

Hepatocellular Carcinoma in an African American Man with a Noncirrhotic Liver Presented Initially as an Occipital Mass

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An 88-year-old African American man with no significant medical history was referred to our hospital for evaluation of a rapidly growing, painless right occipital mass associated with severe, progressively worsening headaches that were unresponsive to over-the-counter drugs, ataxic gait, and an unexplained 20-lb weight loss over a period of 2 months. The patient had no history of blood transfusion, alcohol abuse, or intravenous drug use.

On physical examination he was found to be alert and oriented, with a 15 × 9-cm oval-shaped, nontender, immobile, firm mass palpable in the right occipital area. No lymphadenopathy or jaundice was noted. Cardiac and chest examination were unremarkable. His liver was smooth and nontender, palpable 5 cm below the costal margin, and no ascites or splenomegaly was detected. The patient had normal hair distribution of the chest, axillae, and pubis, no gynecomastia, and normal-sized testicles. Bilateral pedal edema was more pronounced on the right side than left. Neurological examination showed wide-base ataxia and a positive Romberg test. Cranial nerves were grossly intact and there were no pathological reflexes.

The initial laboratory evaluation included a complete blood count, blood chemistry, liver function tests, and coagulation profile; all were within normal range. A chest x-ray was normal, without masses or hilar lymph adenopathy.

Computed tomography (CT) and magnetic resonance imaging scans of the head showed a large soft-tissue

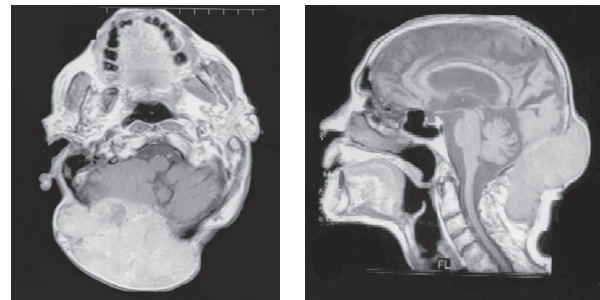


Figure 1. (Left) Axial computed tomography scan of the head showing a large soft-tissue mass involving the right occipital bone, with extension to the overlying soft tissues.

Following administration of gadolinium, axial and T1-weighted images showed a large soft-tissue density mass in the right occipital region, centered in the occipital bone, with extension into epidural space and the right side of the posterior fossa and a large component in the subcutaneous tissues with mass effect of the right side of the cerebellum.

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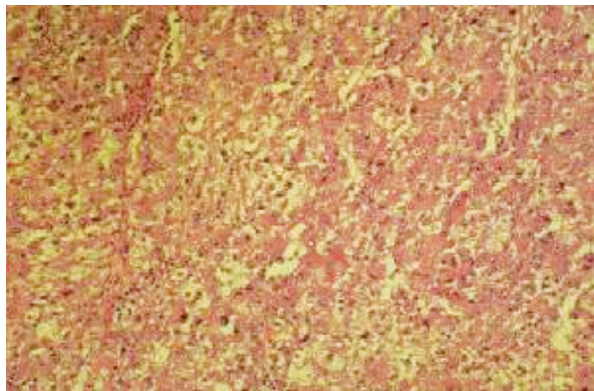


Figure 3. Sheet of tumor cells showing canalicular formations, irregular intracytoplasmic Mallory bodies, and scanty fibrous stroma.

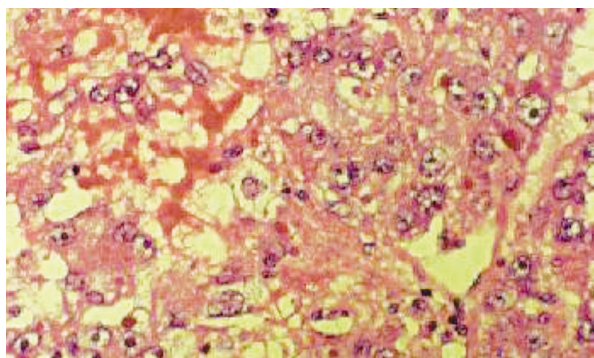


Figure 4. On high magnification, the tumor cells show marked pleomorphism with prominent nucleoli and clear cytoplasm containing eosinophilic globules.

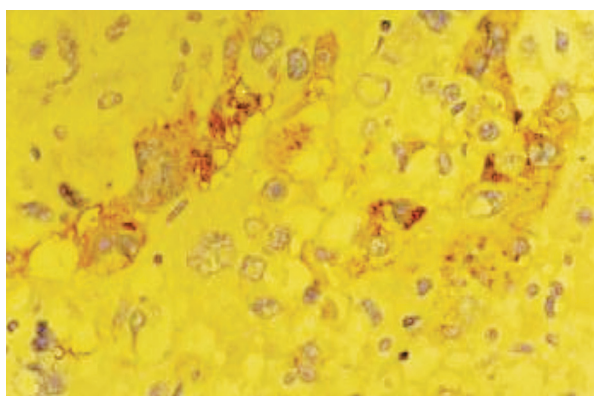


Figure 5. The tumor cells show a positive reaction to α -fetoprotein on immunohistochemical stains.

density measuring $6.0 \times 7.0 \times 12.0$ cm centered in the right side of the occipital bone with epidural extension and mass effect up on the right cerebellar hemisphere. The mass extended to involve the posterior upper neck. There was no evidence of hemorrhage or extra axial fluid collection (Figures 1 and 2). Magnetic resonance angiography/venography showed occlusion of the right transverse sinus by the soft-tissue mass.

Pathology findings from resection of the mass were as follows: multiple irregular fragments of friable hemorrhagic soft tissue measuring in aggregate $5.2 \times 5 \times 1.2$ cm; histopathologic examination revealed a poorly differentiated epithelial tumor with canalicular formation, intracytoplasmic Mallory bodies, and eosinophilic globules suggestive of hepatocellular carcinoma (HCC). The diagnosis was confirmed by immunohistochemical studies (Figures 3–5).

CT scans of the chest, abdomen, and pelvis were normal except for a mass in the posterior segment of the right lobe of the liver measuring 8.0 cm in diameter (Figure 6). Several small satellite lesions were also noted. There was no evidence of biliary dilatation.

The α -fetoprotein (AFP) level was 4,548 ng/mL; hepatitis serology was negative.

The patient was started on glucocorticoids and anti-seizure medication and referred to radiation oncology and neurosurgery.

A subtotal resection was performed followed by 6 weeks of radiation therapy (total cumulative dose: 6,000 cGy in 30 fractions). The mass was significantly reduced to 4 cm in diameter; the patient reported no pain and neurological deficits improved. The patient died 6 months later from severe aspiration pneumonia.

Discussion

Hepatocellular carcinoma is one of the most common internal malignancies of mankind. It ranks fifth in frequency in the world with an estimated 0.5–1 million cases per year, most of which occur in sub-Saharan Africa and Southeast Asia.^{1,2} The disease has a dismal 5-year survival rate of less than 5%.³

North and South America, most of Europe, Australia, and parts of the Middle East have a relatively low incidence of HCC, with fewer than 3 cases reported per 100,000 population per year. In the United States, however, the incidence of HCC has increased during the past 2 decades, from 1.4 to 2.4 per 100,000 during the period from 1991 to 1995. Men are affected 3 times as often as women, and blacks are affected twice as often as whites. Older age is associated with a higher risk, but the incidence among younger persons has also risen progressively.^{4,5}

Important risk factors for the development of HCC in the United States are infection with the hepatitis C virus (HCV) or hepatitis B virus (HBV) and alcoholic cirrhosis.⁶ However, HCC can also occur in patients without known risk factors.⁷

The increased incidence rate is likely to continue because of the large number of patients infected with HCV, HBV, or both in whom the cancer is in the latency period, as well as growing immigration from endemic areas such as Southeast Asia and parts of Africa, where HBV infection and exposure to environmental carcinogens such as aflatoxin are common.⁴

HCC is frequently diagnosed late in its course because of the absence of pathognomonic symptoms.⁸ Many patients have untreatable disease when first diagnosed, with a median survival of about 6–20 months.⁹ Patients with advanced disease may have mild to moderate upper abdominal pain, weight loss, early satiety, or a palpable mass in the upper abdomen⁸ or symptoms related to their chronic liver disease. Only up to approximately 4% of patients with advanced disease present with metastatic lesions and no abdominal complaints.¹⁰

Suspicion for HCC should be heightened in patients with previously compensated cirrhosis who became decompensated with ascites, encephalopathy, jaundice, or variceal bleeding. These complications are often associated with extension of the tumor into the hepatic or portal veins or arteriovenous shunting induced by the tumor.¹¹

Uncommon presentations include obstructive jaundice, diarrhea, intraperitoneal bleeding due to tumor rupture,^{12,13} or paraneoplastic syndromes like hypoglycemia, erythrocytosis, hypercalcemia, or severe watery diarrhea.^{14–17}

Dermatomyositis and pemphigus foliaceus have been described in association with HCC; however, they are not specific for the diagnosis.¹⁸

About 67% of patients without cirrhosis and 50% of those with cirrhosis are found to have extrahepatic metastases at the time of diagnosis.¹⁹ The lungs, regional lymph nodes, kidneys, and adrenal glands are common sites of metastasis. Bone metastases are uncommon, with an incidence ranging from 2% to 16%.²⁰ The most frequent sites of osseous metastases are the vertebrae. Metastases to the skull bones are exceptionally rare, approximately 0.4–1.6%.^{20,21} In Taiwan in 1979, Chang and Chen studied 382 patients with HCC and found only 2 with skull metastases (0.5%).^{10,22}

Skull metastasis without other osseous metastases is rare. However, Yen et al, after studying 33 cases of HCC with intracranial metastasis, hypothesized that HCC can metastasize to the cranium via 1 of 2 pathways: the hematogenous pathway via the lungs to the brain parenchyma and the osseous pathway via Batson's venous plexus to the

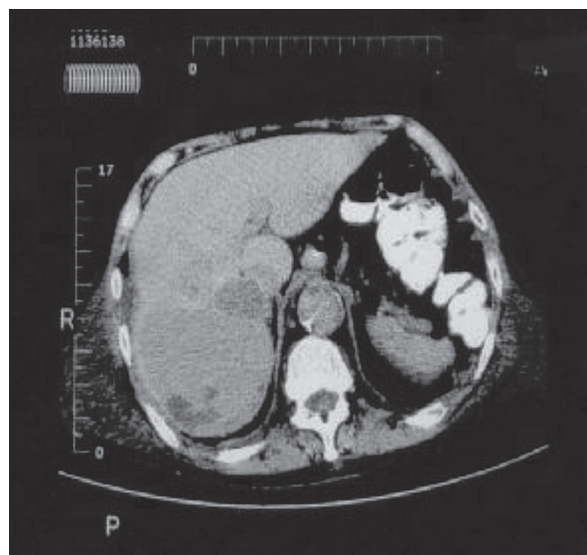


Figure 6. Computed tomography scan of the abdomen showing a large liver mass of approximately 8 cm in diameter, involving a large posterior segment of the right lobe with satellite lesions.

skull,²³ followed by erosion into inner and outer tables producing metastatic lesions in the skull.

Skull metastases have been reported to be associated with acute epidural hematoma causing neurological deficit and coma,²⁴ and with epistaxis.¹⁰ HCC skull metastases most often appear on CT scans as osteolytic, expansile, and well-enhanced masses extending from the skull and accompanied by a soft-tissue mass,²⁵ as in our case. Patients presenting with skull metastases usually have had their primary disease already diagnosed and typically have bony metastases elsewhere. Our patient had no metastasis other than to the skull.

The diagnosis of HCC is suspected when a patient with underlying liver disease develops an elevated serum AFP level. Radioimmunoassay for AFP was reported as elevated in 60–75% of patients with HCC²⁶; however, it can also be normal.²³ Kuratsu and colleagues reported that only 1 of 3 cases of HCC with brain metastases showed a significant increase in serum AFP.²⁷ A level of AFP greater than 500 µg/L in a high-risk patient is diagnostic of HCC.

Serum AFP levels do not correlate well with other clinical features of the disease, such as size, stage, or prognosis.²⁸

Lectin-reactive profiles and des-γ-carboxy prothrombin (also known as prothrombin produced by vitamin K absence or antagonism II [PIVKA II]), tumor-associated isoenzymes of gamma-glutamyl transpeptidase, urinary transforming growth factor-β-1, serum levels of circulating intercellular adhesion molecule-1, and serum

α -L-fucosidase activity have all shown promise in the diagnosis of HCC,²⁹⁻³⁴ but have not demonstrated superior accuracy compared to serum AFP.

Treatment of HCC with skull metastases with either radiotherapy or surgery or both should be considered because of the risk of extradural or intratumoral hemorrhage or underlying brain compression, which have neurological consequences.

A vigilant approach to the treatment of patients known to have HCC or at a high risk of developing HCC can reduce the risk of neurological sequelae and thus improve or maintain patient quality of life, and sometimes prolong life.^{23,35}

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Review

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Introduction

The report by Khalil and colleagues of a patient with HCC who presented with a metastasis in the occipital bone is a timely reminder that this tumor may present in one or more of many unusual ways. Failure to be aware of these presentations may result in the diagnosis of HCC being delayed or even overlooked. Atypical presentations are the result of either the characteristics of the primary tumor, such as vascular invasion or paraneoplastic manifestations, or metastatic spread.

Obstructive Jaundice

Obstructive jaundice is one of the more frequent of the unusual presentations of HCC, being the presenting complaint in as many as 12% of patients.¹⁻⁴ In other patients obstructive jaundice becomes evident later in the course of the illness. The jaundice is moderate or deep and is commonly associated with other features of cholestasis, including pruritus. These symptoms may overshadow the other symptoms of the tumor.

Several causes of obstructive jaundice have been described in patients with HCC.¹⁻⁴ The most common causes are compression of the major intrahepatic bile ducts by a primary tumor located near the porta hepatis, compression of the common hepatic duct by malignant glands in the porta hepatis, or extensive invasion of intrahepatic bile ducts by the tumor. With these causes, the jaundice is unremitting and progressive. When extensive invasion of intrahepatic bile ducts by the primary tumor occurs, the tumor may propagate along the lumen of the ducts towards the hilum of the liver and may reach the extrahepatic biliary tree.^{2,5} In some instances the distal portion of the tumor in the ductal system may separate from the proximal intraductal tumor, becoming a free-floating tumor plug. Rarely, such a tumor plug may result from necrosis of HCC with rupture into an adjacent major bile duct. Hemobilia is another rare cause of obstructive jaundice. This condition results from hemorrhage from the tumor into a major intrahepatic bile duct. The jaundice produced by a free-floating tumor plug or hemobilia may be episodic and be accompanied by colicky upper abdominal pain and cholangitis. Occasionally, HCC may directly infiltrate the wall of the common hepatic or common bile duct with obliteration of the lumen and consequent obstructive jaundice.

Budd-Chiari Syndrome and Inferior Vena Caval Obstruction

HCC has a propensity to invade venous radicles in the liver. This phenomenon occurs particularly with portal venous radicles, but hepatic venous radicles may also be affected, and it is the latter that result in unusual clinical presentations. Naked-eye evidence of invasion of hepatic veins is seen in as many as 14% of necropsies.^{1,6} Patients with this complication show the typical clinical features of the Budd-Chiari syndrome—a uniformly enlarged, tender liver and tense intractable ascites. In approximately two thirds of patients with hepatic venous invasion, the tumor propagates along the lumen of the hepatic veins to reach the inferior vena cava, where it produces partial or complete occlusion of the lumen.^{1,6} Complete occlusion is recognized clinically by the sudden onset of gross bilateral pitting edema of the lower limbs that characteristically reaches as high as the groins and responds poorly to treat-

ment with diuretics. The tumor may propagate down the lumen of the inferior vena cava, reaching as far as the iliac veins, or up the lumen into the right atrium and even the right ventricle. Intracardiac spread is present in 2–4% of necropsies.^{1,6-8} These patients present with syncope, right heart failure, tachycardia, changing cardiac murmurs, or sudden death. Very rarely, pulmonary infarction may result when a large part of the tumor plug in the right side of the heart breaks off and embolizes to the lungs.⁹ Occasionally, HCC invades the inferior vena cava by direct spread.¹

Superior Mediastinal Syndrome

Patients with HCC rarely present with the symptoms and signs of the superior mediastinal syndrome.¹⁰⁻¹² This results from compression of the superior vena cava by a mediastinal mass comprised of lymph nodes infiltrated by metastases. These metastases originate from a primary tumor located in the right hepatic lobe under the bare area. A Virchow-Trossier node or right-sided supraclavicular lymphadenopathy may occur in association with the large mediastinal mass of lymph nodes.¹¹

Acute Abdominal Crisis

A small number of patients with HCC first come under medical attention because of a sudden onset of severe abdominal pain accompanied by the development of board-like rigidity of the anterior abdominal wall, abdominal distension, absent bowel sounds, pallor, and hypovolemic shock.^{1,13-15} This life-threatening complication is caused by rupture of the tumor, or of attenuated liver tissue overlying the tumor, with resulting acute hemoperitoneum. Tumor rupture is usually spontaneous, but may follow blunt abdominal trauma (that need not be severe).¹⁶ Ironically, the latter may carry a better prognosis because tumors ruptured by trauma tend to be smaller and more likely to be resectable than those rupturing spontaneously. Although a rare presenting event, tumor rupture is more likely to occur in the later stages of the illness and is an important terminal event. Tumor rupture is more common in Chinese and black African patients, occurring in 12–26% of these patients^{1,13-15} compared with 2–3% of patients in other countries.^{17,18} Understandably, tumor rupture carries a grave prognosis. At necropsy, smaller ruptures and bleeds are sometimes seen to have been localized by the omentum.

Hepatic tumors that rupture are usually large and necrotic, and are more likely to be in the left lobe and at or near the surface of the liver. The reason for spontaneous rupture of the liver is uncertain. Suggested causes include a sudden increase in intratumoral pressure resulting from hemorrhage into the tumor or a more gradual increase following hepatic vein invasion by the tumor.¹⁵

Very rarely, intraperitoneal bleeding in a patient with HCC is caused by splenic rupture.¹⁹ This is usually the result of splenic metastases.

Respiratory Symptoms

Dyspnea, cough, and hemoptysis are rare presenting complaints in patients with HCC.^{1,20-22} For example, this occurred in 1% of Chinese patients from Hong Kong.²⁰ Less infrequently, these symptoms are present later in the course of the illness when they may be overshadowed by other symptoms attributable to the primary tumor. Respiratory symptoms result from multiple pulmonary metastases, a markedly raised right hemidiaphragm, a large pleural effusion, or a combination of these.^{1,20-22} The lungs, together with regional lymph nodes, are the most common sites for extrahepatic metastases in HCC.^{23,24} For example, Si et al used plain chest radiography and CT of the lungs to show that pulmonary metastases were present in 42% of their patients.²⁴ Pulmonary metastases are seen on plain radiography at the time of admission in 19% of black South Africans with HCC, and they become evident in a further 6% of patients during life.²⁵ Pulmonary metastases seldom cause symptoms, but when they do dyspnea is most likely. A cough may also occur, and if the bronchial lining is eroded, blood-stained sputum is produced. Pathological elevation of the right hemidiaphragm (more than 2.5 cm above the left hemidiaphragm in a conventional plain postero-anterior x-ray of the chest) is a frequent radiologic finding in black African and Chinese patients with HCC, occurring, for example, in 30% of black South African patients.²⁵ The raised hemidiaphragm may show one or more localized bulges or have a uniform outline. Linear atelectases are often seen adjacent to the raised hemidiaphragm. A markedly raised hemidiaphragm may cause dyspnea with or without a nonproductive cough.

Pulmonary infarction rarely occurs as a result of a large tumor-embolus originating from tumor in either the inferior vena cava or the right side of the heart.⁹

Very rarely, multiple tumor emboli to the pulmonary microvasculature may be responsible for a presentation with pulmonary arterial hypertension.²⁶ The pulmonary hypertension may mistakenly be thought to be primary.

Bone Pain

Extrahepatic metastases commonly complicate HCC.²⁷⁻³⁰ The most frequent sites for metastases are the lungs, the regional lymph nodes, and bone. Clinical manifestations of metastases usually become evident following clinical diagnosis, although they are occasionally the presenting or the only symptom. In these instances the presence of the primary tumor may readily be overlooked or both the

metastasis and the enlarged liver may be wrongly attributed to metastases from a primary tumor in an organ other than the liver.

About 3% of patients with HCC experience bone pain induced by osteolytic metastases.¹ However, if skeletal metastases are specifically sought during life with appropriate diagnostic tests, they are found in 7–10% of patients.^{27,28} The prevalence may be as high as 20% at necropsy.³⁰ Metastases, including skeletal metastases, are less frequent when HCC coexists with cirrhosis.³¹ Pathological fractures not infrequently complicate skeletal metastases.

Skeletal metastases may be solitary or multiple. The bones most often affected are the vertebrae, ribs, femur and other long bones, skull bones, sacrum, and clavicle.²⁷⁻³⁰ The frequency of vertebral metastases is attributable to the link between the hepatic circulation and Batson's paravertebral venous plexus. Vertebral metastases are particularly troublesome because of the frequency with which they are complicated by paraplegia or nerve root compression.^{27,28,32,33}

Rare Sites for Metastases

Rare sites for metastases in patients with HCC include the adrenal glands,^{34,35} skin,³⁶ maxillary and mandibular gingiva,³⁷ maxillary sinus,³⁸ parasellar tissue,³⁹ testes,⁴⁰ orbit,⁴² thyroid,⁴² breast,⁴³ brain,⁴⁴ pituitary gland,⁴⁵ esophagus,⁴⁶ spleen,⁴⁷ kidney,⁴⁸ heart,⁴⁹ and rectus abdominis muscle.⁵⁰ An umbilical or periumbilical nodule caused by malignant infiltration (Sister Joseph's nodule) is occasionally found in patients with HCC and may be the presenting complaint.⁵¹

Spread of HCC to regional lymph nodes in the abdomen is common.⁵² On rare occasions HCC spreads to lymph nodes remote from the liver.

Virchow-Troisier Lymph Node: Patients with HCC are occasionally found to have a Virchow-Troisier node⁵³⁻⁵⁵ or metastatic spread to other cervical lymph nodes.¹¹ HCC located under the bare area of the liver may spread to mediastinal lymph nodes and thence into the thoracic duct. Alternatively, malignant cells may gain access to the thoracic duct by way of lymph nodes in the porta hepatis and regional lymph nodes, or as a result of the presence of peritoneal metastases.

Axillary Lymph Node: One patient has been described in whom HCC spread to a lymph node in the right axilla.⁵⁶ Possible routes of this spread are to the mediastinal glands and thence along intercostal lymphatics to the axilla, or spread to the umbilical region and then via subcutaneous lymphatics to the axilla. A number of unusual clinical presentations of HCC are attributed to paraneoplastic phenomena of the tumor.

Paraneoplastic Phenomena

Many of the deleterious effects of neoplasms are caused by neither the local effects of the tumor nor by metastases. Most of these systemic or distant consequences of the tumor result directly or indirectly from production by the neoplasm of substances that enter the bloodstream. HCC produces many diverse such manifestations. Most involve the synthesis and secretion of biochemical substances that have no clinical consequences, but several are biologically active and result in clinically recognizable syndromes.⁵⁷ Although none of the latter occur with high frequency, they are diagnostically important because they may precede the local manifestations of the tumor. In so doing they may direct the attention of an informed clinician to the presence of HCC or divert that of an uninformed clinician away from the correct diagnosis.

Hypoglycemia

Hypoglycemia is one of the more common of the paraneoplastic presentations of HCC. Two types have been described.⁵⁷ Type A hypoglycemia occurs during the last weeks of life in a patient with advanced disease. The blood sugar levels are usually only moderately reduced and overt hypoglycemia is uncommon. Accordingly, type A hypoglycemia is often overlooked unless specifically sought. When symptomatic, type A hypoglycemia is readily controlled. It is not a paraneoplastic phenomenon but results from the inability of a liver extensively replaced by tumor, and often cirrhotic, to meet the combined demands for glucose of a large and perhaps rapidly growing tumor and the other tissues of the body.

Type B hypoglycemia is characterized by severe hypoglycemia that manifests early in the course of HCC and may be the reason for the patient coming under medical attention. These patients present with 1 or more hypoglycemic symptoms, and the underlying tumor may be overlooked. Blood sugar levels are typically very low and the patient requires a continuous intravenous infusion of a high-concentration glucose solution to maintain an adequate blood sugar level. Type B hypoglycemia is unresponsive to corticosteroids, glucagons, thiazides, and diazoxide, and the patient's prognosis is particularly poor. This form of hypoglycemia is a paraneoplastic phenomenon and results from the defective processing by malignant hepatocytes of the precursor of insulin-like growth factor-II (pro-IGF-II).^{58,59} The resulting big pro-IGF-II circulates in 60 kDa complexes that are appreciably smaller than the normal 150 kDa complexes composed of IGF-II, IGF-binding protein-3, and an α -subunit. These smaller complexes transfer more readily across capillary membranes, increasing access of IGF-II to those tissue receptors with which it reacts (IGF-I, IGF-II, and insulin

receptors). This greatly increases uptake of glucose by tissues and results in hypoglycemia.

Erythrocytosis

Erythrocytosis (polycythemia) is another of the more important paraneoplastic complications of HCC.⁵⁷ It occurs in 3–12% of patients, although the lower part of the range is a more usual figure.⁶⁰ Because HCC often coexists with cirrhosis, which may cause hemodilution, anemia, or both, the finding of erythrocytosis in a patient known to have cirrhosis is a strong clue that HCC has supervened. Erythrocytosis present early in the course of the disease may later be 'neutralized' by the anemia of advanced malignant disease or that resulting from blood loss.⁶⁰ Erythrocytosis results from the synthesis and secretion by the tumor of erythropoietin in native or slightly modified form.^{60,61} Ectopically produced erythropoietin is, however, not always biologically active.⁶⁰ Production of biologically active erythropoietin by malignant hepatocytes is not unexpected because the hormone is normally synthesized by the fetal liver.

Hypercalcemia

Hypercalcemia in HCC usually results from osteolytic metastases although it may be a paraneoplastic phenomenon. Paraneoplastic hypercalcemia occurs with a frequency similar to that of hypoglycemia and erythrocytosis. It is most likely to occur with sclerosing HCC.⁶² Paraneoplastic hypercalcemia is often symptomatic and requires treatment.^{62,63} Some of the symptoms, especially drowsiness, confusion, and coma, may mask the presence of the underlying tumor and delay diagnosis. The complication appears to be the result of ectopic production of parathyroid hormone-related protein by the tumor.⁶⁴

Watery Diarrhea Syndrome

Although diarrhea is not uncommon in patients with HCC, in a few instances it is severe and intractable and appears to be part of watery diarrhea syndrome.^{65,66} This syndrome is characterized by a secretory diarrhea, hypokalemia, and achlorhydria. Prostaglandin E₂, vasoactive intestinal peptide, and gastrin can be detected in the tumors, suggesting that they contain amine precursor uptake and decarboxylation cells.⁶⁷ The diarrhea responds to treatment with inhibitors of prostaglandin synthesis.⁶⁷

Sexual Changes

Three types of sexual change have been reported in patients with HCC—isosexual precocity, gynecomastia, and feminization.

Isosexual Precocity: Although the more common association of isosexual precocity with a hepatic tumor is with

hepatoblastoma, it may also occur in boys with HCC.⁶⁸ Sexual precocity is attributed to ectopic production of a gonadotropin by the tumor. Limitation of the syndrome to males suggests that the substance elaborated by HCC possesses mainly interstitial cell stimulating properties capable of stimulating the release of testicular androgens. Affected boys have adult serum testosterone levels.

Gynecomastia: Gynecomastia has been described in a few patients with HCC.^{69,70} Elucidation of the pathogenesis of the breast enlargement is complicated by the frequent coexistence of cirrhosis with HCC, because cirrhosis may itself cause gynecomastia. In the published reports of gynecomastia complicating HCC in the absence of cirrhosis no reason for the breast enlargement has been established.

Feminization: Patients with HCC (including the fibrolamellar variant) may rarely become feminized.⁷¹⁻⁷³ The mechanism appears to be aromatization by the tumor of circulating dehydroepiandrosterone to estrone and, to a lesser extent, estradiol. This conversion of a circulating C19 prehormone to estrogen involves a single metabolic step only and is catalyzed by aromatase P-450, the product of the CYP 19 gene.^{71,73} Aromatase has been shown to be expressed by HCC but not by healthy adult liver tissue.⁷³ In the patient studied in the greatest detail, all signs of feminization were reversed after successful resection of the tumor.⁷¹

Porphyria

Porphyria cutanea tarda asymptomatica is a rare paraneoplastic complication of HCC.^{74,75} The patients present with a light-sensitive dermatosis. Porphyrin excretion patterns in the urine and feces vary among patients but are not consistent with any of the inherited porphyrias. HCC tissue may fluoresce strongly under fluorescence microscopy and show increased activity of the heme biosynthetic enzymes, δ -amino levulinic acid synthase and dehydratase, and porphobilinogen deaminase.⁷⁵ Excessive porphyrin production by the tumor results in the accumulation of porphyrins in the skin, accounting for the photosensitivity.

Systemic Arterial Hypertension

The more common cause of this rare paraneoplastic syndrome is the ectopic production of angiotensinogen (renin precursor) by HCC.⁷⁶⁻⁷⁸ In patients with more severe degrees of hypertension the tumor produces, in addition, renin ectopically.⁷⁷ Lesser degrees of hypertension may respond to angiotensin-converting enzyme inhibitors.

Carcinoid Syndrome

Patients with this syndrome complicating HCC present with diarrhea and syncope.⁷⁹ Increased urinary excretion of 5-hydroxy indole acetic acid, total 5-hydroxy indoles,

and serotonin are found. Indole derivatives and increased tryptophan hydrolase activity can be demonstrated in the tumor.

Hypertrophic Osteoarthropathy

Two patients with this complication have been described.⁸⁰ Only 1 had pulmonary metastases. Ectopic production of growth hormone has been suggested as the cause of this syndrome when it occurs in other tumors,⁸¹ although levels of this hormone were not measured in either of the 2 reported cases with HCC.

Hyperthyroidism

Serum concentrations of thyroid-stimulating hormone, T4, T3, and free T3 were increased in the single HCC patient reported with hyperthyroidism.⁸² Ectopic secretion of a substance that stimulates the secretion of thyroid-stimulating hormone is thought to be the explanation.

In other HCC patients without overt hyperthyroidism, increased levels of thyroxine-binding protein have been present.⁸³ This increase results in high levels of circulating thyroxine.

Cushing Syndrome

Occasional cases of Cushing syndrome complicating HCC have been reported.⁸⁴ The syndrome results from ectopic production of adrenocorticotropin by the tumor.

Osteopenia (Osteoporosis)

Osteopenia has been described in a few children (but never in adults) with HCC.⁸⁵ The cause of the disturbed bone metabolism is unknown.

Skin Rashes

Each of a number of cutaneous changes has rarely been reported in patients with HCC. Whether these rashes are paraneoplastic phenomena or chance associations in a particular patient is uncertain. They include Leser-Trelat sign,⁸⁶ pemphigus foliaceus associated with acanthosis nigricans-like lesions,^{87,88} papuloerythroderma,⁸⁹ acquired perforating dermatosis,⁹⁰ erythema nodosum,⁹¹ psoriasis guttata,⁹² and subacute cutaneous lupus erythematosus.⁹³ Dermatomyositis has been described, but only in children.⁹⁴ Less rare is pityriasis rotunda (circumscripta), although this rash occurs with any frequency only in black Africans with HCC.⁹⁵ It consists of single or multiple, round or oval, hyperpigmented, scaly lesions on the trunk, buttocks, and thighs. The lesions range in size from 0.2 to 25 cm and they may become confluent.

Neuromuscular Disorders

A sensorimotor polyneuropathy affecting all limbs,⁹⁶ polymyositis,⁹⁷ and encephalomyelitis⁹⁸ have occasionally been reported in patients with HCC.

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