

Case Report

Metastatic Hepatocellular Carcinoma: presentation in a rare site

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Abstract

Hepatocellular carcinoma (HCC) is a common malignancy showing extra-hepatic metastases in 30-50% of the patients at the time of diagnosis. However, Patients presenting with metastatic hepatocellular carcinoma are rare and soft tissue metastases in head and neck area are extremely rare.

We report a 54-year-old man presenting with hoarseness of voice and a neck lump. Radiological impression was of a laryngeal carcinoma with local infiltration. Fine Needle Aspiration Cytology (FNAC) revealed a neoplastic lesion, with the incisional biopsy confirming a metastatic hepatocellular carcinoma. A primary HCC was discovered subsequently. Although cytological features are those of HCC, this case highlights the diagnostic dilemma due to its rare metastatic location.

Key words: Metastatic hepatocellular carcinoma, larynx

Introduction

HCC is a malignant tumour of hepatocellular differentiation and is the second most common cancer in Asia and fourth most common in Africa [1]. It is more prevalent in South-East Asia, Japan, Korea and Sub-Saharan Africa [2] with a high incidence in areas with high prevalence of Hepatitis B and C infections [3]. HCC is more prevalent in 6th and 7th decades of life (3,4) and usually presents with symptoms related to liver disease such as abdominal pain, malaise, weight loss, jaundice, hepatomegaly etc. [1].

Although intra-hepatic metastases and multiple lesions within the liver are common with HCC, extrahepatic metastases are seen only in 30-50% of the cases at the time of diagnosis [5]. However, symptoms due to metastases can be the initial manifestation of the disease [6]. Common sites for extra-hepatic metastases are lungs, lymph nodes, bone and adrenal glands. Soft tissue metastases in head and neck area are very rare. Metastatic HCC usually has an aggressive course and poor prognosis [7].

Case Report

A 54-year-old, previously healthy man presented with hoarseness of voice. Examination revealed an anterior neck lump and left vocal cord palsy. Ultrasound and CT scan of the neck were suggestive of a locally advanced laryngeal carcinoma of 4.2 cm size in the subglottic area with few enlarged left supra-clavicular lymph nodes.

FNAC of the neck lump showed moderately cellular smears with cohesive clusters, sheets, and few singly dispersed polygonal cells with mild to moderate pleomorphic nuclei, stippled chromatin and deeply eosinophilic, abundant cytoplasm (*Figure 1 A & B*). Plasmacytoid cells were also noted. However, classic features of squamous cell carcinoma which is the commonest laryngeal carcinoma were not seen. No lymphocytic background was seen to suggest that the lesion was a metastatic deposit in a lymph node. Cytology was reported as a neoplastic lesion, and histological examination was suggested for further evaluation and definitive diagnosis.

Trucut biopsy from the neck lesion showed a malignant tumour composed of sheets of cells arranged in a trabecular pattern. These cells were polygonal and showed enlarged, moderately pleomorphic nuclei containing granular chromatin. Some of these nuclei showed prominent nucleoli and occasional mitotic figures. The cytoplasm was abundant, eosinophilic with some cells showing a brown-coloured granular pigment. Numerous intervening vascular spaces were seen (Figure 2A). The tumour infiltrated into adjacent skeletal muscle with surrounding tissue showing a desmoplastic reaction. The tumour cells showed strong, diffuse, cytoplasmic positivity for Hep Par 1 (Figure 2 B) and were negative for CK7 and CK20. A diagnosis of metastatic HCC was made.

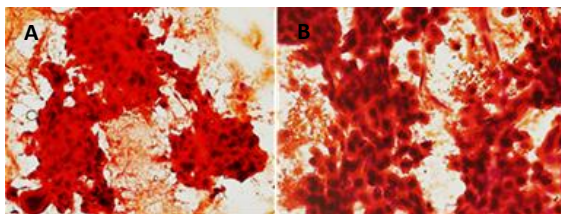


Figure 1: A- Cohesive polygonal cells with mild to moderately pleomorphic nuclei and abundant eosinophilic cytoplasm (H&E x 100) B- Cohesive sheets of tumour cells focally entrapped by endothelial cells (H&E x400).

Subsequent CT scan of the abdomen showed a 7.3 cm, hypodense lesion in liver segments VIII and Iva, compatible with a HCC in a non-cirrhotic liver with para-aortic adenopathy. USS guided biopsy showed liver tissue with no portal tracts, distorted architecture and non-triadal vessels. The cells were arranged in sheets with few vague glandular structures. Some cells showed high nuclear cytoplasmic ratio with coarse chromatin. (Figure 2C) Prominent sinusoidal capillarization was noted and confirmed by CD34 immunostain (Figure 2D). This biopsy was diagnosed as a primary HCC.

Discussion

Most HCC occur in a background of cirrhosis and present with symptoms related to liver disease [1]. Presentation with metastatic

disease occurs in a small percentage of patients [6] and common sites include lungs (47%), lymph nodes (45%), bone (37%) and adrenal glands (12%). Metastases are rarely seen in ovaries, kidneys, muscle, brain, and heart [1,3]. Head and neck metastases are very rare. Documented cases of head and neck metastases were in jaw, orbital cavity, skull and sinonasal area [2].

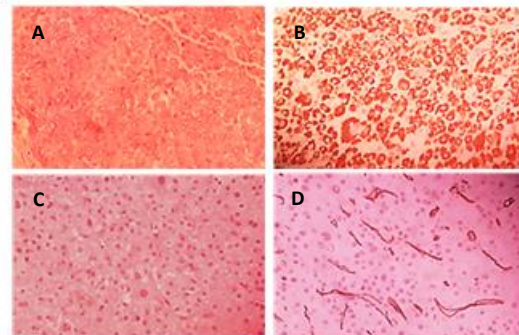


Figure 2: A- Tumour formed of sheets of polygonal cells (H&E x100). B - Tumour cells with diffuse cytoplasmic positivity for HepPar1 (x400). C- Dysplastic hepatocytes arranged in sheets (H&E x100) D- Sinusoidal capillarization is marked with CD34 (x 100)

This patient presented with hoarseness of voice due to metastasis of HCC to the larynx, which is a very rare occurrence. Furthermore, he was previously healthy with no history of liver disease and imaging was suggestive of a primary laryngeal carcinoma. Although cytomorphology of FNAC was suggestive HCC, it was challenging to report this as a metastatic HCC at this stage and biopsy was requested for confirmation.

HCC are commonly seen in cirrhotic livers due to Hepatitis B & C infection and alcohol abuse. None of these aetiologies were evident in this patient and his liver was non-cirrhotic. All these features negated a primary liver lesion at the time of initial presentation.

FNAC smears of HCC are usually hypercellular and show the spread of cells in a uniformly granular pattern. Malignant hepatocytes appear as cohesive clusters with arborizing, tongue-like projections of broad cords of cells representing thickened liver cell plates. They may be wrapped by peripheral endothelium due to sinusoidal capillarization. Pseudo-acini

containing bile or secretions are also common findings. The cells are polygonal and show well defined borders with ample granular cytoplasm and central round nucleus. Mitotic count increases with nuclear grade. Tumour cells may be small, large or similar in size to normal hepatocytes. Well differentiated tumours show small, monotonous cells with subtle increase in nucleus to cytoplasmic ratio while poorly differentiated tumours show more pleomorphic cells. Presence of intra-cytoplasmic bile is a characteristic feature of hepatic origin. Intra-cytoplasmic fat, glycogen and inclusions such as hyaline, pale and Mallory Denk bodies may be seen [8]. Although the cellular features were suggestive of hepatocellular origin, histological assessment was suggested in this patient for definitive diagnosis due to unusual clinical presentation as mentioned above.

Histopathology of classic HCC shows several architectural patterns such as trabecular (plate-like), pseudo-glandular or acinar pattern and compact or solid pattern. Whatever the architecture, finding of sinusoidal capillarization and unpaired or non-triadal arteries are constant. Portal tracts are absent in HCC. The tumour cells usually resemble hepatocytes. Bile production, hyaline bodies, pale bodies and ground glass inclusions are also seen in these tumour cells. Nuclear pleomorphism may vary with grade of the tumour. WHO histological grading is based on tumour differentiation into well, moderately, poor and undifferentiated types [1].

In this patient, the biopsy from the metastatic deposit of the larynx showed a moderate to poorly differentiated HCC while the liver biopsy showed a well differentiated HCC, confirming that metastatic deposits can differ significantly from the primary lesion [5]. HCC cells are positive with HepPar1, CEA, AFP, fibrinogen, CK8 and CK18 and negative for CK19, CK20 and EMA [1,9]. The 3-marker panel which is specifically positive for malignant hepatocytes include glypican-3, heat shock protein-70 and glutamine

synthetase. In this patient, the metastatic deposit in the larynx was Hep Par1 positive.

Spread of HCC occurs via lymphatic and haematogenous routes and the latter is more common. Intrahepatic vascular invasion by tumour cells leads to haematogenous spread of the tumour by two pathways. The common route is via the portal venous system. Arterial involvement occurs through the pulmonary circulation following hepatic vein invasion. Pulmonary metastases precede any other sites via this route. The portal route is common in patients with cirrhosis. Due to increased intra-thoracic retrograde pressure to the jugular system, retrograde flow occurs via pre-vertebral and vertebral venous plexus. With this mechanism, usually lung metastases are absent [2,4,5]. In this patient, neither lung metastases nor cirrhosis was present and lymphatic spread was favoured over haematogenous spread as cervical and para-aortic lymph node enlargement was noted in imaging.

Although many biomarkers have been experimented with a routine biomarker for prediction of metastasis and recurrences of HCC is still unavailable. However, angiogenesis which depends on the net balance between pro and anti-angiogenic factors is closely related to invasiveness of HCC. Angiogenic factors, Vascular Endothelial Growth Factor (VEGF) and Platelet Derived Growth Factor (PDGF) are involved in progression of HCC. Angiogenesis can be evaluated in HCC by CD34 immunohistochemistry [10].

Conclusion

Metastasis of HCC to larynx is very rare and may mimic primary laryngeal carcinoma as highlighted in this case. Although cytological evaluation of the lesion by FNAC is helpful, histological assessment is needed to confirm the diagnosis with detection of the primary liver lesion. Retrospective correlation of cytological and histological features is important for better understanding of the morphology of this lesion.

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