Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Unusual extrahepatic metastatic site of hepatocellular carcinoma with post-therapy disseminating metastases presenting as a primary soft tissue sarcoma: case report

Kuang-Ting Liu, MT, MS[a,b], Yueh-Ching Chang, MT, MS[a,b], Yu-Chieh Lin, MD[a,d], Junn-Liang Chang, MD, PhD[a,c,d,*]

Introduction and importance: Hepatocellular carcinoma (HCC) is a highly malignant primary hepatic tumor. However, extrahepatic metastatic sites of HCC with post-therapy dissemination of metastases mimicking primary soft tissue sarcomas with rib metastases are extremely rare.

Case presentation: The authors report a unique case of hepatitis B virus (HBV)-positive HCC with bilateral lung involvement and widespread right-flank soft tissue and rib metastases. The pathological diagnosis after surgical resection confirmed extrahepatic HCC metastasis. Subsequently, adjuvant-targeted and immune-checkpoint inhibitor therapies were still initiated.

Clinical discussion: Extrahepatic HCC metastasis, which initially presents at distant sites, is uncommon. HCC commonly metastasizes to the lungs, bones, lymph nodes, kidneys, adrenal glands, and peritoneum/omentum. HCC with aggressive post-scheduled adjuvant therapy to the lungs and hypochondriac soft tissue with rib metastasis is very rare and has a poor prognosis.

Conclusion: Although most patients with HCC have disseminated extrahepatic metastases, primary HCC should still be treated. Thus, a review of the history and imaging, histopathology, and immunohistochemical findings is crucial for the definite and differential diagnosis of this tumor.

Keywords: hepatitis B virus, hepatocellular carcinoma, immune-checkpoint inhibitor, immunohistochemistry, transarterial chemoembolization

Introduction

Hepatocellular carcinoma (HCC) is a primary liver malignancy and common cancer worldwide[1–3], with the highest incidence in regions with a high prevalence of cirrhosis, commonly caused by hepatitis B or C virus (HBV or HCV) infection or alcohol consumption, other hepatitis viruses, autoimmune hepatitis, steatohepatitis, and primary biliary and sclerosing cholangitis[4–7]. The incidence of extrahepatic metastasis from HCC varies from 5 to 35% of HCC cases at diagnosis[1,3,8–11], with the most frequent sites being the lungs (18–55%), lymph nodes (26.7–53%), bones, most commonly including the axial skeleton, (5.8–38%), and the adrenals (8.4–15.4%), and indicates a poor prognosis.[3,10,12–15] Extrahepatic metastasis of HCC is relatively rare at initial diagnosis. HCC commonly metastasizes to the lungs, pleura, abdominal cavity, bones, lymph nodes, pancreas, gallbladder, stomach, colon, peritoneum, kidneys, adrenal glands, skeletal muscle, soft tissue, and skin[1,3,6,8–15]. In particular, metastasis of HCC to the lungs, soft tissues, and ribs is extremely rare. We describe a unique case of HBV-positive, alpha-fetoprotin protein (AFP) level elevated advanced HCC with post-therapy bilateral disseminated metastases to the lungs, and extensive metastases to the right-flank soft tissue and ribs, presenting as a primary soft

HIGHLIGHTS

- Hepatocellular carcinoma (HCC) is a common primary malignant tumor of cirrhotic liver caused by hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
- Extrahepatic metastasis of HBV-positive alpha-fetoprotin protein (AFP) elevated HCC is an indicator of poor prognosis despite aggressive treatment.
- Metastasis to the lungs, soft tissues and ribs post-therapy for HBV-positive advanced HCC is extremely rare.
- Extrahepatic metastatic HCC can only be diagnosed based on patient history and imaging, histopathology and immunohistochemical (IHC) examinations.

[a]Department of Pathology and Laboratory Medicine, Taoyuan Armed Forces General Hospital, [b]Hsin Sheng Junior College of Medical Care and Management, [c]Department of Biomedical Engineering, Ming Chuan University, Taoyuan City and [d]Department of Pathology, Tri-Service General Hospital, National Defense Medical Center, Taipei City, Taiwan

K.-T.L., Y.-C.C. contributed equally to this work.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Department of Pathology and Laboratory Medicine, Taoyuan Armed Forces General Hospital, Taoyuan City, Taiwan. 32551, No.168, Zhongxing Rd., Longtan Dist., Taoyuan City, Taiwan. Tel.: +886 347 99595 extent 325571; fax: +886 348 09946. E-mail: junn9liang@yahoo.com.tw (J-L. Chang).

Annals of Medicine & Surgery (2024) 86:5501–5508

Received 19 April 2024; Accepted 13 June 2024

Published online 25 June 2024

http://dx.doi.org/10.1097/MS9.0000000000002307

tissue sarcoma—a type of disseminating disease not previously described in the literature. This case report specifically aims to evaluate the histopathological and immunohistochemical (IHC) characteristics and diagnosis based on clinical evaluation, risk factor assessment, imaging, and prognosis of disseminating metastatic HCC. This case was reported in accordance with the Surgical CAse REport (SCARE) 2023 criteria[16].

Case presentation

A 52-year-old man complained of a progressively palpable nodule associated with a mildly tender mass in the right-flank region for over two years. On admission, his vital signs were as follows: body temperature, 37.2°C; pulse rate, 112/min; respiratory rate, 19/min; blood pressure, 114/78 mmHg. The patient denied consuming alcoholic beverages or illegal drugs. He reported no drug allergies, adverse reactions, addiction, or contributing family history, including relevant genetic information or psychosocial history. The patient did not report any COVID-19 symptoms and had no history of smoking or betel nut consumption. Surveys for travel, occupation, contract history, and cluster history within the past three months were non-contributory. The patient had a history of HCC. He underwent partial liver resection and comprehensive serial adjuvant treatment with entecavir at a local medical center. Two years later, computed tomography (CT) of the lungs revealed HCC recurrence with bilateral lung metastases. He received transarterial chemoembolization (TACE), sorafenib and regorafenib (oral targeted therapies), and pembrolizumab [immune-checkpoint inhibitor (ICI)] at the same local medical center for C1–8 courses. Three months later, he visited our hemato-oncologic outpatient department for continued treatment. He was admitted, and Port-A was implanted for the chemotherapeutic schedule with pembrolizumab, and sorafenib was applied six months later. In the last 2 years, a progressively palpable tender solitary subcutaneous mass was found over the right flank. The patient was transferred to the general surgical division for further evaluation and treatment. On physical examination, the subcutaneous soft tissue mass over the right hypochondrial and flank regions measured ~8 × 4 cm. The extremities showed free movement and no deformities or pitting edema.

Clinical laboratory test results included differential complete blood count, biochemical, and serological results, as shown in Table 1. Epstein-Barr virus and COVID-19, evaluated by polymerase chain reaction (PCR), were negative. The other sample tests exhibited non-contributing profiles.

Lung CT revealed multiple nodular masses of varying sizes (Fig. 1A). Liver CT also revealed multiple nodular masses in segments 5 and 7, with a maximal size of 3.5 cm (Fig. 1B). A subcutaneous soft tissue mass over the right-flank (hypochondriac) region invaded the 12th rib (Fig. 1C). The size of the tumor on CT is ~8 × 4 × 4 cm. Extrahepatic HCC metastasis should be considered based on clinical manifestations, past medical history, and imaging analysis. However, primary malignant soft tissue tumors or sarcomas cannot be completely excluded. The doctor suggested surgical intervention. Surgical tumor resection was performed only after obtaining the patient's informed consent. Subsequently, the patient was instructed to perform an excision of the tumor of the right-flank region to obtain a pathological diagnosis. The patient refused fine-needle biopsy of the liver and lung tissues to complete the pathological diagnosis. However, the patient agreed to undergo direct subcutaneous tumor resection. Subsequently, the senior attending physician in the general surgery department resected the subcutaneous mass in the right hypochondriac region. The postoperative period was uneventful, and there were no complications.

Table 1
Clinical laboratory test results

Laboratory data/items	Results	Reference range (units)
White blood cell	8.93	$4.8–10.8 \times 10^3/\mu l$
Red blood cell	4.64	$4.7–6.1 \times 106/\mu l$
Hemoglobin	13.8	14–18 g/dl
Hematocrit	40.7	42–52%
Neutrophil	74.4	40–74%
Lymphocyte	20	19–48%
Blood urine nitrogen	12.6	6–24 mg/dl
Creatinine	0.78	0.5–1.4 mg/dl
Serum glutamic-pyruvic transaminase (SGPT)	55.7	2–32 U/l
Serum glutamic-oxaloacetic transaminase (SGOT)	55.7	2–32 U/l
Lactate dehydrogenase	201	135–225 U/l
Alpha-fetoprotein (AFP)	157	≤ 7 ng/ml
Carcinoembryonic antigen (CEA)	7.99	≤ 5.2 ng/ml
Carbohydrate antigen 19-9 (CA19-9)	21.6	< 34 U/ml
HBsAg	Reactive	980.12 S/CO
Anti-HBs	0.02 mIU/ml (non-reactive)	
Anti-HBc	0.09 S/CO (non-reactive)	
HCV-PCR	Negative	

anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; PCR, polymerase chain reaction.

Gross findings

Macroscopic examination of the submitted specimen revealed a small soft tissue fragment measuring 7 × 4.5 × 4 cm attached to the surrounding fibrous adipose tissue. The bisections showed ill-defined, lobulated, semi-solid spongy masses, uniformly light yellow to brown in color, with multifocal hemorrhage and necrosis (Fig. 2).

Histopathologic and IHC findings

Microscopic examination of the tumor mass revealed multifocal trabecular HCC morphology composed of hyperchromatic lobulated tumor cells with prominent nucleoli forming a predominantly typical trabecular arrangement (Fig. 3A), sinusoidal pattern, and focal acinar, vacuolated, hyaline, acini or pseudoglandular structure (Fig. 3B) with scattered bizarre, giant cells with eosinophilic cytoplasm (Fig. 3C) with occasional mitotic fingers (Fig. 3D) and scattered sparse thinned fibrous stroma. There was also obvious hemorrhage, necrosis, and local infiltrative growth in the damaged skeletal muscle and surrounding subcutaneous soft tissue. Local lymphovascular and perineural invasions were not observed.

Subsequent IHC analysis revealed that the neoplastic cells were strongly positive for pan-CK, CK18 (Fig. 4A), HepPar-1

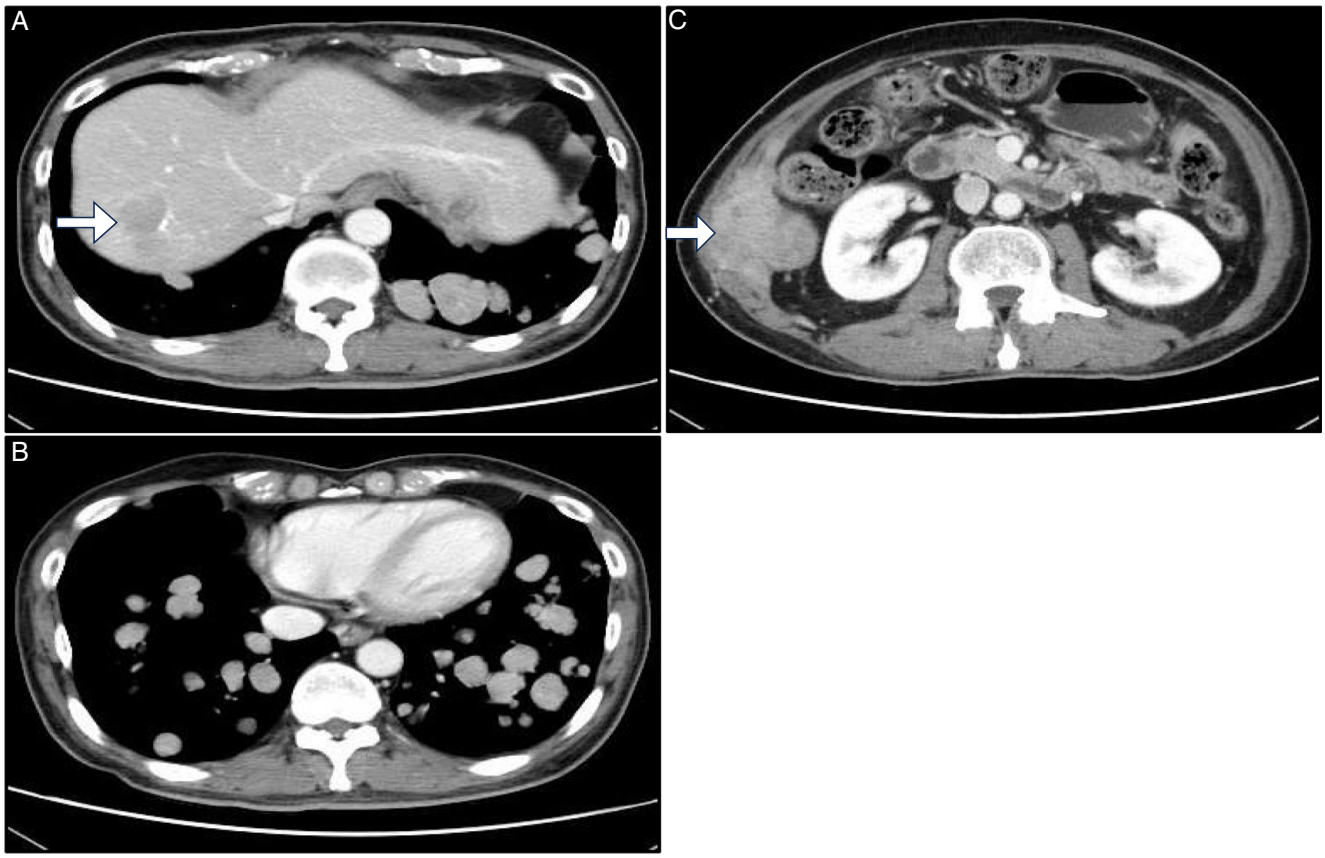

Figure 1. Computed tomography (CT) scan of the lungs shows multiple nodular masses of various sizes in both lungs (A). CT scan of the liver shows nodular masses (whitish arrow) (B). CT scan of the chest shows a subcutaneous soft tissue mass over the right-flank (hypochondriac) region invaded the 12th rib (whitish arrow) (C).

(Fig. 4B). Additionally, the tumor was negative for vimentin, directly excluding the possibility of mesenchymal origin soft tissue sarcomas or other tumors. The p53 also showed overexpression (Allred score 7/4 + 3) (Fig. 4C), and increased expression of proliferative Ki-67 labeling index (> 75%, 3 +) in affected tumor cells (Fig. 4D). Vimentin and CD34 highlighted the trabecular, sinusoid septa, and vascular wall patterns. These tumor cells demonstrated negative immunostaining for HMB45, CK7, CK20, CEA, CDX2, and TTF1. Definite pathological diagnosis of metastatic HCC was supported by histopathology. Although these tumors correspond to poorly to moderately differentiated carcinomas, they have a focal trabecular with pseudoglandular and acinar patterns. Finally, the histopathological and IHC analysis indicated characteristics typical of HCC. Additionally, we excluded soft tissue sarcoma based on the above morphological and IHC examinations. Clinical characteristics, histopathology, and IHC examinations demonstrated an uncommon site of extrahepatic metastatic HBV-positive, AFP-level elevated advanced HCC with metastases to the lungs, right hypochondrium soft tissue, and rib. According to the AJCC 8th edition pathologic prognostic stage groups, p any T any N M1, stage IV was considered.

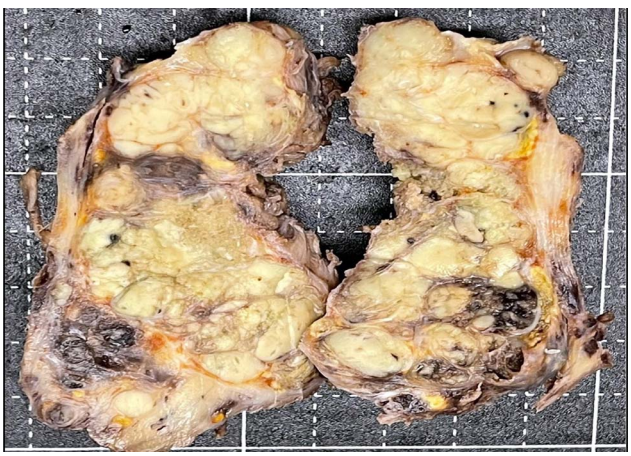

Figure 2. Photograph of bisected right-flank (hypochondriac) tumor reveals an ill-circumscribed heterogeneous lobulated mass with a gray-light to yellowish color and multifocal hemorrhage and necrosis.

Follow-up and workup

The patient recovered uneventfully after surgery. Considering that the disease had disseminated, sorafenib therapy was initiated. He continued to receive targeted therapy with sorafenib plus pembrolizumab and was followed up at our hemato-oncologic department for one month. Unfortunately, the patient died from

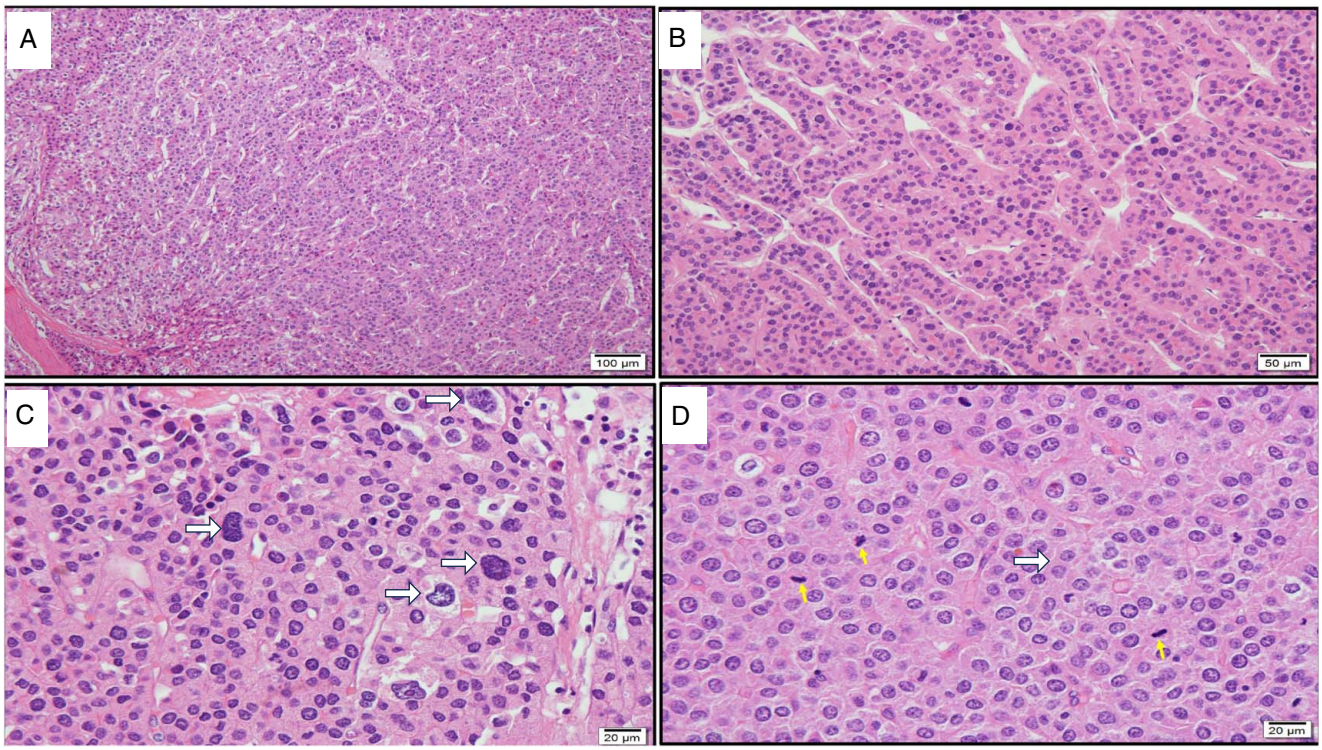

Figure 3. Photographs of metastatic hepatocellular carcinoma of the right-flank region illustrate the predominant architectures with trabecular arrangement pattern [(A, B) hematoxylin and eosin (H&E) stain, original magnification 100×]. These neoplastic cells exhibit cellular and nuclear pleomorphism, bizarre irregular nuclear chromatin, and prominent nucleoli with occasional mitotic figures [(C, D) H&E, original magnification 200×].

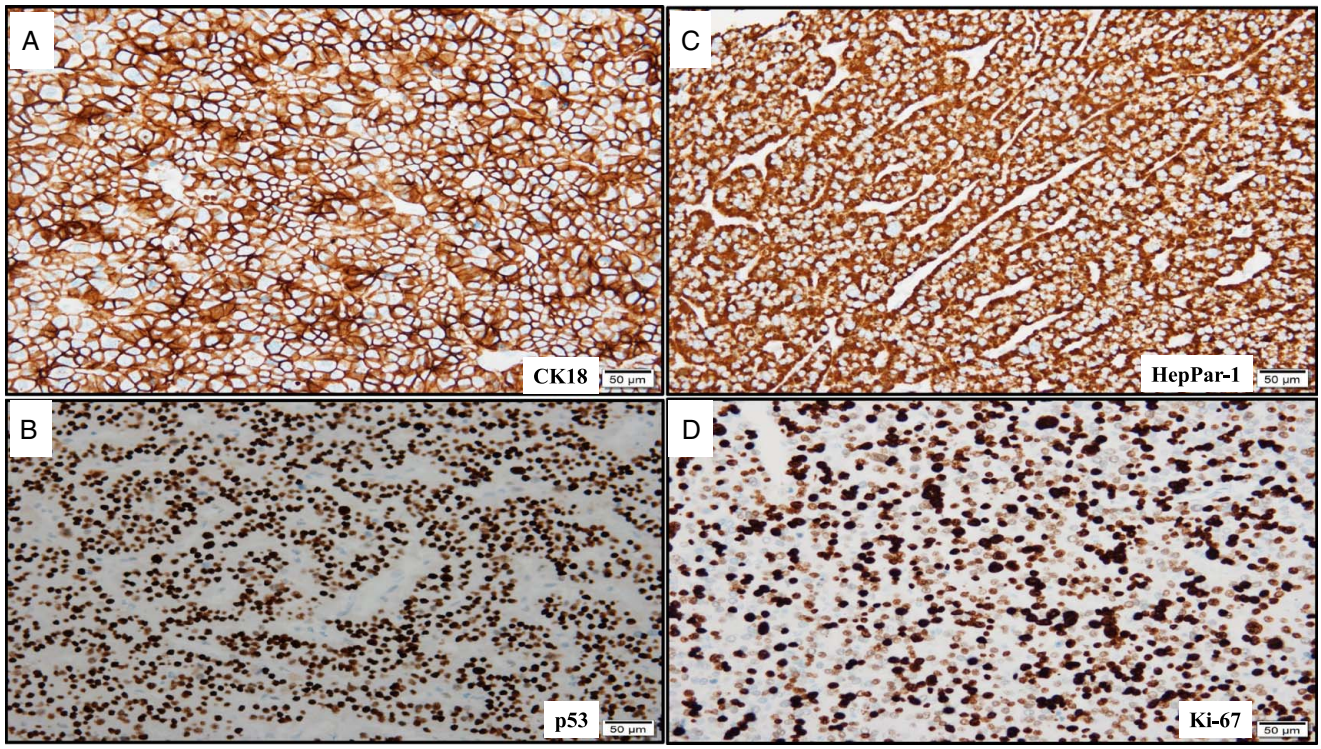

Figure 4. Immunohistochemical analysis of the metastatic hepatocellular carcinoma showed diffuse positivity for CK18 [(A) original magnification 200×], and HepPar-1 [(B) original magnification ×200×], strong nuclear staining for p53 [(C) original magnification 200×], and a proliferative Ki-67 labeling index activity more than 750% of cancer cells [(D) original magnification 200×].

Table 2

The heterogeneity in clinical manifestations, tumor incidence, patient demographics, outcomes, and management for comparison of present case and previously well-documented published case reports of extrahepatic metastatic HCC presenting as soft tissue sarcomas

No./Case report/ [Reference]	Sex/ age	Clinical manifestations	Diagnosis/management	Prognosis/ outcomes	Clinical takeaways
1. Ananthkumar., 2017[1]	M/ 46	Had HCV hepatitis and metastatic HCC with multiple soft tissue, bony and adrenal metastasis.	CT scan, no lung Mets, fine-needle aspiration cytology, subsequent systemic C/T with Sorafenib.	NA*	Consider to evaluate with appropriate imaging and sampling of the mass for histopathological and IHC examination.
2. Kumar *et al.*, 2019[3]	M/ 60	Complaints of rapidly progressing swelling over the left scapular region for 1 month.	CT scan, lung Mets, subsequent core needle biopsy of scapular region, refused any further treatment	Lost to follow-up	Soft tissue metastasis in HCC is a unique rare especially in unusual sites. Early diagnosis and appropriate surgical intervention prolong survival
3. Sanders *et al.*, 2021[6]	F/77	A forehead hematoma with acute onset ascites and cirrhosis of liver, elevated AFP level	CT scan, no lung Mets, subsequent core needle biopsy of forehead lesion, no any treatment	Passed away 2 months later	To differentiate the metastatic HCC and early diagnosis may lead to improved quality of life with early treatment or palliation.
4. Targe *et al.*, 2021[12]	M/ 60	Loss of appetite, generalized weakness, and weight loss, a firm lump in the right hypochondrium	CT scan, no lung Mets, multiple disseminating Mets, subsequent biopsy of right lobe liver and right rectus abdominis muscle lesion, FNA cytology from left axillary lymph node. Immunotherapy treatment with Durvalumab (1500 mg, 9 cycles)	Overall survival of 10 months.	To differentiate the extrahepatic metastatic HCC and accurate diagnosis and prompt appropriate treatment for better prognosis
5. John *et al.*, 2022[15]	F/72	HCC with cirrhosis and chronic HBV, pain in the left shoulder and scapular region	MRI, PET-CT scan, no lung Mets, a biopsy of right scapular. Subsequent treated with R/T to the bone lesion, followed by bisphosphonates, sorafenib, and entecavir	NA*	Clinician add pathologist should keep in mind this rare entity as a differential diagnosis, and multidisciplinary approach to management
6. Present case Liu *et al.*, 2024	M/ 52	HBV-positive AFP-elevated HCC post-C/T for years with right-flank soft tissue mass	CT scan, lungs Mets, suspected soft tissue sarcomas, subsequent excision of right-flank mass, followed adjuvant systemic C/T with targeted and Immune-checkpoint inhibitor therapies	Overall survival of 4 months	To differentiate the extrahepatic metastatic HCC, histopathological and IHC examinations, accurate diagnosis and prompt appropriate treatment

AFP, alpha-fetoprotin protein; C/T, chemotherapy; CT, computed tomography; F, female; FDG, 18F-fluorodeoxyglucose; FNA, fine-needle aspiration biopsy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis B virus; IHC, immunohistochemical; M, male; NA, not available; PET, positron emission tomography; R/T, radiotherapy.

HCC-related causes, hepatorenal failure, coma, and respiratory failure four months postoperatively.

Discussion

The most common risk factors for HCC worldwide are liver cirrhosis, HBV infection, HCV infection, alcohol consumption, and aflatoxin exposure[1,2,4]. The factors associated with the risk of metastasis are AFP level (> 400 μg/ml), vascular invasion, tumor size (> 5 cm)[2,10,11], and multifocal or infiltrative tumors, as in our case. AFP level can be relevant for disease prognosis, normal AFP level should not be used to exclude HCC. This is especially pertinent in cases of HCC without cirrhosis, where the sensitivity of AFP level for detecting the disease ranges only from 31 to 67%.[10,11,13–15]

Extrahepatic metastasis of HCC tends to affect men, especially those over 60 years old, and exhibits characteristics of the primary tumor[14]. The distribution of metastases in these patients was as follows: lung (39.5%), lymph nodes (34.2%), bone (25.4%), adrenal glands (8.8%), brain (1.2%), spleen (0.6%), and breast (0.3%).[12]. We emphasize the importance of a thorough examination to exclude common causes of lungs and bone metastasis. HCC disease, but soft tissue and bone metastases at initial presentation are rare. Extrahepatic metastases to unusually sites from HCC have been reported in a few case reports[1,3,6,8–15]. To the best of our knowledge, extrahepatic HCC with both soft tissue and bony metastases is extremely rare and scarcely described in the literature. The present case, along with previously documented cases of extrahepatic metastatic HCC presenting as soft tissue tumors, is compared in terms of clinical presentation, tumor incidence, patient demographics, prognosis, and management. These comparisons are detailed in Table 2. These findings underscore the rarity and uniqueness of soft tissue metastases in HCC, particularly in atypical anatomical locations. Recognizing and evaluating soft tissue metastases in HCC requires a vigilant clinical approach due to their infrequent occurrence and potential diagnostic challenges[3].

Our patient with HBV-positive, elevated AFP-level HCC exhibited signs of lungs, lytic rib bone, and right-flank soft tissue metastases. No bilateral axillary lymph node involvement was observed. The metastasis to the soft tissue of the right flank likely occurred from the primary tumor involving the upper part of the right liver lobe, spreading via the lymphatic vessels. Poorly differentiated HCC and the absence of cirrhosis were identified as risk factors for extrahepatic metastases, with elevated AFP levels considered as a surveillance modality in high-risk patients[3].

Fukutomi *et al.*[17] analyzed 673 patients with HCC and reported that the most frequent sites of bone metastases from HCC was the vertebrae, followed by the pelvis, ribs, and skull. Extrahepatic metastases to the lungs, bones, and lymph nodes are more frequent in the advanced stages than in the early stages.[4,9,11–13,18] In the present case, patient had HBV-positive, AFP-elevated advanced HCC and underwent partial hepatotectomy with post-systemic chemotherapy extrahepatic HCC metastases to lungs, right 12th rib and flank region soft tissue, indicating extremely unusual sites of extrahepatic disseminating metastasis of HCC.

Extrahepatic metastases were identified through a combination of diagnostic modalities, including CT, MRI, bone scintigraphy, X-ray, and/or positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG). Additionally, histopathological examination of surgically resected specimens or biopsies contributed to the diagnosis[9,11,13,14]. The possibility and clinical features of extrahepatic metastases should be considered when examining patients with HBV-positive, AFP-elevated HCC. This approach enables a precise evaluation of metastatic spread and aids in determining the appropriate treatment method[1,3].

The unique features of this case are the clinical features of atypical HCC manifestations, such as HBV-positive HCC, elevated AFP level, and related risk factors such as chronic HBV infection with abnormal liver function test. Diagnostic challenges presented by this unusual presentation include possible misinterpretation or delayed diagnosis. The final diagnostic challenge and difficulty is based only on past liver surgery, imaging of liver and lung metastases, histopathology of extrahepatic metastases after tissue resection. Microscopic examination revealed soft tissue lesions similar to HCC morphology. The pathological diagnosis of metastatic HCC at extrahepatic sites is relatively easy. In this report, IHC marked evaluation is also used for differential diagnosis and exclusion of commonly suspected mesenchymal origin of soft tissue sarcomas. Biopsy of the tumor mass at the metastatic site confirmed the diagnosis using histopathology and IHC, including cellular morphology, trabecular, pseudoglandular, acinar architectures, the presence of hepatocyte-like cells and IHC markers characteristic of HCC. The final diagnosis was made by comparing the same pattern in primary HCC patterns[13,14]. IHC studies for the histopathology of HCC are valuable in this regard. HepPar-1 is a relatively specific marker for hepatocytes and HCC[6,9,10,13–15,19]. Increased expression of the proliferative Ki-67 labeling index indicates cell proliferation, as in our case. The present case illustrated that HCC can metastasize to various organs other than the lungs and that HepPar-1, CK18, and AFP are good markers of extrahepatic metastases from these unusual sites in extrahepatic HCC[9,13,14,18,20], such as our case.

By considering the assessment of these prognostic factors in the context of extrahepatic HBV-positive, AFP-level elevated HCC metastasis, patient prognosis should be comprehensively assessed and decision-making on treatment strategies should be guided. Extrahepatic HCC metastasis occurs depending on the HCC stage. Prognosis remains poor even after the application of therapy to the primary liver tumor, including surgical treatment, radiation therapy, TACE or systemic therapy with sorafenib[12–14]. Systemic therapy is the mainstay treatment for metastatic disease, and localized cutaneous or soft tissue metastatic lesions can be palliated with surgical resection or radiotherapy[14,20].

The prognostic significance of disseminated HCC has not been fully explored, but studies have shown that the development of bone metastases at any point during the course of the disease carries a poor prognosis[10,13], as shown in Table 2. The overall prognosis of HCC is often grim, with a 5-year survival rate of less than 20%, and patients with extrahepatic spread have an extremely poor prognosis[2,4,8,13,14,20]. Bone metastasis caused by HCC results in an extremely grim prognosis, with a median survival of only 1–2 months[10,14]. Progress has been made in therapeutic procedures such as surgical resection, radiofrequency ablation, percutaneous ethanol injection, and ACE[1,7,8,11], and their combination with molecular targeted therapy enhances the immune response[1,7,10,20]. The median survival time after a diagnosis of extrahepatic metastasis is 8.1 months. Untreated

HCC has a dismal prognosis, with a 5-year survival rate below 10%[11]. The median survival is 4.9 months (0–37 months)[10].

To the best of our knowledge, the unique case of HBV-positive, AFP-level elevated advanced HCC with post-therapy bilateral disseminated metastases to the lungs and extensive right-flank soft tissue and rib metastases, presenting as a primary soft tissue sarcoma is not previously described in the literature as shown in Table 2. Our report suggests that the best outcomes come from a cross-multidisciplinary team, personalized treatment, close surveillance, early detection of relapse, and a multiplicisnary approach. This case report demonstrates the limitations and complexities of pathological diagnosis and treatment.

Although this is a single case, it may increase clinicians' interest in imaging by helping them determine uncommon extrahepatic metastatic sites of HCC, thereby promoting overall patient health and timely treatment. For radiologists, prompt detection of extrahepatic metastatic sites at diagnosis is critical for accurate staging and treatment planning, as well as for assessing recurrence, such as post-resection or post-locoregional therapy.

This study has some important limitations. First, the initial diagnosis of the primary hepatic lesion was not immediately available, and we were unable to compare the disseminating widespread metastatic histopathological and morphological features and phenotypic heterogeneity between the primary and its corresponding metastatic HCC. Second, the patient refused fine-needle biopsy of the lungs and liver for pathological diagnosis. The final pathological diagnosis can only be made based on the patient's clinical presentation, medical history, imaging findings, and histopathological and IHC findings. With the progress in molecular targeted therapy drugs and immunotherapy for HCC, our paper summarizes systemic drugs that have been approved and have shown positive results for treating advanced HCC, providing an outlook on the future of advanced HCC treatment.

Conclusion

We emphasize the importance of a thorough examination to exclude common causes of unusual soft tissue and bone metastasis of HCC. The possibility of metastatic extrahepatic HCC should be considered in patients presenting with rapidly growing soft tissue tumors, particularly those with a history of or risk factors for HBV-associated HCC and elevated AFP levels. Early diagnosis is pivotal, especially when evaluating patients with bilateral lungs metastases, soft tissue and rib invasion in the context of HBV-positive, AFP-level elevated advanced HCC risk factors. Vigilant radiological assessment and timely identification of unusual extrahepatic metastatic sites are essential for accurate staging and treatment planning, necessitating collaboration among multidisciplinary care teams. Despite advancements, the overall prognosis for such patients remains challenging, highlighting the complexities inherent in managing these cases.

Ethical approval

This study was approved by the Institutional Review Board of (IRB) the Tri- Service General Hospital (TSGH), National Defense Medical Center on September 11, 2023.. The reference number for their IRB approval No. is TSGHIRB No. : B202415063.

Consent

The ICF/IC Waiver is granted.

Source of funding

This study was supported by grants from TYAFGH-D-113045 and TYAFGH-A-113013 Taoyuan Armed Forces General Hospital, Taoyuan, Taiwan.

Author contribution

J.-L.C.: drafting manuscript review, corresponding author, data interpretation, evaluation, information acquisition and final approval. K.-T.L.: responsible for operating pathological tissue / specimen processing, information acquisition and final approval, concept and design, critical review and final approval. Y.-C.C.: responsible for operating pathological tissue sections, special chemical staining and immunohistochemical staining, information acquisition, critical review, and final approval. Y.-C.L.: responsible for information acquisition and final approval, concept and design, critical review and final approval.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

NA. This paper is a case report; registration is not required. The datasets in this article are available in the repository, upon request, from the corresponding author.

Guarantor

Junn-Liang Chang.

Data availability statement

Not applicable.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Acknowledgement

The authors thank Dr Yen-Lin Chen, Department of Radiology, for providing the medical images and explanations of the present case. The authors also thank to Dr Zu-Wei Liang, Department of Surgery, for explaining the intraoperative findings. The authors are also grateful to Mei-Ling Li, medical laboratory technician, for assisting in pathological sectioning and processing IHC and histochemical staining.

References

[1] Ananthkumar S. Hepatocellular carcinoma with multiple soft tissue metastasis—a rare case report. J Hepatol Gastrointest Disord 2017;3:156–8.

[2] Alves RCP, Auer LS, Da Cunha Saud LRC, *et al*. Hepatocarcinoma with metastasis to the anterior mediastinum. Hepatoma Res 2016;2:293–6.

[3] Kumar A, Kola GST, Elamurugan TP, *et al*. Metastatic hepatocellular carcinoma masquerading as soft tissue sarcoma. Clin Surg 2019;4:2413.

[4] Aljumah AA, Kuriry H, Faisal N, *et al*. Comparison of clinicopathologic characteristics and outcomes of hepatocellular carcinoma associated with chronic hepatitis B versus hepatitis C infection. Ann Saudi Med 2018;38:358–65.

[5] Feo F, Pascale RM. Multifocal hepatocellular carcinoma: intrahepatic metastasis or multicentric carcinogenesis? Ann Transl Med 2015;3:4.

[6] Sanders K, Thomas A, Isache C, *et al*. A rare case of metastatic hepatocellular carcinoma masquerading as a forehead hematoma. Case Rep Gastrointest Med 2020;2020:1–5.

[7] Kim SB. Hepatocellular carcinoma with distant metastasis cured by 20-day sorafenib treatment. Case Rep Gastroenterol 2021;15:610–5.

[8] Uka K, Aikata H, Takaki S, *et al*. Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. World J Gastroenterol 2007;13:414–20.

[9] Terada T, Maruo H. Unusual extrahepatic metastatic sites from hepatocellular carcinoma. Int J Clin Exp Pathol 2013;6:816–20.

[10] Zainal N, Hasbullah HH. Prolonged survival of metastatic hepatocellular carcinoma: a case report. J Gastrointest Oncol 2018;9:E6–8.

[11] Md Radzi AB, Tan SS. A case report of metastatic hepatocellular carcinoma in the mandible and coracoid process: a rare presentation. Medicine (Baltimore) 2018;97:e8884.

[12] Targe M, Yasam VR, Nagarkar R. Hepatocellular carcinoma with uncommon sites of metastasis: a rare case report, Egypt. J Radiol Nucl Med 2021;52:1–7.

[13] Gupta R, Hirsch J, Guhan M, *et al*. Unusual initial presentation of hepatocellular carcinoma as a clavicular head mass. Oncology (Williston Park) 2023;37:335–8.

[14] Mašulović D, Igić A, Filipović A, *et al*. A rare case of isolated hepatocellular carcinoma metastasis in left mandibular region in a patient with hepatitis C virus liver cirrhosis diagnosed after the onset of COVID-19 infection. Medicina (Kaunas) 2023;59:1992–8.

[15] John AR, Dwivedi S, Varghese J, *et al*. Metastatic hepatocellular carcinoma masquerading as an expansile osteolytic lesion in scapula: a rare case of isolated appendicular skeletal metastatic involvement of hepatocellular carcinoma at initial presentation. World J Nucl Med 2023;22:55–8.

[16] Sohrabi C, Mathew G, Maria N, *et al*. Collaborators. The SCARE 2023 guideline: updating consensus Surgical CAse REport (SCARE) guidelines. Int J Surg 2023;109:1136–40.

[17] Fukutomi M, Yokota M, Chuman H, *et al*. Increased incidence of bone metastases in hepatocellular carcinoma. Eur J Gastroenterol Hepatol 2001;13:1083–8.

[18] Lugli A, Tornillo L, Mirlacher M, *et al*. Hepatocyte paraffin 1 expression in human normal and neoplastic tissues: tissue microarray analysis of 3,940 tissue samples. Am J Clin Pathol 2004;122:721–7.

[19] Ng IO, Srivastava G, Chung LP, *et al*. Overexpression and point mutations of p53 tumor suppressor gene in hepatocellular carcinoma in Hong Kong Chinese people. Cancer 1994;74:30–7.

[20] Zhang H, Zhang W, Jiang L, *et al*. Recent advances in systemic therapy for hepatocellular carcinoma. Biomark Res 2022;10:3.