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Elevated serum α-fetoprotein in a patient with undifferentiated carcinoma of the gall bladder

W K Ng, W F Ng

Abstract
An uncommon case of undifferentiated carcinoma of the gall bladder in a 65 year old Chinese man, who presented with an increased serum α-fetoprotein concentration, is reported. Histologically, the tumour had a primitive appearance and was composed of a pavement-like array of poorly differentiated columnar/polygonal cells. Alpha-fetoprotein was demonstrated in some of the tumour cells using an immunoperoxidase technique. Alpha-fetoprotein secretion in this instance may have occurred because the gall bladder and the liver are of similar embryological origin. Alpha-fetoprotein may also be related to the resurgent expression of oncofetal antigens. This tumour may represent an-
other rare cause of increased serum α-fetoprotein concentrations.


Keywords: α-fetoprotein, undifferentiated carcinoma, gall bladder.

Serum α-fetoprotein concentrations are often noticeably increased in hepatocellular carcinomas and yolk sac tumours. Such increases have also rarely been associated with carcinoma of the stomach,\(^1\) colon, pancreas,\(^2\) and lung.\(^3\) Many gall bladder malignancies are mucin secreting adenocarcinomas and do not secrete α-fetoprotein; however, a rare type of gall bladder carcinoma, previously known as pleomorphic giant cell adenocarcinoma, has been reported to be associated with intra- and/or extracellular α-fetoprotein containing eosinophilic globules.\(^4\) Recently, Vardaman *et al*\(^5\) described seven cases of clear cell carcinoma of the gall bladder.

One of their cases showed features of hepatoid differentiation and was associated with α-fetoprotein secretion. Here, we report a rare case of undifferentiated carcinoma of the gall bladder presenting with persistently increased serum α-fetoprotein concentrations. The morphology of this tumour, however, was different from that of clear cell carcinoma.

Case report

A 65 year old Chinese man first presented with epigastric pain of several days duration. On admission, the patient had an increased total bilirubin concentration (124 μmol/l) and slight derangement of liver function. His serum α-fetoprotein concentration was 32 ng/ml. Ultrasonogram of the biliary system and endoscopic retrograde cholangiopancreatogram were unremarkable. Four months after presentation, the patient's serum α-fetoprotein concentration rose to 256 ng/ml. Liver function remained normal. Hepatic arteriogram and lipoidal computed tomography were performed and did not reveal a definite tumour mass in the liver. The gall bladder wall, however, was thickened with a focal increase in density. The patient's serum α-fetoprotein concentration remained high and was 425 ng/ml one month later. Seven months after initial presentation, the patient was readmitted because of recurrent epigastric pain. His serum α-fetoprotein concentration was 275 ng/ml at this time. The patient died suddenly two days after admission of cardiac failure.

A clinical postmortem examination was performed one day after his death. There was a 4 cm, tan coloured, fungating tumour over the fundus of the gall bladder. The distal part of the common bile duct was obstructed by a 2 cm, cylindrical, necrotic tumour mass which had detached from the main tumour bulk in the gall bladder. Local destruction of adjacent organs was not seen. Gallstones and lymph node enlargement were not present. The liver was mildly enlarged and there was no evidence of hepatocellular carcinoma. Thorough examination of the testes, mediastinum and brain revealed no evidence of germ cell tumours.

Multiple tissue blocks were sampled from the gall bladder tumour, promptly fixed in 10% neutral buffered formalin and embedded in paraffin wax. Sections, 3 μm thick, were cut and stained with haematoxylin and eosin, mucicarmine, periodic acid-Schiff (PAS), alcian blue, Grimalius, and Fontana-Masson. Immunohistochemical studies were carried out using the Streptavidin biotin complex technique using antibodies directed against α-fetoprotein (Dako), AE 1/3 (BioGenex), Cam 5.2 (Becton Dickinson), vimentin (Dako), monoclonal carcinoembryonic antigen (Dako), neuron-specific enolase (BioGenex), chromogranin (BioGenex), and synaptophysin (Boehringer Mannheim).

Histological examination of the gall bladder tumour revealed a superficially invasive carcinoma infiltrating the inner part of the muscle coat. The tumour was composed of a pavement-like array of columnar/polygonal cells (fig
Undifferentiated carcinoma of the gall bladder

1) which contained a moderately pleomorphic vesicular nucleus, inconspicuous nucleoli, frequent mitotic figures, and foamy to granular amphophilic cytoplasm. Occasional tumour giant cell formation was evident. There were no sarcomatoid or clear cell changes. Focal areas with a microtrabecular pattern and palisaded nuclei were identified, but true papillary configurations or hepatoid differentiation was not found. In some of the sections the tumour cells were associated with clumps of acellular eosinophilic squame-like material. True squamous cell components, however, were not identified. The tumour cells were negative for mucicarmine, PAS and alcin blue. They were also non-argyrophilic and non-argentaffinic. On immunohistochemistry, α-fetoprotein was detected in the cytoplasm of some tumour cells (fig 2) as well as among extracellular eosinophilic material. The tumour cells did not express vimentin, carcinoembryonic antigen, neuron-specific enolase, chromogranin, or synaptophysin.

Discussion

Alpha-fetoprotein is a serum glycoprotein produced by embryonic liver cells and yolk sac tissues. It has no confirmed biological function in humans. The serum α-fetoprotein concentration is of particular value in the diagnosis and follow up of hepatocellular carcinomas or yolk sac tumours. It has been proposed that a serum concentration of 400 ng/m in adults may be a useful threshold for diagnosing hepatocellular carcinoma. Other tumour types and non-neoplastic conditions such as viral hepatitis and inflammatory bowel disease are rarely associated with this degree of elevation. This patient represents a rare case of carcinoma of gall bladder associated with a persistent increase in serum α-fetoprotein concentrations.

Histologically, the tumour was an undifferentiated carcinoma of the gall bladder, previously referred to as pleomorphic giant cell adenocarcinoma. This group of neoplasms is characterised by a wide spectrum of morphology and various proportions of polygonal, round, spindle, and multinucleated giant cells. Areas of well differentiated adenocarcinoma are found in about two thirds of the tumours, representing a transition from pleomorphic components to well differentiated elements. Foci of squamoid differentiation may also be present in a small number of cases. The final third, including the case presented here, consists exclusively of undifferentiated elements. Eosinophilic hyaline globules are present in about 10% of the tumours, and some are positive for α-1-antitrypsin or α-fetoprotein. The wide spectrum of morphological features of this group of tumours illustrates their potential to differentiate along different lines including glandular, squamous and hepatoid. In contrast to most of the previously reported cases of α-fetoprotein producing gall bladder carcinomas, this case did not show any evidence of clear cell differentiation. It is possible that the present case and the α-fetoprotein secreting clear cell carcinomas simply represent two extremes of a spectrum with different degrees and stages of hepatoid differentiation.

Secretion of α-fetoprotein by gall bladder carcinomas may occur because the gall bladder and the liver are of similar embryological origin, as well as because of the resurgence of oncofetal antigens. Embryologically, the gall bladder originates from the hepatic diverticulum, which is a ventral outgrowth from the caudal part of the foregut and later divides to form the gall bladder and the liver. In laboratory animals chemically induced liver tumours can differentiate morphologically and biochemically towards either liver tissues or intestinal epithelium. Similarly, because the gall bladder and the liver are closely related at the embryological level, multipotential uncommitted tumour cells in undifferentiated carcinoma of the gall bladder may undergo primitive hepatoid differentiation and acquire the ability to produce α-fetoprotein. Alternatively, resurgence of oncofetal antigen expression by the tumour cells may also explain this phenomenon.

The present case represents another uncommon cause of increased serum α-fetoprotein concentrations. While this phenomenon may help in the understanding of embryological differentiation of undifferentiated gall bladder carcinomas, it may also serve to remind clinicians that increased serum α-fetoprotein concentrations in adults are not always diagnostic of hepatocellular carcinoma. Analysis of follow up serum α-fetoprotein concentrations can also be useful for assessing tumour recurrence.