

# Carcinoid tumour of the common bile duct – a novel complication of von Hippel-Lindau syndrome

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## Abstract

**A 30 year old man with von Hippel-Lindau syndrome presented with obstructive jaundice caused by a carcinoid tumour of the mid- and upper common bile duct. This association is probably causally related in view of the propensity for patients with von Hippel-Lindau syndrome to develop neuroendocrine tumours.**

The von Hippel-Lindau syndrome is a rare genetically determined condition, inherited in an autosomal dominant fashion, caused by a defect of the short arm of the third chromosome.<sup>1,2</sup> At present the precise gene affected is unknown. We describe a patient with von Hippel-Lindau syndrome complicated by obstructive jaundice. This was caused by a carcinoid tumour of the common bile duct, itself a rare condition.

## Case history

A 30 year old unemployed man, born in England to Ukranian parents, presented with a two month history of jaundice, itching, dark urine, and pale stools. His weight was unchanged. There was no history of travel abroad, contact with other people with jaundice, or drug intake. His alcohol consumption was 20 units per week. In childhood he had been treated for a retinal angioma. His father had died in 1968, aged 40 years, after surgery for a

cerebellar haemangioma and he was known to have had bilateral fundal haemangiomas. An older brother had died in 1973, aged 19, from a pheochromocytoma.

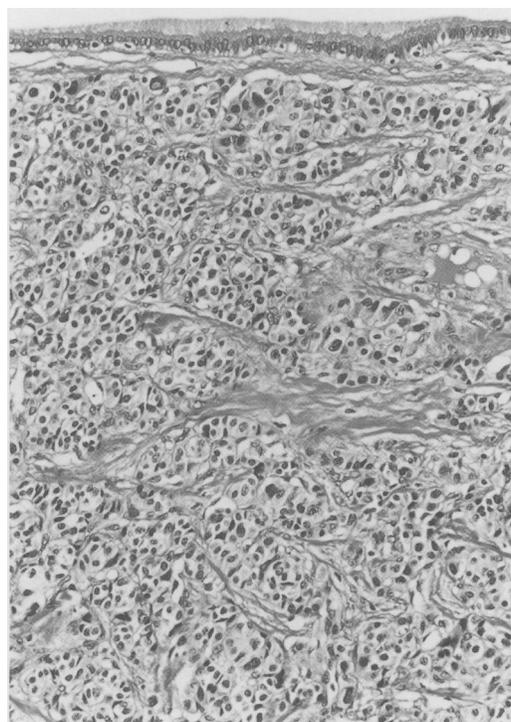
On examination, he was jaundiced but there were no abnormal abdominal signs. His arterial blood pressure was 130/70 mmHg and 120/80 mmHg on separate occasions. His biochemical liver function tests showed serum bilirubin concentration 125  $\mu\text{mol/l}$  (normal 0–17), alkaline phosphatase 1455 IU/l (normal 98–280),  $\gamma$  glutamyl transpeptidase 671 IU/l (normal 11–51), alanine aminotransferase 193 IU (normal 0–40), and albumin concentration 43 g/l (normal 31–51). His international normalised ratio for prothrombin time was abnormal at 1.8 but corrected to 1.1 after intravenous vitamin K1, 10 mg.

The patient's haemoglobin concentration was 14.3 g/dl, white blood cell count  $4.5 \times 10^9/l$ , platelet concentration  $231 \times 10^9/l$ , with erythrocyte sedimentation rate 9 mm/h (Westergren). Serum concentrations of urea, creatinine, and electrolytes were normal. Hepatitis B surface antigen and hepatitis A IgM antibodies were absent, but hepatitis A IgG antibodies were present, reflecting previous infection with hepatitis A. His 24 hour urinary excretion of vanillylmandelic acid was 32  $\mu\text{mol}$  (volume 2.38l; normal less than 35  $\mu\text{mol}$ ). Ultrasound examination showed normal liver architecture but dilatation of the intrahepatic and proximal extrahepatic ducts with a common hepatic duct diameter of 1.3 cm. The gall bladder was normal but it was impossible to visualise the common bile duct because of overlying bowel gas.

A percutaneous transhepatic cholangiogram showed dilatation of the biliary tree as far as the mid-common bile duct where there was a 1.5 cm diameter filling defect, reflecting a probable polypoid tumour. No contrast medium entered the duodenum. Laparotomy showed a cherry sized tumour at the junction of the cystic duct and common bile duct. The gall bladder and common bile duct were removed and the common hepatic duct was anastomosed to a Roux loop of jejunum. The patient made an uneventful recovery and his abnormal liver function tests gradually resolved over the next six weeks.

Histological examination showed a 1.5 cm diameter carcinoid tumour (Figs 1 and 2) of the common bile duct. Electron microscopy confirmed the presence of typical neuroendocrine granules. Immunohistochemistry showed positive staining with S-100, PGP 9.5, cholecystokinin and gastrin, focal staining with somatostatin, and no reactivity with glucagon. The tumour showed expansile and infiltrative growth and extended close to the lateral excision margins, although the proximal and distal cut ends of the common bile duct were free from

*Figure 1: Carcinoid tumour of the common bile duct showing overlying intact biliary mucosa (haematoxylin and eosin  $\times 220$ ).*



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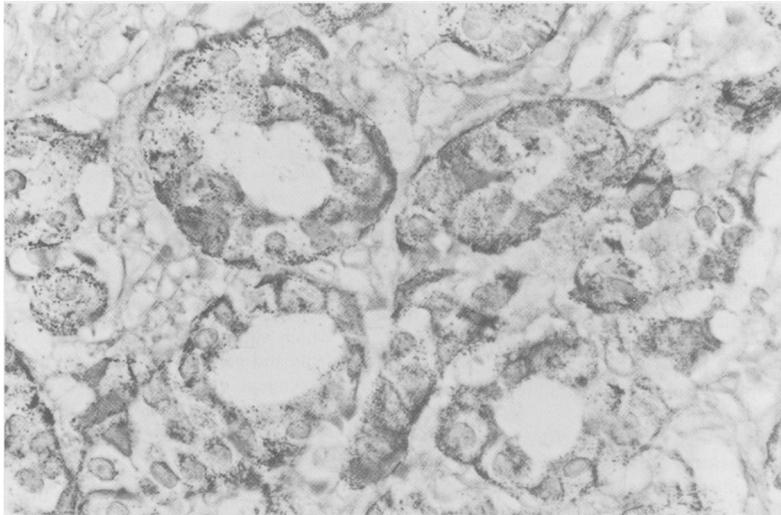


Figure 2: Cytoplasmic granules in the carcinoid tumour (grimalius  $\times 900$ ).

neoplasm. After surgery a urine screen for 5-hydroxyindole acetic acid was negative. A computed tomogram of the abdomen showed no hepatic metastases but there were multiple 1 cm diameter cysts in both kidneys and a 1.5 cm diameter mass in the right adrenal gland. Renal angiography showed small renal cysts in the right kidney and a contrast blush in the region of the right adrenal gland. The left kidney showed multiple cysts in the lower pole with a 2.5 cm diameter mass lesion with pathological circulation in the medial lower pole. A metaiodobenzylguanidine (MIBG) scan was normal.

Computed tomography of the cranium was normal but funduscopy showed angiomas of the right eye. The patient has subsequently had a left nephrectomy. The excised kidney showed multiple cysts, one of which contained adenocarcinoma which was infiltrating but not quite breaching the capsule of the kidney. The non-functioning right adrenal tumour is being reviewed regularly. A screening programme was instituted for his eight surviving siblings.

### Discussion

The biliary tract is a very rare site of origin of carcinoid tumours. A review of the previously published reports up to 1986 showed only six cases arising in the extrahepatic bile ducts,<sup>3</sup> with 17 arising in the gall bladder.<sup>3</sup> Carcinoid tumours can also affect the ampulla of Vater.<sup>4,5</sup> Carcinoid syndrome has not been reported in association with a carcinoid tumour of the biliary system.<sup>4</sup> Most carcinoid tumours (except appendiceal carcinoids) are potentially malignant but the commonly used criteria of malignancy, mitotic rate and degree of anaplasia, are unreliable, with invasive behaviour, either macroscopically or microscopically, being the main indicator.<sup>3</sup> Surgical excision is the usual treatment of biliary tract carcinoid tumours but the prognosis is uncertain because of the rarity of the condition. Previously published data on carcinoid tumours at other sites, however, have suggested five year survival rates of 68–95% in the absence of metastases, falling to 38% in the presence of distant metastases.<sup>6,7</sup>

It seems incontrovertible that the patient described in this paper has von Hippel-Lindau syndrome, since he has retinal angiomas, renal cysts, a renal cell carcinoma, and a possible pheochromocytoma in the presence of a positive family history of phenotypic expression of von Hippel-Lindau syndrome in his father and older brother. There is only one previous report of a malignant carcinoid tumour (primary site unknown, with hepatic metastases) in a patient with von Hippel-Lindau syndrome.<sup>8,9</sup> The present patient is the first to be described in whom a carcinoid tumour of the common bile duct has complicated von Hippel-Lindau syndrome. This finding conflicts with a previous review<sup>10</sup> which found no case of carcinoid tumour in von Hippel-Lindau syndrome and which suggested a sharp demarcation between the association of von Hippel-Lindau syndrome with pancreatic islet cell tumour and pheochromocytoma and that between neurofibromatosis, duodenal carcinoid tumour, and pheochromocytoma. The common bile duct carcinoid tumour in the present study, however, did not show the noticeable glandular pattern, dominant somatostatin positivity, and intraluminal psammoma bodies of the periampullary carcinoids associated with neurofibromatosis.<sup>10</sup> While the link between ampullary carcinoids and neurofibromatosis remains intact, the range of endocrine tumours associated with von Hippel-Lindau syndrome seems broader than envisaged in that review.<sup>10</sup>

The underlying reason for the development of various tumours in von Hippel-Lindau syndrome is uncertain, although the genetic locus of the syndrome is near the *RAF-1* oncogene associated with renal cell carcinoma.<sup>2</sup> It has been proposed that the von Hippel-Lindau gene encodes a tumour suppressive factor whose loss of activity allows oncogene expression and development of neoplasia.<sup>2</sup>

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