Hepatocellular carcinoma

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Liver can be seat of primary malignancy in the form of hepatocellular carcinoma (HCC) or of secondary (metastatic) deposits. It is most frequently affected by metastases.

HCC though a common malignancy, its incidence exhibits a wide geographic variation.The condition develops exclusively on a background of chronic liver disease at the stage of cirrhosis, chronic hepatitis B virus infection and chronic hepatitis C virus infection, and dietary exposure to aflotoxin. The condition may develop in the background of haemochromatosis, tyrosinaemia, alpha-1 antitrypsin deficiency, intake of excessive androgens, and oral contraceptives The incidence of HCC is noted more commonly in elderly male persons. The incidence of HCC is high in Taiwan, Zimbabwe, Hong Kong, Senagal and Japan.[1]

The tumour appears as a single or multiple nodules in the presence of cirrhosis. Microscopically the tumour resembles hepatocytes when well differentiated. HCC is a highly vascular tumour getting blood supply from hepatic artery unlike the normal liver parenchyma which derives its blood supply from portal vein.The tumour is capsulated and contains haemorrhage, necrosis, fat and calcification. The tumour spreads by invasion into the portal vein and its radicals. The tumour metastasizes to the lymph nodes located around porta hepatis, coeliac and para aortic region, lung, bone and adrenal glands.

The clinical manifestations are often noted when the tumour has occupied a greater amount of space in the liver. The condition presents with pain in right hypochondrium, anorexia, weight loss and hepatomegaly. The patient may exhibit features of chronic liver disease in the form of ascites, jaundice and variceal bleeding. Palpation of the abdomen reveals hepatomegaly or a single hypochondrial mass. A bruit may be audible due to tumour vascularity. There are rare chances of rupture of tumour to result in haemoperitoneum with severe abdominal pain and shock. Uncommonly the tumour may secrete insulin-like growth factors, parathyroid-related hormones, and erythropoietin to bring about changes such as hyperglycaemia, hypercalcaemia and polycythaemia respectively.

The alpha-fetoprotein (AFP) is elevated and an amount greater than 400 mircograms/ml is diagnostic of HCC, in patients with cirrhosis and a mass greater than 2 cm in diameter.[2] A rising trend in the level of AFP further confirms the diagnosis. Serum AFP levels rise in presence of active hepatitis B and C viral replication, and acute hepatic necrosis. Ultrasound of the abdomen is useful in the diagnosis, and it can detect lesions as small as 2-3 cms. Often regular screening of high risk patients (cirrhosis due to hepatitis B and C, alcohol, alpha-1 antitrypsin deficiency and haematochromotosis) by ultrasound scanning periodically may help in early recognition of the tumour. Sonographic features of HCC can be hyperechoic, hypoechoic, echogenic or complex. Smaller tumours exhibit an hypoechoic halo corresponding to fibrotic capsule. Often it is hypoechoic due to dense cellular elements, necrosis and sinusoidal dilatations. It may be heterogenously hyperechoic due to the presence of fat, haemorrhage or fat.

CT shows the lesions to be hypodense to the parenchyma. The lesions give a hypervascular appearance on helical CT following intravenous contrast. Four phases of contrast enhancement, following administration of 120 ml of contrast material containing iodine (170 mg/ml), in liver are recognized.[3] The early arterial phase shows enhancement hepatic arteries without any parenchymal enhancement. In the late arterial phase, there is persistence of arterial enhancement along with early portal venous and parenchymal enhancement. There is hepatic venous enhancement. Then there is portal venous phase showing marked parenchymal and portal venous enhancement and opacification of hepatic veins. It is followed by the delayed (equilibrium) phase. Smaller lesions show a uniform enhancement. The larger lesions show heterogeneous enhancement due to presence of different elements within the tumour. Fine needle biopsy of liver has marked limitation in the diagnosis. Often it may fail to detect small lesions. Difficulty may be posed to distinguish a well-differentiated HCC from displasia and adenoma. Biopsy may facilitate tumour seeding along the needle track and often it is recommended to avoid the procedure when a surgical resection or transplantation has been contemplated.

MRI may show iso-, hypo- or hyper-intense shadows to liver parenchyma on T1W1 images and hyperintense in T2W1 image. MRI shows enhancement in the arterial phase with relative hypovascularity (iso- to hypodense) in the portal or late phases. There may be hypertrophy of hepatic artery, presence of hepatic vein and portal vein thrombosis and an arterio-portal shunting. The capsule gives a hypointense image.

Biopsy is not indicated when the imaging features are characteristic. It should be avoided in potentially operable lesions as there is risk of tumour seeding.

Majority of HCC develop on the background of chronic liver disease. The size of the tumour has a distinct role in determining the prognosis as vascular invasion increases with tumour size. However the prognosis is better if it can be resected in the absence of vascular invasion. Underlying cirrhosis often limits the surgical option as resection requires sufficient hepatic reserve for proper function. A fibrolamellar type of HCC that develops in young age group in males and females without any underlying chronic liver disease or hepatitis B infection, offers good prognosis as it can be resected. The tumour attains a large size and AFP is usually normal.

There are many different types of treatment procedures. But the choice is limited to some selected patients. Liver resection is possible in a small number as the condition is not detected in earlier stages. The resection is planned on determining the size, location, relation to blood vessels, cirrhosis and underlying liver status. Hepatic resection is possible if there is no underlying cirrhosis.

Liver transplantation gives some hope to the patients with tumour and underlying cirrhosis. However there is a major limitation for the supply of donor organs. The waiting period is often associated with risk of tumour growing in size making the procedure futile. Patients with hepatitis B and C may recur in the transplant liver.

Liver ablation: In some selected cases, who are not candidates either for resection or transplant, ablation treatment may be tried. However it is difficult to achieve full ablation when the tumour has exceeded 5 cm in diameter. Increasing size facilitates vascular invasion and increases chances of metastases. The procedure is carried under image guidance percutaneously. Percutaneous injection (PEI) of chemical substances (ethanol, acetic acid) into the tumour or by modifying temperature (radiofrequency, laser cryotherapy) have been widely studied. Injection of 90% of ethanol under ultrasound guidance is safe and inexpensive procedure.[4] This is useful in lesions less than 2 cm in size. A localized thermal treatment is carried out by using radiofrequency ablation (RFA). It is recommended in lesions of size between 2 to 5 cm in diameter. There is destruction of tumour when the probe inserted into the tumour is heated to >60 o C.[5]

Transarterial chemo-embolization (TACE): HCC is not radiosensitive. Since the tumour derives its blood supply from hepatic artery, a selective catheterization of the hepatic artery using super-selective microcatheters, is done through which chemotherapy is administered to have a regional effect, and is followed by embolization of tumour-feeding arteries so as to to abolish tumour circulation. Chemotherapeutic agent (adriamycin) often mixed with lipiodol, when injected, it gets preferentially accumulates in the tumour. It facilitates concentration of chemotherapy in tumour and reduces systemic exposure due to impaired venous drainage. Thus it functions regionally. It is to be followed by embolization of tumour feeding arteries to abolish circulation. Such a procedure can't be undertaken when the blood supply from the portal vein (main portal vein thrombosis) to the non-tumour portion of liver is compromized. This procedure is also not advised in advanced cirrhosis and co-morbid conditions. The procedure may rarely lead to liver abscess.[6]

Radioisotopes: Radio-isotopes such as yttrium-131 labeled micro-spheres or iodine-131 containing lipiodol can be delivered through hepatic artery. However the recurrences are frequent.

Systemic therapy: In situations where the carcinoma is multi-focal or has involved both lobes or when it has spread to other regions and exhibits underlying cirrhosis, surgical intervention is not possible and it has to be treated with chemotherapy. Doxorubicin has not shown significant survival benefits. Nolatrexed, a thymidylate synthase inhibitor has been tried, and it has not improved survival benefit. [1]

Attempts are made to inhibit the angiogenesis that facilitates the growth of tumour. [1] Sorafenib, an oral multikinase inhibitor has been tried to inhibit a tyrokinase (TK) that signals the cacade that promotes angiogenesis through vascular endothelial growth factor (VEGF) and it has shown to be effective in bringing disease stability. Sunitinib, also a multikinase inhibitor targeting VGEF is under trial. Bevacizunide, an monoclonal antibody targeted against VGEF is able to prevent its interaction with receptor(R). Epidermal growth factor (EGF) and transforming growth factor-alpha have a role in angiogenesis, and cancer cell proliferation and spread, and they are active through ECF receptors. Eclotinib is able to inhibit EGFR-TK to bring about disease stability. These agents may have an adjunctive role to the systemic therapy.

Prevention: Since hepatitis B virus forms one of the major risk factors for development of HCC, vaccination against hepatitis B virus plays an important role in preventing its occurrence. Use of antiviral therapy on development of hepatitis B virus infection helps in further reducing the incidence of chronic hepatitis B, in turn HCC. There is no vaccine against hepatitis C virus infection.

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