

Obstructive jaundice secondary to neuroendocrine tumour in a patient with von Recklinghausen's disease

D.N. Samonakis^a, A. Quaglia^b, N.M. Joshi^c, J.M. Tibballs^d, A. Nagree^c, C.K. Triantos^a, N. Davies^d, R. Standish^b, A.P. Dhillon^b, B.R. Davidson^a, A.K. Burroughs^a and M.E. Caplin^c

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder, with variable clinical manifestations and unpredictable course, associated with an increased incidence of various tumours. Plexiform neurofibromas are hallmark lesions of NF1; they are slow-growing tumours, which account for substantial morbidity, including disfigurement and functional impairment, and may even be life-threatening. Neuroendocrine tumours (NETs), a rare diverse group of neoplasms, are occasionally associated with neurofibromatosis. Pancreatic NETs are tumours with an incidence of less than 1/100 000 population/year and complex patterns of behaviour, which often need complicated strategies for optimal management. We present the case of a young adult with NF1, having a unique concurrence of plexiform neurofibroma involving the liver with an ampullary NET, and we discuss step

by step the management in a specialist centre. *Eur J Gastroenterol Hepatol* 17:1229–1232 © 2005 Lippincott Williams & Wilkins.

European Journal of Gastroenterology & Hepatology 2005, 17:1229–1232

Keywords: plexiform neurofibroma, liver, neuroendocrine tumour

^aLiver Transplantation and Hepatobiliary Unit, ^bHistopathology Department, ^cNeuroendocrine Tumour Unit and ^dRadiology Department, Royal Free Hospital, London, UK.

Correspondence and requests for reprints to Dr M.E. Caplin, BSc Hons, DM, FRCP, Neuroendocrine Tumour Unit, Centre for Gastroenterology, Royal Free Hospital, Pond Street, London NW3 2QG, UK. Tel: +44 20 7830 2867; fax: +44 20 7472 6728; e-mail: M.Caplin@medsch.ucl.ac.uk

Received 24 March 2005 Accepted 19 July 2005

Introduction

Neurofibromatosis type 1 (NF1) (von Recklinghausen neurofibromatosis) is an autosomal dominant genetic disorder, with an estimated birth incidence of one in 3000–4000 but with variable clinical manifestations and an unpredictable course [1]. The NF1 gene has been identified on chromosome 17q11.2; it is a tumour suppressor gene involved in growth regulation [1]. Inactivation of this gene (through mutation or allelic loss) leads to functional loss and the consequent development of many different types of tumours [2]. A heterogeneous group of benign tumours that grow from intraneural and extraneural tissues are neurofibromas, representing one of the commonest of the protean manifestations of NF1. Neurofibromas may present clinically as discrete tumours (dermal neurofibromas), diffuse tumours, spinal neurofibromas and plexiform neurofibromas [3].

Plexiform neurofibromas are among the most common and debilitating complications of NF1. They are benign, slow-growing, peripheral nerve sheath tumours that involve multiple nerve fascicles or branches of major nerves variably composed of Schwann cells, fibroblasts and other cell types [4]. Plexiform neurofibromas are typically associated with multiple nerves and can grow to large proportions, affecting an entire limb or body

segment; moreover, these lesions often have a rich vascular network and may occasionally result in haemorrhage. Plexiform neurofibromas are often poorly circumscribed and locally invasive (which can give rise to extensive disfigurement), and undergo malignant transformation in 2–16% of cases [2,4,5] into peripheral nerve sheath tumours.

Neuroendocrine tumours (NETs) are slow-growing malignancies derived from the neuroendocrine system, which have distinct biological and clinical characteristics. Sixty per cent of NETs arise in the gastrointestinal tract [6], less than 1% of these occur in the ampulla of Vater and 25% of these cases can be associated with neurofibromatosis. Ampullary NETs are usually non-functioning (i.e. have no associated clinical syndrome related to hormonal hypersecretion). Most are well-differentiated neoplasms with low malignant potential [7,8]. We report a unique case of a patient diagnosed with NF1 presenting with obstructive jaundice due to ampullary NET and we discuss the relevant specialist clinical management.

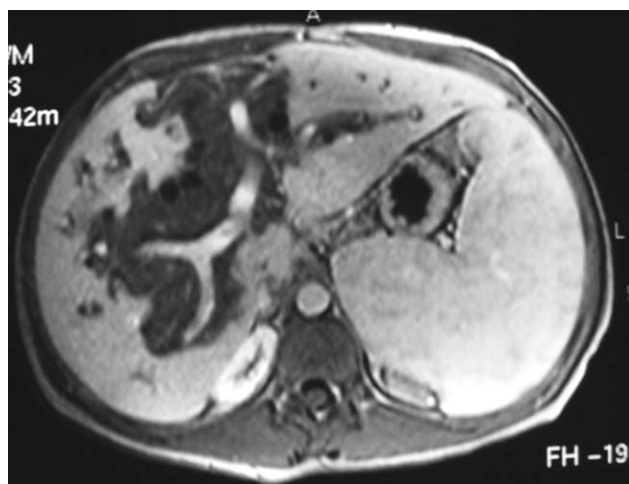
Case presentation

A 23-year-old student was referred to his local hospital with a 2-month history of pruritus and jaundice. He had no significant past medical history and did not drink alcohol or use tobacco. His father died of non-Hodgkin

lymphoma aged 56 years, but his mother was well with no other family history. On clinical examination there were more than 15 café-au-lait spots > 1.5 cm in diameter, and multiple skin fibromas in the trunk and lower extremities. Ophthalmological examination was negative for Lisch's nodules or other NF1-related lesions; audiometry-evoked and auditory-evoked potentials were normal. The clinical picture was compatible with von Recklinghausen's disease. The patient was jaundiced and malnourished. He had an enlarged non-tender liver as well as splenomegaly, but no other cutaneous signs of chronic liver disease. He was referred to our centre for further opinion.

The full blood count was normal; the liver function tests showed a predominant cholestatic profile: alkaline phosphatase, 385 (normal range, 39–150) U/l; gamma glutamyl transpeptidase, 573 (normal range, 0–50) U/l; aspartate transaminase, 131 (normal range, 5–40) U/l; alanine transaminase, 155 U/l; and bilirubin, 6.58 (normal range, 0–1.3) mg/dl. Viral markers, autoantibody and haemoglobinopathy screens were negative. Liver ultrasound confirmed common bile duct (CBD) dilatation, a normal gall bladder but a hilar mass and splenomegaly. Magnetic resonance imaging (MRI) confirmed the CBD dilatation but also a 2 cm mass at the distal common bile duct. MRI additionally demonstrated a soft tissue mass (Fig. 1), extending from the region above the pancreatic head to the porta hepatis and into the liver parenchyma encasing the vessels but without narrowing or occlusion; splenomegaly was also confirmed. An endoscopic retrograde cholangiopancreatography demonstrated an ampullary mass preventing cannulation of the CBD. Ampullary

Fig. 1

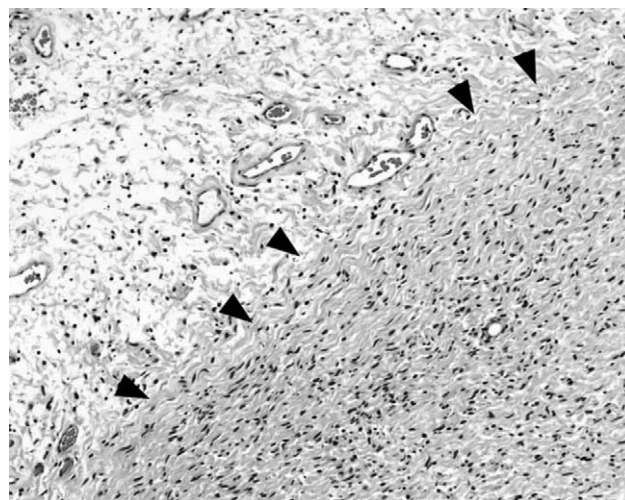


Axial gradient echo T1 post gadolinium magnetic resonance imaging, portal venous phase. The intrahepatic portal vein branches course through portal tracts markedly dilated by non-enhancing tissue.

biopsies showed features typical of a NET with positive staining for synaptophysin, Anticytokeratin antibody CAM 5.2, Protein Gene Product 9.5 and neuron-specific enolase. Very occasional cells showed calcitonin staining while no staining was seen for chromogranin. The tumour had a low proliferative index with Ki67 < 2%. A percutaneous transhepatic cholangiogram was performed and, following a short period of external biliary drainage, an 8.5-French endoprosthesis was placed. After resolution of the biliary obstruction, a liver biopsy was obtained that showed features of secondary biliary cirrhosis with increased hepatic venous pressure gradient (10 mmHg) due to chronic biliary obstruction. A targeted biopsy of the liver hilum lesion showed features of a plexiform neurofibroma (Fig. 2). An indium-111 octreotide scan demonstrated physiological uptake but no avid tumour uptake. An I-123 meta-iodo-benzyl-guanidine scan also showed no avid uptake. The patient had a normal fasting gut hormone profile (vasoactive intestinal peptide, pancreatic polypeptide, gastrin, glucagon, neurotensin) as well as normal chromogranin A (10 pmol/l) and chromogranin B (29 pmol/l). Parathyroid hormone levels were normal as well alpha fetoprotein, Ca19-9, beta human chorionic gonadotrophin, and carcinoembryonic antigen. Surgical resection of the ampullary tumour was planned after a period of biliary decompression and improved nutrition. The patient was discharged with bilirubin of 1.9 mg/dl, aspartate transaminase of 65 U/l, alanine transaminase of 79 U/l, alkaline phosphatase of 145 U/l and an International Normalized Ratio of 1.3.

At 5 months after the initial hospitalization, the patient gained weight and improved exercise tolerance. A repeat

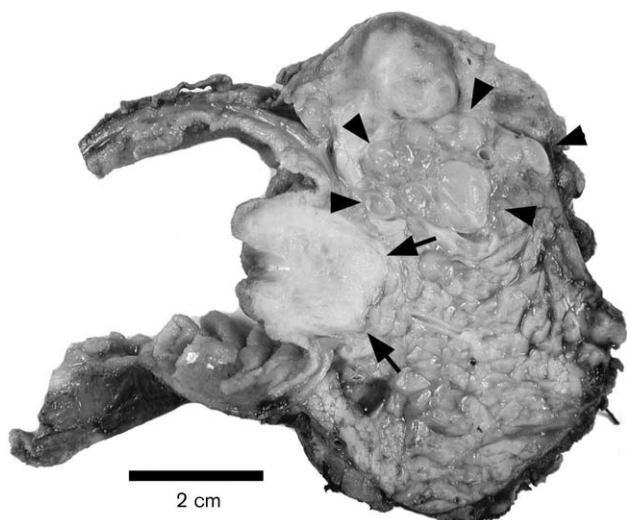
Fig. 2



A tissue sample from the liver hilum shows plexiform neurofibroma composed of wavy neural bundles (arrowheads) and adjacent loose fibrovascular stroma.

MRI scan showed no change in the ampullary tumour, which was still distinct from the plexiform neurofibroma. The liver and an area of plexiform neurofibroma were re-biopsied to exclude malignancy and to assess the liver histological response to biliary decompression. The liver showed less fibrosis, ductular reaction and copper-associated protein than previously. An endoscopic ultrasound confirmed that the ampullary tumour did not extend into the pancreas. Chest computed tomography and bone scans were negative. He underwent resection of the ampullary tumour. At operation, the liver was grossly enlarged but smooth and not obviously cirrhotic. A confluent mass of fibrotic tissue encased the hilum, the gallbladder and extended to involve the duodenum and the head of the pancreas. A 2 cm mass was identified at the ampulla, extending towards the pancreatic head. The remainder of the pancreas was normal. A pylorus preserving partial pancreaticoduodenectomy, and cholecystectomy with a Roux-en-Y loop reconstruction to the remnant pancreas was performed. The patient made an excellent recovery postoperatively. Histologically, the resected specimen contained a 1.6 cm diameter neuroendocrine tumour adjacent to the ampullary region (Fig. 3). The bile duct and pancreas were clear of tumour, with only one of 19 regional lymph nodes that were removed infiltrated with tumour. The mass of fibrotic tissue attached to the pancreatic head was plexiform neurofibromatosis with no evidence of malignancy. The patient was discharged home to be kept under regular follow-up; 6 months after the operation he is very well.

Fig. 3



The partial pancreatotomy specimen shows an ampullary tumour (arrows). Histopathological examination showed a low-grade neuroendocrine neoplasm. The adjacent pancreatic and peripancreatic tissue showed plexiform neurofibromatosis (arrowheads).

Discussion

NF1 (von Recklinghausen's disease) is one of the most common neurogenetic diseases affecting adults and children. It is a complex progressive disease affecting multiple cell types and multiple systems of the body; it can involve the central and peripheral nervous system as well as the skin, bone, endocrine, gastrointestinal and vascular systems. Diagnostic criteria for NF1 highlight these diverse manifestations and include pigmentary lesions, neurofibromas, optic pathway gliomas and bony dysplasias [3].

NF1 is transmitted as an autosomal dominant disorder caused by mutations in the NF1 gene on chromosome 17. The NF1 gene (a large gene, over 350 kb of genomic DNA) encodes a large cytoplasmic protein (neurofibromin) containing 2818 amino acids, which functions in part as tumour suppressor by inactivating the RAS molecule and preventing its mitogenic signalling, resulting in reduced cellular proliferation. Mutations at the NF1 gene result in diminished levels of neurofibromin that may predispose to subsequent development of a variety of tumours [5] (there is variable penetrance of mutations in the NF1 gene and 50% of affected individuals have new mutations). Additionally, there is increasing evidence that other contributing events, which may be under cytokine modulation, are important for neurofibroma development and growth [3].

Plexiform neurofibromas may be present at birth or may become apparent later on (they can remain silent for years and may be revealed only by imaging studies) and their growth can occur at any time in life [9]; their incidence in patients with NF1 in various studies is between 16 and 40% [10]. Plexiform neurofibromas have been reported to occur more commonly on the trunk (44%), followed by the limbs (38%), head and neck (18%) [11]. Liver involvement is very rare and has been described either as an isolated finding or in the context of widespread infiltration of various organs [12–17]. Often there is encasement of the major vessels (hepatic artery, portal vein) [13,18,19], as in this case. The periportal sheath distribution of plexiform neurofibromas is highly suggestive of their growth along intrahepatic nerve fibres accompanying vessels and ducts [19]. The optimal management for plexiform neurofibroma is surgical resection with prevention of possible compromise to vital structures. However, resection may often not be feasible because of the danger of damaging vital structures [13,19]. Moreover, because of the infiltrative nature of the tumours, outcome after surgery is often suboptimal with a high incidence of tumour regrowth [3]. Plexiform neurofibromas do have malignant potential, albeit rare [4], with transformation to malignant peripheral nerve sheath tumours [5]. These spindle cell sarcomas tend to be poorly responsive to therapy, can

metastasize and are associated with a low 5-year survival rate [3]. There are case reports of hepatic angiosarcoma and of both angiosarcoma and malignant schwannoma in the liver [20,21].

Ampullary NETs have been described in association with NF1 [8,22,23], and may present as obstructive jaundice or as acute pancreatitis. None of the published cases of liver involvement is associated with NET. In our patient the tumour was clearly demonstrated by cross-sectional imaging and endoscopic ultrasound, which has an increasingly recognized role in the local staging of ampullary NETs [24]. Somatostatin receptor scintigraphy was negative. This technique is less sensitive in tumours < 2 cm. The meta-iodo-benzyl-guanidine scan was negative, which is often the case in ampullary NETs [25]. The NET in the present case had a low mitotic and proliferative index (Ki67, a protein expressed when cells are in cycle of division), normal plasma chromogranin A (a neuroendocrine marker, high levels of which are associated with poor prognosis), small size and no concomitant liver metastases. Other additional favourable features were male sex, absence of bone metastases or ectopic hormone production. The only prognostically adverse feature was the node involvement [25]. Ampullary NETs have better prognosis than adenocarcinomas. Pancreaticoduodenal resection is the procedure of choice for periampullary NETs (and adenocarcinomas), given the high incidence of lymph node involvement and the inability to predict preoperatively with accuracy any regional spread. For those unable to tolerate extensive surgery, local excision may be considered [26]. With pancreatic NETs, conventional contraindications to surgical resection (such as superior mesenteric vein invasion, nodal disease or distant metastases) are reconsidered, with aggressive debulking surgery recently suggested in centres where morbidity and mortality can be minimized [27].

Our case is unique as it describes for the first time a combination of two rare entities in association with neurofibromatosis: an ampullary NET causing biliary obstruction in continuity with a hilar plexiform neurofibroma. The ampullary tumour with adherent plexiform neurofibroma was resected, relieving the biliary obstruction and facilitating an oncological cure of the underlying NET.

Conflict of interest

None declared.

Authors' contributions

D.N. Samonakis, N.M. Joshi, A. Nagree, C.K. Triantos, B.R. Davidson, A.K. Burroughs and M.E. Caplin were involved with the medical care of the patient and in the writing and/or review of the paper. A. Quaglia, R. Standish and A.P. Dhillon performed and interpreted the immunohistochemistry. N. Davies and J.M. Tibballs performed the biopsies and reviewed the radiological imaging.

References

- Zoller ME, Rembeck B, Oden A, Samuelsson M, Angervall L. Malignant and benign tumors in patients with neurofibromatosis type 1 in a defined Swedish population. *Cancer* 1997; **79**:2125–2131.
- Reynolds RM, Browning GG, Nawroz I, Campbell IW. Von Recklinghausen's neurofibromatosis: neurofibromatosis type 1. *Lancet* 2003; **361**: 1552–1554.
- Packer RJ, Gutmann DH, Rubenstein A, Viskochil D, Zimmerman RA, Vezina G, et al. Plexiform neurofibromas in NF1: toward biologic-based therapy. *Neurology* 2002; **58**:1461–1470.
- Waggoner DJ, Towbin J, Gottesman G, Gutmann DH. Clinic-based study of plexiform neurofibromas in neurofibromatosis 1. *Am J Med Genet* 2000; **92**:132–135.
- Hirsch NP, Murphy A, Radcliffe JJ. Neurofibromatosis: clinical presentations and anaesthetic implications. *Br J Anaesth* 2001; **86**:555–564.
- Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003; **97**:934–959.
- Solcia E, Kloppel G, Sobin LH (editors): *Histological typing of endocrine tumours*. 2nd edn. New York: Springer-Verlag; 2001.
- Hatzitheoklitos E, Buchler MW, Friess H, Poch B, Ebert M, Mohr W, et al. Carcinoid of the ampulla of Vater. Clinical characteristics and morphologic features. *Cancer* 1994; **73**:1580–1588.
- Korf BR. Plexiform neurofibromas. *Am J Med Genet* 1999; **89**:31–37.
- Friedman JM, Birch PH. Type 1 neurofibromatosis: a descriptive analysis of the disorder in 1,728 patients. *Am J Med Genet* 1997; **70**:138–143.
- Huson SM, Harper PS, Compston DA. Von Recklinghausen neurofibromatosis. A clinical and population study in south-east Wales. *Brain* 1988; **111**:1355–1381.
- Cardinale L, Castoldi MC, Mattai Del Moro R, Sangermani R. Intrahepatic neurofibromatosis in childhood. 2 cases. *Radiol Med (Torino)* 2000; **100**:84–86.
- Ghalib R, Howard T, Lowell J, Huettner P, Whelan A, Teehey S, et al. Plexiform neurofibromatosis of the liver: case report and review of the literature. *Hepatology* 1995; **22**:1154–1157.
- Guzman R, Toro F, Hinestroza D, Colmenares D. Von Recklinghausen disease and hepatic neurofibromatosis. *GEN* 1995; **49**:303–306.
- Kakitsubata Y, Kakitsubata S, Sonoda T, Watanabe K. Neurofibromatosis type 1 involving the liver: ultrasound and CT manifestations. *Pediatr Radiol* 1994; **24**:66–67.
- Nguyen KT, Pace R, Ludwin S, Ramsay DA. Plexiform neurofibroma: report of an unusual presentation. *Can Assoc Radiol J* 1990; **41**:103–104.
- Partin JS, Lane BP, Partin JC, Edelstein LR, Priebe CJ Jr. Plexiform neurofibromatosis of the liver and mesentery in a child. *Hepatology* 1990; **12**:559–564.
- Gallego JC, Galindo P, Suarez I, Garcia-Rodriguez JF. MR of hepatic plexiform neurofibroma. *Clin Radiol* 1998; **53**:389–390.
- Malagari K, Drakopoulos S, Broutzos E, Sissopoulos A, Efthimidadou A, Hadjiyiannakis E, et al. Plexiform neurofibroma of the liver: findings on MR imaging, angiography, and CT portography. *Am J Roentgenol* 2001; **176**:493–495.
- Andreu V, Elizalde I, Mallafre C, Caballeria J, Salmeron JM, Sans M, et al. Plexiform neurofibromatosis and angiosarcoma of the liver in von Recklinghausen disease. *Am J Gastroenterol* 1997; **92**:1229–1230.
- Lederman SM, Martin EC, Laffey KT, Lefkowitz JH. Hepatic neurofibromatosis, malignant schwannoma, and angiosarcoma in von Recklinghausen's disease. *Gastroenterology* 1987; **92**:234–239.
- Mayoral W, Salcedo J, Al Kawas F. Ampullary carcinoid tumor presenting as acute pancreatitis in a patient with von Recklinghausen's disease: case report and review of the literature. *Endoscopy* 2003; **35**:854–857.
- Tan CC, Hall RI, Semeraro D, Irons RP, Freeman JG. Ampullary somatostatinoma associated with von Recklinghausen's neurofibromatosis presenting as obstructive jaundice. *Eur J Surg Oncol* 1996; **22**:298–301.
- Fritscher-Ravens A. Endoscopic ultrasound and neuroendocrine tumours of the pancreas. *J Pancreas* 2004; **5**:273–281.
- McStay M, Caplin ME. *GI hormone producing tumours: syndromes and treatment options*. Pancreatic disease – basic science and clinical management. London: Springer; 2004, pp. 31–53.
- Ricci JL. Carcinoid of the ampulla of Vater. Local resection or pancreaticoduodenectomy. *Cancer* 1993; **71**:686–690.
- Norton JA, Kivlen M, Li M, Schneider D, Chuter T, Jensen RT. Morbidity and mortality of aggressive resection in patients with advanced neuroendocrine tumors. *Arch Surg* 2003; **138**:859–866.