Case Report

8-YEAR SURVIVAL WITH A METASTATIC THYMIC NEUROENDOCRINE TUMOR: EMPHASIS ON REDEFINING "TREATMENT OBJECTIVES" USING "PERSONALIZED" PEPTIDE RECEPTOR RADIONUCLIDE THERAPY WITH ^{177}LU- AND ^{90}Y-LABELED SOMATOSTATIN ANALOGS

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ABSTRACT

Objective: Peptide receptor radionuclide therapy (PRRT) with ^{90}Yttrium (^{90}Y)- and ^{177}Lutetium (^{177}Lu)-labeled somatostatin analogs are the accepted standard of care for treatment of metastatic well-differentiated neuroendocrine tumors (NET) of the midgut. More aggressive NETs (e.g., of mediastinal or thymic origin) require regular follow-up and monitoring after therapy, and individualization is very important from the clinical perspective for improving outcomes and avoiding toxicity, thus improving patient quality of life (QoL).

Methods: We report a case of a 58-year-old female with metastatic thymic NET who was treated with "personalized PRRT."

Results: The patient presented with inoperable mediastinal and pleural metastatic lesions. We treated the patient with ^{90}Y- and ^{177}Lu-labeled somatostatin analogs after positive confirmation of receptor expression on ^{68}Gallium (^{68}Ga)-DOTA^{0}-Phe^{1}-Tyr^{3} octreotide (DOTATOC) positron emission tomography/computed tomography (PET/CT). The patient responded well with no associated toxicity. She had three disease relapses and was treated with PRRT each time. However, disease was always confined to the mediastinum and pleura, with no distant extrathoracic spread. No hematotoxicity or nephrotoxicity was documented.

Conclusion: PRRT, when "personalized" as per disease profile and patient condition, yields better outcome and survival. This case emphasizes the need for such practice in order to improve patient QoL. **(AACE Clinical Case Rep. 2015;2:e131-e135)**

Abbreviations:
DOTATOC = DOTA^{0}-Phe^{1}-Tyr^{3} octreotide; **^{68}Ga** = ^{68}Gallium; **^{177}Lu** = ^{177}Lutetium; **NET** = neuroendocrine tumor; **PET/CT** = positron emission tomography/computed tomography; **PRRT** = peptide receptor radionuclide therapy; **QoL** = quality of life; **SMS-R** = somatostatin receptor; **^{90}Y** = ^{90}Yttrium

INTRODUCTION

The aim of palliative treatment in metastatic cancers is to arrest the spread of disease and keep the patient symptom-free. This is especially true in neuroendocrine tumors (NETs), which are often metastatic at diagnosis. Peptide receptor radionuclide therapy (PRRT) using ^{90}Yttrium (^{90}Y)- or ^{177}Lutetium (^{177}Lu)-labeled somatostatin analogs is an emerging standard of care for treatment of metastatic, well-differentiated NETs of the midgut, as well as pancreatic NETs. Fixed-regimen targeted chemotherapeutic agents are still mainly used; however, individualization of therapy becomes increasingly important to improve outcome and avoid toxicity. Here we present the case of a 58-year-old female with metastatic NET of the thymus who was treated with a "personalized" PRRT approach over 8 years. This regiment repeatedly reduced the tumor mass without causing any adverse effects and improved the patient's quality of life (QoL).

CASE REPORT

This 58-year-old female patient was first diagnosed with a nonfunctioning mediastinal neuroendocrine tumor (NET) in 2002, when she presented with acute onset cough

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and breathlessness. A computed tomography (CT) chest scan detected the primary tumor and demonstrated pleural and pericardial metastases. She underwent palliative R2 resection of a mediastinal mass and subsequent external beam radiotherapy to the mediastinum. She was on interferon therapy from 2004 to 2006 and also received octreotide therapy (Sandostatin LAR™ 30 mg/month) from March 2003 to November 2006. Both surgery and interferon therapy were well tolerated. In 2006, though, she again presented with breathlessness. CT confirmed relapse of the pleural and pericardial metastatic lesions, and she was referred to our center. Restaging by ^{68}Gallium (^{68}Ga)-DOTATOC PET/CT (Fig. 1 *A*) in March 2006 demonstrated multiple somatostatin receptor (SMS-R) positive metastases in the thorax (extensive bilateral pleural and pericardial deposits) (Fig. 1 *B-E*). After ensuring good renal function, she received the first course of PRRT (with 4,000 MBq ^{90}Y-DOTATATE) in March 2006. The patient did not receive octreotide therapy after initiation of PRRT. Serial PET/CT studies (June 2006, September 2006, and March 2007) were performed and demonstrated significant molecular partial remission (in terms of the SMS-R expression), as well as morphological regression of the disease burden (size on CT), with no new findings (Fig. 2 *A-D*). She was further treated with 2 courses of ^{177}Lu-DOTATATE therapy (4,500 MBq in October 2006 and 5,000 MBq in April 2007). Follow-up PET/CT in 2008 (Fig. 3 *A*) showed an excellent treatment response. However, in October 2009, PET/CT showed significant molecular progression of pleural and pericardial disease (Fig. 3 *B*), and the patient was treated again with ^{177}Lu-DOTATATE (6,500 MBq). Follow-up PET/CT once again exhibited partial molecular and morphological responses (Fig. 3 *C*). Due to pleural relapse in November 2011 (Fig. 3 *D*), the patient received an additional cycle of PRRT applying ^{177}Lu-DOTATATE (7,500 MBq). Follow-up PET/CT studies showed stable disease (Fig. 3 *E*) until November 2013, when PET/CT re-established disease progression with multiple pleural deposits (Fig. 3 *F*) that further increased in size and number in May 2014 (Fig. 4 *A-C*). During the entire duration of treatment, her renal function parameters were within normal limits, as documented by tubular extraction rate (TER) on technetium mercaptoacetyltriglycine scintigraphy. Serial 2-dimensional echocardiography studies during the course of disease showed no evidence of myocardial involvement. The patient was clinically unremarkable throughout the entire treatment course, with no deterioration in the QoL assessed by Spitzer Quality of Life Index and good functional status indicated by a 100% Karnofsky Performance Score. She received the seventh PRRT cycle (5,900 MBq of ^{177}Lu DOTATATE) in June 2014 with excellent uptake of the radiopharmaceutical in the pleural and pericardial deposits (Fig. 4 *E*). She is due for her next follow-up visit in December 2014.

DISCUSSION

Mediastinal NETs, particularly those of thymic origin, are relatively rare and more aggressive than other tumor entities (1). These neoplasms have a higher propensity to metastasize to distant sites (2). Fukai et al (3) described a series of 15 patients and reported that metastases occurred in 10 of 13 patients despite local resection, and 6 of them died of distant metastases 5 to 25 months after recurrence. Chemotherapy regimens (e.g., 5-fluorouracil and streptozotocin), as well as novel targeted agents like the mamma-

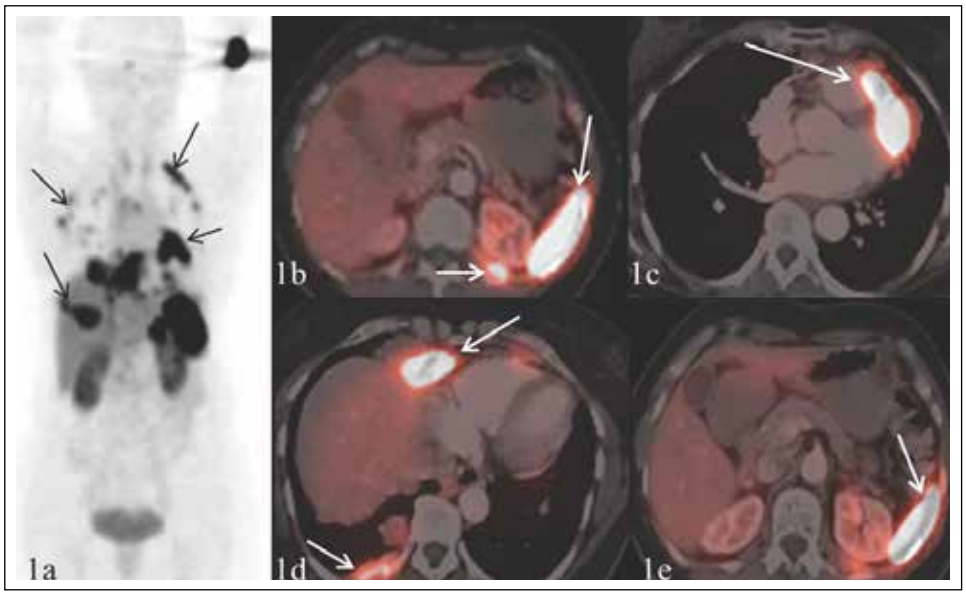

Fig. 1. Maximum intensity projection image showing multiple foci of increased tracer uptake in the thorax (*A*, *arrows*), corresponding to pleural and pericardial metastatic deposits (*B-E*) on axial fused ^{68}Gallium DOTATOC positron emission tomography/computed tomography images.

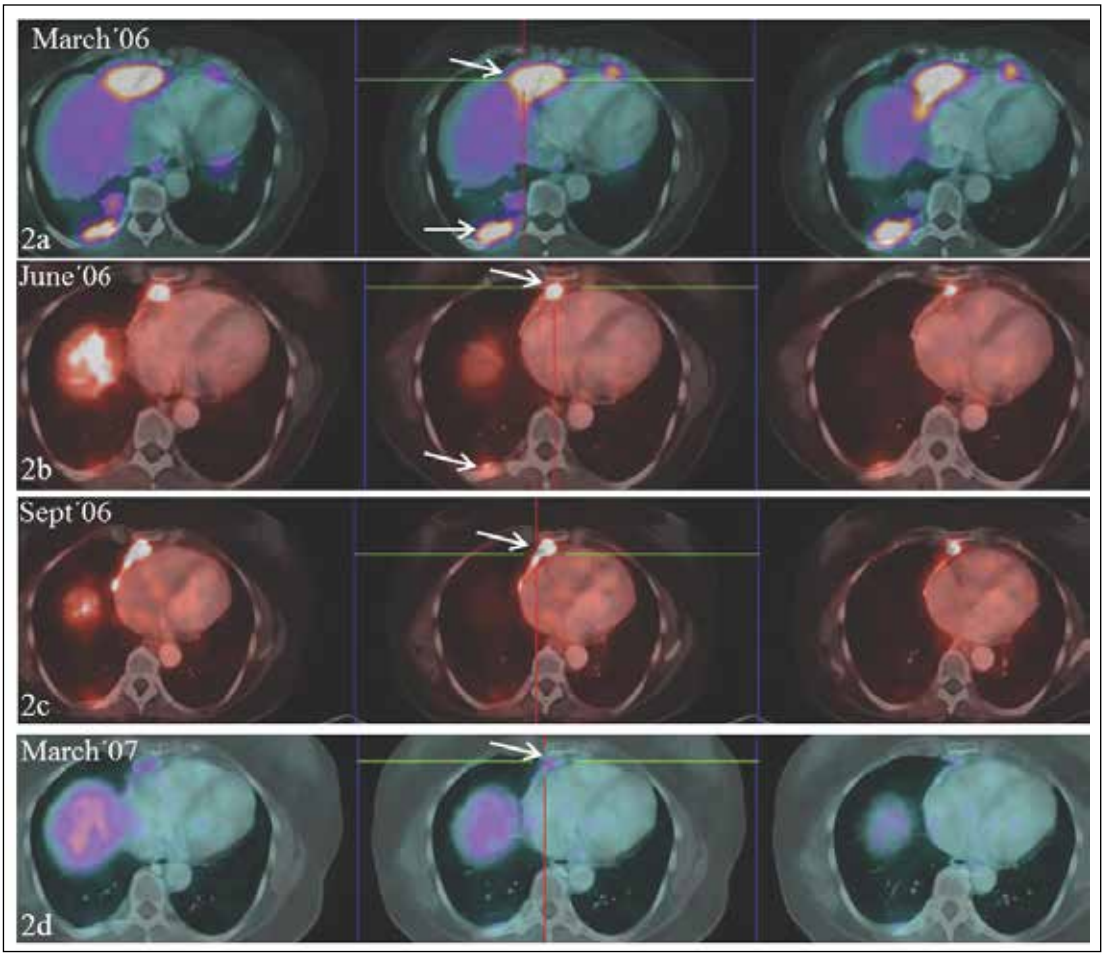

Fig. 2. Serial axial fused ^{68}Gallium DOTATOC positron emission tomography/computed tomography images (March 2006 to March 2007). (*A*) Pericardial and pleural deposits (*arrows*) in the baseline scan in March 2006. (*B*) Received the first PRRT in March 2006, and a partial response was observed in June 2006, with tracer-avid residual pleural and pericardial metastatic deposits (*arrows*). (*C*) Stable disease seen in September 2006 (*arrows*). (*D*) Received the second PRRT in October 2006, and a near complete metabolic and morphological response was seen in March 2007, with a small residual pericardial nodule noted (*arrow*). *PPRT* = peptide receptor radionuclide therapy.

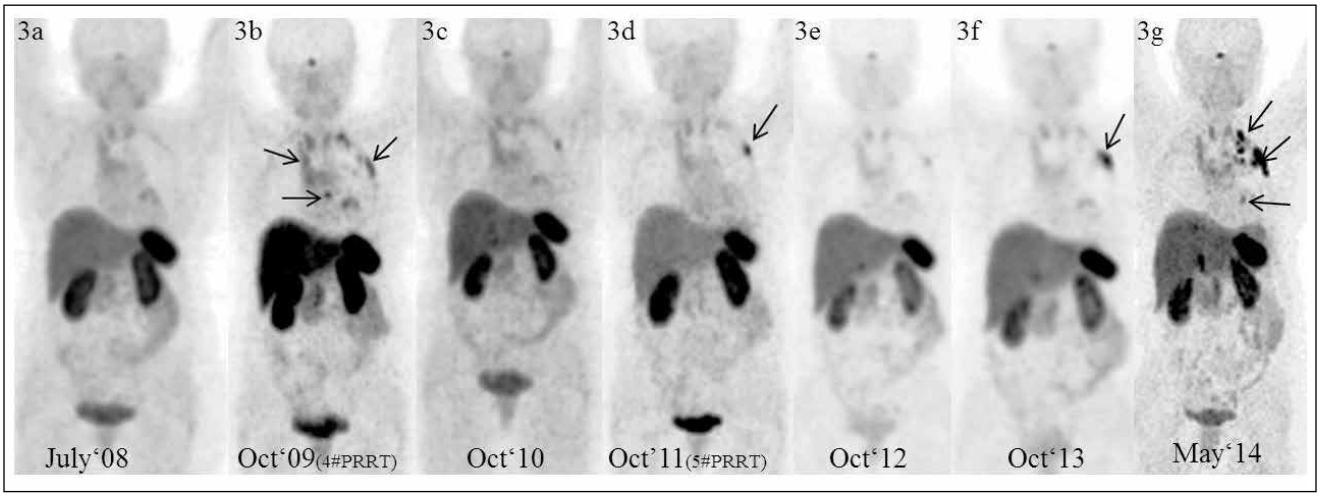

Fig. 3. (*A-G*) Serial MIP images of ^{68}Gallium DOTATOC positron emission tomography/computed tomography studies performed between July 2008 and May 2013 illustrating the "waxing and waning" pattern of disease. Disease relapses (*arrows*) noted in October 2009 (*B*), October 2011 (*D*), and October 2013 (*F*), with disease progression in May 2009 (*G*).

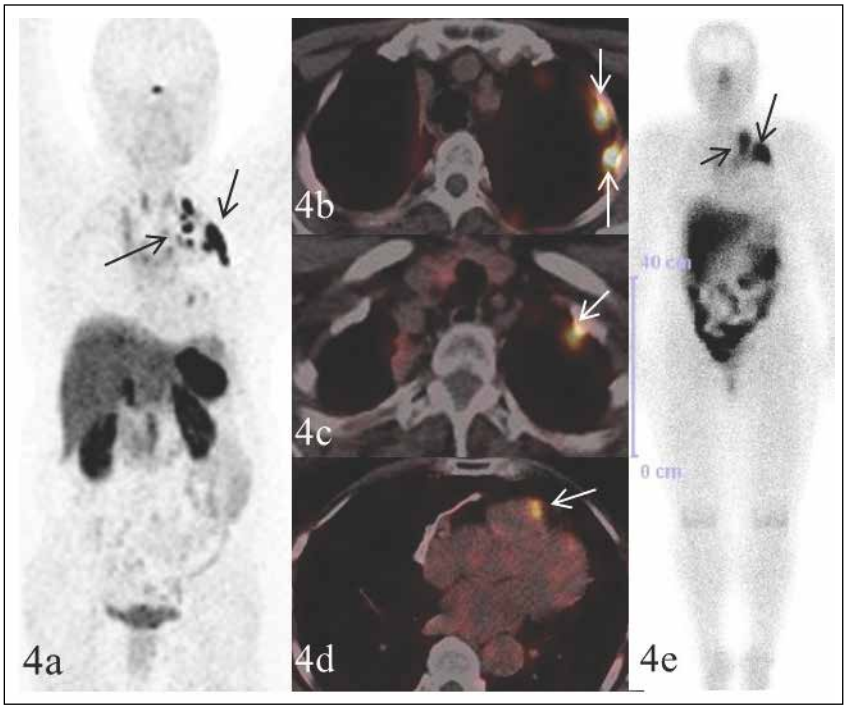

Fig. 4. Maximum intensity projection image (*A*) of ^{68}Gallium DOTATOC positron emission tomography/computed tomography study performed in May 2014, showing multiple tracer foci in the mediastinum, corresponding to pleural and pericardial metastatic deposits on axial fused positron emission tomography/computed tomography images (*B-D*). A post-^{177}Lutetium DOTATATE therapy (June 2014) scan showed tracer uptake in pleural and pericardial metastases.

lian target of rapamycin (mTOR) inhibitor everolimus or the tyrosine kinase inhibitor sunitinib, which are approved for metastatic NET of the pancreas, offer no significant benefit in thymic NET (4). Temozolamide as monotherapy has also been tried, with no great impact on survival (5). PRRT is a treatment option for well-differentiated metastatic SMS-R-expressing gastroenteropancreatic NET, irrespective of previous treatment strategies (6). The available literature on PRRT of mediastinal NET is very limited; van Essen et al treated 2 patients with ^{177}Lu octreotate; 1 showed stable disease, and the other had disease progression (7). With no definite treatment strategy documented in the literature, we followed an individualized approach in the present patient. This involved "personalization" in the sense that the goal was to achieve the maximum "tumor targeting" in the first 3 sequentially administered courses. Hence, we used 1 course of ^{90}Y (particles having a long beta range) and 2 courses of ^{177}Lu (with a range of 2-3 mm), such that the tumor bulk and tiny nodular pleural and pericardial metastases were targeted, respectively. This yielded results as evidence by the patient's ^{68}Ga DOTATOC PET/CT scan performed in March 2007, where there was a near complete metabolic response. Immediately after (i.e., in April 2007), another course of ^{177}Lu was administered, and the patient was in remission for the next 30 months. When the disease relapsed, it was confined to pleural and pericardial regions. The absence of extra-thoracic disease spread at the time of disease relapse justified administration of the fourth course of PRRT to address "micrometastases," even after achieving a "near complete response." Further courses were administered after every relapse (November 2011 and June 2014). The serial images show that the disease volume was lower at every relapse compared to her initial presentation. "Theranostics" involves molecular imaging using ^{68}Ga DOTATOC PET/CT to precisely assess tumor receptor expression; in the present case this was achieved by serial imaging every 6 months (8,9). Hence the "good" response seen on ^{68}Ga-PET/CT after the first 3 PPRT cycles was suggestive of maximum receptor targeting. This was also the reason for administering a single course of PRRT for every relapse, considering the disease volume. The ultimate goal of PRRT has always been prolonging survival with good QoL; however, there is a need to "personalize" the treatment based on disease "behavior" and redefine treatment objectives during the its course. Although the objective of PRRT is "palliation," the "near complete" response prompted us to redefine the objective in this case, which was to achieve "near complete cure," which we ultimately achieved over the last 8 years. Another aspect of PRRT is monitoring for possible toxicity. Considering the potential for nephrotoxicity, renal function parameters were diligently monitored during the entire

course of PRRT. Although the initial courses using ^{90}Y led to a mild reduction in TER, renal function in fact improved with subsequent therapies. Importantly, the patient was clinically asymptomatic with no decline in the QoL index over 8 years.

CONCLUSION

In conventional chemotherapy regimens, dosage is defined based on large patient studies, but such an approach rarely benefits NETs with variable tumor phenotypes and clinical courses (10). We therefore highlight the concept of "individualization" of both imaging and therapy regimen based on tumor behavior, receptor expression, and toxicity profiles for better survival outcomes and QoL scores.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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