

# Clinical and laboratory features of hepatocellular carcinoma

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The clinical presentation of hepatocellular carcinoma (HCC) differs between patients in developing countries (African and Chinese populations) from those in industrialized countries. In industrialized countries, HCC co-exists with symptomatic cirrhosis in 80% of cases and clinical manifestations are usually related to those of the underlying disease. On the other hand, patients from developing countries have HCC and cirrhosis in approximately 40% of cases. Underlying cirrhosis in many cases is not advanced and does not produce any symptoms or associated symptoms are masked by those of the tumor (right upper quadrant pain, mass in the upper abdomen, weight loss and weakness). In a subset of patients, there are no clinical manifestations as HCC may occur in the context of hepatitis B infection without cirrhosis.

## Clinical Manifestations

In Western countries, nearly 35% percent of patients with HCC are asymptomatic. Some of the most common clinical manifestations include: abdominal pain (53-58% of patients), especially in epigastrium or right upper quadrant, abdominal mass (30%), weight loss, malaise, anorexia, cachexia, jaundice or fever.

## Physical Exam

Physical findings vary with the stage of disease. The patient may exhibit slight or moderate wasting when first seen. In patients with cirrhosis, typical stigmata of chronic liver disease may be present. In advanced stages of HCC the liver may be enlarged and there is significant tenderness. An arterial bruit may be heard over the liver. Jaundice is unusual at first presentation and, when present, is mild; it commonly appears or deepens with progression of the disease. A low to moderate, intermittent or remittent fever may be present.

## Unusual Presentations

- Obstructive jaundice: is the initial presentation in 1-12% of cases. It is due to compression of the major intrahepatic bile duct by the tumor, invasion of HCC into the lumen of intrahepatic bile ducts, infiltration of the wall of bile ducts causing obliteration of the lumen, hemobilia, or free-floating tumor plugs into the biliary tree.
- Acute abdomen: is a life-threatening complication caused by rupture of the tumor causing intraperito-

neal bleeding. It occurs in later stages of the tumor and is a frequent cause of death.

- Obstruction of splanchnic veins: tumor may invade the portal vein, hepatic veins and inferior vena cava, resulting in portal hypertension (with ascites and variceal bleeding), Budd-Chiari syndrome and pitting edema of lower limbs.

## Paraneoplastic syndromes

Patients with HCC may develop a paraneoplastic syndrome such as hypoglycemia, erythrocytosis, hypercalcemia or watery diarrhea.

- Hypoglycemia: there are 2 types of hypoglycemia in patients with HCC. Type A hypoglycemia is not a paraneoplastic syndrome, it is related to the inability of a liver extensively replaced by tumor cells to meet the glucose demands of the tumor and the entire body. Typically, this type of hypoglycemia is mild and asymptomatic. In contrast, type B hypoglycemia is due to secretion of insulin-like growth factor-II by the tumor. This factor acts as an insulin agonist, causing severe symptomatic hypoglycemia.
- Erythrocytosis may be due to the production of erythropoietin by the tumor. Although, 23% of the patients with hepatocellular carcinoma have this abnormality, elevations in hemoglobin concentration are uncommon.
- Hypercalcemia may be due to osteolytic metastases of the tumor or more frequently to the secretion of parathyroid-related protein by the tumor.
- Watery diarrhea may be related to the secretion of peptides that cause intestinal secretion, including VIP, gastrin or peptides with prostaglandin-like immunoreactivity.
- Symptomatic porphyria: It is due to excessive production of porphyrin by the tumor with its consequent accumulation in the skin causing photosensitivity.

Other paraneoplastic manifestations are, arterial hypertension (related to the production of angiotensinogen by the tumor), carcinoid syndrome, hypertrophic osteoarthropathy and hyperthyroidism.

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### Laboratory findings

Laboratory examination is usually nonspecific. Most of patients with HCC have cirrhosis and may have thrombocytopenia, hypoalbuminemia, hyperbilirubinemia, and hypoprotrombinemia. Patients are often mildly anemic and may have electrolyte disturbances like hyponatremia, hypokalemia, and metabolic alkalosis, associated with defective water handling or with diuretic use. Serum aminotransferases, alkaline phosphatase and gammaglutamyl transpeptidase are often abnormal in a nonspecific pattern. Some serum markers are useful in diagnosis of HCC. The most commonly used is alpha-fetoprotein (AFP). AFP is a glycoprotein that is normally produced during gestation by the fetal liver and the yolk sac.

In adults, normal values are less than 20 ng/ml and AFP is often elevated in patients with HCC. Serum concentrations of AFP do not correlate with clinical features of HCC, such as size, stage and prognosis but is generally accepted that serum levels greater than 500 ng/ml in a high risk patient is diagnosis of HCC.

Other serum markers - Because of the limitations of serum AFP measurements, other serum markers of HCC used alone or in combination with the serum AFP have been evaluated for diagnosis or determining prognosis in patients with HCC. These include lens culinaris agglutinin-reactive AFP and des-gamma carboxyprothrombin, glypican-3, human hepatocyte growth factor, and insulin-like growth factor.

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