

A rare case of a patient with a high grade neuroendocrine tumor developing neutropenic sepsis after receiving PRRT combined with Capecitabine or Temozolomide: A case report

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Abstract. Neuroendocrine tumors (NET) are rare and demonstrate variable clinical behavior depending on the degree of tumor differentiation. Patients with poorly differentiated tumors (NET G3) have a poor prognosis. Systemic treatment with cytotoxic chemotherapy is considered to be the treatment of choice. In patients that are refractory or intolerant to first-line therapy, experts recommend peptide receptor radionuclide therapy (PRRT) in tumors that express somatostatin receptors. Recently, combinations of PRRT and chemotherapy were tested in patients with NET. Available data have reported promising tumor control rates and an excellent toxicity profile in cases where PRRT had been administered with capecitabine/temozolomide, even when administered as salvage therapy. The current study reported an exceptional case of advanced NET G3 with severe toxicity upon receiving PRRT in combination with capecitabine/temozolomide as third line therapy. The patient developed a life-threatening neutropenic fever, fungal pneumonia and necrotizing mastitis

23 days after the first cycle of therapy was administered. However, the treatment led to a significant reduction in tumor size. A total of 5 months after treatment initiation, the patient was alive and in excellent clinical condition with sustained tumor response. In summary, the current study presented a rare case of high grade NET exhibiting an almost complete response to PRRT in combination capecitabine/temozolomide, despite facing unexpected severe toxicity.

Introduction

Neuroendocrine neoplasia (NEN) are a rare and heterogeneous group of tumors. According to the World Health Organization (WHO) classification, NEN are stratified into low/moderate-[grade (G) 1/2] or high-grade (G3) neuroendocrine tumors (NET) and neuroendocrine carcinoma (NEC) (1). Well-differentiated NET (G1 and G2) are characterized by a low proliferative index, retain the expression of somatostatin receptors (SSTR) and are associated with a good prognosis compared with that in other malignancies. By contrast, G3 NET feature a high Ki-67 proliferation index of >20% and are associated with a poor prognosis.

The systemic treatment of patients with G3 NET has been under investigated. To date, no data from prospective clinical trials are available, and current recommendations for the treatment of G3 NET primarily relies on retrospective analyses and case series. Overall, G3 NET show low objective response rates to platinum-based therapies, when compared with that in NECs (2). Therefore, alternative, less toxic chemotherapy regimens, such as capecitabine/temozolomide are recommended (3). Data on second- or third-line therapy in the treatment of G3 NET are even rarer, and current recommendations are primarily based on expert opinions rather than on systematic clinical studies. In the case of SSR-positive tumors, peptide receptor radionuclide therapy (PRRT) has been recommended by several expert research groups. PRRT is a tumor-targeted systemic radiotherapy that enables the specific delivery of radionuclides directly into tumor cells inducing tumor cell death. The high-level expression of SSR on the tumor cell surface in NEN provides the rationale for a therapy

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Abbreviations: CUP, cancer of unknown primary; ECOG, Eastern Cooperative Oncology Group; GBq, gigabecquerel; G, grade; MBq, megabecquerel; mGy, miligrays; NEN, neuroendocrine neoplasia; NET, neuroendocrine tumors; PRRT, peptide receptor radionuclide therapy; PET, positron emission tomography; PFS, progression-free survival; SSA, somatostatin analogue; SSTR, somatostatin receptors

Key words: peptide receptor radionuclide therapy, capecitabine, temozolomide, neuroendocrine poorly differentiated tumors, hematologic toxicity, response

with radioisotope-labeled somatostatin analogs (4). While PRRT has emerged as a highly effective and well-tolerated treatment in SSR-positive, well-differentiated NET (5-7), few data exist on patients with high-grade NET. Zhang *et al.* (8) reported a median progression-free survival (PFS) time of 9.6 months and a median overall survival (OS) time of 19.9 months in 69 patients with G3 NET treated with PRRT. Notably, in these patients PRRT was well-tolerated without any decline in renal function, hepatotoxicity or grade 3/4 hematotoxicity. Combinations of PRRT with systemic chemotherapy (e.g. capecitabine with and without temozolomide) might be associated with both additive and synergistic effects, since chemotherapeutic agents might serve as a radiosensitizer, as well as targeting cells non-responsive to PRRT (9). However, at present, there are only a few case reports and small number of case series, which have reported the outcome of patients treated with a combination of PRRT and chemotherapy. In the present case study, a patient with disease progression following 4 cycles of PRRT, who was subsequently treated with a combination of PRRT and capecitabine/temozolomide at our institution has been described.

Case report

The case of a 58-year-old female patient who was diagnosed with a G3 NET of unknown primary location and synchronous liver metastases in October 2017 (Table I) has been described. The proliferation according to Ki-67 was high (20%). Multi-slice computed tomography (CT) and DOTATOC-positron emission tomography (PET)/CT revealed multiple SSR-positive liver metastases; however, it did not provide any evidence of a primary tumor. Immunohistochemical analysis of a biopsy obtained from a liver metastasis showed strong expression of synaptophysin and a slightly weaker expression of chromogranin. Staining for serotonin, CDX2 and TTF1 were negative and membranous PD-L1 expression was found in <1% of tumor cells.

Treatment with lanreotide Autogel (120 mg) was administered every 28 days. In addition, the patient underwent 4 cycles of PRRT with 7.4 gigabecquerel (GBq) ¹⁷⁷Lu DOTATOC over a period of 6 months (last dose June 2018). Notably, this treatment resulted in a partial remission lasting until December 2018 (Fig. 1A-C). At this time point a follow-up DOTATOC-PET/CT scan revealed disease progression in the liver (only in the right lobe, with stable disease on the left-hand side). No other distant metastases was evident. Based on the short duration of tumor control, another systemic treatment was not administered; however, the patient was admitted to undergo hemihepatectomy to resect the progressive lesions. Histopathological analysis of the resected tumor confirmed the diagnosis of NET with Ki-67 >20%, leading to the diagnosis of G3 NET (Fig. 2A-C). However, a DOTATOC-PET/CT scan performed four months following surgery showed further hepatic and lymphatic progression with an increase in tumor size of >20% according to the Response Evaluation Criteria in Solid Tumors (RECIST). Considering the initial partial response to PRRT and the systemic progression at that time point, systemic therapy was not administered but simultaneously continuation of PRRT sessions. Capecitabine/temozolomide was chosen as the chemotherapeutic agent due to the high response rates

observed in patients with NET (10,11) and since it represents the most common therapy regime used in studies investigating PRRT in combination with chemotherapy (12-14). At the time point of treatment initiation, the patient was in good general condition [Eastern Cooperative Oncology Group (ECOG) 0] and had recovered from the side effects of previous therapies. Nevertheless, the therapy was administered at a reduced dose, since (reversible) anemia and a lower platelet and leucocyte count had occurred, as some of the side effects from the initial 4 cycles of PRRT (Fig. 3A and B).

As timing between chemotherapy and PRRT has been found to have an impact on outcome parameters in animal studies, wean already established protocol was used (15,16). Of note, this particular protocol was selected, as it has been reported that therapy was only accompanied by modest reversible myelosuppression, which was not greater than that in conventional PRRT therapies. Therefore, the combination of PRRT plus capecitabine/temozolomide was administered according to the protocol recently published by Strosberg *et al.* (10) using 750 mg/m² capecitabine (which was reduced to 538 mg/m²) and temozolomide 200 mg/m² (which was reduced to 150 mg/m²). Chemotherapy with oral capecitabine started five days prior to PRRT. In particular, 7.0 GBq ¹⁷⁷Lu-DOTATOC was administered intravenously, followed by oral temozolomide in the last five days of the 14-day period of the capecitabine cycle. Dosimetric calculations revealed that the radiation absorbed doses were 1.09 milligrays (mGy)/megaBq (MBq) for the kidneys, 0.288 mGy/MBq for the liver, 0.41 mGy/MBq for the spleen and 0.03 mGy/MBq for bone marrow, while hepatic metastases demonstrated a higher uptake of 4.56 mGy/MBq, which was in line with previously published results from patients receiving combinations of chemotherapy and PRRT (17).

The treatment was initially well-tolerated without any side effects. However, 23 days after PRRT, the patient was hospitalized due to recurrent episodes of fever, dyspnea, as well as pain, redness and swelling in the right mamma. Laboratory testing revealed pancytopenia and slightly elevated inflammatory markers, while an ultrasound of the mamma showed distinct edema with induration of the tissue without evidence of an abscess formation. Chest CT revealed a mass-like pulmonary infiltrate in the right upper lobe with surrounding ground glass opacity, suggesting fungal pneumonia (Fig. 4A and B).

Blood, sputum and swab cultures did not identify any pathogens. For further evaluation of the pancytopenia, a bone marrow puncture was performed, which revealed toxic bone marrow damage (Fig. 5). As a result of the clinical investigations, neutropenic fever, a right-sided necrotizing mastitis and fungal pneumonia, as clinical complications of toxic bone marrow aplasia (most likely due to hematotoxicity of PRRT and chemotherapy) was diagnosed. The patient, treated in an external rural hospital at that time, was then sent to an Oncology unit in a tertiary University hospital. An empirical combination therapy with piperacillin/tazobactam, vancomycin, aciclovir and Caspofungin was initiated and was later changed to a combination of vancomycin, ciprofloxacin and voriconazole. Furthermore, stimulation therapy with granulocyte-colony stimulating factor was performed, along with the administration of several red blood cell and platelet transfusions. After 11 days, the blood cells started to regenerate (Fig. 3A and 3B). Follow-up imaging two weeks

Table I. Course of disease.

Year	Month	Therapy	Staging
2017	October	-	G3 NET CUP with synchronous hepatic metastases: First biopsy of a hepatic metastasis, Ki 67 20%, Synaptophysin+++, CGA++, SSTR-2A+++
	November	SSA therapy (Somatuline 120 mg) every 28 days	Staging CT and DOTATOC-PET: SSR-positive multiple hepatic metastases primarily in the right liver lobe. No evidence of primary tumor
		-	Second biopsy of a hepatic metastasis: Ki67 35-40%, Synaptophysin+++, CGA++, SSTR-2A+++, ISLET1-positive, TTF1- and CDX2-negative
	December	First cycle PRRT 7,4 GBq ¹⁷⁷ Lu-DOTATOC	-
2018	February	Second cycle PRRT 7,4 GBq ¹⁷⁷ Lu-DOTATOC	-
	April	Third cycle PRRT 7,6 GBq ¹⁷⁷ Lu-DOTATOC	Staging CT: Hepatic progressive disease
		-	Staging CT and DOTATOC-PET: Hepatic progressive disease
	June	Fourth cycle PRRT 7,7 GBq ¹⁷⁷ Lu-DOTATOC	-
	July	Continuation of SSA therapy	Staging CT: Partial remission with hepatic tumor size reduction
	September	-	Staging CT and DOTATOC-PET: Partial further hepatic tumor size reduction
	December	-	Staging CT and DOTATOC-PET: Hepatic progressive disease (progress of right lobe liver metastasis). No pathological lymph node enlargement
2019	January	Right hemihepatectomy	Histopathology of liver specimen: Ki 67 >20%, synaptophysin +++, CGA++, MLH1+, MSH2+, MSH6+, PMS2+serotonin, CDDX2 and TTF1 negative. PD-L1+
	May	-	Staging CT and DOTATOC-PET: Hepatic and lymphatic progressive disease (>20% according to RECIST)
	June	Fifth PRRT 6,941 GBq ¹⁷⁷ Lu-DOTATOC in combination with capecitabine (540 mg/m ²) and temzolomide (150 mg/m ²)	-
	July	Hospitalization due to clinical complications (neutropenic fever, transfusion obligatory pancytopenia, right sided necrotizing mastitis, fungal pneumonia) after PRRT in combination with capecitabine/temzolomide	Staging CT: Partial remission (55% according to RECIST). No pathological lymph node enlargement. No primary tumor detectable
	August	Continuation of SSA therapy	-
	October	-	MR: Partial remission (68% according to RECIST)

PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue therapy; CT, computer tomography; MR, magnetic resonance; PET, positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumors.

later revealed a clear regression of the infiltrations in the right upper lobe. The inflammatory markers decreased, along with an improvement in the healing process of the wound tissue of the mamma (Fig. 6).

Despite the critical clinical condition caused by combination PRRT, CT staging conducted one month following PPRT plus capecitabine/temzolomide showed a liver tumor mass reduction of at least 55% according to RECIST, without any

signs of pathological lymph node enlargement. Subsequent magnetic resonance imaging four months later revealed a further tumor reduction of at least 68% according to RECIST (Fig. 1D and E).

In consideration of the severe bone marrow damage and the critical condition of the patient, the combination of PRRT plus capecitabine/temzolomide was discontinued and somatostatin analogue (SSA)-therapy was restarted again. The

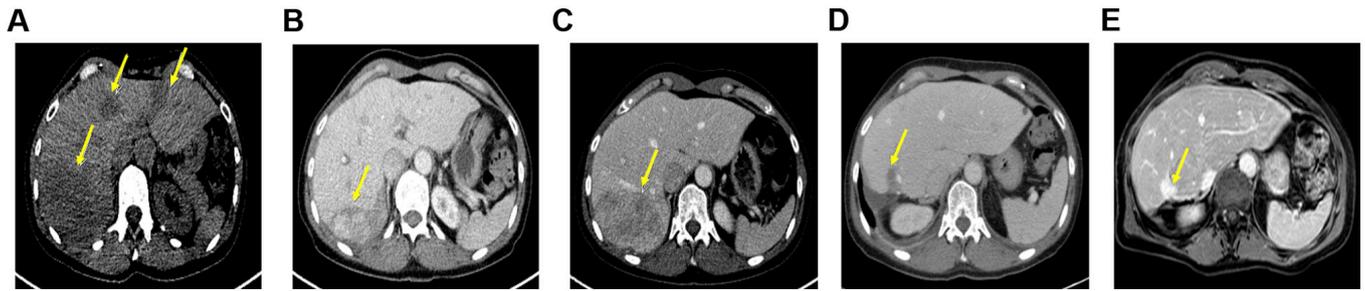


Figure 1. Hepatic metastases in axial abdominal CT and MRI scans during the course of treatment in a 58-year-old female patient with neuroendocrine CUP and synchronous hepatic metastases. Tumor lesions are indicated by yellow arrows. (A) Axial non-contrast-enhanced CT scan demonstrates multiple hepatic metastases at initial diagnosis (November 2017). (B) Axial-contrast enhanced (venous phase) CT scan displays a reduction in the size of hepatic metastases after 4 cycles of PRRT (July 2018). (C) Axial-contrast enhanced (venous phase) CT scan demonstrates progression in the size of hepatic metastases primarily in the right liver lobe (December 2018). (D) Axial contrast-enhanced (venous phase) CT scan demonstrates tumor reduction of at least 55% (according to RECIST v11.1) 1 month after PRRT in combination with capecitabine/temozolomide (July 2019). (E) Axial contrast-enhanced (venous phase) MRI depicts a hepatic tumor reduction of at least 68% (according to RECIST v11.1) after one cycle of PRRT in combination with capecitabine/temozolomide (October 2019). CUP, cancer of unknown primary; PRRT, peptide receptor radionuclide therapy; RECIST, Response Evaluation Criteria in Solid Tumors.

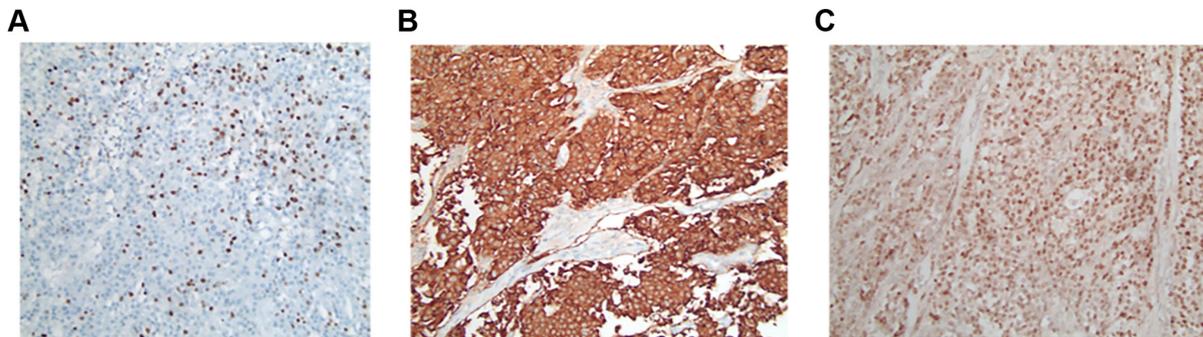


Figure 2. Immunohistochemical expression of cells from hepatic metastasis (hemihepatectomy resection from January 2019). Pathological analysis and immunohistochemical expression of cells from hepatic metastasis obtained following hemihepatectomy resection. (A) Ki-67 expression was >20%. (B) Synaptophysin expression of tumor cells. (C) Chromogranin expression of the tumor cells (all, magnification x20).

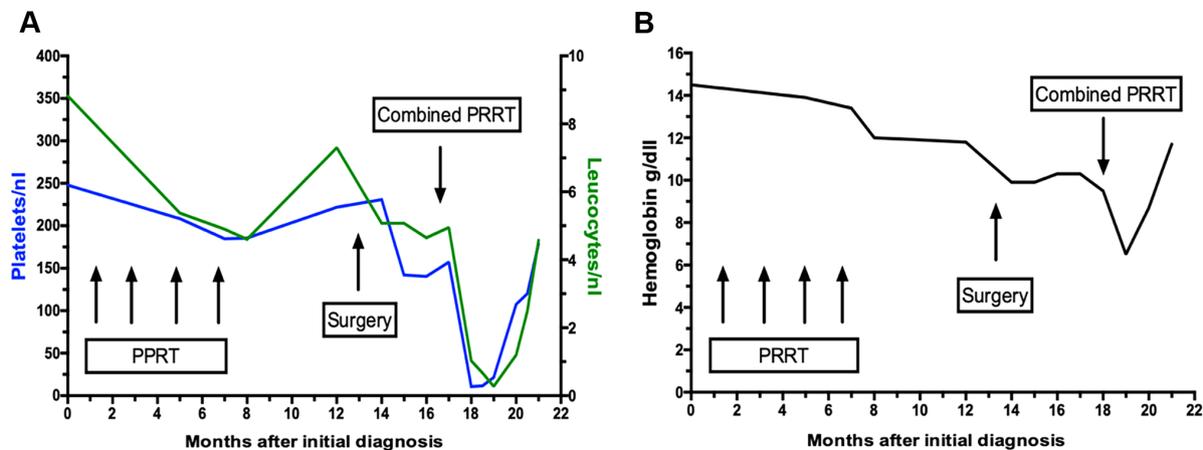


Figure 3. Platelet and leucocyte count during the course of treatment. (A) Platelet (blue curve) and leukocyte count (green curve) during the course of treatment. The graph illustrates a large decrease in leucocyte and platelet count 23 days after PRRT in combination with capecitabine/temozolomide. The results also exhibit a decline in platelet and leucocyte count after the administration of four cycles of PRRT, which rapidly increased subsequently, and stabilized during partial remission, with a decrease as the disease progressed. (B) Hemoglobin levels during the course of treatment. The graph illustrates a progressive decrease in hemoglobin levels after initial diagnosis resulting in chronic anemia. Despite a decrease in hemoglobin levels after four cycles of PRRT, the anemia may have been cancer-related, showing a decline with progressive disease. Subsequent to granulocyte-colony stimulating factor stimulation and the administration of erythrocyte concentrates during hospitalization in July 2019, hemoglobin levels normalized. PRRT, peptide receptor radionuclide therapy.

blood count stabilized and remained normal. The following staging investigations in October 2019 revealed further

sustained tumor response. To date, the patient is alive and fully recovered from the therapy-related side effects.

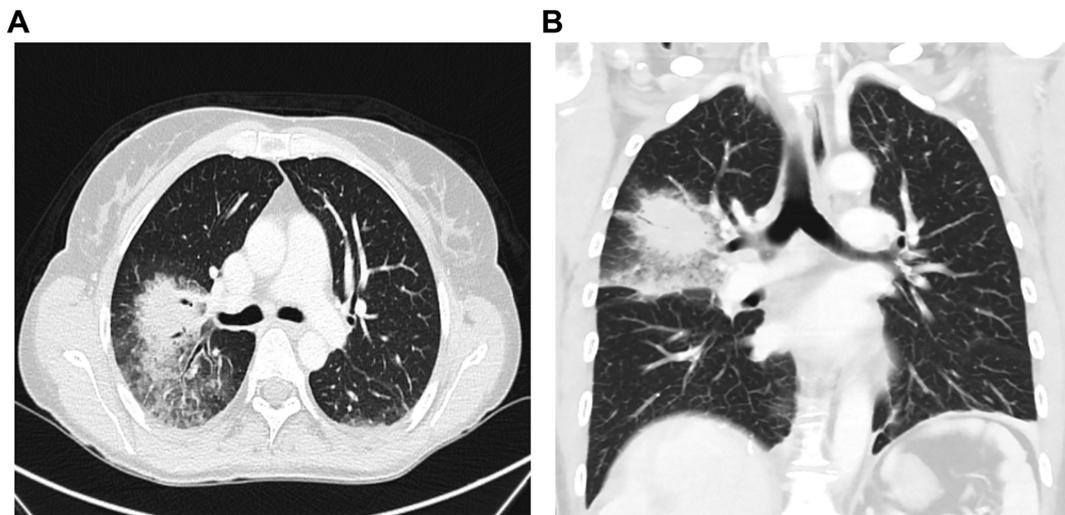


Figure 4. Axial contrast-enhanced CT scan of the chest, suggesting fungal pneumonia. (A) Axial- and (B) coronal contrast-enhanced CT scan of the chest demonstrated a mass-like pulmonary infiltrate in the right upper lobe with surrounding ground glass opacity, suggesting fungal pneumonia.

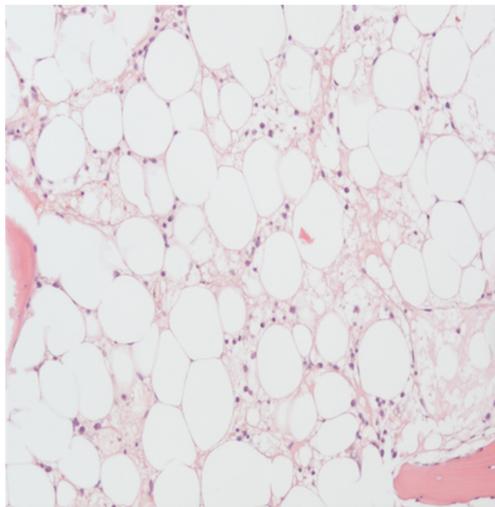


Figure 5. Bone marrow aspirate stained with H&E showing severe bone marrow hypoplasia. For further evaluation of the unexplained pancytopenia, a bone marrow puncture was performed. Results suggested that toxic bone marrow damage most likely due to hematotoxicity of PRRT and chemotherapy.

Discussion

The present case report described the case of a patient diagnosed with a G3 NET of unknown primary origin accompanied by synchronous liver metastases. The patient received a combination of PRRT and capecitabine/temozolomide chemotherapy, as part of a multi-modal treatment concept at our institution. After receiving only one cycle of therapy, the patient exhibited severe bone marrow toxicity, as well as neutropenic fever and critical infectious complications (necrotizing mastitis and fungal pneumonia); however, demonstrated an effective tumor response. The patient in the present case report provides several notable aspects: First, the combination of chemotherapy and PRRT was associated with an effective tumor response, leading to a sustained tumor control >5 months after only one cycle; second, this response was achieved in a patient with high-grade NET, representing a cohort of patients with

limited treatment options; third, the toxicity of the treatment exceeded the toxicity reported in the current literature by far, highlighting the requirement for careful patient selection and close monitoring of patients receiving PRRT in combination with chemotherapy.

Until now, different experimental approaches and strategies have been investigated to optimize the effectiveness of PRRT and to minimize potential side effects (18). Research groups, such as Claringbold *et al* (12-14) have tried to combine PRRT with chemotherapy (capecitabine with and without temozolomide) in cases of patients with advanced low-grade GNETs, in which either of the two treatment options alone failed (12-14,16). With the intention to use chemotherapy, as a radiosensitizing agent to enhance the efficacy of PRRT, effective tumor control rates were achieved, with disease control in up to 55% of the patients (13,19). A study, investigating pNET in particular, revealed an overall response rate of 80%, including complete remission in 13% and partial response in 70% of the cases (14). Accordingly, the effective tumor response of at least 68% tumor reduction was in line with previous studies.

Both combined PRRT and PRRT alone have been presented as procedures leading to an increase in long-term survival with a low complication rate (20-28). The patient in the present case study received the combination of ¹⁷⁷Lu-octreotate and capecitabine and temozolomide, which was considered feasible and safe, regarding the acute and subacute side effects (12-14). According to previous studies, acute side effects are typically mild and self-limiting (most commonly nausea), whereas long-term side effects include loss of renal function, myelodysplastic syndrome and acute leukemia. However, hematological toxicity was the most significant potential adverse event following PRRT, caused by irradiation of the bone marrow and primarily presenting as reversible, limited grade cytopenia. Current research studies suggest that WHO grade 3 or 4 toxicity could only occur in up to 15% of patients. According to Kesavan *et al* (16) this number was not significantly increased in patients receiving PRRT in combination with radiosensitizing chemotherapy, which has the potential to enhance the efficiency of the therapy. Research by Kesavan *et al* (16) retrospectively analyzed long-term outcomes

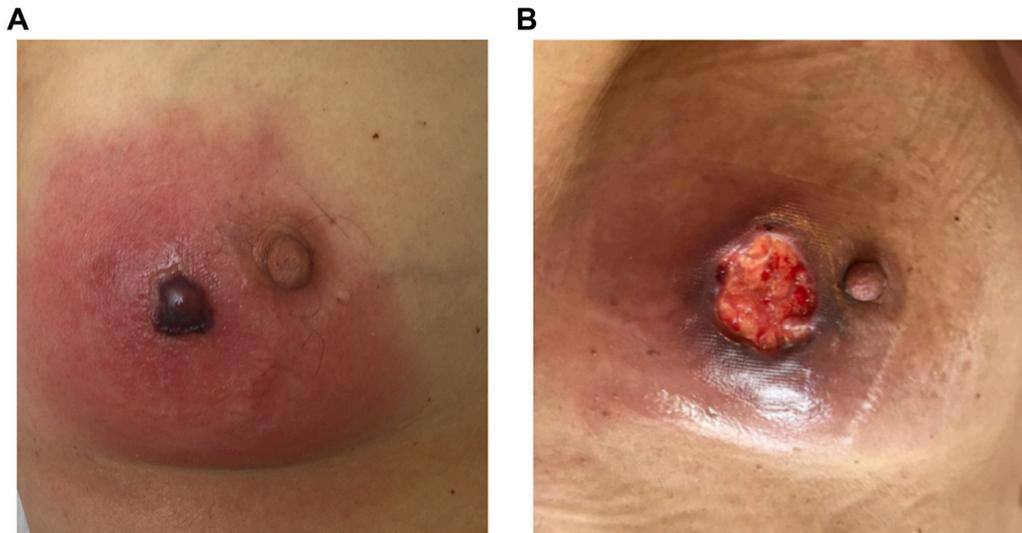


Figure 6. Necrotizing mastitis (with cutis and subcutis involvement) of the right mamma prior to and during treatment. (A) Mastitis before treatment initiation, showing erythema, edema and necrosis. Previous ultrasound imaging of the patient's mamma showed distinct edema with induration of the tissue without evidence of an abscess formation. (B) Mastitis of the right mamma during the healing process after treatment initiation. As a result of therapy, edema and erythema regressed, while necrosis could still be detected.

of the two cohorts from their ^{177}Lu -octreotate and chemotherapy study (37 patients treated with capecitabine/temozolomide and 28 patients treated with ^{177}Lu -octreotate and capecitabine). In both cohorts, only modest reversible myelosuppression was observed. In patients treated with capecitabine/temozolomide, long-term follow-up revealed significant thrombocytopenia in 2.7% (n=1), neutropenia in 2.7% (n=1) and anemia in 10.8% (n=4), while no short-term hematological toxicity grade 3/4 (n=0) was reported. In patients receiving ^{177}Lu -octreotate and capecitabine, long-term hematotoxicity, such as anemia and thrombocytopenia was only detected in 3.5% of the cases (n=1). However, an exact measure of the adverse events due to PRRT plus chemotherapy can be challenging, which is why the procedure is still considered investigational (29).

The patient in the present case report developed severe bone marrow toxicity, along with critical infectious complications (necrotizing mastitis and fungal pneumonia) after only one session of PRRT in combination with capecitabine/temozolomide at a reduced dose. Despite the fact that only one cycle of combined PRRT, at a reduced dose was administered, severe bone marrow damage was observed, leading to myelotoxic cytopenia most likely caused by prior therapy with PRRT, which was not seen in association with previous SSA therapy (30,31). Fig. 3A and B revealed the myelotoxic damage after two PRRT sessions causing a lower platelet and leucocyte count, counts as well as persistent anemia after several months. However, an increased radiation uptake can be excluded, as dosimetric calculations revealed the radiation absorption doses, which were in line with previously published results from patients receiving combinations of chemotherapy and PRRT (17). Therefore, it was concluded. Therefore, we can conclude that the patient in the current study was already predisposed to develop pancytopenia during PRRT in combination with capecitabine/temozolomide. Pretreatment with radiation-based therapy or alkylating agents has also been considered a significant factor to predict myelotoxicity, as research by Kesavan *et al* (16) showed a significant

difference in significance between increased risk of short- and long-term toxicity and the presence and number of previous treatments. Thus, a reduced dose of capecitabine/temozolomide was administered to the patient in the present case report.

As aforementioned, there are several approaches to prevent adverse effects of PRRT, such as using amino acid infusion or gelifusine and optimization of antiemetic regimens (32-35). Furthermore, it has been suggested that early therapy with PRRT-containing regimens could not only improve the outcome, but also reduce myelotoxicity (36). However, early treatment with PRRT was not successful in preventing severe bone marrow damage in the patient in the present case report, suggesting the requirement for additional approaches to prevent myelotoxicity. In this regard, establishment of specific algorithms incorporating predictors for myelotoxicity are highly desirable to select optimal treatment strategies, with respect to dosage and the number of cycles for each individual patient.

Another primary finding of the present case report was that the tumor reduced in size by at least 55% after only one month, followed by a further reduction of up to 68% (Fig. 1D). This supports several previous studies, which consider PRRT in combination with radiosensitizing chemotherapy an effective therapeutic option in this challenging disease (12-14). The rapid response seen in the patient in the current case report indicates the requirement for close clinical and radiological monitoring in patients treated with such regimens, to adjust the therapeutic strategy according to its efficacy and toxicity. Long-term follow-up would be a requirement to investigate sustainability of the tumor response after one cycle, as well as the occurrence of long-term adverse effects.

However, the present case report has some limitations, as only one patient with radiosensitizing chemotherapy in combination with PRRT was treated at our institute, which makes further conclusions difficult. Furthermore, the primary tumor in the patient is still unknown. However, there is a high incidence of, CUP (10-15%) in patients with NET (37-40) and no correlation between an improved therapy response

and/or higher toxicity with respect to tumor origin after PRRT combination combined with chemotherapy has been analyzed or reported yet (12-14,19).

Despite the high tumor reduction rate and several successful approaches to reduce the side effect profile in the field of radio sensitizing chemotherapy in combination with PRRT, the serious problem of myelotoxicity could not be addressed. Clinical trials on this type of therapy are rare, but are urgently required to further investigate the toxicity, as well as to develop preventive measures and predictors of response and long-term survival in patients receiving a combination of PRRT and systemic chemotherapy.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

BÖ, HA, IS, PEG, MTM, UF, FT, HJ and CR were involved treated the patient. BÖ, HJ and CR wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the publication of patient data and images according to the Declaration of Helsinki.

Competing interests

The authors declare that they have no competing interests.

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