



METASTATIC HEPATOCELLULAR CARCINOMA – PATHWAY TO THE ORAL CAVITY: A REVIEW

Oral Medicine

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ABSTRACT

Metastatic malignancies of the oral cavity are a rare phenomenon, accounting for only about 1% of all oral malignancies. The metastatic tumor cells may affect the jaw bones or the oral soft tissues or even both. The primary tumors commonly implicated in oral metastasis are usually from the lungs, breast, kidney and bone. The Batson's paravertebral plexus is usually implicated as the pathway for distant metastasis into the oral cavity. Hepatocellular carcinoma (HCC) is the most common malignant neoplasm affecting the liver and about two thirds of HCC metastasize, usually to the lungs and regional lymph nodes. Such secondary neoplasm's do not have any pathognomonic clinical or radiologic findings and therefore they pose a diagnostic challenge. We review the various risk and predisposing factors and the key route of metastasis of Hepatocellular carcinoma to the oral cavity involving both the maxilla and mandible.

KEYWORDS

Oral metastasis, Hepatocellular carcinoma, Batson's paravertebral plexus, viral hepatitis.

INTRODUCTION

Malignancy is characterized by anaplasia, invasiveness, and metastasis. Malignant tumors commonly metastasize to the bone, the different parts of the skeleton and also to the maxilla and mandible.^{2,3}

Metastasis to the jaw bones is relatively rare with only about 1- 4% of all oral malignancies being secondaries from distant primary sites.⁵ However in the differential diagnosis of malignant tumors of the oral cavity, it is essential to consider the occurrence of both primary as well as metastatic tumors, despite the low incidence of the latter.⁴

The most common primary sources of metastatic tumors to the orofacial region are the breast, lung, kidney, bone, colon and rectum, prostate, thyroid, stomach, testis, bladder, ovary and cervix.^{6, 7} The breast is the most common primary site for tumors metastasizing to the mandible, whereas lungs are the most common source for metastases to the oral soft tissues.⁸ Cervical lymph nodes, mandible and gingiva are the most commonly affected sites.⁹ In the mandible, metastatic lesions are reported more frequently in the premolar – molar area¹⁰ and also to the angle of mandible probably due to loads of hematopoietic tissue marrow, which favors angiogenesis of the tumor mass to embed and proliferate.^{7,15}

HCC accounts for 85-90% of all primary liver malignancies occurring as a complication of chronic hepatitis B (HBV) and C virus (HCV) infection. Approximately 50–75% of patients with HCC develop metastases during the disease course but less than 1% of cases show oral involvement.^{1, 11} Extra-hepatic metastases of Hepatocellular carcinoma have been reported in majority of cases with involvement of lung, diaphragm, or skeleton.^{9, 12, 13} Yoshimora et al¹⁴ reported bone metastases most frequently involving the vertebrae followed by ribs, sternum and pelvis.

We review the various risk and predisposing factors and the key route of metastasis of Hepatocellular carcinoma to the oral cavity involving both the maxilla and mandible.

TEXT

Metastatic oral malignancies are rare and, only 1–3% of oral malignancies are secondaries from a distant primary site, from the breast, adrenal gland, colorectal system, genital organs and thyroid in females; and from lung, prostate, kidney, bone and adrenal gland in males.^{9,16} The most common sites of metastasis from HCC are the lung, lymph nodes, bone and adrenal glands.^{17,18}

Metastatic tumors to the jaws are far more common than in the oral mucosa. In case of metastases to the jaw bones, there is slight female

predilection; whereas in cases of metastases to the oral mucosa, there is almost equal gender predilection. The breast is the most common primary site for tumors metastasizing to the jaw bones while lung was the most common source for metastases to the oral mucosa.⁸ It was also reported that mandible was the most common site affected in Cranio-facial metastasis¹⁹⁻²¹ and molar premolar area is the most common site involved in the mandible.¹⁰ In the oral soft tissues, the gingiva is the most common site for metastatic colonization and the mandibular attached gingiva is more commonly involved than maxillary attached gingival.^{22,23} It may be hypothesized that due to persistent inflammation in the attached gingiva it serves as a common site for metastasis.

Hepatocellular carcinoma (HCC) also called Hepatocarcinoma, is a primary malignancy of the liver and is the fifth leading cause of cancer deaths worldwide.²⁴ A literature search in pubmed shows only 56 reported cases of metastatic hepatocellular carcinoma to the oral cavity - 45 to the mandible, 9 to the maxilla, 1 to both mandible and maxilla and 1 to the tonsil.²⁵ Most cases of HCC occur predominantly in patients secondary to either a viral hepatitis infection (Hepatitis B & C) or due to underlying chronic liver disease and cirrhosis.²⁶

The various predisposing factors [Figure 1] that play a role in liver cancer are viral hepatitis B & C,^{27, 28} Aflatoxins,²⁹ cirrhosis of liver, alcohol, post necrotic and hemochromatotic cirrhosis in low prevalence areas,^{30 - 32} obesity, and hypertension, metabolic disorders – Type I Tyrosinemia,³³ Dyslipidemia and Type II Diabetes,³⁴ chemicals and drugs – vinyl chloride,³⁵ Thorium dioxide,³⁶ polychlorinated biphenyls and organochlorides,³⁷ and genetics



Figure 1: Predisposing factors for Liver carcinoma

The incidence of occurrence of HCC varies greatly in different regions of the world, being highly prevalent in Asia and Africa due to the high

prevalence of viral hepatitis (Hepatitis B & C).^{38, 39} Viral hepatitis may strongly predispose to the development of chronic liver disease that may eventually lead to the development of HCC (Figure 2).

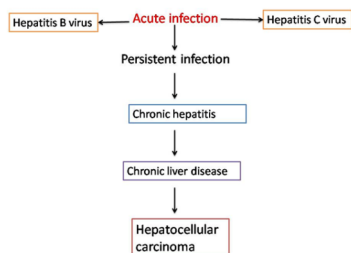


Figure 2: Role of viral hepatitis in HCC

Hepatitis B virus (HBV) predisposes to 80 – 90% cases of HCC while Hepatitis C virus (HCV) being the second most common predisposing factor. Inflammation, necrosis, fibrosis and regeneration, which are the characteristics of liver cirrhosis may also predispose to the development of HCC. In patients with HBV infection, HCC can develop in the absence of cirrhosis; while in patients with HCV, HCC can develop more or less with cirrhosis. This difference is due to the fact that HBV is a DNA virus that becomes incorporated into the host genome of infected hepatocytes and produces HBX protein that may play a vital role in the malignant transformation^{40,41} whereas HCV is an RNA virus that replicates in the cytoplasm and does not get incorporated in the host DNA.

In the subtropical region, ingestion of Aflatoxins (fungal toxins) contaminated food is also believed to play a role in HCC development. Aflatoxins can bind covalently with cellular DNA and cause mutations in proto-oncogenes or tumor suppressor gene mainly p53 and consist of a transversion of guanine to thymine at codon 248.⁴² In the low prevalence area such as North America and Europe, where HBV/HCV vaccinations are prevalent, the underlying cause proposed to be alcohol, post necrotic and hemochromatotic cirrhosis.^{43 - 45} Recent literature suggests that HCC may develop from hepatic stem cells that proliferate in response to chronic regeneration caused by viral injury.⁴⁶ The metastasis of liver cancer (Figure 3) occurs by 2 routes – hematogenous and lymphatogenous and it is believed that hematogenous route is more important than lymphatic spread. There are two main pathways of tumor metastasis from the liver to the maxillofacial region by means of hematogenous route.^{15, 47} The first is through the portal hematogenous route, involving the major vessels of the liver – hepatic artery and portal vein, leading to widespread metastases frequently to the lungs, which may later reach the maxillofacial region. According to this pathway, most of the metastatic deposits of HCC in the maxillofacial region are often accompanied by lung metastases.

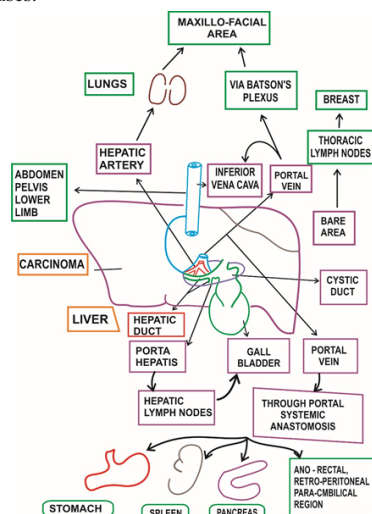


Figure 3: Spread of Liver carcinoma

The second route is by Batson's paravertebral plexus (BPP) or the venous plexus of Batson. This plexus named after Oscar Vivian Batson⁴⁸ is a system of valveless vein located in epidural space between

the spinal column and dura mater.^{49,50} This plexus of veins has no valves to control the flow of blood, so that any increase in pressure in the vena cava system leads to increase in flow into the BPP. Malignant cells entering the plexus get embedded in the venous and sinusoidal system of bones that are connected to BPP,⁵¹ thus bypassing the pulmonary, caval and portal systems. The route of venous drainage is outlined in (Figure 4).

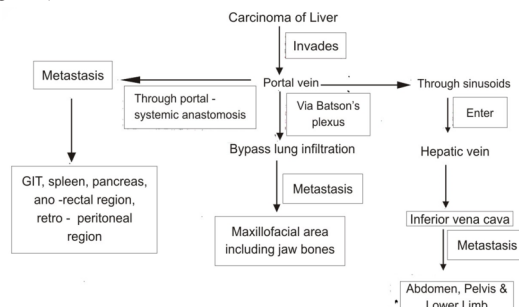


Figure 4: Venous spread of liver cancer

Once the carcinoma invades the lymphatic system, malignant cells from liver spreads via lymphatic channels to the hepatic lymph nodes in the porta hepatis, then to the celiac nodes and finally involves the thoracic duct. Hence, hepatic, peri-pancreatic, celiac and para-aortic lymph nodes are invaded first before finally spreading to the head and neck region. The spread of cancer cells from the lymphatic route is outlined in (Figure 5). The immune-histochemical markers that can be used to diagnose HCC are α -feto protein, Glypican-3, HepPar1 and CD34.⁵²⁻⁵⁴

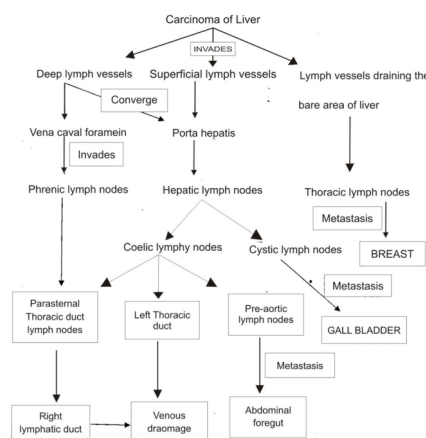


Figure 5: Lymphatic spread of liver cancer

The possible cause of death in HCC may be due to liver failure, portal hypertension and massive intraperitoneal hemorrhage (Figure 6).

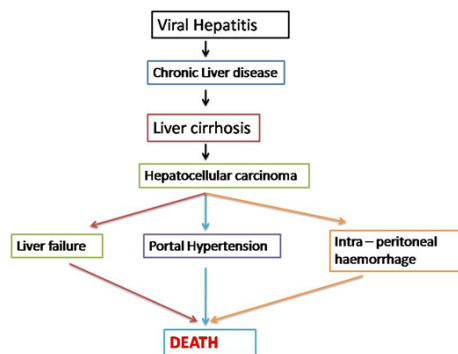


Figure 6: Complications in HCC

CONCLUSION

Oral cavity has been described as a mirror of systemic diseases. Hepatocellular carcinoma is a common primary liver malignancy in the developing world and though oral metastasis is very rare but oral manifestations are often the sole indication of the disease.^[55] Diagnosis of metastatic lesions is quite challenging and detection of these lesions

in the oral cavity is even more important as these may be diagnosed first by the oral physician/dental surgeon. Since there are no pathognomonic clinical or radiographic signs of oral metastatic disease, it poses a diagnostic challenge. Moreover metastatic HCC may be undifferentiated, or have a pseudoglandular pattern, mimicking other glandular malignancies so that the primary cell of origin is not detected. With the advent of Immuno – histochemical markers, advancement in molecular techniques and introduction of therapies targeted at molecular level, the diagnosis is easier and specially targeted therapies may be introduced to halt the tumor proliferation, thereby improving the quality of life as well as life expectancy of the patients.

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