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Case report

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Neurofibromatosis Type 1 and pancreatic islet cell tumours: an association which should be recognized

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Case report

A 75-year-old female with known NF-1 was being investigated for episodes of recurrent collapse. During one episode, she lost consciousness and on the arrival of the paramedics her capillary glucose was reported as 1.7 mmol/l: 1 mg intramuscular glucagon was administered and blood glucose was 2.7 mmol/l on admission to the Emergency Department, where she received intravenous dextrose. She described a 3-year history of episodes of collapse which begun with the onset of visual disturbance followed by the sensation of leg weakness. They occurred after fasting and her symptoms resolved on eating. The patient had a known diagnosis of aortic stenosis and a recent echocardiogram had shown an aortic valve area of 1 cm^2, with a peak gradient of 57 mmHg. A gastrointestinal stromal tumour had been resected several years previously.

An inpatient 72-h fast was performed. The patient developed symptomatic hypoglycaemia with a blood glucose of 2.1 mmol/l some 12 h into the fast. A concomitant insulin was 82 pmol/l, C-peptide 0.81 nmol/l and β-hydroxybutyrate 0.9 mmol/l, with a plasma sulphonylurea screen which was negative. The IGF-2: IGF-1 ratio was below 10, excluding the probability of an IGF2-secreting tumour. These results confirmed the presence of endogenous hyperinsulinism according to recent guidelines.[1,2] The patient was hypertensive and two sets of 24-h urinary collections showed elevated metadrenaline levels of 2.51 umol/24 h and 4.31 umol/24 h, respectively (laboratory upper limit of normal for urinary metadrenaline 1.40 umol/24 h).

An MRI scan with gadolinium showed a hypervascular lesion in the body of the pancreas and bilateral adrenal nodules. Endoscopic ultrasound revealed a hypoechoic lesion within the body of the pancreas. Selective pancreatic arteriography with calcium stimulation testing failed to localize the insulinoma. ^{123}I-mIBG scintigraphy showed increased uptake only in the right adrenal nodule (Figure 1).

Diazoxide was initiated but, despite dose titration, the patient experienced ongoing symptomatic hypoglycaemia and prednisolone was added: alpha- and beta-adrenoceptor blockade was commenced. The patient underwent a combined laparoscopic distal pancreatectomy and right adrenalectomy. The pancreatic body tumour measured 15 mm × 12 mm × 8 mm. Microscopically, it was a well-differentiated neuroendocrine tumour (Figure 2) with no lymphovascular or perineural invasion. No mitoses or necrosis were seen. The cells stained strongly positive for synaptophysin and chromogranin. There was positive, moderate intensity staining in most cells for insulin (Figure 3) and somatostatin. The adrenal tumour measured 35 mm and histology was consistent with a phaeochromocytoma with no untoward characteristics.

Following surgery, diazoxide was stopped and prednisolone reduced gradually. The patient had

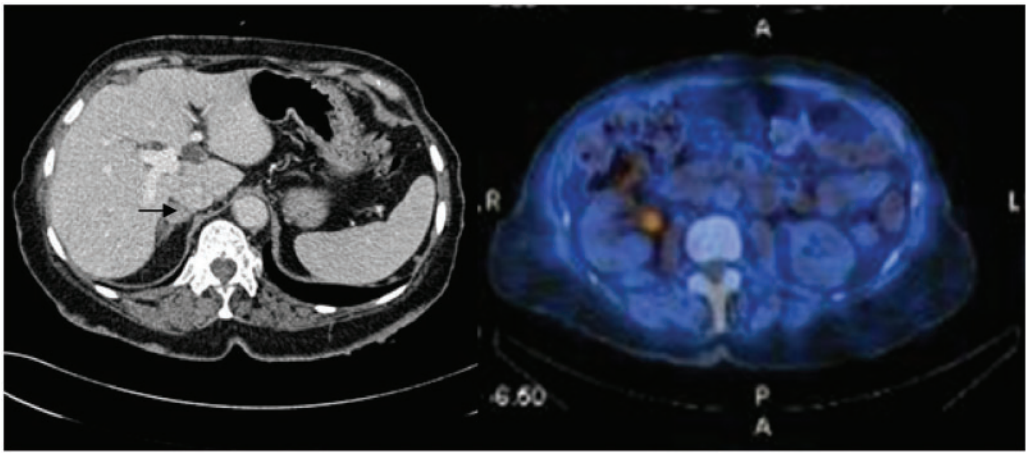

Figure 1. Right adrenal nodule (arrow) seen on CT scan (left image) and ^{123}I-mIBG scintigraphy showing avid uptake in the right adrenal nodule.

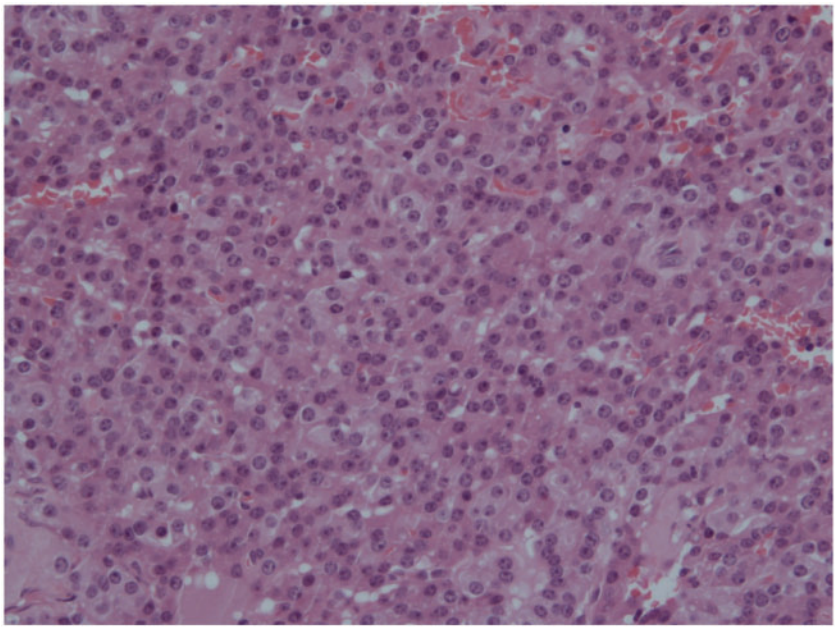

Figure 2. Monomorphic cells with neuroendocrine type nuclei and no mitoses (medium power magnification).

no further episodes of hypoglycaemia. Alpha- and beta-adrenoceptor blockade was stopped. A post-operative 24-h urinary metanephrines collection was normal, and the patient remains well 6 months after surgery.

Discussion

NF-1 is a common genetic disorder with an incidence of 1 in 3000 per year and a prevalence of 1 in 4000.[3] The NF-1 gene is located at 17q11.2 and contains 60 exons: 50% of the mutations arise *de novo*. It encodes neurofibromin, a 2485 amino-acid Ras-GTPase-activating protein which has a negative regulatory effect on the Ras oncogene signal transduction pathway. Patients with NF-1 are at a 2- to 4-fold higher risk of developing tumours compared to the general population.[4]

It is well known that NF-1 patients are predisposed to phaeochromocytomas, paragangliomas and duodenal somatostatinomas. However, there are also several reports of pancreatic neuroendocrine tumours in these patients, and these can be clinically significant. We report a case of an NF-1 patient presenting with an insulinoma in conjunction with a phaeochromocytoma. Our literature review identified that insulinomas in NF-1 have

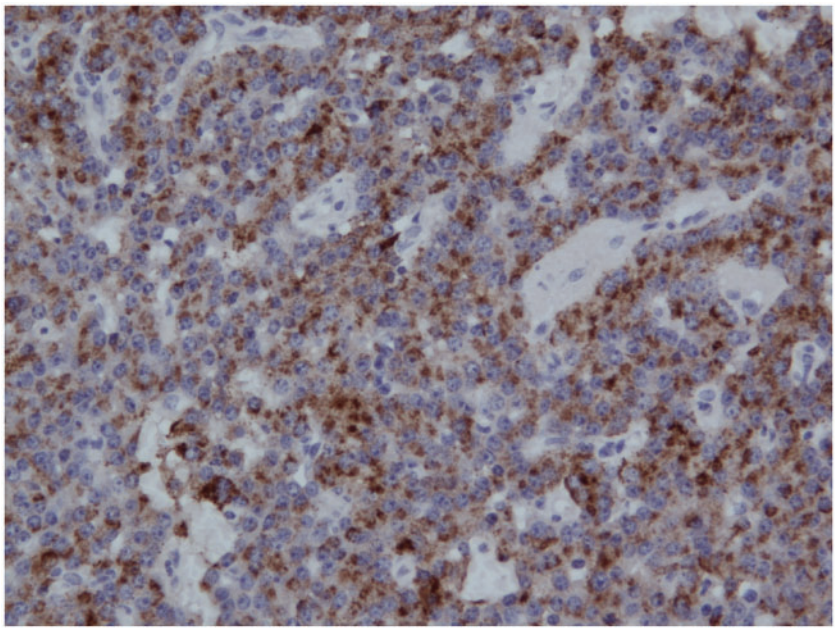

Figure 3. The majority of the tumour cells showed positive, moderate intensity immunostaining for insulin.

been reported but appear to be infrequent: our case is the fourth demonstration of an insulinoma in an NF-1 patient to be reported.

The first case reported in 1965 was that of a 66-year-old female with NF-1 who presented with a 3-year history of transient episodes of altered consciousness and seizures.[5] She had gained 20 kg in weight in the 3 years prior to diagnosis; 75% of her pancreas was resected and she also underwent a splenectomy. Histological examination confirmed a 1.5 cm × 2 cm well-encapsulated β-cell carcinoma of low-grade malignancy. The patient died from post-operative complications. Fung and Lam[6] described the case of a 45-year-old male with NF-1 who presented with a 12-month history of generalized seizures not responding to phenytoin. He had biochemical evidence of endogenous hyperinsulinism: laparatomy and enucleation of a 0.75 cm tumour in the body of the pancreas was performed. Histology confirmed an islet cell tumour with positive immunostaining for insulin.

The third case reported in the literature by Perren *et al.*[7] provides us with evidence that insulinomas are a rare manifestation of NF-1 rather than a chance sporadic occurrence. They performed molecular analysis of a malignant insulinoma from an NF-1 patient: loss of heterozygosity analysis of the insulinoma confirmed retention of both wild type and mutant NF-1 alleles in the tumour tissue. Reverse transcriptase-polymerase chain reaction of tumour extract showed expression of the mutant NF-1 allele but not the wild type. They also showed that neurofibromin protein expression was absent in the tumour tissue. They postulated the reduced expression of the wild-type NF-1 transcripts and protein was due to epigenetic mechanisms.

Our case was diagnosed with a synchronous phaeochromocytoma. Phaeochromocytomas and paragangliomas are the most commonly occurring endocrine tumours in NF-1 and are seen in 1–2% of patients. The mean age of phaeochromocytoma onset is 42 years,[8] and 84% have solitary adrenal tumours, 9.6% have bilateral adrenal disease and 6.1% have ectopic phaeochromocytomas, while they are malignant in 11.5% of cases.[8] These findings are not dissimilar to sporadic cases.

Somatostatinomas are by far the most commonly occurring GEP-NET seen in NF-1.[9] They are most frequently located in the duodenum with NF-1 accounting for 48% of all duodenal somatostatinomas.[10] Duodenal somatostatinomas are most commonly located in the periampullary region and tend to be hormonally silent.[11] The somatostatinoma syndrome, characterized by steatorrhoea, hypochlorhydria, anaemia, cholelithiasis and mild non-ketotic hyperglycaemia, is rarely seen with extra-pancreatic somatostatinomas.[10] Bettini *et al.*[12] noted 34 cases of peri-ampullary somatostatinomas associated with NF-1 in the literature between 1981 and 2006. They typically present clinically with abdominal pain, nausea, vomiting, bleeding, pancreatitis and jaundice.[11] Pancreatic somatostatinomas in NF-1 are only rarely reported.

Our literature review revealed two case reports of gastrinoma[13,14] and two case reports of VIPomas associated with NF-1.[15,16] Both the VIPomas were

extra-pancreatic and due to secretion of vasoactive-intestinal peptide from phaeochromocytomas. The patients presented with the WDHA (watery diarrhoea, hypokalaemia and achlorhydria) syndrome. Adrenalectomy of the affected gland resulted in normalization of the VIP levels and resolution of symptoms in both cases. No cases of glucagonoma associated with NF-1 are currently reported in the literature.

In conclusion, while it is well known that phaeochromocytomas, paragangliomas and duodenal somatostatinomas are seen in NF-1, we now report the fourth case in the literature of an insulinoma in an NF-1 patient. Clinicians should be aware of the possibility of insulinoma in patients with NF-1 and consider this in their differential diagnosis when investigating an NF-1 patient with episodic symptoms.

Conflict of interest: None declared.

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