CORRESPONDENCE

Poorly differentiated hepatocellular carcinoma with unusual tubular structures

The patient was a 70 year old woman. A tumour in liver segment 8 arose in a background of cirrhotic liver with chronic hepatitis C and reached a size of 6.0 cm in six months. The patient’s serum concentration was raised (17101 ng/ml), and the tumour was suspected to be hepatocellular carcinoma (HCC) based on various image findings. An extended liver anterior segmentectomy was performed, and serum α fetoprotein returned to normal immediately after surgery.

Although the macroscopic findings were compatible with conventional HCC (fig 1A), the histology of the tumour was atypical—the tumour cells mainly formed irregular tubular structures filled with a bloody/serous or bloody fluid (fig 1B), and small tubular or acinar-like structures were also found (fig 1C). Solid structures were seen in a small portion of the tumour (fig 1D), and vascular invasion, or Alcian blue/periodic acid Schiff positive mucin was seen. In addition, a typical moderately differentiated HCC (measuring 1.0 cm) with trabecular pattern was also found.

Immunohistochemical examination revealed that the tumour cells showed diffuse and strong reactivity for vimentin and pan-keratin (AE1/3), focal reactivity for α fetoprotein and HepPar 1, and negativity for calretinin. Wilms’ tumour 1 protein, c-kit, CD34, cytokeratin 7, cytokeratin 19, cytokeratin 20, low molecular weight cytokeratin (CAM5.2), epithelial membrane antigen, chromogranin A, synaptophysin, neuron specific enolase, carcinoembryonic antigen, CA125, 2A2, 2G10, and 4C4. The tumour cells had a high proliferative activity, scoring 60% on the MIB-1 labelling index.

All candidate tumour types with the exception of HCC (cholangiocellular carcinomas, metastatic adenocarcinomas, primary malignant mesotheliomas, carcinoid tumours, and germ cell tumours) were ruled out clinically and histologically. Pseudo-glandular formation is a common histological manifestation of HCC, and peloid-type HCC shows large vascular lakes within the tumour, mimicking peliosis hepatis. Therefore, we consider this tumour to resemble such types of HCC.

Recently, intermediate liver carcinomas and hepatic stem cell malignancies have been reported. However, an apparent stem cell component was not prominent in the present tumour, and the negativity for c-kit, the hypochromatic nuclei, and the absence of desmoplastic stroma were not compatible with these types of tumours. The reticular-like pattern suggested a yolk sac tumour, and an association between hepatitis C virus infection and yolk sac tumours has been suggested. However, specific features, such as Schiller-Duval bodies, a cystic pattern, and hyaline globules, were not detected. In addition, the tumour was immunohistochemically negative for 2A2, 2G10, and 4C4, which have been reported to be specific to yolk sac tumours. A strong reactivity for vimentin is associated with metastatic HCCs or sarcomatous HCCs, indicating a highly malignant form of HCC. Clinically, this tumour showed rapid growth and a high proliferative activity of 60% as assessed by the MIB-1 labelling index.

Considering the various findings described above, we finally diagnosed this tumour as an unusual type of HCC with poorly differentiated features presenting with a high degree of malignancy. Thirteen months after surgery, a new tumour was detected in liver segment 2 and percutaneous ethanol injection therapy was performed.

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The patient gave informed consent for this letter to be published.

References

Metastasis of a caecal neuroendocrine carcinoma to the thyroid gland

Metastatic tumours to the thyroid have been reported to arise from several organs. We describe a unique case of caecal neuroendocrine carcinoma (NEC) metastatic to the thyroid gland, mimicking a primary medullary thyroid carcinoma (MTC).

A 56 year old woman was referred after complaining of dysphagia and hoarseness.
Fifteen months before, she underwent surgery because of a well differentiated caecal NEC, low grade malignant, with metastases to the left ovary, the omentum, and the abdominal lymph nodes (World Health Organisation classification). The tumour was composed of spindle shaped cells, exhibiting scanty eosinophilic cytoplasm, salt and pepper nuclei, and inconspicuous nucleoli (fig 1). Neoplastic cells showed intense reactivity with antibodies against CAM 5.2, AE1/AE3, cytokeratin 7, cdx-2, chromogranin A, synaptophysin, serotonin, and neuron specific enolase; there was weak reactivity for calcitonin and carcinobryonic antigen. In contrast, no immunoreactivity was detected for thyroid transcription factor 1 or vimentin. On examination, a firm nodule was felt in the left lobe of the patient’s thyroid gland; attempts at fine needle aspiration biopsy did not yield adequate material for a cytological diagnosis. The patient underwent thyroidectomy, and histological examination disclosed a tumour in the left thyroid lobe, with the same pathological and immunohistochemical features as the previously excised caecal lesion (fig 2). Nonetheless, it was negative for Congo red, S-100 protein, and thyroglobulin stain; again, cdx-2 staining was positive, further confirming the caecal origin of this tumour (fig 3). Twenty one months after surgery, the patient died as a result of multiple organ failure.

To the best of our knowledge, this is the first case of a rare caecal NEC with metastasis to the thyroid to be reported. The differential diagnosis included several primary neoplasms. MTC is characterised by positive immunostaining for calcitonin; nonetheless, calcitonin can also be produced ectopically. In our patient, weak positivity for calcitonin was found at immunohistochemical examination; however, staining for thyroid transcription factor 1, a marker of thyroid or lung origin, was negative, whereas cdx-2, a transcription factor involved in the proliferation and differentiation of intestinal epithelial cells encoded by a homeobox gene, was positive, excluding MTC. Parangangioma was ruled out by both the intense reactivity of neoplastic cells for cytokeratins, and the absence of sustentacular cells, as shown by negativity for S-100 protein. Insular carcinoma could be excluded by the absence of a microfollicular pattern, the negative immunoreaction against thyroglobulin, and the positive immunostaining for neuroendocrine markers. Finally, a few cases of primary small cell carcinoma of the thyroid have been described, which share identical pathological and immunohistochemical features with primary lung small cell carcinoma. Some of them are positive for calcitonin, and are therefore regarded as small cell variants of MTC. In our patient, small cell carcinoma was ruled out firstly because of patient history and also by positive immunostaining for cdx-2.
Liesegang rings were related to duct ectasia. The ring has developed within an areolar tissue of the duct ectasia and the adjacent tissue with an associated foreign body giant cell reaction. Liesegang rings are laminated spherical ring-like structures that develop usually in relation to cystic or inflammatory lesions. The rings are composed of a mixture of calcium, iron, silicone, and sulfur and form by periodic precipitation from a supersaturated colloidal solution. Liesegang rings are rare and have been described primarily in the lung but have also been reported in other sites.

In their recent letter, the group of Rubio et al. in the March 2005 issue of *J Clin Pathol* reported the discovery of a foregut cyst in a 63-year-old woman. The cyst was located in the gastric fundus and contained a mucous lining. The authors suggested that the cyst might be a bronchogenic cyst, but further studies were needed to confirm the diagnosis. The case was discussed in the context of other foregut cysts, such as esophageal, oesophageal, and cardiac cysts, which are known to have characteristic histological features.

The authors of the letter emphasized the importance of distinguishing foregut cysts from other cystic lesions, as they can have similar histological features. The use of tissue microarrays for rapid linking of molecular markers in tissues is recommended to help standardize the reporting of molecular markers in the literature. The objective of the analysis was to demonstrate that vascular endothelial growth factor (VEGF) is upregulated independently of activated HIF-1α in most human tumours. This may imply constitutive overexpression or, more likely, reactive upregulation in response to other factors in the tumour microenvironment. The validity of this observation is not affected by the choice of tissue microarrays or whole sections. Indeed, a report by Torhorst and colleagues suggests that the assessment of biomarker status in arrayed tissue cores may carry greater prognostic value than assessment in whole sections.

In summary, we strongly support any move that would help to standardize the reporting of the expression of molecular markers in tissues. However, we stand by our observations that the upregulation of VEGF in human tumours is largely independent of HIF-1α activation. The assumption that the analysis of HIF-1α expression in whole sections is prognostically superior to tissue microarrays is unfounded at this time. Indeed, a report by Torhorst and colleagues suggests that the assessment of biomarker status in arrayed tissue cores may carry greater prognostic value than assessment in whole sections.

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