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Unusual extrahepatic sites of hepatocellular metastases: case series

Neha Chhabra [1]*, Puneet Somal [1], Sankalp Sancheti [1]

[1] Department of Radiodiagnosis and Interventional Radiology, Homi Bhabha Cancer Hospital and Research Centre, Tata Memorial Centre, New Chandigarh, Punjab, India

Abstract

Introduction: Hepatocellular carcinoma (HCC) is a major global health burden and a leading cause of cancer-related mortality. Patients typically present with symptoms related to the primary hepatic tumor, while extrahepatic metastases are generally associated with advanced disease and poor prognosis. Rarely, HCC may initially manifest through symptoms arising from metastatic involvement before the primary hepatic lesion is identified.

Case Presentation: We report two cases of hepatocellular carcinoma that initially presented with symptoms attributable to extrahepatic metastases to the rare sites. Both cases had normal AFP levels and were CT negative, with HCC detected only on MRI of the abdomen.

Case 1: A 63-year-old male presenting with epistaxis and a destructive maxillary sinus mass, which on histopathology and immunohistochemistry was diagnosed as metastatic HCC. Subsequent MRI of the liver revealed a small LI-RADS 5 lesion that was occult on CT.

Case 2: A 60-year-old chronic alcoholic male presenting with gastrointestinal bleeding due to a duodenal mass. Biopsy confirmed metastatic HCC, and subsequent MRI demonstrated two hepatic lesions categorized as LI-RADS 5 and LI-RADS 4, which were not definitively detected on initial CT imaging.

Discussion: Extrahepatic metastases from HCC most commonly involve the lungs, lymph nodes, and bones, while involvement of unusual sites such as the maxillary sinus and duodenum is exceedingly rare. Presentation with metastatic disease prior to identification of the primary tumor may delay diagnosis and management. These cases highlight the limitations of CT in detecting small or infiltrative hepatic lesions and emphasize the superior sensitivity of MRI in lesion characterization. Immunohistochemical markers such as HepPar-1 and arginase play a crucial role in establishing the diagnosis of metastatic HCC, particularly when serum alpha-fetoprotein levels are normal or only mildly elevated.

Conclusion: Hepatocellular carcinoma may rarely present with symptoms related to extrahepatic metastases before the primary hepatic lesion becomes clinically or radiologically apparent. A high index of suspicion, combined with comprehensive imaging using MRI and appropriate immunohistochemical analysis, is essential for early diagnosis. Recognition of such atypical presentations can prevent diagnostic delay and facilitate timely initiation of appropriate therapy

Keywords: Hepatocellular carcinoma, Extrahepatic metastases, HepPar-1

Corresponding Authors: Neha Chhabra

✉ Email: nhchhabra@yahoo.com

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common primary hepatic malignancies and a leading cause of cancer-related mortality worldwide. According to the World Health Organization, approximately 900,000 new cases of HCC are diagnosed annually, with a marked male predominance (male-to-female ratio ~2.7). The global distribution of HCC is uneven, with Asia accounting for nearly 72.5% of new cases. HCC is currently the fourth most common cause of cancer-related death worldwide (1,2).

Chronic infection with hepatitis B virus or hepatitis C virus remains the most important etiological factor for HCC, followed by alcohol-related liver disease (1,3). Extrahepatic metastases are an adverse prognostic feature and are reported in up to 50% of patients during the disease course. The lungs, lymph nodes, and bones are the most frequent sites of metastatic spread (4). In the majority of cases, patients initially present with symptoms related to the primary hepatic tumor, with metastatic manifestations developing later in the disease course (5).

The Liver Imaging Reporting and Data System (LI-RADS) provides a standardized framework for the non-invasive diagnosis of HCC in at-risk patients. Imaging features such as arterial phase hyperenhancement, non-peripheral washout, enhancing capsule, and threshold growth on multiphase CT or MRI are highly specific for HCC (6,7). Several meta-analyses have demonstrated that MRI offers higher sensitivity and comparable specificity to CT for HCC detection, particularly when liver-specific contrast agents are used, improving detection of lesions smaller than 2 cm (8). Histopathological confirmation is generally reserved for patients without cirrhosis or chronic hepatitis B infection, as LI-RADS criteria are not applicable in this group. Serum alpha-fetoprotein (AFP) has limited diagnostic utility, especially in poorly differentiated tumors that may not secrete AFP (9).

Despite advances in imaging, early-stage HCC lesions may remain occult on CT, particularly in the presence of chronic liver disease. Presentation with symptoms related to extrahepatic metastases before identification of the primary hepatic lesion is uncommon and may lead to diagnostic delay. In this context, MRI plays a crucial role in detecting small or infiltrative hepatic tumors not visualized on CT.

We report two cases of early-stage HCC that initially presented with symptoms attributable to unusual extrahepatic metastases, in which the primary hepatic lesions were not detected on CT but were subsequently identified on MRI. These cases underscore the diagnostic value of MRI in CT-negative patients and highlight the need to consider metastatic HCC in patients presenting with atypical metastatic disease of unknown primary.

Case presentation

Case 1

Chief Complaint

Nasal bleeding and progressively increasing right facial swelling for one week.

History

A 63-year-old male presented to the head and neck outpatient department with a one-week history of recurrent epistaxis associated with a rapidly enlarging swelling over the right maxillary region. There was no history of trauma, visual disturbance, or neurological deficits. The patient was a known case of chronic hepatitis C virus infection. There was no prior history of malignancy or hepatic decompensation.

Examination

Local examination revealed a firm, non-tender swelling over the right maxillary region. No cervical lymphadenopathy was detected. Systemic examination was unremarkable.

Investigations

Contrast-enhanced CT of the neck and chest demonstrated a large, aggressive soft-tissue mass

involving the right maxillary sinus with infiltration into the right ethmoid, frontal, and sphenoid sinuses, right pterygopalatine fossa, high infratemporal fossa, right orbit, and intracranial extension into the right temporal region. Associated erosion of the right greater wing of the sphenoid and right mandibular condyle was noted (Figure 1).

Biopsy from the maxillary mass revealed features of metastatic carcinoma. Immunohistochemistry showed diffuse and strong positivity for HepPar-1 and focal positivity for arginase, while PAX-8 and S-100 were negative, confirming metastatic hepatocellular carcinoma. Serum alpha-fetoprotein levels were within normal limits (3.5 ng/mL).

Triphasic CT of the abdomen showed features of chronic liver parenchymal disease without a definite focal hepatic lesion. Subsequent triphasic MRI of the upper abdomen demonstrated a focal lesion in segment VIII of the liver, appearing hyperintense on T2-weighted images with mild capsular retraction. Dynamic contrast-enhanced images revealed a 3.2 × 1.9 cm lesion showing non-rim arterial phase hyperenhancement, portal venous washout, and delayed capsular enhancement (Figure 2).

Diagnosis

Early-stage hepatocellular carcinoma (LI-RADS 5) with extrahepatic metastasis to the maxillary sinus.

Treatment

The patient received palliative radiotherapy to the maxillary lesion, followed by systemic therapy as per oncology protocol.

Follow-up / Outcome

The patient was placed on regular follow-up under medical oncology and hepatology services for disease monitoring and supportive care .Patient is stable with no clinical or radiological progression .

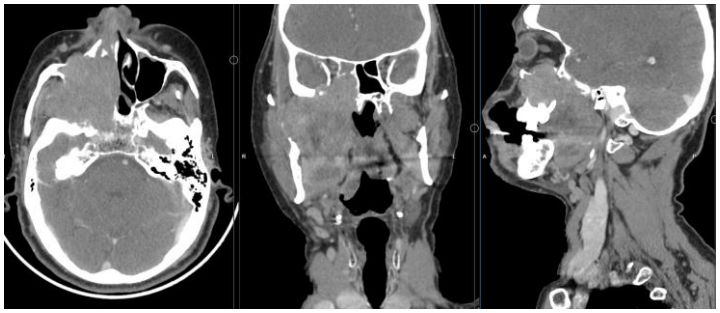

Figure 1. Large heterogeneously enhancing soft tissue swelling in right maxilla which on biopsy showed metastatic hepatocellular carcinoma.

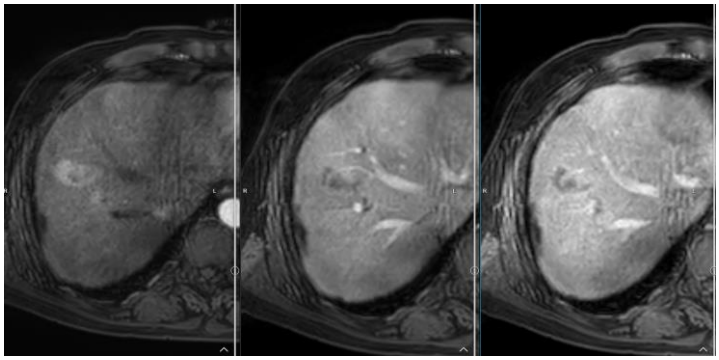

Figure 2. LI-RADS 5 lesions was detected in segment 8 of liver showing nonperipheral rim enhancement on arterial phase and washout on portal venous phase with enhancing capsule in delayed images . HCC was discovered incidentally in patient presenting with large solitary maxillary swelling.

Case 2

Chief Complaint

Intermittent melena for 10 days.

History

A 60-year-old male with a history of chronic alcohol consumption presented with intermittent episodes of melena for 10 days. There was no history of abdominal pain, hematemesis, or prior gastrointestinal bleeding. The patient had no known history of liver malignancy.

Examination

Physical examination revealed pallor. Abdominal examination showed no palpable mass or ascites. There were no signs of hepatic encephalopathy.

Investigations

Contrast-enhanced CT of the abdomen revealed diffuse circumferential wall thickening of the second part of the duodenum, along with features of chronic liver parenchymal disease. No definite focal hepatic lesion was identified (Figure 3).

Upper gastrointestinal endoscopy demonstrated an ulceroproliferative lesion in the second part of the duodenum, and biopsy samples were obtained. Immunohistochemistry showed diffuse positivity for HepPar-1 and AE1/AE3, with negative staining for CK7, CK20, INSM1, synaptophysin, chromogranin, CDX2, and BerEP4, consistent with metastatic hepatocellular carcinoma. Serum alpha-fetoprotein levels were 28.4 ng/mL.

Subsequent dynamic contrast-enhanced MRI of the abdomen revealed two hepatic lesions: A 3.9 × 2.7 cm lesion in segment IV and a 2.0 × 1.9 cm lesion in segments II/III. Both lesions demonstrated non-rim arterial phase hyperenhancement with portal venous washout and were categorized as LI-RADS 5 and LI-RADS 4 respectively (Figure 4).

Diagnosis

Hepatocellular carcinoma with duodenal metastasis.

Treatment

The patient was initiated on systemic palliative therapy under the care of medical oncology.

Follow-up / Outcome

On follow-up, the patient reported no further episodes of gastrointestinal bleeding and continues to remain under oncologic surveillance.

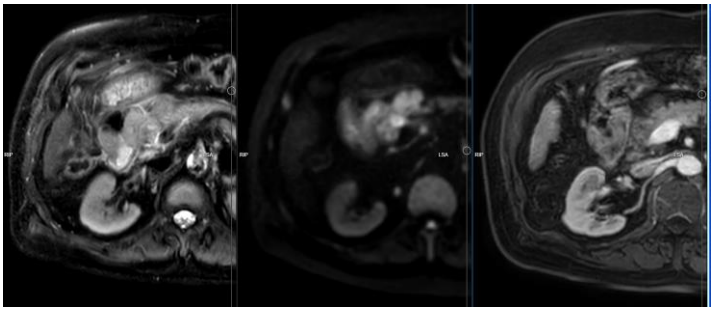

Figure 3. Circumferential mural thickening noted in second part of duodenum. Biopsy came out as metastatic hepatocellular carcinoma.

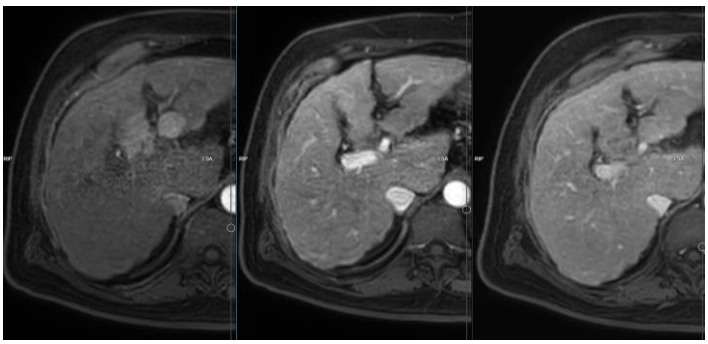

Figure 4. LI-RADS 4 and 5 lesions were discovered in segment 2/3 and 4 of liver . HCC was discovered incidentally in patient presenting with malena and duodenal thickening.

Discussion

This case series highlights several unique considerations regarding HCC presenting with extrahepatic metastases.

Primary presentation with metastases: Both cases initially presented with symptoms from metastatic sites rather than the primary liver tumor. Such presentations are rare, reported in only 5–10% of HCC cases (10,11). Clinicians should consider HCC in the differential diagnosis of carcinoma of unknown origin.

Unusual metastatic sites: The maxillary sinus and duodenum are exceptionally rare sites for HCC metastases. Other uncommon sites reported in literature include the orbit, omentum, adrenal glands, kidney, brain, and skin (12,13). By contrast, the most frequent metastatic sites are the lungs, lymph nodes, and bones (14). Awareness of these atypical sites is critical to prevent misdiagnosis.

Imaging findings: In both cases, CT imaging failed to detect the hepatic lesions, which were subsequently identified on dynamic contrast-enhanced MRI. This underscores the superior sensitivity of MRI, especially for small HCC lesions, consistent with prior studies (8).

Serum biomarkers: AFP levels were not significantly elevated in either case. Usually the normal range of AFP is < 10 ng/ ml , though some allow upto 40 ng/ ml . Markedly elevated levels of AFP ,particularly > 400 ng/ml are highly suggestive of HCC. While AFP is commonly used for monitoring disease progression, it is often normal in poorly differentiated HCC and cannot reliably establish a diagnosis (9).

Stage at presentation: Most patients with extrahepatic metastases present at advanced intrahepatic stages (T3 or T4) according to the TNM - AJCC staging system. Interestingly, in our cases, the primary hepatic tumors were early-stage (LI-RADS 5 in segment VIII for Case 1 was T1b ; LI-RADS 5 and 4 in segments IV and II/III for Case 2 was T2). Early metastasis despite limited intrahepatic disease may be due to tumor-intrinsic metastatic potential, early vascular invasion, or patient-specific genetic and regional factors affecting metastatic behavior as reported previously by Budhu et al (15).

Site-specific considerations and management:

- **Maxillofacial metastasis (Case 1):** HCC metastasis to the head and neck is rare, often presenting as large soft-tissue masses. These lesions spread via vertebral or azygous venous pathways or lymphatics. Palliative radiotherapy (30 Gy/10#) followed by systemic therapy with lenvatinib, atezolizumab, and bevacizumab was administered.

- **Duodenal metastasis (Case 2):** Isolated hematogenous metastasis to the small bowel is exceedingly rare as compared to local invasion of small bowel from HCC; isolated duodenal metastasis has been reported only twice previously (16,17). GI bleeding was the presenting symptom. The patient was managed with palliative systemic therapy (atezolizumab and bevacizumab) and remained stable without recurrent bleeding.

Immunohistochemistry (IHC): Accurate diagnosis of HCC metastases relies on a panel of IHC markers. Arginase-1 and HepPar-1 have the highest sensitivity for well-differentiated tumors, though HepPar-1 may also stain adenocarcinomas of the esophagus, stomach, and lung (20). Glypican-3 is more sensitive for poorly differentiated lesions. In practice, HCC typically shows positivity for hepatocytic markers (HepPar-1, Arginase-1, Glypican-3) and is negative for CK7 and CK20. Panels combining these markers are essential to differentiate metastatic HCC from other carcinomas (18–20).

Comparison of cases: While both cases share the unusual feature of presenting with metastatic symptoms, the maxillary metastasis was associated with a solitary early-stage hepatic lesion, whereas the duodenal metastasis coexisted with two early hepatic lesions. Both cases illustrate that early-stage primary HCC can metastasize to atypical sites, emphasizing the importance of high-sensitivity imaging and IHC panels for diagnosis (Table 1).

Limitations of the study

Due to short-term clinical follow-up, long-term survival, disease progression, and treatment response could not be adequately assessed.

Conclusion

Extrahepatic metastases of HCC can present with two unusual patterns:

1. Spread to rare sites such as the maxillary sinus, orbit, adrenal glands, and small bowel.

2. Metastatic-first presentation, where the primary hepatic tumor is detected after metastatic symptoms manifest.

These findings underscore the need to consider HCC in cases of carcinoma of unknown origin. Dynamic contrast-enhanced MRI should be preferred when CT fails to detect primary lesions. For immunohistochemical confirmation, a panel

including HepPar-1 and Arginase-1 is recommended to accurately identify metastatic HCC. Early recognition of such atypical presentations facilitates timely management and appropriate palliative or systemic therapy.

Table 1. Depicts the salient features of both the cases.

Characteristic	Case 1	Case 2
Clinical presentation	Nasal bleeding, right maxillary swelling	Intermittent melena, fatigue
Metastatic site	Right maxillary sinus (head & neck)	Second part of duodenum (small bowel)
Imaging findings	CT: large maxillary mass; MRI: 3.2 × 1.9 cm lesion in liver segment VIII (arterial enhancement, portal washout, delayed capsular enhancement, LI-RADS 5)	CT: circumferential duodenal thickening; MRI: two hepatic lesions – segment IV (3.9 × 2.7 cm, LI-RADS 5), segments II/III (2.0 × 1.9 cm, LI-RADS 4) with arterial enhancement and portal washout
Pathology / IHC profile	Metastatic HCC; HepPar-1 (+), Arginase (+ focally), PAX-8 (-), S-100 (-)	Metastatic HCC; HepPar-1 (+), AE1/AE3 (+), CK7 (-), CK20 (-), INSM1 (-), synaptophysin (-), chromogranin (-), CDX2 (-), BerEP4 (-)
AFP level	3.5 ng/mL	28.4 ng/mL
Stage (intrahepatic HCC)	Stage IB (solitary lesion)	Stage II (two lesions)
Treatment	Palliative radiotherapy (maxilla) + systemic therapy (lenvatinib, atezolizumab, bevacizumab)	Palliative systemic therapy (atezolizumab + bevacizumab)
Outcome / Follow-up	Stable, no progression reported at last follow-up	Stable, no further GI bleeding reported

Author contribution

NCH wrote main radiology manuscript and complined it with images. **PS** wrote the pathology part of manuscript. **SS** reviewed and made correction in final manuscript.

Conflicts of interest

There are no conflicts of interest.

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