Clinical Case Report

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The prognostic influence of the proliferative discordance in metastatic pancreatic neuroendocrine carcinoma revealed by peptide receptor radionuclide therapy

Case report and review of literature

Nathanaëlle Montanier, MD[a,*], Juliette Joubert-Zakeyh, MD[b], Caroline Pétorin, MD[c], Pierre François Montoriol, MD[d], Salwan Maqdasy, MD, PhD[a,e], Antony Kelly, MD[f]

Abstract

Rationale: Pancreatic neuroendocrine tumors (pNET) are rare slowly growing tumors with a high metastatic potential. Peptide receptor radionuclide therapy (PRRT) with radiolabeled analogues has been developed as a new tool for the management of metastatic well-differentiated (grade 1 and 2) neuroendocrine tumors expressing somatostatin receptor (SSTR2). Chemotherapy is the mainstay in the management of grade 3 (G3) unresectable pancreatic neuroendocrine carcinoma (pNEC). To date, no study has evaluated the efficacy of PRRT in such tumors.

Diagnoses and interventions: We describe a case of a progressive G3 pNEC with huge liver metastases successfully treated with PRRT (^{177}Lu DOTATATE).

Outcomes: Complete remission was obtained for 3 years. Indeed, the mitotic index was low (as G2 tumors) but with a very high Ki-67 index (45%–70%). Such discordance between the proliferative markers should consider the use of PRRT before chemotherapy in unresectable metastatic G3 tumors expressing SSTR2.

Lessons: This case supports the hypotheses highlighting the heterogeneity of G3 pNEC. The latter should be subdivided into 2 distinct categories: proliferation-discordant (well differentiated) and concordant (poorly differentiated) NEC. PRRT could be suggested for the former group before the conventional chemotherapy.

Abbreviations: 5-FU = 5-fluoro-uracil, CK-19 = cytokeratin 19, ENETS = European Neuroendocrine Tumor Society, GEP-NET = gastro-entero-pancreatic-neuroendocrine tumors, Grade 1, 2, 3 = G1, G2, G3, LAR = long acting release, NEC = neuroendocrine carcinoma, NET = neuroendocrine tumor, ORR = objective response rate, PFS = progression-free survival, pNEC = pancreatic neuroendocrine carcinoma, pNET = pancreatic neuroendocrine tumor, PRRT = peptide receptor radionuclide therapy, SSTR2 = Somatostatin receptor of type 2, WHO = World Health Organization.

Keywords: discordance, neuroendocrine carcinoma, pNET, proliferative markers, PRRT

1. Introduction

Pancreatic neuroendocrine tumors (pNET) are rare slowly growing tumors with a high metastatic potential. Distant metastases, mainly to the liver, are present in about 60% of the cases at diagnosis.[1] Biotherapy and chemotherapy are the main steps in the management of inoperable metastatic tumors.[2] Since 2 decades, peptide receptor radionuclide therapy (PRRT) with radiolabeled analogues has been developed as a new tool for the management of metastatic well-differentiated neuroendocrine tumors (grades 1 and 2 according to WHO and ENETS classification of NET), with promising results. However, because of lack of prospective studies, it is considered only as a second-line therapy for G1 and G2 pNET.[3] Indeed, recent studies demonstrated the benefits of PRRT as a first-line treatment for progressive diseases.[4,5] To date, no study has evaluated the efficacy of PRRT in G3 NET or neuroendocrine carcinoma (NEC). The latter are poorly differentiated tumors for which chemotherapy is indicated as a first-line therapeutic option. Recently, NECs were described to be more heterogeneous and their prognosis seems variable.[6] Indeed, the histopathological study of NEC is characterized by a high Ki-67 and/or mitotic index according to ENETS and WHO criteria. Some of them

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[a] CHU Clermont-Ferrand, Service d'endocrinologie, diabétologie et maladies métaboliques, [b] CHU Clermont-Ferrand, Service d'anatomopathologie, [c] CHU Clermont-Ferrand, Service de chirurgie et oncologie digestive, [d] Centre de Lutte Contre le Cancer Jean Perrin, Service de radiologie, Clermont-Ferrand, [e] UMR CNRS 6293, INSERM U1103, Université Clermont-Auvergne, Génétique Reproduction et Développement, Aubiere, [f] Centre de Lutte Contre le Cancer Jean Perrin, Service de Médecine nucléaire, Clermont-Ferrand, France.

[*] Correspondence: Nathanaëlle Montanier, CHU Gabriel Montpied, 58, Rue Montalembert, 63000 Clermont-Ferrand, France (e-mail: nathanaelle.montanier@etu.udamail.fr).

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could have very high Ki-67 with low mitotic index or inversely. Discordance between these proliferative markers could be in favor of a better prognosis compared to tumors with both markers elevated. In this article, we describe a case of progressive poorly differentiated metastatic pNEC with a complete remission for >3 years, thanks to PRRT! Furthermore, we review further predictive factors of good response to PRRT besides somatostatin receptor (SSTR2) expression. The proliferative discordance in our case could be one of these factors. This element should consider the use of PRRT in unresectable metastatic pNEC expressing SSTR2. This case supports the few theories suggesting that G3 pNEC should be subdivided into 2 distinct categories: well (proliferation-discordant) and true poorly differentiated ones (proliferation concordant with both Ki-67 and mitotic index over 20). PRRT could be suggested for the former group before conventional chemotherapy.

2. Case report

In 2007, a 57-year-old woman has presented with abdominal discomfort. The computed tomography identified a 45-mm-diameter tumor occupying both the body and the tail of the pancreas, invading the splenic vessels, with a secondary lesion of 20 mm in the segment IV of the liver. She did not have secretory symptoms. Surgical excision of the pancreatic and liver masses was decided owing to the doubtful histopathological results on the endoscopic biopsy and the excellent performance of the patient. The final histopathological analysis revealed a poorly differentiated neuroendocrine carcinoma of the pancreas with 4 mitoses in 10 high-power fields and a very high Ki-67 (45%–70% in some focal areas). The tumor revealed a positive immunostaining for CK19 and Vimentin (Fig. 1). It was graded as NEC (G3) and staged as T3N0M1 according to ENETS-2006 classification.[7] The postoperative somatostatin receptor scintigraphy (OctreoScan) revealed massive liver invasion by multiple lesions overexpressing somatostatin receptors (grade 3 isotope uptake). She received a treatment by somatostatin analogues (Octreotide LAR 20 mg) that temporarily stabilized the lesions. In May 2009, she presented a symptomatic carcinoid syndrome in parallel with disease progression; new liver lesions on segment VI and VIII appeared. Despite medical treatment with somatostatin analogues, the liver metastases progressed and invaded up to 50% of the liver. Owing to her excellent physical status (Karnofsky Performance Score = 100%) and to the intensive

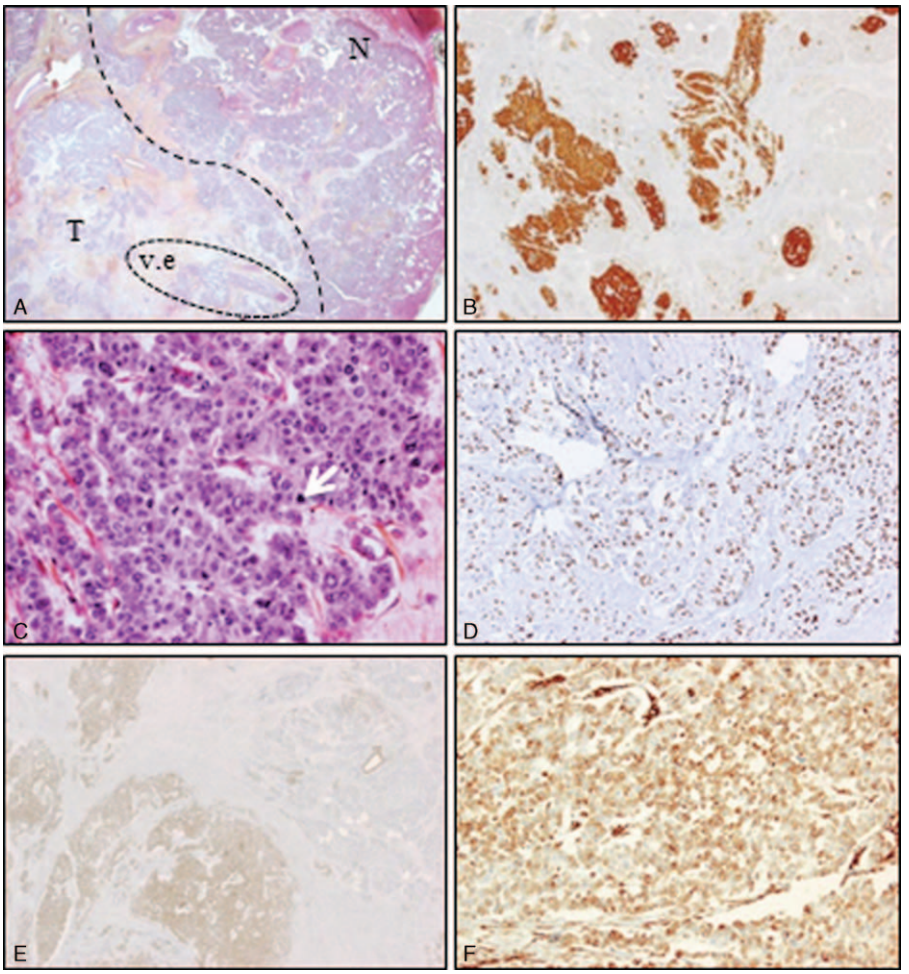

Figure 1. Characterization of pancreatic neuroendocrine carcinoma (G3) with discordant proliferative markers. E and F represent the markers of aggressiveness (please see[18]). (A) Hematoxylin-eosin (125×) showing normal tissue (N) separated from the tumor (T) by a dashed line. Note the presence of vascular emboli (v.e). (B) Immunohistochemical study showing chromogranin A staining within the tumor (400×). (C) Haematoxylin-eosin (400×) showing the mitotic rate within the tumor (arrow). The number of mitoses per field was <5. (D) Immunohistochemical evaluation of Ki-67 (100x) expression that varies from 45% to 75%. (E) Immunohistochemical study showing positive reactivity for CK19 (400×). (F) Immunohistochemical study showing positive reactivity for Vimentin (200×).

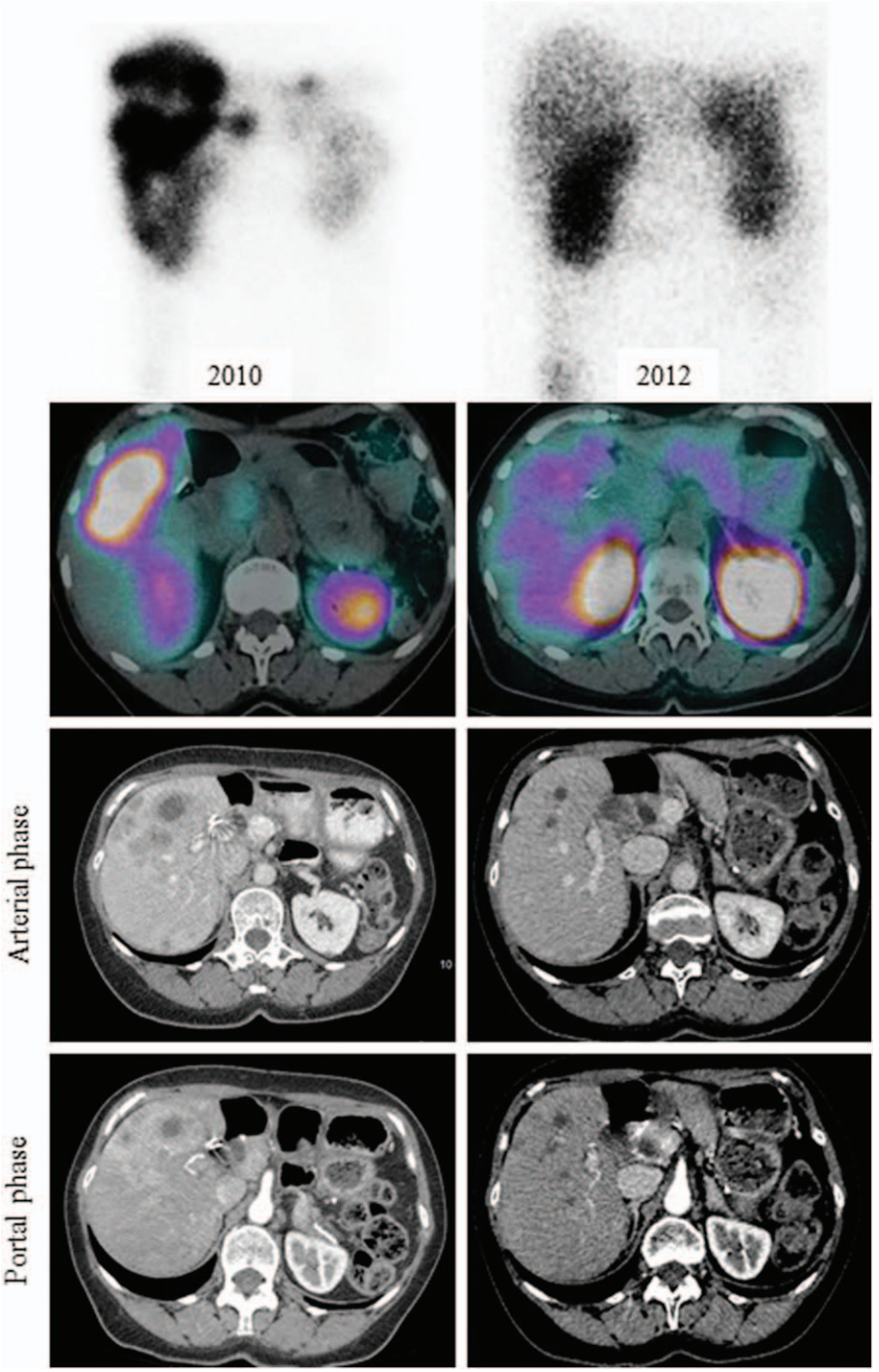

Figure 2. Complete remission of liver metastases after 4 cures of peptide receptor radionuclide therapy with ^{177}Lu DOTATATE confirmed on somatostatin receptor scintigraphy (OctreoScan) and computed tomography (CT) imaging. In the column on the left, note the high burden of liver metastases overexpressing SSTR2, with a high score of tumor uptake (grade 3 fixation) on Octreoscan. CT shows an enhanced contrast uptake during the arterial and portal time with diffuse liver damage. In the second column, complete remission of the metastases after 4 cures of ^{177}Lu DOTATATE with a consequent persistence of scars in the segment VIII, without contrast uptake on CT imaging and no fixation on OctreoScan.

fixation of the tumor on the OctreoScan, it was decided to manage her with PRRT using ^{177}Lutetium-radiolabeled somatostatin analogue (DOTATATE) in the Erasmus Center of Rotterdam. From September 2010 until March 2011, she received 4 sessions of 7.5GBq, every 2 months, each session was followed by an injection of Lanreotide LAR 120 mg. The Chromogranin A decreased progressively from 209 μg/L in the pre therapeutic stage (July 2010) to 39 μg/L at the end of the treatment. In March 2012, the liver metastases completely disappeared on tomography and OctreoScan, suggesting a complete response to ^{177}Lu DOTATATE (Fig. 2). After 36 months of complete response, several liver metastases reap-

Table 1

Main studies assessing the efficacy of peptide receptor radionuclide therapy with ^{177}Lu in neuroendocrine tumors including the pancreatic neuroendocrine tumors.

Articles	n	Age	Grade	Liver metastases	Treatment already received	CR	PR	SD	PD	ORR	OS, mo	PFS, mo
Kwekkeboom et al, 2008[5]	pNET (n=72)	—	—	—	—	4 (6%)	26 (36%)	19 (26%)	10 (14%)	43 (60%)	—	—
	Whole cohorte (n=310)	59 (21–85)	—	276 (89%)	153 S (49%) 16 RT (5%) 52 CT (17%) 168 SSA (54%)	5 (2%)	86 (28%)	107 (35%)	61 (20%)	142 (46%)	46	33
Bodei et al, 2011[14]	pNET (n=14)	—	—	—	—	0	8 (57%)	2 (14%)	3 (21%)	9 (64%)	—	—
	Whole cohorte (n=51)	57 (30–79)	—	41 (80%)	35 S (68%) 43 SSA (48.3%) 11 CT (12.4%) 30 S+SSA (58%)	1 (2%)	14 (27%)	14 (27%)	9 (18%)	28 (55%)	NR	36
Ezziddin et al, 2011[15]	pNET (n=37)	—	G1: 30% G2: 62% G3: 8%	—	—	0	21 (57%)	6 (16%)	5 (13.5%)	—	—	—
	Whole cohorte (n=81)	61 (33–83)	G1: 25% G2: 61% G3: 9%	—	29 SSA (36%) 23 CT (28%) 40 S (49%) 18 O (32%)	0	30 (370%)	25 (34%)	8 (11%)	—	—	—
Sansovini et al, 2013[13]	pNET (n=52)	61 (26–82)	G1: 23% G2: 60% Unknown: 17%	42 (81%)	22 S (42%) 14 CT (27%), 34 SSA (65%), 14 PRRT (27%), 8 O (15%)	**0** 4 (8%)	1 (14%) 11 (21%)	1 (14%) 27 (52%)	5 (71%) 10 (19%)	15 (29%)	–	29
Ezziddin et al, 2014[4]	pNET (n=68)	62 (37–82)	G1: 28% G2: 72%	65 (97.1%)	30 S (44.1%), 20 SSA (29.4%), 17 CT (25%), 7 LR (10.3%)	0	41 (60%)	9 (13.2%)	10 (14.7%)	49 (72%)	53	34
Total	Whole :562 pNET (243)	59 (21–85)	G1: 25% G2: 64% G3: 3.4%	89%	S 280 (49%) CT 117 (20%) 294 SSA (52%)	2.4%	42.3%	37.3%	17% pNET: 15%	57.4%	—	33

Previous treatment received by patients: S, CT, SSA, LR, PRRT, or O. OS and PFS are reported in months. Percentage of tumors classified grade 1, 2, or 3 (G1, G2, or G3) according WHO 2010. CR and PR are defined according to the RECIST criteria (Response Evaluation Criteria in Solid Tumors) for Kwekkeboom et al and Bodei et al's studies or SWOG criteria (Southwest Oncology Group solid tumor response) in Sansovini et al and Ezzidin et al's studies. Overall objective tumor response rate comprises CR, PR, and MR (25%–49% of tumor regression). CT=chemotherapy, CR=complete response, LR=loco regional treatment, MR=minor response, NR=not reached, O=other treatments, ORR=objective response rate, OS=overall survival, PRRT=peptide receptor radionucleide therapy, PR=partial response, PRS=progression-free survival, S=surgery, PD=progressive disease, SD=Stable disease, SSA=somatostatin analogues.

peared. Chemotherapy with 5FU-ZANOSAR was administered together with Lanreotide LP 120 mg, before switching to Sunitinib because of disease progression.

Informed consent was obtained from the patient for publication of this case report.

3. Discussion

The incidence of pNET is about 2 per 1,000,000 persons, and represents about 20% of the neuroendocrine tumors.[1,8] The median survival of the nonfunctional pNETs is about 38 months, with 5-year survival obtained in 43% of the patients. The presence of distant metastases and the degree of differentiation are the most powerful predictors of survival.[3] Indeed, Grade 3 or poorly differentiated NEC (>20 mitoses per 10 high-power fields and/or a Ki-67 index of >20%) are of poor prognosis; the 5-year survival rates vary between 6% and 11%.[9,10] Such tumors are disseminated in 50% to 70% of cases at diagnosis and are rarely accessible to surgery or locoregional methods.[10] Systemic chemotherapy with cisplatin/etoposide remains the standard management of grade 3 NEC with an objective response obtained in 41% of the patients and a median survival of 9.2 months.[2]

In the 1990s, PRRT with radiolabeled somatostatin analogues was introduced into the management of NETs, offering promising results in the well-differentiated metastatic tumors. Radiolabeled somatostatin analogue consists of a radionucleotide (^{111}Indium, ^{90}Ytrium, or ^{177}Lutetium) linked to a chelator (DTPA or DOTA) and bound to a somatostatin analogue (Octreotide or Octreotate). It delivers radionuclides to its target (tumors expressing somatostatin receptors). To-date, ^{177}Lu-DOTA^0 [Tyr^3]-Octreotate stands out as the treatment of choice when PRRT strategy is adopted, thanks to its higher affinity to SSTR2.[11,12]

According to the European Neuroendocrine Tumor Society (ENETS), PRRT is recommended as a second intention treatment, after the medical biotherapy (SST analogues), in patients with G1/G2 NETs strongly expressing SSTR2 on pretherapeutic imaging.[3]

Several studies reported an excellent response to ^{177}Lu-Octreotate during the management of NETs. A prospective study of Kwekkeboom et al evaluated the efficacy of ^{177}Lu-Octreotate in 310 patients with gastroenteropancreatic NETs (GEP-NET). Among them, 72 had pNET; 4 patients with pNET (6%) showed a complete response and 43 (60%) reached an objective response rate (ORR). However, no subgroup information about tumor grades was available.[13] We analyzed all the articles studying PRRT efficacy in the NETs and the data are summarized in the table. Indeed, the objective response rate was obtained for 57% of the patients, whereas only 17% of NETs progressed with PRRT (Table 1).

Compared to the conventional chemotherapy, PRRT seems to be safer and well tolerated with fewer adverse effects. Indeed, ^{177}Lu-DOTATATE safety was studied in 504 patients with GEP-NET.[5] Digestive and hematological side effects were reported in 25% and 3.6% of patients, respectively. Serious adverse effects were rarely reported.[14]

PRRT offers better results in terms of efficacy in G1-G2 NETs than chemotherapy. The median time to progression-free survival (PFS) in PRRT-treated patients is about 34 months, and the overall survival rate up to 53 months.[4] The response to PRRT was maximal in G1/G2 GEP-NETs (Ki-67 <20%).[15] In pNEC treated by chemotherapy, PFS and overall survival do not exceed 8 to 18 and 20 to 40 months, respectively.[5] These data suggest the efficacy of PRRT in the management of metastatic pNET compared to chemotherapy. However, it is important to emphasize that a great heterogeneity exists between different study populations and we compare different populations with different tumor grades. Randomized controlled trials comparing PRRT and chemotherapy are necessary to confirm the superiority of PRRT.

To date, PRRT is not recommended in G3 pNEC.[15] A case of response to PRRT has been reported in a poorly differentiated neuroendocrine carcinoma of unknown primary progressing despite 2 different chemotherapy regimens.[16] In a retrospective study assessing the impact of Ki-67 proliferation index on the response to PRRT, disease progression has been reported in 71% of the G3 subpopulation of GEP-NEC (5/7 patients G3, with only one patient with a stable disease and another with partial response).[15] But, in this cohort, only 3 pancreatic NEC were included, and the response in such tumors was not detailed, but seemed better in pNEC than in the other gastrointestinal NEC. Moreover, despite a Ki-67 >30% in 2 patients, their response to PRRT was better than the 5 other patients. This suggests that Ki-67 alone is not sufficient to predict the bad prognosis of such tumors and their response to PRRT.

Despite the presence of poor prognostic factors like high hepatic burden of ≥25%, positive staining for CK-19 and Vimentin (Fig. 1), and grade 3 NEC, surprisingly, our patient successfully responded to PRRT while belonging to the poorly differentiated G3 group and presenting aggressive components in immunochemistry.[4,17,18] Thus, the drastic response to PRRT in our case highlights the importance of Octreoscan fixation and the proliferative discordance. Indeed, a high uptake of the radiolabeled diagnostic isotope (^{111}In-DTPA) constitutes a predictive factor of response to PRRT. Kweekkeboom and Ezziddin separately identified a relationship between the chances of tumor remission after treatment with ^{177}Lu-DOTATE and the radioisotope uptake degree on pretherapeutic Octreoscan.[4,11] Second, the dissociation between the proliferative markers (the mitotic index and Ki-67 rate) in our case supports few data demonstrating the heterogeneity of G3 tumors.[6,10,19] Many studies highlighted the importance of Ki-67 rate to predict the prognosis of NETs; PFS was longer for G2 tumors with Ki-67 <10% compared to those with Ki-67 >10% (31 vs. 19 months).[17] Furthermore, 2 distinct categories of tumors are described within the G3 tumors: differentiated but highly proliferating NEC with Ki-67 between 20% and 50% and true poorly differentiated NEC with Ki-67 typically >50%.[20] Indeed, our patient belonged to the second group, but with a discordant low mitotic index. Recently, Basturk et al studied the clinical course and pathological features of 19 patients with grade discordant G3 pNEC (mitotic index from 2 to 20 with Ki-67 index >20%), compared to 53 patients with grade concordant G2 pNET (both mitotic count and Ki-67 index <20%) and to 43 true poorly differentiated pNECs. Patients with grade discordant pNET had significantly longer survival time compared to patients with poorly differentiated NEC (54 vs. 11 months). Thus, grade 3 NECs are heterogeneous and could have a variable prognosis.[19] The discordance between the proliferative markers could classify such patients in the G2 group. These data suggest that G3 NEC should be reclassified to restratify the management opportunities including PRRT.

4. Conclusion

PRRT was successful to obtain a significant disease remission in a patient with a pancreatic neuroendocrine carcinoma despite an

important tumor burden within the liver. This is the first case highlighting the efficacy of PRRT to treat metastatic G3 pNEC and revealing the prognostic significance of the proliferative discordance. Randomized controlled trials are needed to confirm the superiority of PRRT over chemotherapy in the proliferative discordant pNEC expressing SSTR2. This case demonstrates the heterogeneity of G3 tumors, separating them into well and poorly differentiated ones. Such proliferative discordance greatly influenced the prognosis in our patient and requires further analyses to reclassify such tumors as G2 rather than G3.

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