behaviour is unpredictable; tumours with increased malignant potential, by virtue of size and cytology, being termed atypical carcinoids. In addition to positive staining with routine epithelial and neuroendocrine markers, they usually express CEA but not S100. Although commonly presenting as a primary lesion, metastases are not unusual and silent primary tumours have been described.¹ Neurological complications are present in 40% of metastatic carcinoids and true central nervous system metastases have been documented both within the brain and spinal cord.²

Primary paragangliomas of the cauda equina are well described³ and, although malignant behaviour is rare, metastatic spread has been documented.⁴ Nuclear atypia and necrosis are unusual features. Positive staining for cytokeratin is uncommon and has not been reported for CEA to our knowledge. The supporting sustentacular cells are classically S100 positive, although they are not always present.⁵

Pituitary carcinomas are a well recognised albeit rare entity. Generalised spread has been reported⁶ although central nervous system spread is more common. Metastasis to the cauda equina has been documented.⁷ Most carcinomas are histologically identical to adenomas; however, nuclear atypia has been recorded and said to indicate increased malignant potential.⁸ Cytokeratin positivity has been reported⁹ but is uncommon; however, the pituitary is a relatively common site for metastatic carcinoma from other sites.¹⁰

Conclusion

This widespread tumour illustrates the problem of classifying neuroendocrine tumours when there is no obvious primary site. The diagnoses of atypical carcinoid, malignant paraganglioma, and pituitary carcinoma were all considered; however, our favoured diagnosis was atypical carcinoid.

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Effusion cytology of hepatocellular carcinoma with in situ hybridisation for human albumin

M R Stephen, K Oien, R K Ferrier, R A Burnett

Abstract

While the cytological features of hepatocellular carcinoma on fine needle aspiration cytology are well described, cases of hepatocellular carcinoma with malignant cells in ascitic fluid and their characteristics are not. A patient is described with cirrhosis resulting from chronic hepatitis B virus infection, ascites, and hepatocellular carcinoma diagnosed by effusion cytology. The malignant cells in the effusion were shown to be positive for α fetoprotein using immunocytochemistry, and for human albumin using in situ hybridisation, confirming the diagnosis of hepatocellular carcinoma. Further investigations in a terminally ill patient were thus avoided.

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Keywords: ascitic fluid; hepatocellular carcinoma; albumin; in situ hybridisation

Ascites is a common complication of both cirrhosis and hepatocellular carcinoma. The yield of malignant cells from hepatocellular carcinoma is generally low (approximately 10% in the series described by Falconieri *et al*¹), and they may be more often identified in cases of hepatocellular carcinoma without cirrhosis.¹ There may be difficulty distinguishing the malignant cells from reactive and atypical mesothelial cells which are commonly seen in effusions from cirrhotic patients. The immunocytochemical staining profile of hepatocellular carcinoma expressing positivity for keratins and negativity for CEA² does not help to distinguish hepatocellular carcinoma cells from mesothelial cells. Positive staining for α fetoprotein, while helpful, is not specific.¹ Albumin gene detection by in situ hybridisation is a highly specific aid to the confirmation of the origin of the malignant cells in an effusion.³

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Figure 1 A group of dispersed malignant cells with mildly pleomorphic nuclei and granular chromatin surrounded by moderate amounts of granular cytoplasm containing intracytoplasmic vacuoles some of which were bile droplets. (Cytospin haematoxylin and eosin, $\times 600$.)

Figure 2 (A) Two malignant cells strongly reacting to a fetoprotein antibody (cytospin AP-Vector SK-5100, $\times 600$). (B) Strong diffuse cytoplasmic staining for human albumin mRNA in a malignant cell. (The hybridised probe was visualised using nitroblue tetrazolium/bromo-chloro-indolyl-phosphate (NBT/BCIP) substrate. Cytospin $\times 600$.)

Case report

The patient was a 60 year old woman of Chinese extraction who had made many trips to Hong Kong. She had chronic hepatitis B virus infection (HbsAg and HbeAg positive), which had been diagnosed 18 months before the most recent admission and had been confirmed by liver biopsy, the report of which concluded that although there was some fibrous scarring, cirrhosis was not established. Focal areas of hepatocyte dysplasia, however, were noted. She presented terminally with rapid clinical deterioration with malaise, anorexia, deepening jaundice, and diuretic resistant ascites. Ultrasound and computerised tomography suggested a multicentric hepatocellular carcinoma. Her α fetoprotein serum concentrations were grossly raised at 2070 KU/l (normal < 5 KU/l). In view of her gross ascites and disturbed coagulation, a repeat liver biopsy was not performed. Paracentesis was done, largely for symptomatic relief. Confirmation of the hepatocellular carcinoma was made from the effusion cytology. In view of the poor prognosis, symptomatic treatment only was continued. Permission for necropsy was refused.

Cytology findings

Cytospin preparations were made and were moderately cellular. Small lymphocytes and reactive mesothelial cells were present in the background. The malignant cells lay in small groups and as single cells. The nuclei tended to be large and hyperchromatic without prominent nucleoli. The cytoplasm was faintly granular. A striking feature was the presence of small round cytoplasmic vacuoles (fig 1). Some of the vacuoles contained PAS positive material while others stained positively for iron and bile. Many apoptotic cells were noted. The abnormal cells stained strongly on immunocytochemistry with antibodies for α fetoprotein (fig 2A), which is a hepatocellular product but is not absolutely specific for malignant cells from a hepatocellular carcinoma. Albumin is a specific product of normal and transformed hepatocytes. In situ hybridisation for the detection of the albumin gene was strongly positive in this case (fig 2B).

Discussion

The diagnosis of hepatocellular carcinoma is important because many cases present late and the patients may have systemic problems such as coagulopathy that prevent invasive procedures to obtain diagnostic material. The cytological features on fine needle aspiration of hepatocellular carcinoma are well described, but are of little use when applied to effusion cytology—for example, endothelial rimming of neoplastic cell groups and intranuclear inclusions are not notable features in an ascitic fluid.

Metastatic malignancy—for example from lung or gastrointestinal tract in peritoneal effusions, shows a relatively limited range of cytological expression, and confusion with reactive mesothelial cells can be a disturbing problem. The application of a technique which is specific to the hepatocyte is clearly a great benefit in defining the site of origin of a neoplasm.

An in situ hybridisation procedure to reveal albumin mRNA on formalin fixed hepatic tissue using a digoxigenin labelled oligonucleotide probe has been developed by Murray *et al.*⁴ In our case a 2 kb cDNA sequence corresponding to a coding sequence of human albumin provided by ATCC (Rockville, Maryland, USA) was used to produce a SP6 transcribed, digoxigenin 11 UTP labelled anti-sense riboprobe. The cytospin preparations were formalin fixed and the method of in situ hybridisation developed by Stewart *et al.*⁵ was employed. The patient had clinical signs strongly suggestive of hepatocellular carcinoma, supported by serological, ultrasound, and computerised tomography findings. The peritoneal effusion contained single neoplastic cells and groups of neoplastic cells showing nuclear pleomorphism and granular chromatin surrounded by moderate amounts of rather granular cytoplasm. These cytological features were certainly in keeping with the appearances of hepatocellular carcinoma as described in fine needle aspirate,⁶ and after demonstrating human albumin mRNA in these

cells we felt that the diagnosis of hepatocellular carcinoma in the ascitic fluid was certain.

We feel that application of this rapid, reliable, and specific technique of in situ hybridisation for human albumin can confirm the diagnosis of hepatocellular carcinoma on cytospin preparations of ascitic fluid, thus making further invasive diagnostic procedures unnecessary.

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Dilutional hyponatraemia: a cause of massive fatal intraoperative cerebral oedema in a child undergoing renal transplantation

A Armour

Abstract

A four year old boy with polyuric renal failure resulting from recurrent urinary tract infections and vesicoureteric reflux from birth underwent renal transplantation. In the past he had had five ureteric reimplant operations and a gastrostomy, as he ate nothing by mouth. He required peritoneal dialysis 13 hours a night, six nights a week. His fluid requirements were 2100 ml per day. This included a night feed of 1.5 litres Nutrizon. Before operation he received 900 ml of Dioralyte instead of the Nutrizon feed, and peritoneal dialysis was performed as usual. The operation itself was technically difficult and there was more blood loss than anticipated, requiring intravenous fluids and blood. The operation ended about four hours later but he did not wake up. Urgent computed tomography revealed gross cerebral oedema. He died the next day. At necropsy the brain was massively oedematous and weighed 1680 g.

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Keywords: cerebral oedema; operation; intravenous fluids

There are various causes of cerebral oedema including inflammatory conditions, ischaemia, trauma, space occupying lesions, anoxia, tox-

ins, and metabolic disorders—in particular hyponatraemia¹ and water intoxication.² Cerebral oedema has been defined as an increase in brain volume due to an increase in its water content.³ It can be localised or generalised. In the conscious patient it produces symptoms of raised intracranial pressure, but in the unconscious the symptoms are masked. Cerebral oedema developing as a result of hyponatraemia is well documented⁴⁻⁶ but most of these cases have developed postoperatively or following intravenous administration of fluids in a conscious patient. The event described here occurred during anaesthesia, and at the end of the operation—about four hours later—the patient, a child, did not wake up and had developed papilloedema. Urgent computerised tomography showed gross cerebral oedema with slit-like ventricles. Brain stem tests were carried out and he was declared dead the next day, about 26 hours from the start of the operation. This case illustrates the complexity of fluid management in an intraoperative fatality. To pathologists carrying out these necropsies—it is important to realise that asymptomatic dilutional hyponatraemia can occur intraoperatively when the symptoms of hyponatraemia and cerebral oedema are masked due to anaesthesia and unconsciousness. Arief *et al.*⁴ studied 16 cases of symptomatic postoperative

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