels for hepatitis B virus (HBV) and hepatitis C virus (HCV) showed HBsAg (-), HBeAg (-), Anti-HBc (-), Anti-HBs (+), Anti-HBe (-), HBV-DNA (-); Anti-HCV (-), HCV-RNA (-). A chest radiograph was performed and showed multiple, round, bilateral pulmonary solid lesions of variable sizes (Fig. 1). Metastatic malignancy was suspected, and a contrasted computed tomography (CT) scan of the chest, abdomen and pelvis was performed. Chest CT revealed multiple bilateral, well-circumscribed pulmonary nodules (8-11 mm) with a density of 40 Hounsfield Units (HU) and contrast-enhanced to 51 HU (Fig. 2). This pattern is known as "cannonball" lesions. CT scan of the abdomen and pelvis revealed a heterogeneous lesion located in the right lobe of the liver measuring 174 by 172 mm with a density of 47 HU in single phase and 61 HU in contrast-enhanced phase. Retroperitoneal lymph node growths with diameters of 12 mm were reported. The patient was classified as Class A according to the Child Pugh classification system. Pulmonary metastases secondary to HCC were suspected, so ultrasound-guided tru-cut biopsy of the right hepatic lobe mass was performed. Histopathologic examination revealed liver tissue with replacement of normal parenchyma at the expense of a neoplasm with acinar and trabecular pattern, atypical hepatocytes, polygonal cells with severe pleomorphism, dense granular cytoplasm and eosinophilic nucleolus, atypical mitoses, and necrosis. Immunohistochemistry tests were positive for HepPar1 and CD34, and negative for CK7, CK20, P40, GATA3 and TTF1. These findings were consistent with poorly differentiated invasive HCC (Fig. 3). Due to the advanced stage of the disease, the patient refused chemotherapy and received palliative care and expired two months later.

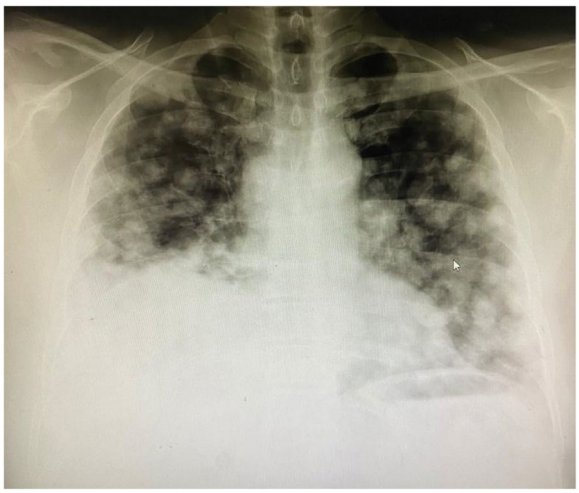

Fig. 1 Chest radiograph showing multiple, round, well-circumscribed, bilateral lung lesions of different sizes

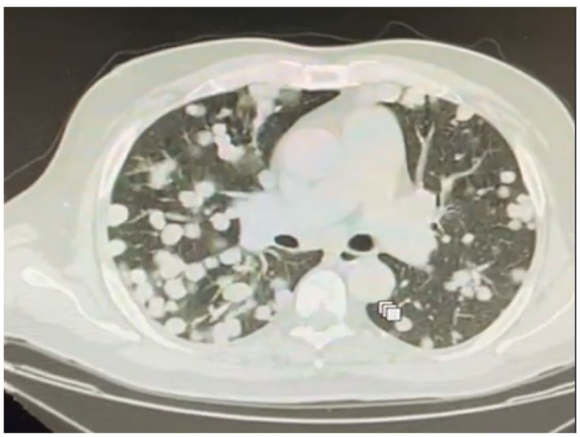

Fig. 2 Chest CT (lung window) revealing multiple bilateral, well-circumscribed pulmonary nodules (8-11 mm). These are 'cannonball' in appearance

Discussion

HCC accounts for the majority of primary liver cancers. The global HCC incidence ratio of men to women is 2.8:1. Over 90% of HCC cases occur in the setting of chronic liver disease. Cirrhosis from any etiology is

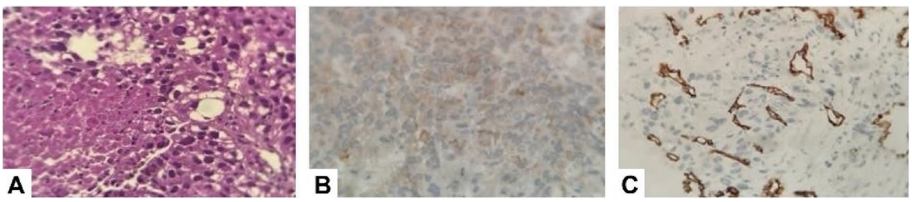

Fig. 3 (A-C) Histopathological images showing typical microscopic appearance of poorly differentiated HCC. (A) Atypical hepatocytes, polygonal cells with severe pleomorphism, atypical mitoses and necrosis, H&E stain (x 400). (B) Immunohistochemical stain reveals positive marking result in HepPar1 (x 400). (C) Immunohistochemical marker CD34 is positive (x 400)

the strongest risk factor for HCC. Other risk factors for HCC include chronic alcohol consumption, diabetes or obesity-related non-alcoholic steatohepatitis, and infection (even in the absence of cirrhosis) by hepatitis B or C virus [1, 3]. The pathophysiology of HCC is a complex multistep process and although the mechanism of disease varies depending on the underlying etiology, the usual sequence is liver injury, chronic inflammation, fibrosis, cirrhosis, and HCC [3].

Clinical manifestations depend on the underlying liver disease. They range from the absence of tumor-related symptoms, mainly in those diagnosed with HCC at an early stage through regular surveillance, to features of hepatic decompensation (variceal hemorrhage or ascites) due to invasion of HCC into adjacent structures in patients with more advanced hepatic disease [1]. It is estimated that 50% of HCC cases worldwide are diagnosed incidentally, by identifying a liver mass on an imaging study performed for other reasons or owing to symptomatic advanced-stage HCC after developing abdominal pain, weight loss or worsening liver dysfunction, as in the case of our patient. This demonstrates the need for continued screening, especially in developing countries [1].

Both hematogenous and lymphatic spreading are common in HCC. Extrahepatic HCC metastases are present at the time of diagnosis in 10-15% of cases, their most common sites are lung, followed by the lymph nodes, bone, adrenal gland, and brain. The presence of this finding represents end-stage HCC [2]. Other rare sites of metastasis have been reported, including the atrium, colon, uterus, orbit, muscle, and skin [4–8].

Cannonball lesions refer to multiple, round, well-circumscribed pulmonary nodules of different sizes. They are classically associated with metastatic disease, commonly seen in renal cell carcinoma and choriocarcinoma, and less frequently in endometrial cancer, prostate cancer, and synovial sarcoma [9]. Nevertheless, other non-malignant causes have also been reported, such as fungal infections, tuberculosis, granulomatosis with polyangiitis and sarcoidosis [10]. However, cannonball metastases in HCC are a rare finding with, to our knowledge, less than ten cases reported in the literature. Since in most cases the presence of cannonball metastases is usually associated with disseminated malignancy at an advanced stage, it indicates a poor prognosis, such as the present case.

In our literature review, we found seven cases of cannonball pulmonary metastases in HCC (Table 1). After inclusion of the present case, out of the eight patients, six (75%) were male and the mean age was 54.75 years. Four (50%) of the reported cases had chronic hepatitis B infection and one (12.5%) had chronic hepatitis C infection. Among the clinical manifestations, the most common was dyspnea, present in six (75%) of the cases, followed by right upper quadrant abdominal pain and cough, both present in 50% of cases. The most common clinical findings were some alteration in pulmonary auscultation present in four (50%) of the patients and anorexia/weight loss also present in half (50%) of the cases. The average survival rate was 19.25 days.

Currently, immunotherapy-based combinations have now become preferred first-line therapy options for advanced HCC, given their increased efficacy, and encouraging survival outcomes. The role of cytotoxic chemotherapy, with modest efficacy for HCC at best, has diminished with the advent of newer immunotherapy and molecularly targeted therapy approaches. Nonetheless, chemotherapy continues to be offered to patients when other treatments are not available, compatible with our case presentation [11].

Metastasectomy may be a treatment option only in some cases of pulmonary metastases. To be a candidate, the patient must present a good risk for surgical intervention, and factors such as the number, location, and size of the lesions (<3 cm) must be considered. However, since most pulmonary metastases are multiple, they are usually unresectable, like our case [12].

The prognosis for patients with HCC remains poor, with a five-year survival rate of 18%. While the five-year survival rate is 2% in metastatic disease [2, 11].

Table 1 Cannonball pulmonary metastases in hepatocellular carcinoma reported cases

Author, Year	Age, Sex	Medical History	Clinical Manifestations	Biopsy	Treatment	Survival, Outcome
Sundriyal et al., 2015 [13]	65, Male	Chronic hepatitis B infection	Hemoptysis, low grade fever and non-tender hepatomegaly	HCC	Sorafenib and anti-viral therapy	N/A
Chao et al., 2015 [14]	72, Male	Chronic hepatitis C, liver cirrhosis and hepatocellular carcinoma	Progressively dyspnea, cachexia appearance and bilateral rhonchi with scattered crepitation over bilateral lung fields	N/A	Palliative care	2 months, Death
Lock et al., 2015 [15]	71, Male	Hypertension, Type 2 diabetes, ex-smoker, history of asbestos exposure, and pulmonary embolism	Dyspnea, right-sided chest wall and upper quadrant abdominal pain and fatigue	HCC	Radiotherapy; hepatic artery embolization with doxorubicin and cisplatin	N/A, Complete resolution of pulmonary metastases and primary site complete response
Emeruwa et al., 2015 [16]	49, Male	Chronic hepatitis B infection	Persistent back pain, weight loss, progressive dyspnea with associated cough and hemoptysis, cachexia, hypoxia requiring supplemental oxygen and globally decreased breath sounds throughout all lung fields	HCC	Palliative care	8 days, Death
Mnyani et al., 2015 [17]	30, Female	Caesarean delivery, HIV-infected, anemia, thrombocytopenia, pre-eclampsia, preterm labor	Fever, dyspnea, cough, right upper quadrant pain, hepatomegaly, splenomegaly, ascites and bilateral pitting edema on the thighs	N/A	Declined	Lost to follow-up
Amusa et al., 2017 [18]	51, Female	Chronic hepatitis B infection	Cough, palpitations, chest pain, orthopnea, paroxysmal nocturnal dyspnea, bilateral pitting pedal oedema, right upper quadrant pain, swelling, anorexia, early satiety, constipation and pruritus.	N/A	Palliative care	N/A, Death
Myat et al., 2022 [19]	41, Male	Chronic hepatitis B infection	Abdominal discomfort, progressive dyspnea, hepatomegaly and crepitations in both lungs	N/A	Tenofovir and lenvatinib	9 days, Death
Ibarra-Sifuentes et al., 2023	59, Male	Type 2 diabetes remission	Asthenia, loss of appetite, involuntary weight loss, subacute cough and decreased breath sounds in the right lung	Poorly differentiated invasive HCC	Palliative care	2 months, Death

HCC Hepatocellular carcinoma, *HIV* Human immunodeficiency virus, *N/A* Non-available

Conclusion

Cannonball metastases are not a common finding in HCC, their presence at diagnosis is an indicator of advanced stage disease and poor prognosis. This case should raise the interest of clinicians in the need for accurate diagnosis in patients presenting with this radiographic appearance and thus achieve appropriate staging and treatment planning.

Abbreviations

HCC Hepatocellular carcinoma
CT Computed tomography
HU Hounsfield units
HBV Hepatitis B virus
HCV Hepatitis C virus

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Not applicable.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by HRIS, GACA, JIGA and CJRA. The first draft of the manuscript was written by GACA and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

This work was approved by the Research Ethics Committee of the North Unit Medical School, Autonomous University of Coahuila.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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