Radical resection of large metastatic non-functioning pancreatic neuroendocrine carcinoma complicated by splenic vein thrombosis and sinistral portal hypertension

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INTRODUCTION AND IMPORTANCE: There are limited reports in the literature of radical surgical resection for pancreatic neuroendocrine carcinoma (PNEC) within the tail of the pancreas tumours can cause splenic vein thrombosis (SVT) and subsequent sinistral portal hypertension (SPH). Radical surgical resection in such patients with concomitant liver metastasis has not previously been reported.

CASE PRESENTATION: We present a 67-year-old female patient who presented with a large NF-PNEC within the tail of the pancreas with liver metastasis. We performed a distal pancreatectomy, splenectomy, partial gastrectomy and liver resection to achieve radical resection.

DISCUSSION: All patients with NF-PNEC within the tail of the pancreatic should be considered for radical surgical resection. In the presence of multi-visceral involvement and complications such as SVT and/or SPH multi-speciality surgical expertise is likely to be required.

CONCLUSION: Radical multi-visceral resection for large NF-PNEC can be safely performed in the presence of SVT and SPH.

1. Introduction

Pancreatic neuroendocrine tumours (PNETs) can occur anywhere within the pancreas and account for 1–3% of all pancreatic malignancies [1]. PNETs originate in the endocrine cells of the pancreas and in some instances are able to secrete specific hormones outside of the normal negative feedback regulation. Thus PNETs can be classified as functional PNETs or non-functioning PNETs (NF-PNETs) on this basis. Due to their lack of symptoms NF-PNETs can become relatively significant in size. In addition, NET can be graded as well-differentiated tumors (G1-G3) or poorly differentiated neuroendocrine carcinomas (NECs) based on Ki67 index. The term NEC G3 covers all high-grade neuroendocrine malignancies (NET G3 and NEC).

Although G1 PNETs are often considered indolent malignancies with an associated good prognosis [2], large NF-PNETs can present with rare complications such as splenic vein thrombosis (SVT) and sinistral portal hypertension (SPH) [3,4]. These factors can make surgical resection of large NF-PNETs challenging and significantly increase risk of bleeding complications. Previous reports have shown that distal pancreatectomy and splenectomy is feasible and safe in the presence of SVT [4]. However, there are limited reports of curative resections of pancreatic neuroendocrine carcinomas (PNECs) in the literature. Furthermore multi-visceral resection of metastatic PNEC in the presence of SPH secondary to SVT has not been previously reported. We report a case of metastatic grade 3 PNEC with SVT and SPH requiring multi-visceral resection. We outline surgical approaches and peri-operative management of this unusual case. The work and case report have been reported in line with SCARE 2020 criteria [5].

2. Case history

CR, a 67-year-old female, presented with new onset back pain in July 2020 and screening tests for osteoporosis demonstrated hypercalcaemia (2.85 mmol/L) with a suppressed parathyroid hormone level (<1.0 pmol/L). Remaining routine haematological and
biochemical parameters were within normal parameters. She was an ex-smoker with no other comorbidities and a performance status of 0. Due to the high index of suspicion of underlying malignancy, a computed tomography (CT) of the thorax, abdomen and pelvis (TAP) was performed that demonstrated a $12 \times 11 \times 12$ cm necrotic heterogeneously arterial enhancing mass within the left upper quadrant that was arising from the tail of the pancreas and was inseparable from the spleen (Fig. 1A–D). The splenic vein was occluded with multiple large varices seen draining into the proximal splenic vein. Radiological features consistent with SPH were present and portal vein was patent. The mass appeared separate from the stomach and appeared to be consistent with a large neuroendocrine tumour arising from the tail of the pancreas. In addition, there were 3 arterially-enhancing lesions in the left lobe of the liver consistent with metastasis (Fig. 1A–D). Further investigations revealed normal urinary 5-HIAA (18 μmol/24 h) but raised chromogranin A (249 pmol/L) and B (231 pmol/L). Given the clinical features were consistent with a NF-PNET, a CT-PET DOTATATE scan and percutaneous biopsy of the liver lesions was undertaken. This demonstrated intense DOTATATE uptake in the pancreatic tail tumour with segments of relative photopenia reflecting areas of likely necrosis. This scan demonstrated that the NF-PNET was possibly involving the gastric body. There were at least three DOTATATE avid lesions in the left liver (Fig. 2). Biopsy of the left liver lesion demonstrated a tumour composed of epithelioid cells with columnar morphology that were strongly positive for Synaptophysin and CD56 with Ki67 index 8% consistent with grade 2 PNET. Following multidisciplinary team (MDT) discussion, the patient was offered systemic chemotherapy in the form of capecitabine and temozolomide primarily to attempt to reduce tumour size and burden prior to surgery. However after 2 cycles of chemotherapy, CT TAP demonstrated no radiological response with the mass measuring $11 \times 10 \times 13$ cm and persistent splenic vein thrombus. The liver metastasis remained stable in size and number (Fig. 3). Given the lack of response to systemic chemotherapy, surgery was considered and offered to the patient. Pre-operative cardiopulmonary exercise testing demonstrated an anaerobic threshold 10.5 ml/kg/min and the patient was deemed ASA 2. Pre-operative splenectomy vaccinations were administered to the patient.

Prior to laparotomy, the patient underwent diagnostic upper GI endoscopy, which demonstrated one fundal varix in the gastric body. Following this, a transverse upper abdominal incision was made. Intra-operatively, a large (approx. 13 cm diameter) pancreatic tail mass was noted with no discernible tissue plane noted between the mass, spleen and gastric fundus. Large splenic varices secondary to SPH were noted consistent with pre-operative imaging. The liver metastases were all in the anatomical left lateral sector. Prior to dissection, an intra-operative ultrasound (IOUS) of the liver demonstrated good portal vein flow. The gastrocolic ligament was opened widely using a Ligasure® device. The pars flaccida was opened with diathermy and a Pringle tape was passed around the porta hepatitis. Prior to mobilisation, the splenic artery was dissected free at superior aspect of the pancreatic neck and clamped with a bulldog clamp. The splenic artery remained clamped until resectability of the mass had been proven. Next, the lateral peritoneal attachments of the spleen were divided with diathermy and

**Fig. 1.** Initial triple phase CT scan. (A & B) arterial phase imaging demonstrating a large arterially enhancing pancreatic tail lesion (red arrows) with large peri-pancreatic and peri-splenic varices (green arrows). In addition there are liver metastasis noted. (C & D) the venous demonstrates addition varices lower in adjacent to the transverse colon (green arrows).
the spleen was fully mobilised away from the transverse colon and splenic flexure. At this stage, the splenic varices had reduced in size making it possible to dissect the inferior border of the pancreas. The mass was found to be involving the gastric greater curve/fundus and a retrogastric tunnel was fashioned. The mass was deemed resectable by 2 Upper GI surgeons at this stage and thus a retropancreatic tunnel was fashioned lateral to the portal vein ensuring that the proximal patent splenic vein could be divided 1 cm from the portal confluence. The splenic artery was now ligated with Hem-O-Lock® clips 2 cm distal to its origin and divided. The pancreatic body was divided by slowly closing a linear vascular stapler with the staple line re-enforced with a continuous 4/0 absorbable suture. Following this, the large retro-splenic, peri-pancreatic and gastric varices were individually dissected and stapled with a vascular stapler (all above performed by RHB). The stomach was then divided using an Endo-GIA stapler ensuring that the gastro-oesophageal junction was not compromised (Figs. 4 & 5) - the gastric staple line was underrun with 3/0 absorbable suture (performed by SK). The remaining large retro-splenic varices were divided with a vascular stapler and the resection was completed with preservation of the left adrenal gland. A segment 2/3 liver resection was then performed with CUSA without inflow control (performed by RHB). Haemostatic agents were applied to the resection sites and abdominal drainage was achieved with Robinson drains. Post resection OGD revealed resection of the fundal gastric varix and no staple line bleeding. The patient was haemodynamically stable at the end of surgery requiring no inotropic support with an estimated blood loss of 1600mls. Post-operatively, the patient was given total parental nutrition for 5 days and intra-venous antibiotics for 72 h. Following this, the patient was commenced upon prophylactic pencillin V (post-splenectomy). Prior to oral feeding, the patient underwent upper GI contrast swallow on post-operative day (POD) 5 (Fig. 5) that demonstrated no leak from the remnant stomach and satisfactory filling of the small bowel. Prior to abdominal drain removal, a CT TAP was performed on POD 6 (Fig. 5), which demonstrated post-operative fluid at the splenic bed and patent portal vein with satisfactory appearances to the liver. The splenic varices had completely resolved. The patient made an uneventful recovery and was discharged on POD 12. The final histopathological diagnosis demonstrated complete resection (R0) grade PNEC that demonstrated focal involvement of the stomach wall. Ki67 index was 30%. Three metastatic liver lesion were also completely resected. There was no lymph node metastasis noted giving a final stage of pT3pN0M1 (Fig. 6). The patient has been referred for further chemotherapy.

3. Discussion

NF-PNETs comprise up to 90% of PNETs with PNECs being very rare clinical entities. NF-PNETs are often asymptomatic meaning these tumours commonly present at advanced disease often with liver metastatic disease as in the reported patient [6]. In general, the liver disease tends to be bilobar and multifocal [7]. 90% of NF-PNETs are sporadic with up to 10% having a genetic association. The literature regarding NECs and, in particular PNECs, remains limited. It is now being appreciated that NEC G3 are a heterogeneous group of tumours. Indeed gastro-enteric-pancreatic (GEP) NECs are usually highly aggressive with a propensity for early metastases and a poor prognosis although the data is very limited [8]. Data on the NET G3/NECs is scarce with NET G3 mainly located in the pancreas and having a better prognosis than NECs [9,10]. Analysis of the SEER database demonstrates the median survival for GEP NECs...
Fig. 4. Post-operative surgical specimen. (A) demonstrates the tumours position in-situ. * represent the main tumour mass. The pancreatic (red arrow) and gastric (green arrow) resection are shown. Posterior to the pancreas and stomach the large varices are visible. (B) demonstrates a medial view of the specimen. The large varices are visible with the forceps applied to the gastric resection margin. (C) the complete resection of the hepatic metastasis.

Fig. 5. Post-operative Imaging. (A) Upper GI contrast swallow demonstrating no leak and satisfactory filling of the small bowel. (B&C) CT CTAP demonstrating post-operative appearances of the upper abdomen and patent portal vein.

was 34 months for those with localized disease, 14–16 months with regional disease and 5 months with distant disease [11,12].

Where feasible, curative or palliative surgical resection should be considered for patients with PNETs [7] although there is no consensus for patients with PNECs. Some authors advocate that NET G3 patients should probably receive the same approach to surgery of the primary and metastatic disease as patients with NET G2 [13,14]. Adopting this approach in PNETs results in a 10-year overall survival rate of 60% and a disease free survival rate of 30% [15]. Hill et al. reported that patients with all stages of NF-PNETs demonstrate survival benefits after surgery with median survival being 114 months after surgery versus 35 months in patients not undergoing surgical resection [16]. For patients with PNETs within the pancreatic tail, distal pancreatectomy ± splenectomy is the standard of care as per ENETS consensus guidelines [17]. In cases, such as the reported patient, where there is SVT and SPH, splenectomy is mandatory [7,18]. In addition ENETS guidelines suggest that patients may undergo primary tumour resection with hepatic metastasis resec-
tion concomitantly if indicated. Furthermore any lesion >2cm or lesions with calcification are recommended to undergo simultaneous lymphadenectomy as in the reported patient. However, our case does demonstrate that multi-visceral resections for PNECs can be safely performed in conjunction with liver resection in a curative setting.

The complexity of surgery was increased in our patient because of SVT and SPH. The first reported case of a splenic vein tumour thrombus secondary to a PNET where the PNET had also invaded the spleen, stomach, left kidney and left colic flexure in association with SVT was reported in 1992 [19]. As seen in our patient, the SVT phenomenon exacerbates blood flow and backpressure on short gastric and gastroepiploic veins leading to substantial left sided varices and risks of upper GI haemorrhage [20]. Indeed, PNETs are more commonly implicated in causing SVT and subsequent SPH than other pancreatic tumours [4,21–26] although this is not an absolute contraindication to radical resection. The cause of SVT in the presence of PNETs is multifactorial and can be due to direct invasion from tumour, compression by the PNET or as a result of a fibrotic and/or vascular reaction to vasoactive secretion from the tumour - although our patient had NF-PNEC [27,28].

In the presence of substantial left sided varices, we strongly recommend that an early step during surgery should include dissection, control and clamping of the splenic artery to reduce splenic inflow, decrease portal pressure and venous collateralisation within the operative field. The splenic artery should only be divided when resectability is proven. In addition, keeping the CVP low during splenic and pancreatic mobilisation helps reduce portal pressure and decreases blood loss. Communication with anaesthetic team is critical throughout this procedure. In this case, minimising blood loss was essential as subsequent liver resection was also planned. We also suggest that in this unusual clinical scenario that the portal confluence is not formally dissected given the numerous large collaterals in the peri-pancreatic tissue. Rather, we suggest that each major varix is dissected free, followed by trial clamping and only division after IUS to confirm satisfactory portal venous blood flow. In a retrospective review of 61 patients with PNETs by Moyana et al., 8 patients had SVT with 4 having SPH [22]. These latter 4 patients had large pancreatic tail PNETs with extrapancreatic extension and invasion of the splenic vein. Interestingly, none of these patients had liver metastasis but given the tumour burden, curative resection was not considered. Three of these patients subsequently required emergency surgical intervention.

In summary, PNETs and where feasible PNECs that are complicated by SVT and/or SPH can be resected together with liver metastasis. To our knowledge, this is the first report of PNEC resection with metastatic disease in the presence of SVT and SPH.

Declaration of Competing Interest

The authors have no conflict of interests to declare.

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Ethical approval

Ethical approval for the case report was provided by the hospital board.

Consent

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Author contribution

Study concepts: RHB, Study design: RHB, SK, Data acquisition: RHB, RR, MT SK, Quality control of data and algorithms: SK, DW, RHB, Data analysis and interpretation: SK, DW, RR, RHB, Statistical analysis: SK, RHB, Manuscript preparation: RHB, Manuscript editing: SK, RHB, Manuscript review: SK, RHB.

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Fig. 6. Post-operative histology. Haematoxylin and Eosin micrograph of the surgical resection (20X) The red arrow represents gastric body type mucosa with the on blue arrow demonstrating the PNEC with a trabecular pattern. The green arrow represents the muscularis propria of the stomach that has been infiltrated by the PNEC.
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