

CASE REPORT WITH REVIEW OF LITERATURE

Potentially fatal crisis after ^{177}Lu -DOTATATE therapy for paraganglioma: a case report with review of literature

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Abstract. Pheochromocytoma/paraganglioma (PPGL) is a rare neuroendocrine tumor with metastatic potential. Peptide receptor radionuclide therapy with ^{177}Lu -DOTATATE, a radiolabeled somatostatin analog, has been used for the treatment of somatostatin receptor-positive PPGLs and has shown promising efficacy and generally mild toxicity. However, rare instances of fatal crises following treatment have been reported. A 50-year-old man with pheochromocytoma was admitted for ^{177}Lu -DOTATATE therapy. At the age of 49, he received ^{131}I -MIBG therapy for the recurrence of pheochromocytoma with bone metastasis. He rejected additional radionuclide treatment because of work commitments. However, the patient's plasma normetanephrine levels increased to $>7,200$ pg/mL, which worsened his pain from bone metastasis. Therefore, the patient resumed radionuclide treatment. Because his markedly elevated catecholamine levels might have induced a hypertensive crisis, ^{177}Lu -DOTATATE therapy was applied to reduce staff radiation exposure in an emergency. He developed a fever and tachycardia approximately 30 hours after ^{177}Lu -DOTATATE administration followed by cardiopulmonary arrest with hemoptysis approximately 35 hours after the administration. He was not revived. Postmortem imaging suggested alveolar hemorrhage. ^{177}Lu -DOTATATE administration might induce a fatal crisis, alveolar hemorrhage, and subsequent death. This is the first detailed report of a patient with PPGL who died shortly after ^{177}Lu -DOTATATE therapy. A review of five reported cases of fatal crises after ^{177}Lu -DOTATATE treatment suggests that high catecholamine levels are associated with a risk of crisis. In conclusion, while ^{177}Lu -DOTATATE therapy is generally considered safe, our findings underscore the potential risks of fatal crisis after therapy. Careful monitoring of patients with PPGL should be performed after treatment.

Key words: Paraganglioma, ^{177}Lu -DOTATATE, Fatal crisis, Peptide receptor radionuclide therapy

Introduction

Pheochromocytoma/paraganglioma (PPGL) is a rare neuroendocrine tumor originating from chromaffin cells, and all PPGLs have the potential for metastasis [1]. The radionuclide therapy ^{131}I -metaiodobenzylguanidine (MIBG) is currently available for treating metastatic, unresectable PPGLs. Additionally, peptide receptor radionuclide therapy (PRRT) with ^{177}Lu -DOTATATE, a somatostatin analog labeled with ^{177}Lu , can be used for PPGL as somatostatin receptor (SSTR)-positive neuroendocrine tumors. This peptide binds to SSTRs on tumor cells and is taken up intracellularly, causing cytotoxicity and cell death primarily through beta rays emitted by ^{177}Lu .

PPGLs are a type of neuroendocrine tumor, many of which express somatostatin receptors, especially SSTR2 [2], making ^{177}Lu -DOTATATE a viable treatment option [3]. ^{177}Lu -DOTATATE therapy for unresectable PPGLs is highly effective for disease control and is generally well-tolerated with minimal toxicity [4-6]. Consequently, it is recommended for PPGL treatment by the National Comprehensive Cancer Network and the Working Group on Endocrine Hypertension of the European Society of Hypertension [7]. However, rare instances of fatal crises following treatment have been reported. Here, we present a case of a patient receiving ^{177}Lu -DOTATATE treatment for pheochromocytoma (PCC) and its multiple bone metastases. He subsequently experienced alveolar hemorrhage and died one day after the treatment. We also review previous reports of fatal crises following this therapy.

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Case Presentation

A 50-year-old man with PCC and multiple bone metastases was admitted to our hospital for ^{177}Lu -DOTATATE therapy. There was no family history of PPGL or other endocrine disorders. At the age of 45, he presented with right chest pain and was subsequently found to have a right adrenal tumor of 3 cm and elevated urinary normetanephrine levels. Pathological findings of the adrenal tumor demonstrated PCC. Although genetic testing for hereditary PPGL was not conducted, succinate dehydrogenase B staining of the pathological tissue was negative, indicating a mutation in the succinate dehydrogenase gene. During postoperative follow-up, his plasma normetanephrine levels began to rise at roughly the age of 48 (Fig. 1). ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) (Fig. 2A) and ^{123}I -MIBG scintigraphy (Fig. 2B) revealed high uptake in multiple bones, confirming recurrent PCC with multiple bone metastases. The somatostatin receptor 2 expression of his PCC was high (Fig. 2D) although ^{111}In -pentetreotide scintigraphy with fair sensitivity for somatostatin receptor showed weak uptake in multiple metastases (Fig. 2C). 7.4 GBq of ^{131}I -MIBG therapy, given at age 49, decreased normetanephrine levels (plasma free: from 4,263 pg/mL to 2,589 pg/mL [reference range: below 506.0 pg/mL], urinary: from 9.7 mg/g creatinine (Cr) to 4.7 mg/gCr). His symptoms, such as constipation and bone pain, also improved. He rejected additional radionuclide treatment because of work com-

mitments. Additionally, metyrosine was suggested but not administered due to the patient's financial constraints. However, his plasma normetanephrine levels increased to >7,200 pg/mL, which worsened his pain from bone metastasis. Therefore, the patient decided to resume radionuclide treatment. Because markedly elevated catecholamine levels might induce hypertensive crisis, ^{177}Lu -DOTATATE therapy, which has a shorter isolation period for radiation safety than ^{131}I -MIBG therapy does, was chosen. The clinical course and normetanephrine levels leading up to and upon admission are illustrated in Fig. 1.

At the time of admission, the patient's height, weight, and body mass index were 168.0 cm, 87.6 kg, and 31.0 kg/m², respectively. He exhibited excessive sweating. He was treated with 32 mg of doxazosin and 80 mg of nifedipine for hypertension, with a blood pressure (BP) of 133/80 mmHg and a pulse rate (PR) of 70 beats per minute. He received 180 mg of loxoprofen, 450 mg of pregabalin, and 30 mg of oxycodone for pain due to bone metastases. Laboratory findings upon admission revealed normal renal function, with plasma epinephrine levels at 0.05 ng/mL (reference range: below 0.17 ng/mL), plasma norepinephrine levels at 17 ng/mL (reference range: 0.15 to 0.57 ng/mL), plasma metanephrine levels at 59.1 pg/mL (reference range: below 130.0 pg/mL), plasma normetanephrine levels at >7,200 pg/mL, urinary metanephrine levels at 0.04 mg/gCr, and urinary normetanephrine levels at 10.6 mg/gCr. On the day of admission, 7.4 GBq

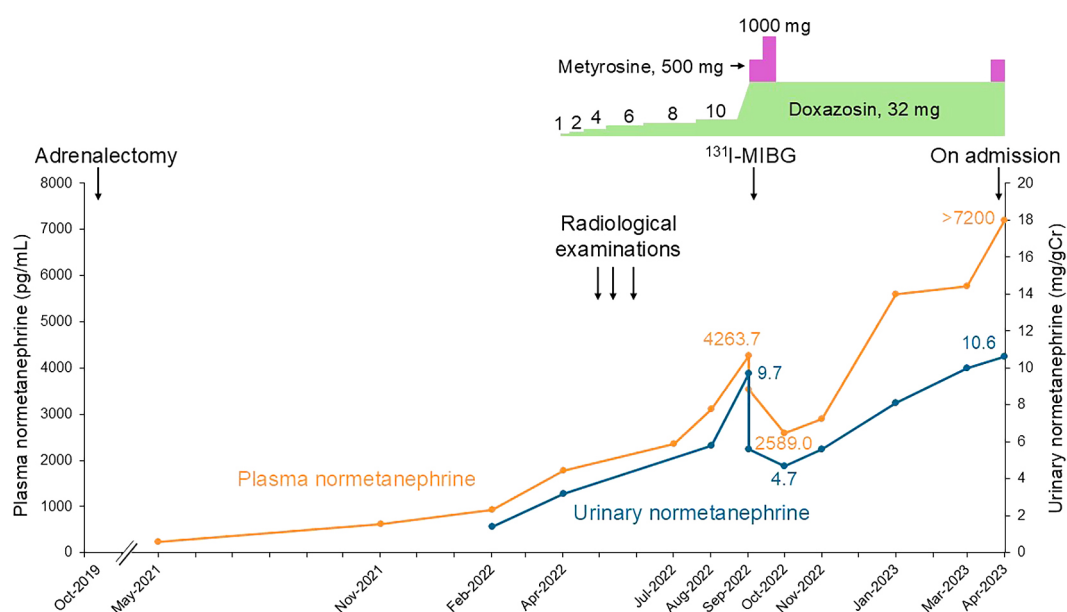


Fig. 1 Clinical course and normetanephrine levels prior to and upon admission. Radiological examinations were performed in the following order: ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography scan, somatostatin receptor (^{111}In -pentetreotide) scintigraphy, and ^{123}I -metaiodobenzylguanidine (MIBG) scintigraphy.

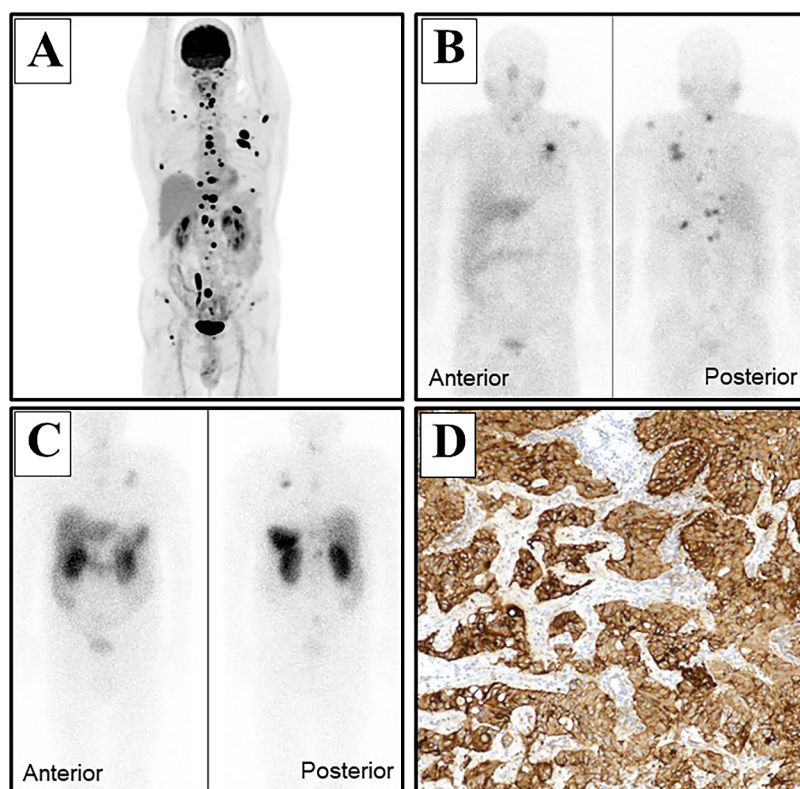


Fig. 2 Radiological examinations of multiple bone metastases. (A) ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography scan. (B) ^{123}I -metaiodobenzylguanidine scintigraphy. (C) Somatostatin receptor scintigraphy (^{111}In -pentetreotide). (D) Somatostatin receptor 2 expression in pheochromocytoma.

^{177}Lu -DOTATATE was administered at approximately 2 pm. Additionally, 500 mg of metyrosine, a catecholamine synthesis inhibitor, was initiated. We cautiously monitored his vital signs, although frequent monitoring was not feasible because of radiation protection protocols for medical staff. Immediately after the administration of ^{177}Lu -DOTATATE, his BP, PR, and body temperature (BT) were 110/97 mmHg, 97 bpm, and 36.3°C , respectively. At 10 am on the following day (approximately 20 hours after ^{177}Lu -DOTATATE administration), his vital signs did not significantly change (BP: 135/78 mmHg, PR: 109 bpm, BT: 36.6°C). At approximately 4 pm (approximately 26 hours after ^{177}Lu -DOTATATE administration), his PR and BT increased, but his BP did not (BP: 127/71 mmHg, PR 114 bpm, BT: 37.0°C). At approximately 8 pm (approximately 30 hours after ^{177}Lu -DOTATATE administration), the patient developed a fever of 38.0°C and sinus tachycardia of 123 beats per minute, although his BP was 141/81 mmHg. However, he had no other symptoms and could eat meals as usual. Therefore, the patient was carefully observed. At approximately 0:40 am (approximately 35 hours after ^{177}Lu -DOTATATE administration), he was found to be in cardiopulmonary arrest with

hemoptysis. Despite resuscitation efforts, he could not be revived. Postmortem CT revealed extensive infiltration and frosted shadows in both lungs, suggesting alveolar hemorrhage (Fig. 3A). In addition, intratracheal fluid was confirmed (Fig. 3B). An autopsy was not performed due to the lack of family consent.

Discussion

We experienced a fatal case of PCC after ^{177}Lu -DOTATATE treatment. The patient suffered multiple bone metastases and markedly elevated catecholamine levels. The postmortem image suggests alveolar hemorrhage (Graphical Abstract). To the best of our knowledge, this is the first report of a patient with PPGL who died shortly after receiving initial ^{177}Lu -DOTATATE therapy.

The meta-analysis of PRRT for PPGL, which included 149 patients treated with ^{177}Lu -DOTATATE, revealed minimal non-hematologic toxicity, manageable hematologic toxicity, and no treatment-related deaths [4], similar to those reported for midgut neuroendocrine tumors [8]. These findings suggest that ^{177}Lu -DOTATATE is a relatively safe therapy. On the other

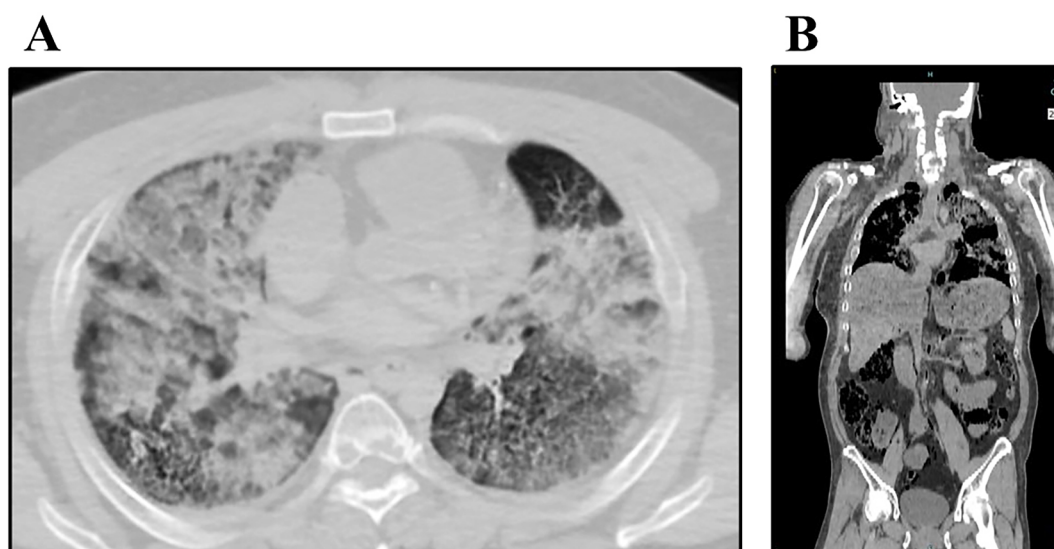


Fig. 3 Postmortem computed tomography scan. (A) Image of the lung, showing extensive infiltration and frosted shadows in both lungs, suggestive of alveolar hemorrhage. (B) Image of the mediastinal window, showing intratracheal fluid.

hand, ^{177}Lu -DOTATATE therapy is reported in rare cases to induce a hypertensive crisis. Moreover, ^{131}I -MIBG therapy for PPGL has been reported to lead to the development of catecholamine-induced hypertensive crises due to tumor collapse in several cases [9], with two reports of death due to myocardial infarction after treatment [10]. There are several reported cases of posttreatment fatal crises in patients receiving ^{177}Lu -DOTATATE therapy for PPGL, although some of the details were not provided [11, 12]. Table 1 shows 5 cases reported in detail. De Keizer *et al.* reported one case of catecholamine crisis in three patients after ^{177}Lu -DOTATATE treatment for PPGL [13]. A marked increase in urinary normetanephrine levels was observed in this patient. Makis *et al.* reported two cases of catecholamine crisis in three patients after initial ^{177}Lu -DOTATATE therapy [14]. Additionally, Malaza *et al.* reported refractory hypertension and tachycardia along with elevated plasma norepinephrine levels after ^{177}Lu -DOTATATE administration, which were successfully managed with multiple drugs, including ivabradine [15]. Phelps *et al.* reported a severe hypertensive reaction in which the patient developed a systolic BP of 240 mmHg within minutes after ^{177}Lu -DOTATATE infusion, which was controlled with nicardipine infusion in the ICU [16].

These reports suggest that patients with high baseline catecholamine levels are at risk of developing a crisis. Similarly, the norepinephrine level of the patient in the present case was markedly greater than that in the other patients without ^{177}Lu -DOTATATE adverse events at our institution (Table 1). However, the precise characteristics of high-risk patients for posttreatment crises

remain unclear because of the limited number of cases. Additionally, a recent report revealed that plasma norepinephrine and normetanephrine levels significantly increase 24 hours after ^{177}Lu -DOTATATE administration, peaking within 48 hours [17]. The present patient might have had increased catecholamine levels after ^{177}Lu -DOTATATE administration because he developed fever and tachycardia approximately 30 hours after administration. However, there was no measurement of catecholamine levels after ^{177}Lu -DOTATATE administration in the present case. Therefore, it is not clear whether the crisis in the present case was attributed to catecholamine release from the PCC. However, close monitoring for signs of a crisis may be required for a certain period after ^{177}Lu -DOTATATE administration. The third case of Table 1 had an onset of catecholamine crisis. Therefore, ^{177}Lu -DOTATATE treatment for PPGL might require longer follow-up than for the other neuroendocrine tumor. A probable mechanism for catecholamine elevation is the spillage of catecholamines caused by direct cytotoxicity from the ^{177}Lu radionuclide on chromaffin cells of the PPGL [17].

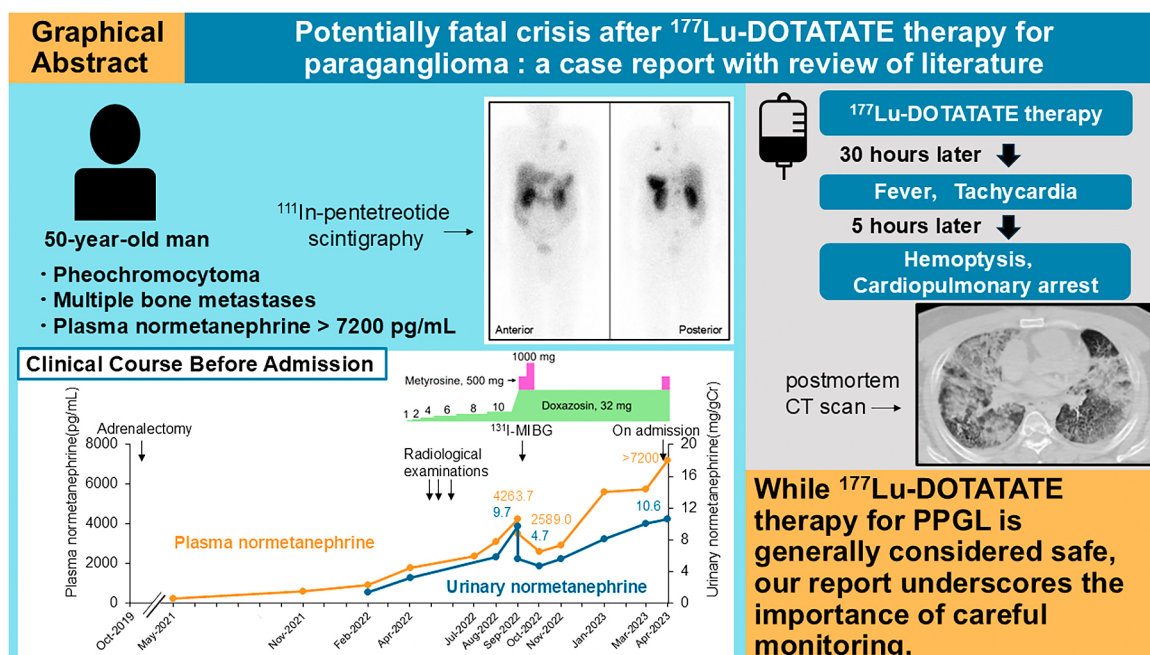
Our patient presented with alveolar hemorrhage on a postmortem CT scan, although he had no history of immunological disease or drugs known to cause alveolar hemorrhage. ^{177}Lu -DOTATATE-associated alveolar hemorrhage has not been reported. However, there are some cases of PPGL with diffuse alveolar hemorrhage [18–20]. One possible mechanism of alveolar hemorrhage is that paroxysmal hypertension elevates pulmonary vein pressure and induces capillary rupture [20]. Undetected paroxysmal hypertension in our patient

Table 1 Characteristics of patients with a catecholamine crisis after ^{177}Lu -DOTATATE therapy and the patient in the present case.

Case	Age/Sex	Treatment before ^{177}Lu -DOTATATE	Laboratory findings before ^{177}Lu -DOTATATE	Laboratory findings after ^{177}Lu -DOTATATE	Onset of crisis	Predominant symptoms	Treatment of crisis
de Keizer B 2008 [13]	63/M	Adrenalectomy, alpha-and beta-blocker, octreotide	uNMN 14.4 mg/day, uMN 1.97 mg/day	uNMN > 110 mg/day	After 1 day	Hypotension, extensive sweating, cardiac ischemia	Phentolamine, octreotide, bisoprolol, morphine
Makis W 2015 [14]	40/F	Paraganglioma resection, nine cycles of sunitinib, two cycles of ^{131}I -MIBG	uNMN 4.03 mg/day, uMN 4.41 mg/day	N/A	Approximately 30 minutes into the infusion	Tachycardia, profound sweating, shortness of breath, hypertension, lability of blood pressure, flash pulmonary edema, low output failure, acral cyanosis, somnolence, tumor lysis syndrome	Stabilized in the ICU
Makis W 2015 [14]	29/F	N/A	uNMN 2.43 mg/day, uMN 0.11 mg/day	N/A	After 3 days	Dizziness, shortness of breath, palpitations, low blood pressure	Hospitalized for 2 days
Malaza G 2019 [15]	54/M	Phenoxybenzamine, metoprolol, metyrosine	pNE 20,500 pg/mL, pE <20 pg/mL	pNE 172,500 pg/mL	N/A	Hypertension, tachycardia, heart failure, acute kidney injury	Phentolamine, esmolol, labetalol, diltiazem, ivabradine
Phelps TE 2024 [16]	78/F	Carvedilol, doxazosin, metyrosine, clonidine patch, amlodipine, sodium chloride	pNE 7,270 pg/mL, pNMN 2,625 pg/mL	pNE 9,135 pg/mL, pNMN 3,026 pg/mL	Within a few minutes into the infusion	Severe hypertension, tachycardia	Intravenous nicardipine, monitoring in the ICU
The present case	50/M	One cycle of ^{131}I -MIBG therapy, doxazosin, metyrosine	pNMN >7,200 pg/mL, uNMN 10.6 mg/gCr	N/A	After 30 to 35 hours	Tachycardia, fever, hemoptysis, cardiopulmonary arrest	N/A
The other cases without significant adverse events	Median age 63/F 1, M 3	Adrenalectomy, ^{131}I -MIBG therapy, doxazosin	Median pNMN 1,022 pg/mL Median uNMN 1.44 mg/day	N/A	None	None	None

The two bottom rows represent the present case and the other cases at our institution. The dose of ^{177}Lu -DOTATATE was 7.4 GBq in all patients at our institution.

M, male; F, female; MIBG, metaiodobenzylguanidine; uNMN, urinary normetanephrine; pNE, plasma norepinephrine; pE, plasma epinephrine; pNMN, plasma normetanephrine; ICU, intensive care unit; N/A, not available



Graphical Abstract Postmortem computed tomography image of lungs after ^{177}Lu -DOTATATE therapy, showing extensive infiltration and frosted shadows in both lungs.

may have induced alveolar hemorrhage, although his BP was not significantly high after ^{177}Lu -DOTATATE administration. However, diffuse alveolar hemorrhage has been reported to be associated with dilated cardiomyopathy and sleep apnea syndrome (SAS). Upper airway obstruction in SAS is suggested as a cause of alveolar hemorrhage [21]. Our patient had SAS. Therefore, his alveolar hemorrhage may have been attributed to SAS.

Stabilization of BP and PR by the use of alpha- and beta-blockers has been proposed for the prevention of posttreatment catecholamine crisis [22, 23]. The BP in our patient upon admission was controlled with the maximum dose of doxazosin and nifedipine. His PR was controlled without medication. Additionally, he received 500 mg of metyrosine after ^{177}Lu -DOTATATE administration because metyrosine might be effective in preventing a catecholamine crisis during ^{177}Lu -DOTATATE treatment. However, metyrosine dose titration before admission for ^{177}Lu -DOTATATE treatment was not performed because of financial constraints. Safe ^{177}Lu -DOTATATE treatment might require optimal control of catecholamine excess by alpha- and beta-blockers and metyrosine. Additionally, prolonging the ^{177}Lu -DOTATATE infusion time, reducing the initial dose of ^{177}Lu -DOTATATE [14], and administering intravenous nicardipine infusion before ^{177}Lu -DOTATATE treatment [16] have been suggested as effective measures to prevent a crisis. However, the second, third, and fifth cases of Table 1 received a decreased dose of ^{177}Lu -DOTATATE

[14, 16]. Therefore, lower dose could also require careful attention.

This case report has several limitations. First, radiation protection inhibited continuous monitoring of the patient's BP, PR, and catecholamine levels from the time of ^{177}Lu -DOTATATE administration to death. Therefore, we could not evaluate these parameters continuously. Second, the diagnosis of alveolar hemorrhage was exclusively based on postmortem CT imaging without an autopsy. Therefore, the cause of death remains inconclusive. Third, alveolar hemorrhage and death may have been dependent solely on the exacerbation of PCC but not ^{177}Lu -DOTATATE therapy because the patient had markedly elevated catecholamine levels upon admission. Despite these limitations, this is a valuable case, highlighting potential risks in the treatment of PPGL with ^{177}Lu -DOTATATE.

In conclusion, we present a case of a patient with multiple bone PCC metastases who died after ^{177}Lu -DOTATATE treatment. While ^{177}Lu -DOTATATE therapy for PPGL is generally considered safe, our findings underscore the importance of careful monitoring. Elevated catecholamines and signs of crisis should be evaluated after treatment. Further accumulation of case studies on ^{177}Lu -DOTATATE treatment for PPGL is essential to identify high-risk patients for fatal crises and elucidate effective strategies to prevent crises following radiotherapy.

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Disclosure

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