Paraneoplastic phenomena in patients with hepatocellular carcinoma

Abstract
A significant proportion of the consequences of hepatocellular carcinoma result from phenomena caused by the tumor and referred to as paraneoplastic phenomena. These phenomena exert their effects on distant organs or tissues, and they play a meaningful role in the progress of the tumor and contribute to its poor prognosis. The four major phenomena are erythrocytosis (polycythemia), hypoglycaemia, hypercholesterolemia and hypercalcemia. Erythrocytosis results from the synthesis and secretion by the tumor of erythropoietin in its native form. It is one of the less rare and fully investigated of the phenomena, and patients with erythropoiesis have slightly longer survival times than those with the other phenomena. Hypoglycemia is usually present in the terminal stages of the tumor, and is not infrequently the cause of death. Cholesterol biosynthesis by the tumor appears to be autonomous and more than 90% of the cholesterol produced is released into the circulation. The excess circulating calcium is released from bones.

Keywords: polycythemia, hypoglycaemia, hypercholesterolemia, hypercalcemia, hepatocellular carcinoma

Introduction
The deleterious effects of hepatocellular carcinoma (HCC) are not invariably the result of either the local effects of the tumor or of its metastases. Many of the systemic, metabolic, or distant consequences of HCC result, either directly or indirectly, from production by the neoplasm of substances that gain access to the blood stream, thereby exerting their effects on distant organs or tissues. These consequences, referred to as paraneoplastic phenomena, are independent risk factors that play an appreciable role in the progress of the tumor and contribute significantly to its poor prognosis. Patients with HCC may present with one (or occasionally more than one) of the paraneoplastic phenomena.1 Because these phenomena may precede the local manifestations of the tumor, they may direct the clinician’s attention to the presence of HCC. With the exception of erythrocytosis, the presence of a paraneoplastic phenomenon in patients with HCC is an independent predictor of a poor prognosis.1, 12, 13 With a mean survival time which may be as short as 36 days.1, 2

The major paraneoplastic phenomena in patients with HCC are erythrocytosis (polycythemia), hypoglycaemia, hypercholesterolemia and hypercalcemia. Erythrocytosis and, to a lesser extent, hypercholesterolemia, tend to develop earlier in the course of the disease than do hypoglycaemia and hypercalcemia, which are more commonly short-lived near-terminal complications. Apart from the tumors tending to be larger and the survival times shorter in patients with HCC result, either directly or indirectly, from production by the neoplasm of substances that gain access to the blood stream, thereby exerting their effects on distant organs or tissues. These consequences, referred to as paraneoplastic phenomena, are independent risk factors that play an appreciable role in the progress of the tumor and contribute significantly to its poor prognosis. Patients with HCC may present with one (or occasionally more than one) of the paraneoplastic phenomena.1 Because these phenomena may precede the local manifestations of the tumor, they may direct the clinician’s attention to the presence of HCC. With the exception of erythrocytosis, the presence of a paraneoplastic phenomenon in patients with HCC is an independent predictor of a poor prognosis.1, 12, 13 With a mean survival time which may be as short as 36 days.1, 2

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Erythrocytosis (Polycythemia)
Erythrocytosis (polycythemia) complicating HCC is the result of secretion of erythropoietin by the tumor. It is one of the less rare and more fully investigated of the paraneoplastic phenomena that may occur in patients with HCC. For example, clinical experience in sub-Saharan Black Africans with HCC has shown incidences of erythrocytosis that range between 1.0 and 15.6%, with the lower incidences in the range (1.0 to 3.0%) being the more common.2, 5, 6, 8, 10, 11, 13 Of southern African Blacks with HCC living on the Highveld of South Africa (altitude 1,750meters above sea-level), 3.9% have a hemoglobin level of greater than 19.2grams% (the upper limit of normal at that altitude) at the time of admission to hospital.2, 4, 5, 8, 10, 11, 13 In two early studies in countries not in Africa, the incidence of the syndrome was 3% and 12%, respectively.14, 15 A possible reason for the lower incidence of the phenomenon in the sub-Saharan Black African population is the late recognition of the tumor in these patients, by which time any erythrocytosis present earlier may already have been counteracted by the anaemia of the advanced malignant disease. Prevalences in Chinese patients range from 2.0 to 5.0%,12 and patients in the U.S.A.5, 14, 15 have similar prevalence’s to those in sub-Saharan Africa.

Erythrocytosis in a patient with liver disease is a strong pointer to the presence of HCC. No difference in clinical characteristics in patients with HCC with or without erythrocytosis has been reported, apart from the important difference in the shorter survival time in the former.2, 3, 5, 6, 8, 10, 19 Nevertheless, patients with erythrocytosis tend to have slightly longer survival times than those with one of the other paraneoplastic phenomena.1 Higher than usual serum α-fetoprotein levels have been recorded in HCC patients with erythrocytosis.20

Erythrocytosis complicating HCC results from the synthesis and secretion by the tumor of erythropoietin in its native form.21 Production of biologically active erythropoietin by malignant hepatic tissue is not unexpected, because this hormone is normally synthesised by the fetal liver.14 Ectopically produced erythropoietin in patients with HCC is, however, not always biologically active.21 Erythrocytosis present early in the course of HCC may later be “neutralized” by the inhibition of erythropoiesis...
that occurs in the advanced stages of malignant disease, as well as the hemodilution that may occur at this time as a result of the presence of cirrhosis. This possibility is supported by the observation in southern African Blacks with HCC that 23 of a group of these patients had a raised serum erythropoietin concentration, but only one of these had an increased hemoglobin concentration and packed cell volume. 

Increased erythropoietic activity has been demonstrated in the majority of patients with HCC in which it was looked for Jacobson RJ, Goldberg RB, although assay of the tumor tissue itself has, more often than not, failed to show such activity. 

Hypoglycemia

Patients with HCC typically develop severe hypoglycaemia as a paraneoplastic phenomenon in the later or final stages of the natural history of the tumor. However, this complication may occur relatively early in the natural history of HCC, although it is rarely the reason for the patient coming under medical attention rather than the symptoms and signs of the tumor per se. 

Hypoglycemia is probably the most common, and certainly one of the more dangerous, of the paraneoplastic syndromes attributed to HCC, and it may be the terminal event. There are no differences in the other clinical characteristics between patients with HCC with or without hypoglycemia at the time of diagnosis. However, patients with this paraneoplastic syndrome have a significantly worse prognosis than those without this complication. The patients are also younger and have higher rates of portal vein thrombosis, bilobar tumor involvement, and tumor size greater than 10cm in diameter than do patients without the syndrome. 

Hypoglycemia has been reported to occur in 2.5 to 6.7% of Black Africans, 4.6% of North Americans, 24% of South Americans, and 27 to 40% of Hong Kong Chinese patients with HCC. The reason for the obvious discrepancy between the very high and the low incidences of the hypoglycaemia in different populations remains to be determined. 

Hypoglycemia is usually present in the terminal stages of the illness, with survival times from the occurrence of this syndrome to the time of death being as short as 36days. In some populations or patients, however, hypoglycemia occurs early in the course of the tumor, and these patients have a longer survival time. 

In general, the larger the tumor size the more likely is the patient to develop hypoglycaemia. In Type A hypoglycaemia, which occurs more commonly and is poorly differentiated, the hypoglycaemia is mild or moderate in severity, and is a late event which is not too difficult to control. By contrast, in Type B hypoglycaemia, in which the tumor is less common, well-differentiated and slower growing, the hypoglycaemia occurs early and is difficult to control. 

Patients with the paraneoplastic syndrome present with confusion, drowsiness, convulsions, or coma, and the presence of the tumor may, not infrequently, be overlooked initially. Once established, large quantities of intravenous glucose are required, both to reverse the hypoglycaemia, and to maintain a normal serum glucose concentration there after. When the hypoglycaemia is severe, carbohydrate intakes of as much as 1,500grams per day may be insufficient to maintain the blood sugar at normal levels. This type of hypoglycaemia does not respond to the administration of glucagon, corticosteroids, thiazides or diazoxide, and carries a particularly grave prognosis. 

One possible explanation for the presence of hypoglycaemia in patients with HCC is that it is the result of consumption of large amounts of glucose by the tumor. Another is that it is caused, at least in Black Africans, by the production by HCC of an abnormal precursor of insulin-like growth factor 11 (pro-IGF-11). These smaller complexes transfer more readily across capillary membranes, increasing access of IGF-11 to tissue receptors, with which it reacts, significantly increasing the uptake of glucose by tissues, with consequent hypoglycaemia. 

Hypercholesterolemia

Another important paraneoplastic phenomenon and metabolic disturbance in patients with HCC is hypercholesterolemia. This occurs, for example, in 13.6% of sub-Saharan Black Africans, 11% of southern African Blacks, and 20 to 33% of Black Africans in Nigeria with HCC. The serum cholesterol level in healthy southern African Blacks is 4.3±0.8mMol/L, and a raised serum level in that population is rarely the result of dietary influences. It follows that the finding of a raised serum cholesterol concentration in the Black African population may be an indirect but useful pointer to the presence of HCC. 

Cholesterol biosynthesis by the tumor appears to be autonomous, and more than 90% of the cholesterol produced is released into the circulation. Hepatic cholesterol synthesis is normally suppressed by exogenous cholesterol in a sensitive negative feedback system. This occurs primarily through an effect on the mucosal enzyme, hydroxyl-β-methyl glutamyl coenzyme A’s conversion to mevalonic acid, which has a limiting effect in cholesterol biosynthesis. Autonomous tumor cells produce large quantities of mevalonic acid and cholesterol, 90% of which is released into the circulation. Moreover, feedback regulation of cholesterol synthesis has been shown to be absent from HCC cells. 

Malignant cells lack cell surface receptors for chylomicron remnants. Cholesterol is therefore prevented from entering the hepatocytes, and exerting feedback inhibition of de-novo cholesterol biosynthesis by its effect on hydroxyl-β-glutamyl co-enzyme A reductase synthesis. Thus, in comparison with normal hepatocytes, the rate of cholesterol synthesis in malignant cells is not affected by diet or fasting. In addition, the normal feedback mechanism of low density lipoprotein (LDL) cholesterol may be altered in HCC and may contribute to the hypercholesterolemia. 

Hepatic cholesterol synthesis in higher animals is normally markedly suppressed by dietary cholesterol. Recent observations suggest that the rate of endogenous cholesterol biosynthesis is regulated by chylomycin ‘remnants’, which attach to receptors on the sinusoidal membranes of hepatocytes, and are then internalized by endocytosis. The intracellular concentration of cholesterol esters modulates endogenous cholesterol biosynthesis by its effect on the microsomal enzyme, β-hydroxyl-β-glutaryl coenzyme A conversion to mevalonic acid, and is rate limiting in cholesterol biosynthesis. 

Extensive studies have been carried out in-vitro in transplatable animal HCCs and in-vivo in the hepatoma-bearing rat. Only a few patients with HCC have been investigated in such detail. Both animal and human studies have consistently shown that a raised serum cholesterol concentration in HCC is associated with increased cholesterol synthesis by the tumor. 

This in turn appears to result from the complete absence in the
malignant cells of the normal negative feedback system. Over 90% of the sterols produced as a result of deletion of the feedback control are released into the circulation.

A possible explanation for the autonomy of cholesterol biosynthesis was considered to be an abnormality of HMG co A reductase itself, such that cholesterol could not exert its inhibitory effects of the enzyme. However, experiments using several physico-chemical methods have not shown any abnormality in HMG co. A reductase from animal hepatoma tissue. Other possible explanations might be defective uptake of chylomicron “remnants” into hepatocytes because of the lack of the appropriate receptors on the malignant hepatocytes, or a defect in intracellular binding of cholesterol.47

Hypercalcemia

Relatively few patients with HCC and hypercalcemia have been reported in the literature and the exact information on the frequency by which this complication occurs has not been established. Nevertheless, evidence is available that hypercalcemia occurs with a frequency similar to that of hypoglycemia and erythrocytosis.36–38 Serum calcium concentrations in neoplastic disease are usually greater than 3.75mmol/L, for example, values of this order are present in 11.7% of southern African Blacks with HCC.39

Hypercalcemia in malignant disease is most often caused by the release of calcium from bone as a result of osteolysis by skeletal metastases. However, the latter occurs rarely in HCC. More than one pathogenetic mechanism may be responsible for hypercalcemia in the absence of metastatic osteolysis.40 Each involves a hormone or a hormone-like substance which is produced by the tumor and appears to alter bone metabolism with release of calcium. The exact mechanism involved in an individual patient is difficult to ascertain.

Ectopic production of a peptide with parathormone-like immunoreactivity has been described in malignant tumors.40 The patients present with metabolic changes which mimic those of primary hyperparathyroidism. The syndrome is therefore referred to as pseudo-hyperparathyroidism. Whether or not this mechanism occurs in patients with HCC has not been established. Small fragments of parathormone, as well as polypeptides larger than native parathormone have been described in association with malignant disease, but their role remains unclear. As many as 50% of cancer patients with hypercalcemia and hyperphosphatemia, have had no parathormone immunoreactivity demonstrable in blood or tumor tissue.36 In some of these patients, with breast or renal carcinomas, excretion of a metabolite of prostaglandin E, was found to be increased, and it returned to normal after treatment of inhibitors of prostaglandin synthetase. Concurrently, serum calcium concentrations fell.41

Prostaglandins of the E series are capable of stimulating bone resorption in-vitro.41 Support for the hypercalcemic role of prostaglandin E, in malignant disease is provided by animal studies. Mice bearing HSDM, fibro sarcoma and rabbits carrying VX, carcinoma develop hypercalcemia in the absence of skeletal metastases.42 High concentrations of prostaglandin are found in the tumors and their venous drainage. The part played by prostaglandins in hypercalcemia has yet to be determined. Of the humoral factors that may play a role in the hypercalcemia of malignant disease are vitamin D and its metabolites, phytosterols and osteoclast-activating factors.43 These have been shown to cause osteolysis in-vitro, and some have been demonstrated in breast tissue and in the blood of patients with this tumor. What role, if any, these factors play in hypercalcemia remains to be determined.

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Conflict of interest

Author declares that there is no conflict of interest.
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