Complete and Sustained Response After Peptide Receptor Radionuclide Therapy in a 66-Year-Old Filipino Male with Metastatic Pancreatic Neuroendocrine Tumor: A Case Report

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ABSTRACT

The introduction of peptide receptor radionuclide therapy (PRRT) to the Philippines has allowed for novel approaches in the management of neuroendocrine tumors (NETs). This case report details the management of a 66-year-old Filipino man diagnosed with metastatic pancreatic NET after biopsy and staging with Ga-68 DOTATATE PET-CT. After poor response to somatostatin analogue therapy, the patient was advised to undergo PRRT. Upon completing four cycles of PRRT with Lu-177 DOTATATE, the metastatic hepatic lesions showed resolution and the pancreatic tail tumor exhibited regression, allowing the patient to undergo surgical resection of the primary tumor. On follow-up, he was declared to be in remission with good quality of life and no imaging evidence of recurrence. The case underscores the diagnostic and therapeutic utility of radiolabeled somatostatin analogues along with the importance of a multidisciplinary approach in the management of an initially unresectable metastatic pancreatic NET

***Keywords**: peptide receptor radionuclide therapy, metastatic pancreatic neuroendocrine tumor, Ga-68 DOTATATE, Lu-177 DOTATATE*

INTRODUCTION

The emergence of novel radiopharmaceuticals for theranostics has launched countless possibilities in the management of various malignancies. Although several radionuclides and biomolecules are presently being studied for the targeted delivery of radiation to tumors of diverse pathologies, the burgeoning era of theranostics has primarily been led by peptide receptor radionuclide therapy (PRRT) for neuroendocrine tumors (NETs), closely trailed by prostate-specific membrane antigen radioligand therapy for metastatic castrate-resistant prostate carcinoma [1].

By exploiting the molecular biology of NETs that overexpress somatostatin receptors (SSTR), PRRT selectively delivers therapeutic doses of radiation to target neuroendocrine tissues using radionuclides, such as Yttrium-90 (Y-90) or Lutetium-177 (Lu-177), attached to somatostatin analogues.[2] Decades of research and development have contributed to the vast literature supporting the use of radiolabeled somatostatin analogues for therapy. From the initial studies using Iodine-123 Tyr3-octreotide (TOCT) in 1987 to the advent of Indium-111 pentetreotide along with Y-90 and Lu-177 tetraazacyclododecanetetraacetic acid (DOTA)-Tyr3-octreotide (DOTATOC) in the 1990s to the first clinical application of Lu-177 DOTA-Tyr3- octreotate (DOTATATE) in 2000,[3] PRRT has undergone significant growth in the preceding decades. This growing bulk of clinical evidence eventually culminated in the NETTER-1 trial, which demonstrated the efficacy of adding PRRT to somatostatin analogue therapy for gastroenteropancreatic (GEP) NETs with a markedly higher response rate and progression-free survival at 20 months compared to somatostatin analogue therapy alone [4]. This was eventually followed by the US FDA approval of Lu-177 DOTATATE (Lutathera) [5] and its integration into the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology in 2022 as a front-line treatment option for metastatic GEP NETs alongside somatostatin analogue therapy, immunotherapy, cytotoxic chemotherapy, and other local therapies directed to the liver and/or bones [6].

Although much of the existing literature has come from high volume centers in Europe and Oceania, theranostics

has slowly found its foothold in developing countries in recent years. Case reports detailing local experience with PRRT have shown its utility in eliciting response and establishing disease control in various NETs.[7,8] The following case report will delve into the use of PRRT as a neoadjuvant treatment for metastatic pancreatic NET in a tertiary referral institution in the Philippines. The objective of the study is to underscore the growing role of PRRT and SSTR positron emission tomography (PET) - computed tomography (CT) in the management of NETs in the Philippine setting.

CASE REPORT

A 66-year-old Filipino man initially presenting with diarrhea underwent work-up with ultrasound and MRI, which revealed a 2.5 x 3.8 cm mass at the pancreatic tail. Fine needle aspiration biopsy of the aforementioned mass revealed cytomorphologic findings suggestive of a low-grade neoplasm. Immunohistochemical testing showed that the samples were positive for synaptophysin and chromogranin, but negative for anti-trypsin and carbohydrate antigen 19-9, supporting the diagnosis of a pancreatic neuroendocrine neoplasm; however, the paucity of cells in the sample precluded evaluation of the Ki-67 index, which is needed to characterize the degree of tumor differentiation.

In lieu of performing another biopsy, the medical oncologist requested for a Ga-68 DOTATATE PET-CT scan (Figure 1.A), which showed SSTR overexpression in the inhomogeneously enhancing pancreatic tail tumor with a maximum standardized uptake value (SUVmax) of 31.3. The scan also revealed increased DOTATATE uptake in an inhomogeneously enhancing nodule at hepatic segment VI, measuring 2.1 x 2.5 cm, along with several smaller DOTATATE-avid foci in both hepatic lobes, with an SUVmax of up to 38.5. Non-specific DOTATATE uptake was likewise noted in the prostate gland, attributed to benign prostatic hyperplasia. Although the left adrenal gland was nodular on CT, its DOTATATE uptake appeared physiologic. Overall, the SSTR overexpression in the primary pancreatic lesion and hepatic metastases suggested a well-differentiated (WHO grade I) neuroendocrine tumor, and the patient was started on long-acting somatostatin analogue injections.

After four months of somatostatin analogue therapy, a repeat whole body Ga-68 DOTATATE PET-CT scan (Figure 1.B) was requested to evaluate treatment response. The pancreatic tail mass demonstrated a 176.7% interval increase of DOTATATE uptake, now with an SUVmax of 86.6. Slight increase by 8.6% of DOTATATE uptake was also seen in several of the hepatic nodules, with an SUVmax of up to 41.8, with concurrent progression in size and number on CT.

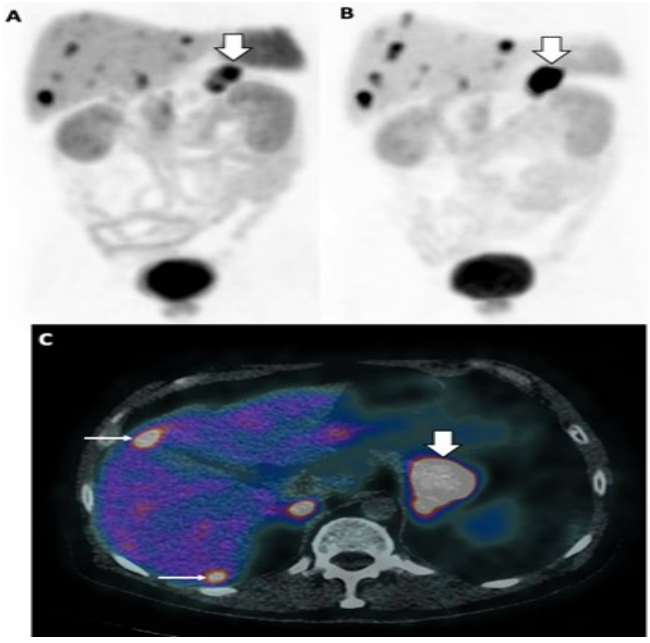

FIGURE 1. Maximum intensity projection (MIP) images of the Ga-68 DOTATATE PET-CT scans on baseline dated September 2018 (A) and after four months of somatostatin analogue therapy dated January 2019 (B) showing interval increase of SSTR expression in the pancreatic tail tumor (thick arrow). Fused PET-CT image (C) shows DOTATATE-avid lesions in the pancreatic tail (thick arrow) and liver (thin arrows).

With evidence of progressive disease based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 after somatostatin analogue therapy, the patient was advised by his Filipino and Singaporean oncologists to undergo PRRT and was referred to the nuclear medicine service. Initial evaluation showed acceptable baseline hematologic, renal, and hepatic functions. The patient then underwent a total of four cycles of PRRT over the course of eight months. In each cycle, anti-emetic and anti-inflammatory medications were given shortly before therapy. Gelofusine was administered for renal protection and adequate hydration was ensured orally and intravenously. A diuretic was given after every therapy to reduce the radiation dose delivered to the kidneys.

On the first cycle of therapy, 6.5 gigabequerels (GBq) of Lu-177 DOTATATE was administered. The 48-hour post-therapy scan showed Lu—177 DOTATATE uptake in the

pancreatic tail tumor and the hepatic metastases, similar to the findings of the prior (January 2019) Ga-68 DOTATATE PET-CT scan. Two months after the first cycle of therapy, the patient underwent a repeat Ga-68 DOTATATE PET-CT scan (Figure 2.A), which demonstrated significant decrease of DOTATATE uptake by 71.6% in the pancreatic tail tumor, now with an SUVmax of 24.6. Resolution of DOTATATE uptake was noted in all of the hepatic metastases with corresponding morphologic regression to resolution, the largest of which measures 1.3 x 1.1 cm.

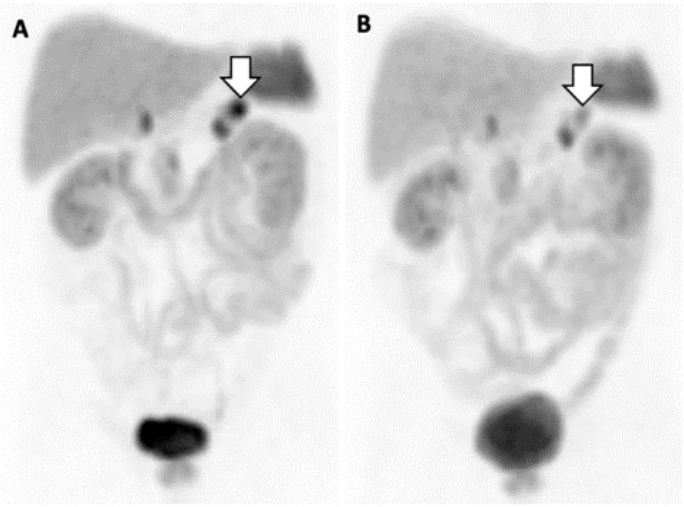

FIGURE 2. Maximum intensity projection (MIP) images of the Ga-68 DOTATATE PET-CT scan after the first cycle dated March 2019 (A) and after the fourth cycle of PRRT dated December 2019 (B). The previously noted DOTATATE-avid hepatic lesions in Figure 1 have resolved after the first cycle, while gradual regression of DOTATATE uptake is seen in the pancreatic tail tumor (thick arrow).

In the absence of clinical or imaging evidence of residual metastatic disease, the patient was referred to a hepatobiliary surgeon for laparoscopic distal pancreatectomy with left adrenalectomy, frozen section biopsy and wedge resection of a liver nodule that was seen intraoperatively. The histopathologic findings reported a low-grade well-differentiated (WHO grade I) pancreatic NET. Immunohistochemical stains were positive for synaptophysin (Figure 3.A), chromogranin (Figure 3.B), and neuron specific enolase (NSE) (Figure 3.C). Ki-67 index (Figure 3.D) was 1.2% and mitotic count was < 2 mitosis/10 hpf, consistent with a well-differentiated pathology. The nodular left adrenal gland was negative for tumor, while the resected liver nodule was shown to be benign hepatic parenchyma with steatosis.

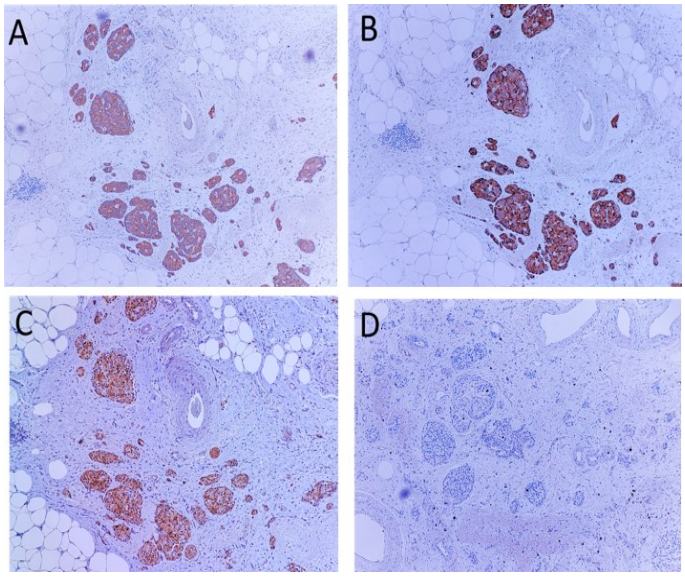

FIGURE 3. Immunohistochemical stains (20x magnification): (A) synaptophysin, (B) chromogranin, (C) neuron specific enolase, and (D) Ki-67

The patient then had his second (6.2 GBq), third (6.7 GBq) and fourth (6.5 GBq) cycles of Lu-177 DOTATATE therapy every three months, which were well-tolerated without impairment of hematologic, renal, and hepatic functions. The post-Lu-177 therapy scans noted decreasing DOTATATE avidity in the pancreatic tail tumor with no new DOTATATE-avid lesions detected. Two months after the fourth cycle of Lu-177 DOTATATE therapy, a repeat Ga-68 DOTATATE PET-CT scan (Figure 2.B) was done for treatment response evaluation. The scan showed further regression of SSTR expression by 52.4% in the stable-sized pancreatic tail tumor, now only with an SUVmax of 11.7. All hepatic nodules have likewise resolved on CT.

On follow-up Ga-68 DOTATATE PET-CT scan (Figure 4) two years after surgery, no tumor recurrence was noted and no SSTR-overexpressing hepatic metastases were seen. There was no hematologic toxicity or nephrotoxicity on follow-up laboratory tests. His initial complaint of diarrhea has resolved. At 54 months since the diagnosis, the patient remains asymptomatic with good social and occupational functions including an Eastern Cooperative Oncology Group (ECOG) performance status of 0.

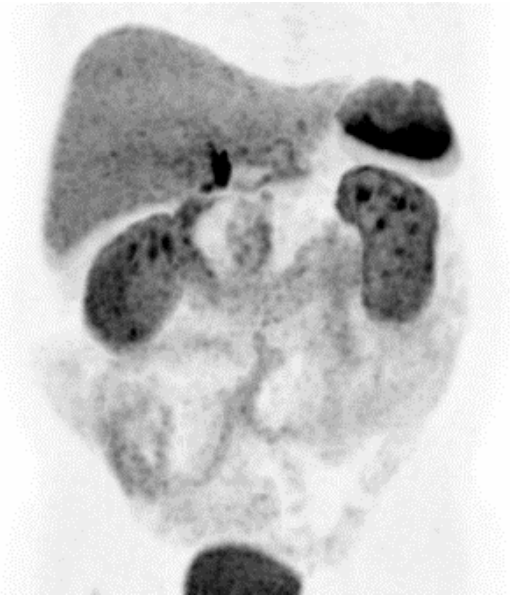

FIGURE 4. Maximum intensity projection (MIP) image of the Ga-68 DOTATATE PET-CT scan 29 months after the last PRRT dated March 2022, s/p laparoscopic distal pancreatectomy with left adrenalectomy

DISCUSSION

Pancreatic NETs make up about 7% of all NETs and less than 2% of all pancreatic neoplasms. Their incidence is less than 1 case per 100,000 people annually, but it has increased in recent years due to improvement in imaging techniques and diagnosis [9]. The 3-to-5-year survival of pancreatic NET patients without hepatic metastasis is 75-99%, but this drastically drops to 13-54% in the setting of hepatic metastasis [10].

Nuclear medicine has long been involved in the management of NETs; however, for several years, this was largely confined to diagnostics. In the aforementioned case, since tissue samples from initial biopsy were insufficient to determine differentiation in the primary lesion, SSTR PET-CT played a critical role as a surrogate "whole body molecular biopsy", as coined by Chan and colleagues [11] and guided patient management by establishing eligibility for therapy, evaluating response, and providing long-term surveillance.

Theranostics expanded the role of the nuclear medicine physician beyond the reading room. Lu-177, with its high energy beta particles and medium energy gamma photons, allows imaging after therapy. Attaching it with a somatostatin analogue enables it to bind to somatostatin receptors in tumor cells directly exposing them to its cytotoxic beta radiation with a maximum particle range of 2 mm. The NETTER-1 trial established the efficacy of adding PRRT to the treatment of GEP NETs and other studies have since shown that PRRT can significantly improve overall survival and considerably decrease tumor burden [4,12,13]. Ultimately, PRRT has the benefit of dramatically improving quality of life [14]. In the patient, PRRT led to regression of the primary tumor and resolution of hepatic metastases, paving the way for definitive treatment in the form of surgery. A few studies have demonstrated the value of PRRT as neoadjuvant therapy, which facilitated resection in a few patients that were initially poor candidates for surgery [15,16,17]. To date, however, this is the first demonstration of the neoadjuvant application of PRRT in the local setting since its introduction to the Philippines in 2018 [7].

Finally, the multidisciplinary team plays an important role in optimizing the management of NETs. After close communication with the pathology service regarding the histopathologic and immunohistochemical findings, the medical oncologist then requested for the appropriate diagnostics and started the patient on somatostatin analogue therapy. Upon recognizing poor response, the medical oncologist then referred to the nuclear medicine theranostician for PRRT. The excellent response to PRRT then allowed the surgical team to successfully remove the tumor, which has since shown no evidence of recurrence after two years.

CONCLUSION

The case has shown that Ga-68 DOTATATE PET-CT can be a valuable tool in the different stages of management and that PRRT with Lu-177 DOTATATE can lead to a marked reduction of tumor burden. The effective use of these modalities radically changed the course of an initially inoperable patient and facilitated surgical resection of the residual tumor. In addition, multidisciplinary team engagement, as demonstrated in this case, can optimize the management of a metastatic well-differentiated pancreatic NET leading to a complete and sustained response with good quality of life for the patient.

ETHICAL CONSIDERATIONS

This report was conducted in adherence to the Principles of the Declaration of Helsinki and the Guidelines of the International Conference on Harmonization-Good Clinical Practice (ICH-GCP), and National Ethical Guidelines for Health and Health-Related Research [18,19].

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