MALIGNANT EPITHELIAL TUMOURS OF THE LIVER IN INFANCY AND CHILDHOOD

ALFRED AZZOPARDI
M.D., Ph.D.
Department of Pathology,
Medical School, Royal University of Malta

Malignant epithelial tumours of the liver are the most common carcinomas of infancy and childhood. (Edmondson, 1958) Embryonic and adult type tumours occur; the morphological similarity of embryonic hepatic tumours to embryonic tumours of other viscera and the similar clinical presentation and behaviour of these tumours are two diagnostic pitfalls. In addition the distinction between adult type primary carcinoma of the liver and some embryonic hepatic tumours is not always possible histologically. This distinction may not be "theoretically valid" since it might only imply a different time of origin; embryonic tumours appearing during the development phase, the adult type tumours appearing later (Willis, 1967). Moreover, one cannot separate embryonic and adult type tumours on the basis of the time factor since the liver retains the power to regenerate actively throughout adult life. This inherent potential to regenerate presumably accounts for the occasional occurrence of an embryonic type tumour in an adult patient.

Aetiological factors

Primary tumours of the liver in childhood and infancy usually occur without antecedent cirrhosis and most case reports appear to be from parts of the world where, primary carcinoma of the liver with its possible relationship to cirrhosis, is a rare entity (Bigelow Wright, 1953). The occurrence of such a tumour in a 10 month old child with biliary cirrhosis has, however, been reported and the presence of giant cells throughout the parenchyma of the liver suggested a possible aetiological relationship between giant cell hepatitis, biliary cirrhosis and primary carcinoma liver (Roth and Duncan, 1955). In a few cases primary tumours follow glycogen storage disease (Edmondson, 1958). That the tumour is congenital in some cases is suggested by the incidental finding of a liver cell carcinoma in a 7-hour-old infant who died of massive cerebral haemorrhage (Wilfer *et.al,* 1944). In one case reported by Shorter *et.al.* (1960) a haemangioma of the right lobe of the liver had been irradiated with x-rays six years before the development of the malignant hepatic tumour. Christopherson and Collier (1953) rule out a possible relationship between hamartomas and primary liver cell carcinomas as hamartomas lack the property of uncontrolled growth; adenomas, however, are possible precursors since they are potentially malignant lesions. The presence of pre-existing adenomas is, however, difficult to establish. Review of the family histories does not usually reveal any significant findings.

Histologic classification

Primary malignant epithelial tumours of the liver in infancy and childhood can be classified histologically into three main varieties viz. primary carcinoma of the adult type, primary carcinoma originating from bile ducts and embryonic hepatic tumours. Embryonic tumours can be further subdivided into embryonic hepatomas (hepatoblastomas) and mixed hepatoblastomas.

The adult type liver-cell carinomas, usually developing in older children, can be regarded as "late-appearing embryonic hepatomas or early-appearing carcinomas of adult type" (Willis, 1962). The structure

of the tumour reflects the degree of maturation of the liver parenchyma ad provided the obviously embryonic. Moreover the liver parenchyma retains the ability to regenerate into late adult life; when this occurs the liver cell assumes an embryonic character which is partly reflected in the structure of some adult type tumours. As a general rule, however, most tumours appearing in infancy or early childhood are typically embryonic tumours while most of those occurring in late childhood are identical in structure to the hepatic cancers of adults. Various reports of adult type tumours, appearing in late childhood, are found in the literature. Kilfoy and Terry (1929) reviewed 44 cases of both hepatoblastomas and adult type tumours in children and reported an adult type tumour accompanied by cirrhosis in a 9-year old girl.

Hansen *et. al.* (1940) reported a liver-cell carcinoma in a 10-year old boy who also had lung metastases. Bodian and White (1952) reported two multifocal liver-cell carcinomas of adult type, one in a 6-year old girl and the other in a 12-year old girl, both with blood-borne metastases to the lungs and central nervous system.

One possibility that has to be considered in connection with the pathogenesis of the adult type tumours is that, like the nephroblastoma (Willis, 1962) and the neuroblastoma (Goldman *et. al.* 1965); Williams 1954) embryonic hepatomas may sometimes mature to form more benign, less embryonic tumours. The maturation process would result in an adult type liver cell carcinoma or perhaps an adenoma (Otaki, *et al,* 1960). Although differentiation of an embryonic tumour with loss of malignancy probably occurs in some cases de-differentation and enhanced malignancy is a more common event.

Hepatic tumours originating from bile ducts are very rare in children. Bigelow and Wright (1953) refer to only 3 cases in their review of the literature. Shorter *et al* (1960) describe a tumour in which the neoplastic cells were forming definite tubular structures resembling bile ducts in a 2-year old boy and suggested the term cholangiohepatoma for this type of tumour.

Embryonic hepatomas or hepatoblastomas are predominantly epithelial tumours more or less resembling embryonic or foetal liver parenchyma. These occur chiefly in young infants and some of them are congenital (Wilbur *et. al.* 1944; Knox *et. al.* 1958). In seven cases referred to by Willis (1962) the ages ranged between four months and seven years and six of the cases were below the age of three. Most of these embryonic hepatomas are highly malignant and metastasize rapidly within the liver, to lungs and bone. Reference has already been made to the possibility that some of these tumours could mature and develop into a more quiescent tumour. This is largely dependent on the rate of growth of the original tumour for most hepatoblastomas would kill the patient from liver replacement and metastases before they mature sufficiently to assume a less aggressive, perhaps benign character.

The *mixed hepatoblastomas* contain, in addition to embryonic hepatic parenchyma, mesodermal components in the form of osteoid, cartilage, bone and myxomatous connective tissue. The majority are seen in infants and in children under the age of eight years; although a few have been reported in adults (Milman and Grayzel, 1951). The epithelial components include liver cell tissue, bile-duct like structures or squamous cell foci with keratinization. The mesenchymal component may be highly cellular and undifferentiated or show varying degrees of differentiation into the above-mentioned components. Although some benign mixed tumours are reported in the literature it is doubtful whether any of these are truly benign. In a malignant mixed tumour either the epithelial or the mesodermal component is malignant; in a few cases both components are malignant. Malignant epithelial growths containing benign mesodermal derivatives are the most common. As the metaseases from these tumours may also contain osteoid it is doubtful whether the mesodermal component is truly benign. Three reported tumours (Sheeham 1930; Williams 1954; Wuester and Knauer, 1961) differed from other mixed tumours of the liver in that the epithelial component consisted mainly

of bile ducts and cysts and not of liver cells and the mesenchymal component consisted predominantly of rhabdomyoblastic tissue and not cartilage or bone. Willis (1967) refers to these tumours as Rhabdomyoblastic Mixed Tumours and classifies them separately. However, this different terminology entailing a separate classification is not justified since the mesodermal component differs only in character but not in histogenesis. As for the prominent bile duct component this has been a feature of other epithelial tumours of the liver (Shorter *et. al.* 1960)

The first reported case of a mixed hepatoblastoma was that of Misick (1898) who labelled the tumour a "teratoma". The mesodermal derivatives found in mixed tumours, unlike the multiple tissues found in teratomas, are not foreign to the part; they represent metaplasia in the host stroma stimulated by a predominantly epithelial tumour or else from the second neoplastic component of a composite tumour.

Clinical findings

Most of the reported cases are in patients of Caucasian stock; there are only two cases reported in children from Japan (Bigelow and Wright 1953; Stainer 1938). In the 11 cases reported by Shorter *et al* (1960) the ages of the patients at the onset of signs and symptoms varied from 5 months to 13 years. In another series of 11 cases (Report, 1952) the first symptoms were noted between 5 months and 7 years of age; in one instance the abdomen was said to be prominent from birth. The adult type liver cell tumours tend to occur in the older age groups while the embryonic are found in infancy and early childhood.

The main symptom is gradual enlargement of the abdomen with development of a definite mass in the right upper quadrant. In most cases, at the time of first admission, the liver is enlarged down to the level of or just below the umbilicus. In the mixed hepatoblastomas calcification of the liver is often visible in the roentgenogram of the abdomen. Apart from this, the commonest presenting symptoms are gastro-intestinal viz. vomiting and loss of appetite.

Pain in the right upper quadrant, becoming extremely severe in the terminal phases of the disease, is the rule. In some cases this pain radiates to the right shoulder; it is not usually related to food, movement or respiration. Jaundice and ascites are not often seen; the latter occurs in a few cases and is a late finding in the course of the disease.

In rare instances these tumours may be accompanied by hemihypertrophy and by serious disturbances in mineral and lipid metabolism (Report, 1952; Hansen. *et. al.* 1940). In two cases (Report, 1952) disproportionate enlargement of the right arm and leg was noted and subsequently at postmortem the right kidney was also found to be enlarged. An appreciable degree of lipid storage in the reticulo-endothelial system, believed to be the result of hyperlipaemia due to liver insufficiency was found in two of eight children with hepatoblastoma and two primary adult type liver carcinoma (Report, 1952). The demineralization of the skeleton has been attributed to deficient calcium absorption due to lack of bile which is necessary for the action of fat soluble vitamin D (Roberts and Sullivan, 1955).

Anaemia, usually of the normochromic and normocytic type occurs as a complication in 80% of cases. Hypochromic anaemia with nail changes consisting of longitudinal ridging and brittleness is described in some cases; these were observed to regress after iron therapy. The total leucocyte count and differential percentages are usually within normal limits.

Serum proteins are usually normal and the serum electrophoretic pattern, may show an increase in the α_2 and β-globulin fractions with hypoalbuminaemia or agammaglobulinaemia (Otaki *et al.*, 1960; Report. 1952).

Prognosis: The duration of life from the onset of symptoms varies from 2 months to 2 years.

References

BIGELOW, W.H. and WRIGHT, A.W. (1953). Cancer *6*: 170.

BODIAN, M. and WHITE, L.L.R. (1952). Gt. Ormond Street Journal, No. *4*: 105.

CHRISTOPHERSON, W.H. and COLLIER, H.S. (1953). Cancer *6*: 853.

EDMONDSON, A.H. (1958). AFIP Atlas of Tumour Pathology. Section VII, Fascicle 25.

GOLDMAN, R.L., WINTERLING, A.M. and WINTERLING, G.C. (1965). Cancer *18*: 1510.

HANSEN, A.E., ZIEGLER, M.R. and McQUARRIE, I. (1940). J. Pediatrics *17*: 9.

KILFOY, E.J. and TERRY, M.C. (1929). Surg. Gyn. Obst. *48*: 751.

KNOX, W.G., ZINTEL, H. and BEGG, C.F. (1958). Cancer *11*: 1044.

MILMAN, D.H. and GRAYZEL, D.M. (1951). Am. J. Dis. Child., *81*: 408.

OTAKI, A. *et al* (1960). Brit. Med. J. *2*: 256.

REPORT (1965). British Empire Cancer Campaign. 30th Annual Report: 168.

ROBERTS, M.H. and SULLIVAN, C. (1955). J. Amer. Med. Assn. *159*. 1002.

ROTH, O. and DUNCAN, P.A. (1955). Cancer *8*: 986.

SHEEHAN, H.L. (1930). J. Path. Bact. *33*: 251.

SHORTER, R.G., BAGGENSTOSS, A.H., LOGAN, G.B. and HALLENBECK, G.A. (1960). Pediatrics *25*: 191.

STEINER, M.M. (1938). Am. J. Dis. Child. *55*: 807.

SWAEN, G.J.V., SLOOFF, J.L. and STOELING, C.B.A. (1965) J. Path. Bact. *90*: 333.

WILBUR, D.L., WOOD, D.A. and WILLETT, F.M. (1944). Ann. Int. Med. *20*: 453.

WILLIAMS, A.W. (1954). Brit. J. Surg. *41*: 13.

WILLIS, R.A. (1962). The Pathology of the tumours of children. Oliver and Boyd Ltd. (Publishers).

WILLIS, R.A. (1967). Pathology of Tumours. Butterworth and Co. (Publishers) Ltd.

WUESTER, W.O. and KNAUER, W.H. (1961). Cancer *14*: 361.