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CASE REPORT

A Tumultuous Journey of Metastatic Pancreatic Neuroendocrine Tumor with Carcinoid Syndrome

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Abstract

A 25-year-old woman presented with metastatic pancreatic neuroendocrine tumor with carcinoid syndrome. She was refractory to octreotide and did not respond well to chemotherapy. Although surgical debulking remains the primary approach for managing these tumours, it entails inherent risks, including potentially exacerbating carcinoid syndrome. We strategically delivered the one Peptide Receptor Radionuclide Therapy cycle before tumor debulking, a decision that yielded a remarkable response, stabilizing her condition.

Key words: pancreatic neuroendocrine tumor, metastatic, octreotide refractory, peptide receptor radionuclide therapy, norepinephrine

INTRODUCTION

Pancreatic neuroendocrine tumors (pan-NETs) present a formidable challenge in clinical practice, particularly when metastatic. We present the case of a patient with metastatic pan-NET, whose clinical course and management were determined after thorough deliberation and discussion within the framework of a multidisciplinary team.

CASE

A 25-year-old woman was doing well until 2019 when she noticed facial flushing followed by dry cough, vomiting and diarrhea that lasted for 4-5 hours, suggestive of carcinoid syndrome. These episodes happened 3-5 days a week. A computed tomography (CT) scan of the abdomen was done, which showed a well-defined heterogenous arterial enhancing mass of 7.2 x 5.3 cm in the body and tail of pancreas suspicious of NET with metastasis to the liver, periportal lymph nodes and T10 vertebra, as shown in Figure 1. Laparoscopy guided biopsy of pancreatic mass revealed a well-differentiated Grade 2 NET with MIB-1 index of 12%. She was started on a monthly injection of octreotide LAR 30 mg. However, her symptoms recurred 18 days after treatment. After medical oncology consultation, everolimus was added to octreotide. Her symptoms were well controlled for almost a year, however, she began experiencing carcinoid syndrome episodes again. Everolimus was discontinued, based on its waning efficacy. Repeat liver biopsy showed a MIB-1 index of 30%, suggestive of tumour progression to Grade 3, and O6-Methylguanine-DNA Methyltransferase (MGMT) staining was positive.

She underwent a successful transarterial embolization (TAE) of the liver via the right hepatic artery, which precipitated a carcinoid crisis. Considering the higher grade of the tumour and MGMT methylation status, she was given sunitinib, temozolomide and capecitabine. However, these were discontinued after four cycles as her quality of life did not improve.

At this point, she transferred to our institution and had ^{18}Fluro deoxyglucose positron emission tomography (^{18}FDG-PET/CT) and ^{68}Ga DOTATATE PET/CT done (Figure 2). Following the scan, she developed a carcinoid crisis that progressed to acute kidney injury (Figure 3). She was put on octreotide infusion, which was gradually increased to 200 mcg/hour, and she recovered over 3 days. However, she suffered two more crises within a week despite being on daily short-acting octreotide. A multi-disciplinary team (MDT) comprising experts in Surgical-gastroenterology, Medical-Oncology, Endocrinology and Nuclear Medicine was constituted to develop a comprehensive management protocol. It was decided that one cycle of peptide receptor radionuclide therapy (PRRT) would be given, followed

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by surgical debulking and three more cycles of PRRT. Lu^{177} DOTATATE 150 mCi was given. She responded well after the first PRRT and successfully underwent a repeat TAE of the right hepatic artery two weeks later. The following week, she was taken for surgery with short-acting octreotide infusion started 24 hours prior to the procedure. Despite that, several carcinoid spells occurred during tumour manipulation. During resection of liver metastasis, she developed profound hypotension (70/40 mm Hg). She was stabilized with noradrenalin infusion, and pancreatic masses were removed (Figure 4). After ligating the pancreatic vessels, her blood pressure improved significantly, indicating no release of hormonal mediators further into the circulation. At the end of surgery, both octreotide and noradrenalin were stopped. She has not developed any further episodes of carcinoid crisis following surgery, and she has subsequently received three cycles of PRRT. A follow-up DOTATATE scan showed evidence of metastasis only in the T10 vertebra and periportal lymph nodes, as depicted in Figure 5. She remains stable and

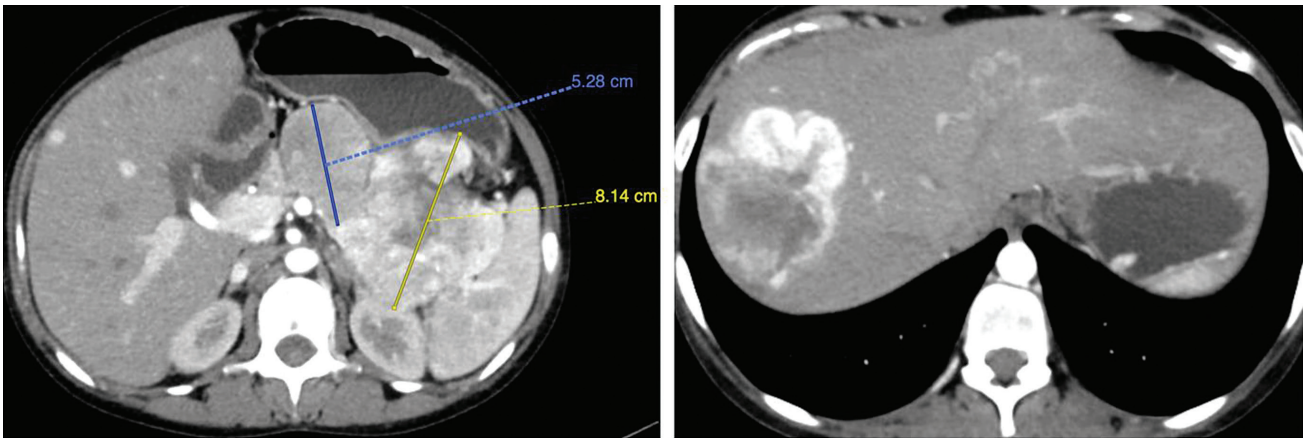

Figure 1. Triphasic CT shows lobulated, heterogenous, hyperenhancing partly exophytic focal lesion with central hypodense area with necrosis without calcification involving distal body and tail of pancreas. An irregular hyperenhancing focal lesion with central necrosis noted in segment 7/8 of liver. Few tiny well defined hyperattenuating lesions also noted in segments 6 and 4.

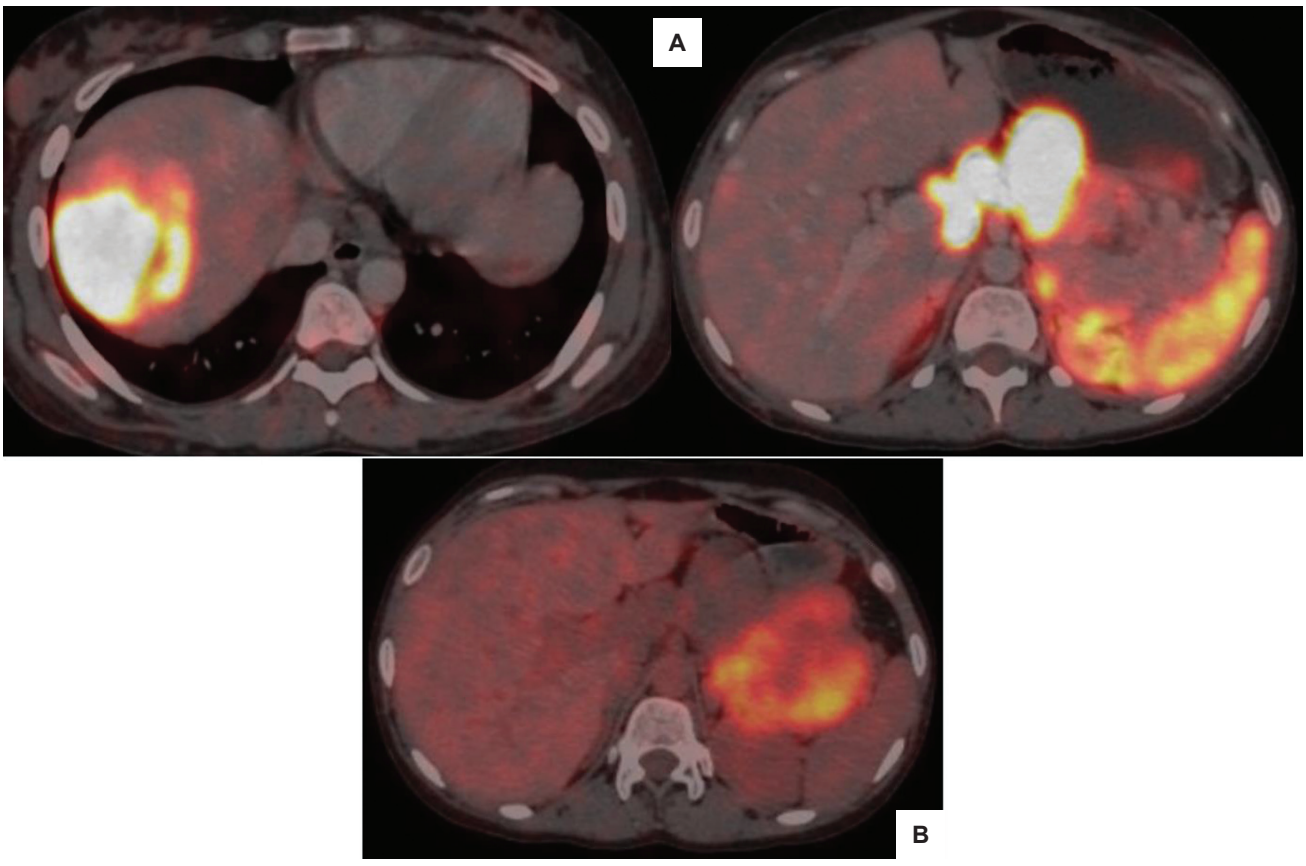

Figure 2. (A) ^{68}Ga DOTATATE PET/CT image before surgery shows avid uptake seen in segment 8 of liver and pancreatic head and body; **(B)** ^{18}FDG-PET/CT image before surgery shows uptake is present in mass in tail of pancreas.

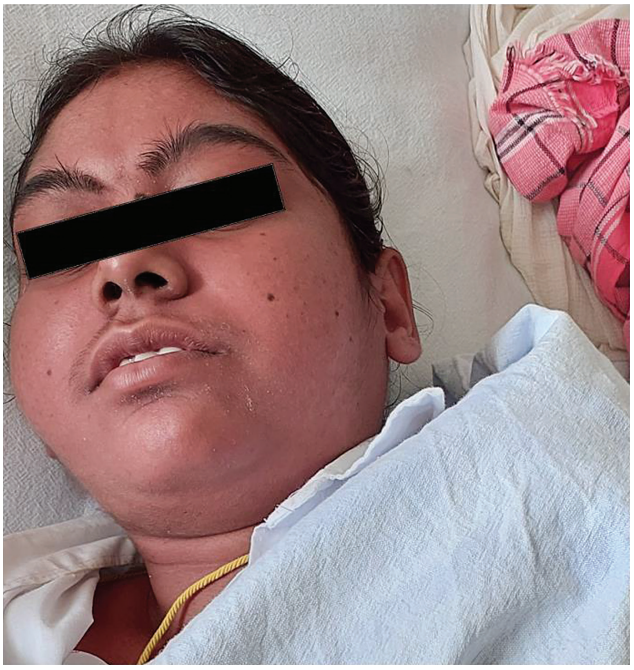

Figure 3. Clinical picture of carcinoid syndrome showing with facial flushing and erythema.

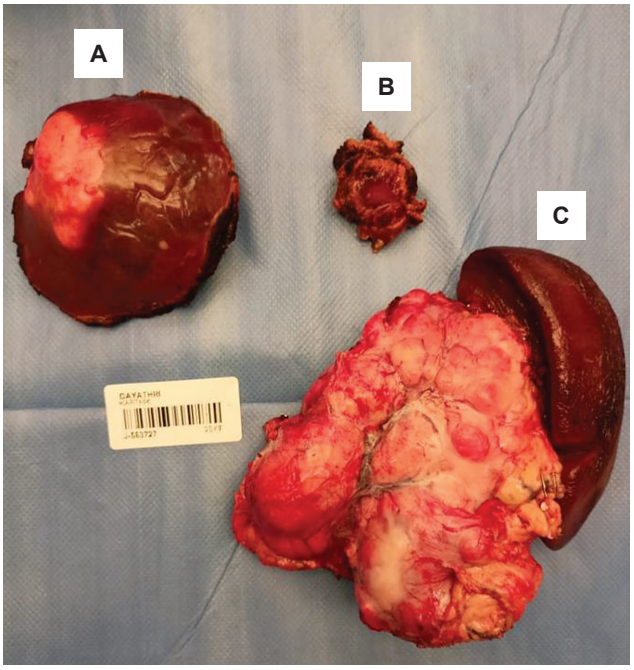

Figure 4. She underwent non anatomical resection of liver. **(A)** Liver segment 8; **(B)** Liver segment 2; **(C)** Distal pancreatico-splenectomy specimen.

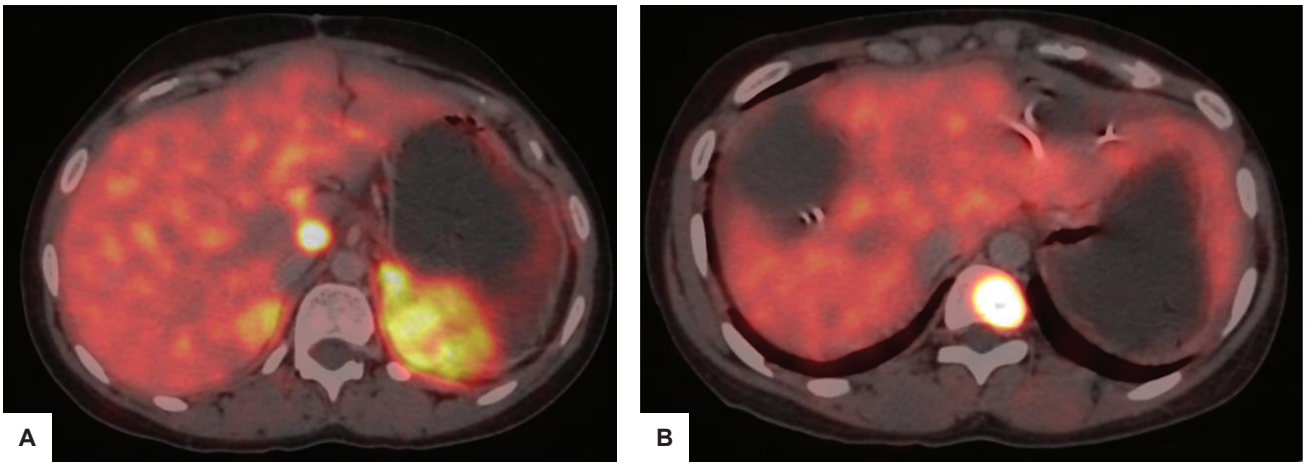

Figure 5. Follow up ^{68}Ga DOTATATE PET/CT scan after surgery. **(A)** Scan shows avid uptake in Periportal lymph node; **(B)** Avid uptake in D10 vertebra.

asymptomatic. The timeline of treatment is shown in Figure 6.

DISCUSSION

Pancreatic NETs present formidable obstacles to curative surgical interventions because they are often diagnosed in advanced stage with widespread metastases. Somatostatin analogues (SSAs) emerge as invaluable palliative agents, mitigating hormonal hypersecretion and reducing tumor burden. Therefore, the European Neuroendocrine Tumor Society advocates its use as initial therapy. However, our patient gradually deteriorated despite being on octreotide. PRRT and targeted molecular therapies are typically reserved for these SSA refractory cases.[1] At the molecular level mTOR pathway stimulates cell growth and it is aberrantly activated in NETs. Everolimus exerts antineoplastic effect by inhibiting the mTOR pathway. The latest European Society for Medical Oncology guidelines endorse the use of everolimus in Pan-NETs considering its synergistic benefit with SSAs.[2] Although she initially responded to this combination for almost a year, recurrence happened due to exhaustion of the antineoplastic effect of everolimus, which is a known fact. Long-term disease control seems achievable by integration of surgery and targeted molecular therapies. Surgery and PRRT can be combined in various clinical situations, such as in neoadjuvant settings for initially unresectable NETs or adjuvant settings to reduce recurrence risk following major surgery. PRRT is a targeted radiation therapy that

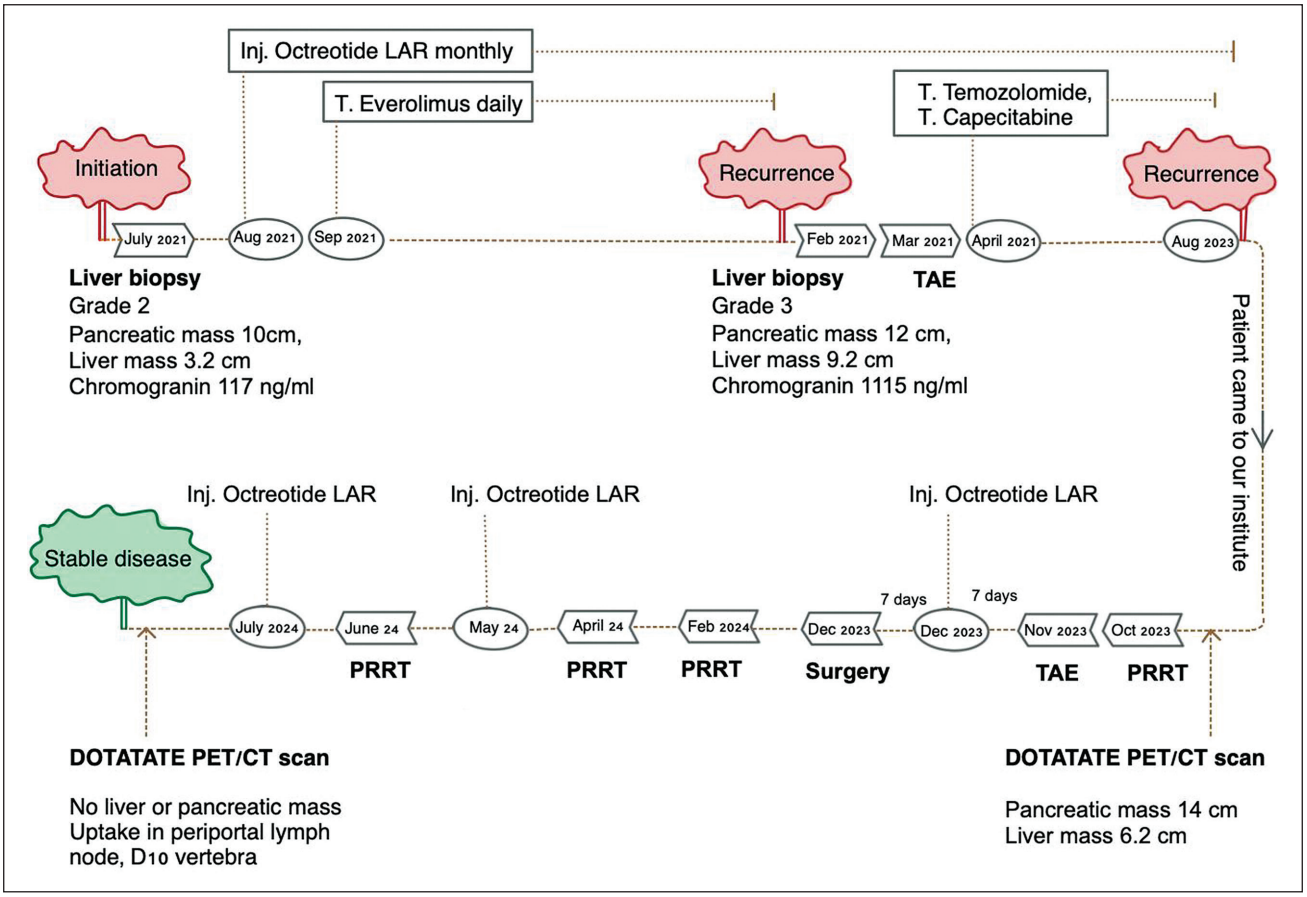

Figure 6. Timeline of events.

delivers radiation to the tumor precisely by delivering a radionuclide chelated to a peptide that targets Somatostatin receptor (SSTR), which is overexpressed on the surface of NET cells. She had a high disease burden when she came to our institute. Although the size of liver metastasis decreased from 9.2 cm to 6.6 cm following TAE, she was symptomatic with recurrent carcinoid spells. Our MDT found that the tumors exhibited a low NET-PET score of P2 (Figure 2) which could explain the failure of chemotherapy that she received outside. Despite the high grade (Grade 3) of the tumors, significant DOTATATE uptake was observed, favouring PRRT over chemotherapy. According to Bertani et al., patients who had surgery as first line treatment had a better median overall survival (112 vs 65 months) compared to patients who just received PRRT.[3] So, tumor debulking was identified as crucial to maximise the effectiveness of PRRT. Moreover, debulking liver metastasis by 70% is helpful for palliation of carcinoid symptoms.[4] However, surgical debulking entails inherent risks, including potentially exacerbating carcinoid syndrome. Two of the six patients in a Polish series with incurable NET had excision following PRRT-induced tumor size reduction.[5] Similarly, an Italian series revealed that the neoadjuvant PRRT group had a much lower incidence of nodal metastases and significantly longer progression-free survival than the group who underwent surgery as first line therapy.[6] PRRT also causes fibrosis, which lowers the chance of a pancreatic fistula formation following surgery. Hence, we strategically gave her one PRRT cycle before tumor debulking which stabilized her condition significantly. She was able to undergo surgery without major complications. The other three cycles of PRRT were given after surgery to improve outcomes. This kind of combination surgery and PRRT technique has been described in few specialized centers with small cohorts with encouraging results; nonetheless, to definitively evaluate this intriguing treatment approach, a randomized controlled study comparing neoadjuvant PRRT with adjuvant PRRT is essential.[7]

One more interesting observation was her hemodynamic improvement with norepinephrine. Since sympathomimetic drugs may paradoxically worsen hypotension by triggering further release of peptides from tumors, vasopressin or selective α1 agonist phenylephrine are the preferred vasopressors in this context. She showed no response to these treatments; but responded well through the administration of norepinephrine.

CONCLUSION

Metastatic pan-NET is a rare entity that has no clear treatment algorithm. Surgical debulking remains the mainstay in managing pan-NET, even in the presence of liver metastases. To mitigate the risk of carcinoid crisis during tumor manipulation the option of pre-surgery single-cycle PRRT can be considered, followed by three

subsequent cycles of PRRT to address any residual or micro-metastases. SSAs play a role in preventing crises, yet their efficacy in treating hemodynamic crises is limited. In such cases, norepinephrine serves as a primary treatment modality. This case illustrates successful individualized therapeutic paradigm in managing a challenging metastatic pan-NET.

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Ethical Consideration
Patient consent form was obtained before manuscript submission.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
SG: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data Curation, Visualization**; SK:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Writing – review and editing, Visualization, Supervision, Project administration; **KR:** Methodology, Validation, Investigation, Resources, Writing – review and editing; **NP:** Methodology, Validation, Investigation, Resources, Writing – review and editing, Project administration; **DN:** Validation, Formal analysis, Resources, Writing - review and editing, Project administration; **JS:** Supervision, Project Administration.

Authors Disclosure
The authors declared no conflict of interest.

Data Availability Statement
No datasets were generated or analyzed for this study.

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