

PostScript

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 massive bleeding was also seen. The tumour cells had abundant eosinophilic granular cytoplasm and round nuclei with moderate variations in size and shape. The typical trabecular pattern was not seen, and no evidence of desmoplastic stroma, extracapsular proliferation, 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 pankeratin (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, neurone 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. Pseudoglandular formation is a common histological manifestation of HCC, and pelioid-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.^{1,2} 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.³ 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,^{4,5} 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.

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Metastasis of a caecal neuroendocrine carcinoma to the thyroid gland

Metastatic tumours to the thyroid have been reported to arise from several organs.^{1,2} 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.

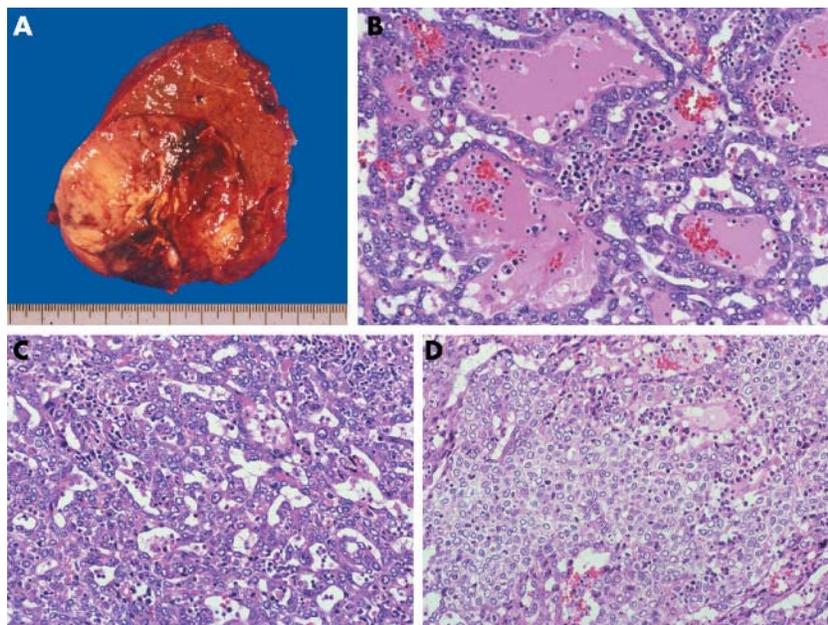


Figure 1 (A) Macroscopically, the nodular S8 tumour has a fibrous capsule. The cut surface of the tumour is well circumscribed, expanded, and yellow/white to dark red in colour. (B) The tumour cells have abundant eosinophilic granular cytoplasm and round nuclei with moderate variations in size and shape. The irregular trabecular structures are filled with a bloody/serous or bloody fluid without mucin production and desmoplastic tissue. The typical trabecular pattern was not seen (haematoxylin and eosin (H&E) stain, original magnification, $\times 200$). (C) Small tubular or acinar-like patterns are also visible (H&E stain; original magnification, $\times 200$). (D) Solid structures are seen in a small portion of the tumour (H&E stain; original magnification, $\times 200$).

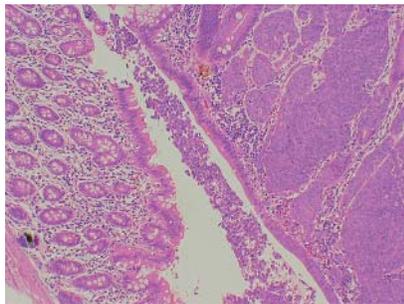


Figure 1 Primary neuroendocrine carcinoma of the caecum. Haematoxylin and eosin stain; original magnification, $\times 10$.

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).³ 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 neurone specific enolase; there was weak reactivity for calcitonin and carcinoembryonic 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 thyroidectomy, 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

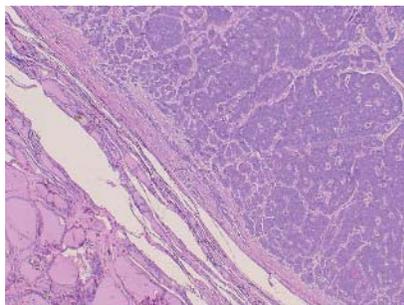


Figure 2 The caecal neuroendocrine tumour (right side of the figure) metastatic to the thyroid gland (on the left side) grew in a predominantly solid and trabecular architectural pattern, surrounded by a fibrovascular stroma. Haematoxylin and eosin stain; original magnification, $\times 10$.

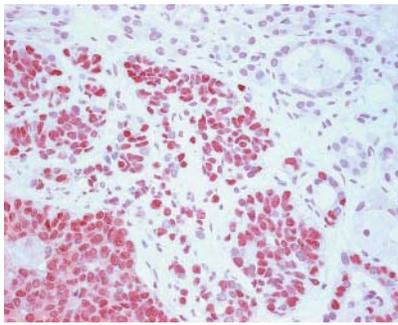


Figure 3 The thyroid metastasis was composed of spindle shaped cells with poorly defined cell borders, exhibiting scanty eosinophilic cytoplasm, salt and pepper nuclei, and inconspicuous nucleoli. The tumour cells showed intense nuclear staining for cdx-2; in contrast, thyroid epithelium was negative for this marker. Cdx-2 staining; original magnification, $\times 40$.

immunostaining for calcitonin⁴; nonetheless, calcitonin can also be produced ectopically.⁵ 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,⁶ was negative, whereas cdx-2, a transcription factor involved in the proliferation and differentiation of intestinal epithelial cells encoded by a homeobox gene,⁷ was positive, excluding MTC. Paraganglioma 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.⁸ 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,⁹ 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.

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Liesegang rings in inflammatory breast lesions

We present two examples of Liesegang rings occurring in association with duct ectasia. Liesegang rings are a rare phenomenon usually found in association with cystic or inflammatory lesions, and may be mistaken for parasites.

The first patient, a 52 year old woman, had a radiological code 4 mass lesion on screening mammography. Needle core biopsy (NCB) showed breast tissue infiltrated by sheets of single cells, with abundant foamy cytoplasm and slightly eccentric nuclei. Cytological atypia was minimal and there was no significant mitotic activity. The cells were admixed with lymphocytes, plasma cells, and neutrophil polymorphs. Immunohistochemical studies showed that the lesional cells were strongly CD68 positive and cytokeratin negative, confirming the haematoxylin and eosin impression of an inflammatory process, and excluding histiocytoid carcinoma. The aetiology of the inflammatory process was not apparent on NCB and, in view of the radiological suspicion of malignancy, the patient proceeded to excisional biopsy. This revealed a 1 cm slightly irregular lesion with a white cut surface and yellow foci centrally, bordered by fatty breast tissue. Microscopically, the lesion was composed of an irregular dense aggregate of histiocytes, lymphocytes, plasma cells, and neutrophil polymorphs, as seen on NCB. Within the aggregate of inflammatory cells, foreign body type giant cells were identified, some of which were associated with round acellular structures. These structures typically comprised a double layered outer wall containing evenly spaced radial cross striations, surrounding dense amorphous non-refractile orangophilic material, interpreted as Liesegang rings (fig 1). There was evidence of fat necrosis and florid duct ectasia in the immediate vicinity. The overall histological appearances were thought to represent a predominantly histiocytic inflammatory process incorporating Liesegang rings, secondary to a ruptured ectatic duct. There was no evidence of malignancy.

The second patient, a 54 year old woman, had a radiological code 5 mass lesion in the upper inner quadrant of her right breast on

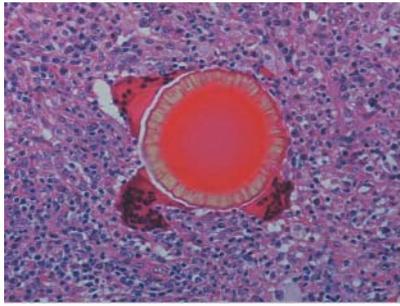


Figure 1 Liesegang ring characterised by a double layered outer wall containing evenly spaced radial cross striations, surrounding dense amorphous non-refractile orangophilic material. The ring has developed within an area of chronic inflammation and is associated with a foreign body giant cell reaction.

screening mammography. After a needle core biopsy diagnosis of invasive ductal carcinoma with associated ductal carcinoma in situ, she underwent therapeutic wire guided breast wide local excision and sentinel lymph node biopsy. The breast specimen showed a 15 mm, grade 3, invasive ductal carcinoma, with extensive high grade ductal carcinoma in situ. Three sentinel lymph nodes were negative for metastatic carcinoma. The tissue lateral to the tumour showed features of duct ectasia. Liesegang rings were present in the lumen of one of the ectatic ducts and in the adjacent tissue with an associated foreign body type giant cell reaction.

Liesegang rings are laminated spherical ring-like structures that develop usually in relation to cystic or inflammatory lesions. The rings are typically composed of a mixture of calcium, iron, silicone, and sulfur and form by periodic precipitation from a supersaturated colloidal solution.¹ Liesegang rings are rare and have been described primarily in the setting of renal cysts,² but have also been observed occasionally in association with breast cysts, endometriotic lesions, and cysts at other sites.³⁻⁵ In the above two cases, the Liesegang rings were related to duct ectasia and in the first case were an integral part of the mammographic lesion. Liesegang rings may be mistaken for psammoma bodies or parasites. Liesegang rings lack the internal organs of true parasites and have a characteristic histological configuration, as described above. Accurate identification of Liesegang rings supports the diagnosis of a cystic or inflammatory process, and decreases the possibility of erroneous misdiagnosis as another type of pathological process.

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Full consent was given for the publication of these cases.

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Congenital bronchogenic cyst in the gastric mucosa

We read with interest the letter by Rubio *et al*, "Congenital bronchogenic cyst in the gastric mucosa" in the March 2005 issue.¹ In their report, the cyst they discovered contained pseudostratified ciliated epithelium with a lymphatic follicle. No cartilage was noted and no respiratory seromucous glands were mentioned. Although all bronchogenic cysts must have ciliated epithelium (pseudostratified ciliated columnar or cuboidal epithelium), they must also have cartilage or bronchial mucous glands.²⁻⁵

Foregut cysts include bronchogenic, oesophageal, gastroenteric, and pericardial types. The most common location for these cysts is in the mediastinum; however, cutaneous, cervical, diaphragmatic, abdominal, retroperitoneal, and gastric locations have all been described. Although gastroenteric and pericardial cysts are straightforward to differentiate, the distinction between oesophageal and bronchogenic cysts can be difficult because of their similar histological features, as a result of their close embryological development. All bronchogenic cysts must have ciliated epithelium (pseudostratified ciliated columnar or cuboidal epithelium). They also must have cartilage or bronchial mucous glands. Oesophageal cysts can have ciliated or non-ciliated epithelium of columnar, squamous, or mixed types. This epithelium sits on two well developed layers of smooth muscle with no cartilage or respiratory glands. When a cyst is only lined by ciliated columnar epithelium with none of the above mentioned distinguishing features, a foregut cyst is the appropriate description.²⁻⁵

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Expression of HIF-1 α in human tumours

In their recent letter,¹ van Diest and colleagues make a valid point that the expression

of molecular markers in the literature is often discordant because investigators do not use standard methodologies. The use of tissue microarrays or whole tissue sections is one example of this, and van Diest and colleagues correctly point out that the core redundancy in tissue microarrays necessary for an accurate reflection of hypoxia inducible factor α (HIF-1 α) expression must be determined in a prospective fashion. Nevertheless, our evaluation of HIF-1 α staining was carefully controlled; we stained all tissues with a single antibody, at the same time, and used positive internal cell line standards on each section.² The assumption that the analysis of HIF-1 α 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.³

The objective of our analysis was to demonstrate that vascular endothelial growth factor (VEGF) is upregulated independently of activated HIF-1 α 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 Mizukami and colleagues suggests that certain human cancers may exploit an HIF-1 α independent mechanism to upregulate VEGF in response to hypoxia.⁴

In summary, we strongly support any move that would help to standardise 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-1 α activation.

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CORRECTION

Salashor S, Woodgett JR. The links between axin and carcinogenesis. *J Clin Pathol* 2005;**58**:225-36. The third sentence of the abstract should read: "Overexpression of mutant axin..." and in fig 5 parts A and D are β catenin and B and E are axin 1. The authors apologise for these mistakes.