Modified Liver-free Multivisceral Transplantation for a Metastatic Small Bowel Neuroendocrine Tumor: A Case Report

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ABSTRACT

Neuroendocrine tumors originating from the small bowel frequently metastasize to the lymph nodes and/or liver. Although surgical extirpation of the primary tumor and locoregional metastases epitomizes the management of patients with such tumors, this is not always possible with conventional surgical techniques. Nonresectable, slow-growing tumors involving the mesenteric root represent a generally accepted indication for deceased donor intestinal and multivisceral transplantation. Furthermore, vascularized sentinel forearm flaps offer opportunities for monitoring graft rejection and tailoring immunosuppression regimens. Here, we report the first documented case of modified liver-free multivisceral transplantation preceded by neoadjuvant 177-lutetium peptide receptor radionuclide therapy in a patient with a small bowel neuroendocrine tumor and extensive lymph node metastases in the mesenterium. At a follow-up of 21 months the patient is biochemically and radiologically disease-free.

NEUROENDOCRINE TUMORS (NETS) originating from the small bowel (SB) frequently metastasize to lymph nodes and/or the liver. Up to 90% of patients with SB NET present with mesenteric lymph node metastases at initial diagnosis irrespective of the primary tumor size [1]. Complete resection of locoregional disease and liver metastases represents the mainstay of treatment of patients with SB NET as it has impact on both the patient's quality of life and survival [2,3]. Extensive mesenteric tumor mass may lead to intestinal obstruction and ischemia due to obstruction of the superior mesenteric vessels. While removal of the primary tumor and adjacent lymph node metastases may be achieved by segmental resection of the mesentery and only limited resection of the small intestine, lymph node metastases involving the mesenteric root and extending retroperitoneally posterior or superior to the pancreas (stage IV) [4] present a technical challenge and are frequently considered inaccessible with standard surgical approaches. Various advanced techniques for the management of tumor masses involving the celiac and superior mesenteric vessels have been reported, including free-dissection of the superior mesenteric artery and vein on the level of inferior pancreatic border [4], ultrasound-guided stenting of the superior mesenteric vein [5], and intestinal and multivisceral ex vivo auto-transplantation [6–8].

Slow growing tumors involving the mesenteric root account for a generally accepted indication for deceased donor intestinal (ITx) and multivisceral transplantation (MVT) [9–12]. In the 2 largest single-center series on MVT, 5/100 (5%) [10] and 11/100 (11%) of transplants, respectively, were performed for central abdominal tumors. Of these, 6 were for NET. Here we report on a patient with a SB NET metastasised to the root of the mesentery as well as in the aortocaval groove who underwent a modified liver-free multivisceral transplantation (MMVT) with a simultaneous vascularized sentinel forearm flap (VSFF) to monitor for rejection. This was preceded by 4 cycles of lutetium-177 (^{177}Lu) peptide receptor radionuclide therapy (PRRT). Furthermore, we provide an overview of published experience with ITx in NET.

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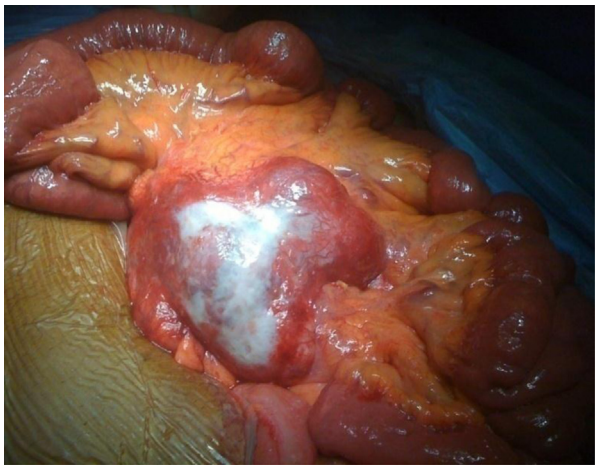

Fig 1. Mesenteric lymph node metastases as seen at laparotomy.

CLINICAL COURSE

Our patient is a 44-year-old man of Caribbean ethnicity who developed hematuria and occasional abdominal pain in 2009. He was otherwise fit and well, and his medical and family histories were unremarkable. Computed tomography (CT) imaging demonstrated a complex cyst within the lower pole of the left kidney that contained calcification and a 10 × 9 × 6 cm heterogeneously enhancing mass within the small bowel mesentery. An ultrasound-guided biopsy of the mesenterial mass confirmed a well-differentiated NET positive for chromogranin A and synaptophysin on immunohistochemistry.

Based on a Ki-67 proliferation index score of <1%, the lesion was classified as a grade (G) 1 NET. His serum chromogranin A was elevated at 395 pmol/L (normal range 0–60), chromogranin B was 349 pmol/L (normal range 0–150), and 5-hydroxy indole acetic acid (5-HIAA) in 24-hour urine was 643 μmol/L (normal range 0–40). Serum intestinal hormones including somatostatin, glucagon, vasointestinal peptide, pancreatic polypeptide (PPP), and gastrin were within normal ranges. On gallium-68 (^{68}Ga)–DOTATATE positron emission tomography (PET)/CT, significant uptake in the mesenteric tumor bulk (standard uptake value [SUV] of 27) and in an aortocaval lymph node (SUV of 10) was observed. Physiological uptake was seen in all other regions. At laparotomy in April 2010, a large stage IV tumor bulk circumferentially encasing the mesenteric root and several smaller enlarged lymph nodes in close proximity to small bowel loops were evident (Fig 1). In total, 7 subcentimeter tumors were scattered over the ileum. The liver appeared normal on exploration and intraoperative ultrasound. The tumor mass was deemed as conventionally nonresectable and the procedure was terminated. Subsequently, the option of MMVT in combination with neoadjuvant PRRT was considered after multicentric conference discussion of the case, followed by referral to an ITx center.

The patient underwent four cycles of [^{177}Lu-DOTA^{0}Tyr^{3}] octreotate (^{177}Lu-DOTATATE) therapy with 12-week intervals between each cycle and a cumulative dose of 28 GBq. No side effects were observed. A follow-up ^{68}Ga-DOTATATE PET/CT performed in February 2013 demonstrated high tracer uptake in the mesenteric and aortocaval tumor foci with significantly higher SUV than on the aforementioned imaging (Fig 2). No other areas of abnormal uptake were seen. There was no change in size of either the mesenteric or the aortocaval lesions. Chromogranin A and chromogranin B were raised at 2200 (normal range 0–60) and 450 (normal range 0–150), respectively (Fig 3).

In March 2013 he underwent an MMVT with a VSFF from the same donor, which was carried out at the Oxford

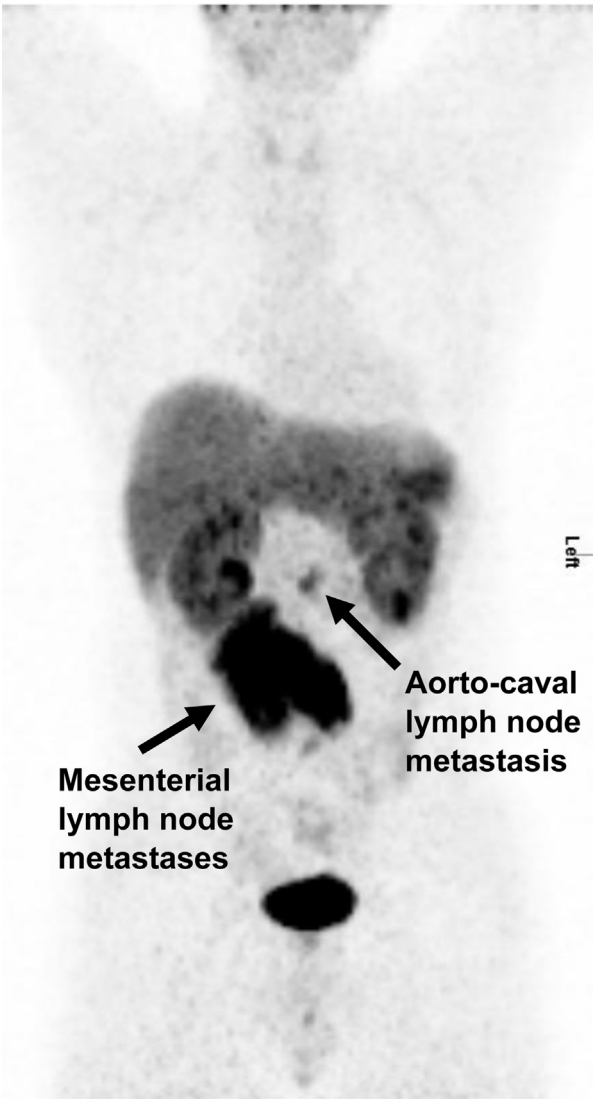

Fig 2. Pretreatment ^{68}Ga-DOTATATE positron-emission tomography (PET) imaging demonstrating pathologic uptake in the mesenterium (arrow) and in the aortocaval grove (arrow).

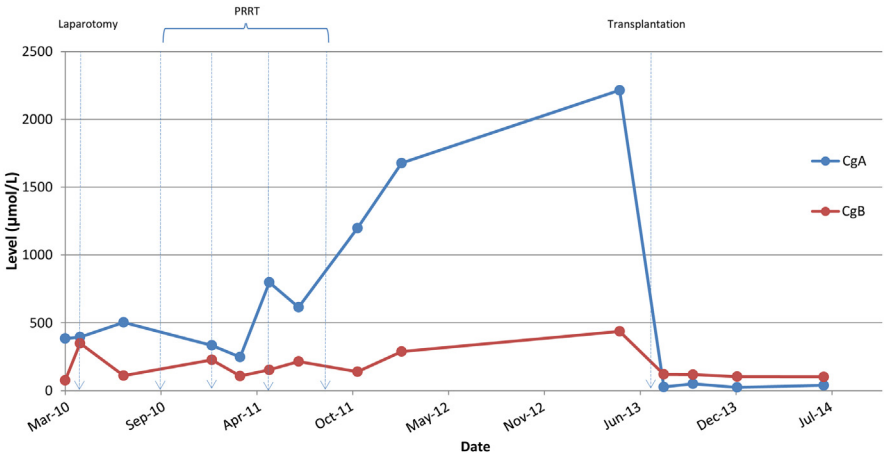

Fig 3. Plasma levels of chromogranin A and B throughout the patient journey (PRRT, peptide receptor radiotherapy; MMVT, modified multivisceral transplantation; VSFF, simultaneous vascularized sentinel forearm flap).

Transplant Centre, Churchill Hospital, Oxford, U.K. Compared to the intraoperative findings in 2010, the mass in the root of the mesentery was now involving the duodenum and pancreas, and there was a lymph node in the aortocaval groove. The liver was free of disease. Exenteration of the stomach, pancreas, spleen, small bowel, and colon (left hemicolon spared) and excision of the lymph node in the aortocaval groove were performed. A jump graft from the recipient's infrarenal aorta was constructed using donor thoracic aorta. This was the arterial inflow for the MMVT. The venous outflow of the graft was constructed via a portoportal anastomosis. The VSFF, a composite vascularized allograft of a flap from the donor's radial forearm to the recipient's left forearm, was created as a tool to monitor for rejection [13,14]. The VSFF was procured from the same donor as the intestinal graft. A 10 × 5 cm elliptoid composite skin island flap was marked in the territory of the radial artery (RA) of the donor. The incision was deepened to include the subcutaneous tissue, fascia, cephalic vein, lateral cutaneous nerve of forearm, and the RA with its vena commitantes (VC). This block of tissue was then flushed with cold preservative solution and transported without freezing. The donor site skin was closed directly.

Under a tourniquet, the recipient's nondominant arm was prepped and an incision made over the ulnar artery (UA) axis in the mid forearm. The incision was taken down to the artery and its VC. The VSFF was vascularized via a run-through anastomosis between the donor RA and the recipient's UA. The outflow was between the donor and recipient's VC, and cephalic vein to basilic vein. The nerve was coapted to a branch of the medial cutaneous nerve of the forearm. The skin was inset longitudinally on the forearm of the recipient.

Histology confirmed a well-differentiated G1 (Ki-67 $<1\%$) multifocal SB NET (7 nodules, the largest 11 mm in size) with lymph node metastases, 1 of them a 120-mm mesenteric mass surrounding the mesenteric vessels and in contact with the duodenum and the pancreas. The disease was staged as pT3 N1 M0 L1 V0 R0. There was strong positive immunostaining with chromogranin, synaptophysin, and CD56, focal staining with CK19, and no staining with PPP, gastrin, glucagon, insulin, and somatostatin.

The induction immunosuppression (IS) consisted of Campath 30 mg intravenously within 6 hours after reperfusion and repeated 24 hours later. The reperfusion of the organs was covered with 500 mg of methylprednisolone. The maintenance IS was based on tacrolimus (trough levels 8–12 ng/mL). The postoperative course was free of any morbidity. Two months after transplantation, the appearance of a maculopapular rash on the skin of the sentinel flap was considered to be rejection and was biopsied. The biopsy was interpreted using the Banff 2007 Working Classification of Skin Containing Composite Tissue Allograft Pathology [15] and confirmed acute rejection. A concurrent endoscopy and biopsy of the visceral intestine were routinely done, and the results from the biopsies of intestine and skin were correlated. At the same time, a small bowel transplant biopsy still showed normal findings. After treatment with 3 pulses of 500 mg methylprednisolone and tacrolimus topical cream, the macroscopic appearance of the skin graft returned to normal. Furthermore, the patient was commenced on 10 mg of oral prednisolone in addition to his tacrolimus. In January 2014, he underwent an uneventful reversal of his ileostomy.

At the last follow-up 21 months post-transplant, he is asymptomatic on tacrolimus and oral prednisolone. He has never demonstrated any rejection in his bowel and is on full enteral nutrition, maintaining his weight and back to full physical activity. His serum chromogranin A and B are within normal ranges (Fig 3), as is his urinary 5-HIAA. There is no evidence of disease recurrence on imaging, including CT and ^{68}Ga-DOTATATE PET/CT. There are plans to add everolimus to his immunosuppressive regimen and lower his tacrolimus dose to achieve trough levels between 3–5 ng/mL.

DISCUSSION

Neuroendocrine tumors metastatic to the liver account for a generally accepted indication for liver transplantation. Although the results were rather dismal as liver transplantation

Table 1. Published Series of Multivisceral Transplantation Including Neuroendocrine Tumors as an Indication

Author	Year	Patients With NET in Cohort (n)	NET Patients With Liver Metastases (n)	Primary Tumor Location/Type	Survival	Recurrence
Tzakis [10]	2005	2/100	NS	Carcinoid, VIPoma	1 death at 24 mo (recurrence)	1 (24 mo post-Tx)
Olausson [23]	2007	5/5	5	Pancreas	2 pts died within 4 mo post-Tx, 1 death at 27 mo	2pts, 25 mo and 48 mo post-Tx
Gedaly [22]	2007	13/13	13	NS	OS: 80% at 1 y, 64% at 3 y, 48% at 5 y*	23% at 1 y, 50% at 3 y, 68% at 5 y*
Mangus [9]	2013	4/95	4	Insulinoma, gastrinoma, carcinoid, VIPoma	10 mo (carcinoid), alive at 40 mo (gastrinoma)	10 mo (carcinoid) and 23 mo (gastrinoma) post-Tx
Varkey [24]	2013	6/20	6	Pancreas	67% at 2 y	100%

Abbreviations: NET, neuroendocrine tumor; mo, months; y, year; pts, patients; Tx, transplant; NS, not stated; OS, overall survival; VIP, vasointestinal peptide.
*Results are combined with those obtained from isolated liver transplantation.

was first implemented in the treatment of patients with advanced NET, identification of strict selection criteria for transplantation, refinement of surgical techniques, better monitoring of transplanted patients, and improved immunosuppressive regimens have yielded 3- and 5-year overall survivals ranging from 57% to 77% and 33% to 90%, respectively, in the recent series [16–21]. The overall outcomes are encouraging and comparable to those achieved in hepatocellular carcinoma. Nevertheless, recurrence rates as high as 50% to 90% at 5 years represent the Achilles heel of the concept, necessitating novel neoadjuvant and adjuvant regimens [22]. The role of multivisceral transplantation for neuroendocrine liver metastases is discussed more controversially. Some centers report encouraging overall survival results comparable to those achieved in NET patients undergoing isolated liver transplantation [9,22,23]. Others consider the indication for multivisceral transplantation in this scenario debatable and call for caution [24].

Not more than 30 ITx and MVT for NET—the vast majority of them of pancreatic origin—have been reported worldwide [9,10,20,22–24] (Table 1). Well-documented cases of ITx for SB NET have not been described, and there are no data available on post-transplant oncologic outcome specifically for this subgroup of NET. Of note, other patients with NET requiring MVT had diffuse liver metastases in addition to their primary disease. In the Indiana University series, over 8 years, 10 patients with nonresectable NET with metastasis to the liver received a multivisceral graft. The recurrence rate was 20% and overall survival was 80% [9, personal communication].

Herein, we report a case of a patient with SB NET with extensive mesenteric lymph node metastases not amenable to conventional surgical approaches who underwent modified liver-free multivisceral transplantation. The surgical principle consisted of 2 distinct components. These included radical clearance of the macroscopic tumour by exenteration of the abdominal viscera, with microscopic lymphatic clearance in the aortocaval groove, followed by restoration of the abdominal anatomy and physiology with an MMVT. In addition, a VSFF was used to aid in the immune monitoring of the visceral graft, the rationale being that it would help the physician to distinguish the cause of any bowel dysfunction in the post-transplant course from an infective cause (no preceding rash on the VSFF) as opposed to an immunologic cause (preceding rash on VSFF). The histology of bowel dysfunction from an infective cause may mimic that of rejection, yet the therapy is diametrically opposite. Furthermore, in a patient with a background of an NET, any attempts of "tailoring" the IS would be desirable [25].

Liver metastases and mesenteric lymph node metastases have been demonstrated to be independent prognostic factors for survival in patients with SB NET. In the largest reported series on the effect of surgery on the outcome of SB NET, 5- and 10-year overall survival was 77% and 52%, respectively, after radical resection of mesenteric lymph node metastases, compared to 65% and 38%, respectively, if mesenteric lymph node disease remained [2]. Furthermore, a median survival of 9.92 years after resection of locoregional disease compared to 4.68 years when no such resection took place in a group of patients with SB NET and liver metastases has been reported [26].

Our patient presented with a multifocal SB NET with nonresectable metastatic mesenteric tumor burden at the initial diagnosis of his disease. The timing of transplantation was a matter of a pro and con debate regarding 2 options: either exenteration of the small intestine and the mesenteric mass followed by transplantation at a later date, or an "all-in-one" approach. The first approach would render the patient with an ultrashort gut and difficulties with managing an ultrashort stoma and would also put his liver at risk from rapid deterioration due to the effects of total parenteral nutrition. The second option would not give us a chance to see the effect of radical cytoreductive surgery without immunosuppression on disease progression. If hepatic micrometastases were present at that time, these may have become evident at a later date due to the immunosuppression. As undetected micrometastases were our main concern and the tumor showed high expression of somatostatin receptors on imaging, the decision was made to offer the patient ^{177}Lu-DOTATATE PRRT as a first step therapy with the potential to target macro- and microdisease before proceeding with the second step of the aforementioned "all-in-one" approach.

To our knowledge, this is the first description of a case in which transplant techniques were used to achieve radical clearance of an NET and restoration of the abdominal

anatomy and physiology with concurrent implementation of an immunological tool (VSFF) to tailor the postoperative IS. We believe that the novelty of this surgical approach is enhanced by the use of neoadjuvant PRRT.

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