INTERNAL MEDICINE

□ CASE REPORT □

Challenging Differential Diagnosis of Hypergastremia and Hyperglucagonemia with Chronic Renal Failure: Report of a Case with Multiple Endocrine Neoplasia Type 1

Takaaki Murakami[1], Takeshi Usui[2], Yuji Nakamoto[3], Akio Nakajima[4], Yuki Mochida[4], Sumio Saito[5], Takahiro Shibayama[6], Nobuhisa Yamazaki[7], Tomonobu Hatoko[1], Tomoko Kato[1], Shin Yonemitsu[1], Seiji Muro[1] and Shogo Oki[1]

Abstract

A 53-year-old woman developed end-stage renal failure during a 15-year clinical course of primary hyperparathyroidism and was referred to our hospital for evaluation of suspected multiple endocrine neoplasia type 1 (MEN1). Genetic testing revealed a novel deletion mutation at codon 467 in exon 10 of the *MEN1* gene. Systemic and selective arterial calcium injection (SACI) testing revealed hyperglucagonemia and hypergastrinemia with positive gastrin responses. A pathological examination revealed glucagonoma and a lymph node gastrinoma. The findings in this case indicate the importance of early diagnosis of MEN1 and demonstrate the utility of systemic and SACI testing in renal failure cases.

Key words: MEN1, glucagonoma, renal failure, calcium test, gastrinoma, AIMAH

(Intern Med 56: 1375-1381, 2017)
(DOI: 10.2169/internalmedicine.56.7230)

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder which appears to be associated with heterozygous germinal mutations of the *MEN1* tumor suppressor gene. MEN1 is clinically diagnosed by confirming the presence of neoplastic disease in at least two of the commonly affected organs: the parathyroid gland, endocrine pancreas, and anterior pituitary gland. The clinical presentation of MEN1 varies among individuals, with less common lesions including adenomas of the adrenal glands and neuroendocrine tumors (1, 2). However, previous studies have reported a substantial delay in the diagnosis of MEN1, and late diagnosis remains a clinical issue (3, 4).

The diagnosis of gastroenteropancreatic neuroendocrine tumors (GEPNETs), including gastrinomas and glucagonomas, remains challenging, which often leads to a delayed diagnosis in clinical settings (5). The measurement of plasma glucagon and serum gastrin levels has proven useful in the diagnosis of GEPNETs (6, 7), but it can be affected by various factors such as the renal function (7, 8). The clinical interpretation of hypergastrinemia and/or hyperglucagonemia in patients with both GEPNETs and renal impairment has yet to be fully elucidated and remains clinically challenging. Therefore, the impact of renal failure on the accuracy of GEPNET diagnosis remains unclear.

We herein report a case of a patient with MEN1 who presented with hypergastrinemia and hyperglucagonemia. We further describe the findings on endocrine evaluation under the conditions of renal failure, likely due to a 15-year history of primary hyperparathyroidism. The findings in the present case demonstrate the importance of early diagnosis of MEN1 and the clinical utility of systemic calcium infu-

[1]Department of Diabetes and Endocrinology, Osaka Red Cross Hospital, Japan, [2]Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Japan, [3]Department of Diagnostic Imaging and Nuclear Medicine, Graduate School of Medicine, Kyoto University, Japan, [4]Department of Surgery, Osaka Red Cross Hospital, Japan, [5]Department of Gastroenterology and Hepatology, Osaka Red Cross Hospital, Japan, [6]Department of Pathology, Osaka Red Cross Hospital, Japan and [7]Department of Respiratory Surgery, Osaka Red Cross Hospital, Japan
Received for publication February 2, 2016; Accepted for publication April 19, 2016
Correspondence to Dr. Takaaki Murakami, tmurakam@kuhp.kyoto-u.ac.jp

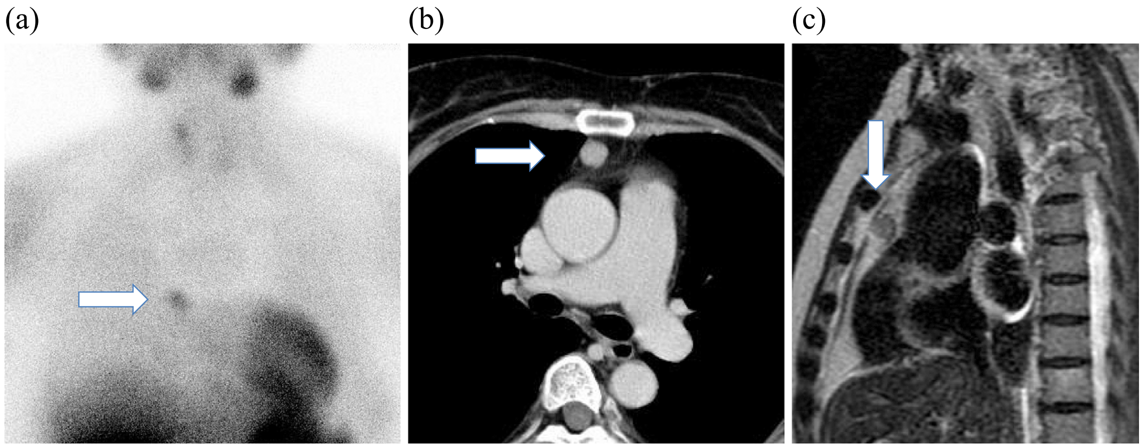

Figure 1. **(a) 99m technetium-sestamibi (^{99m}Tc-MIBI) scintigraphy demonstrating significant uptake in the right superior parathyroid gland and an anterior mediastinal tumor (shown with an arrow). (b) Cervicothoracic computed tomography (CT) and (c) T2-weighted magnetic resonance imaging (MRI) demonstrating a well-circumscribed tumor in the anterior mediastinum (shown with an arrow).**

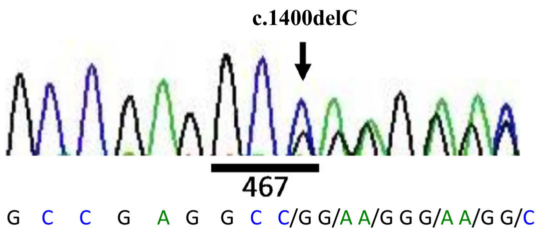

Figure 2. **Direct sequence analysis of the *MEN1* gene. The sequencing analysis demonstrated a novel deletion mutation at codon 467 in exon 10.**

sion and SACI testing in renal failure cases.

Case Report

A 53-year-old woman was referred to our hospital for evaluation of primary hyperparathyroidism and suspected MEN1. Primary hyperparathyroidism had developed at age 38, for which she underwent 3 separate parathyroidectomies of the bilateral inferior glands and left superior gland over a 12-year period at another hospital. However, her intact parathyroid hormone (PTH) levels had not normalized. She developed recurrent nephrolithiasis, and consequently, her renal function declined. She began renal dialysis at the age of 50 years and was followed-up at a hemodialysis clinic. Her mother had presented with recurrent primary hyperparathyroidism, non-functional pancreatic neuroendocrine tumors, and a left adrenocortical tumor leading to a diagnosis of MEN1 at our hospital, with genomic DNA polymerase chain reaction (PCR) testing demonstrating a deletion mutation (c.1400delC) at codon 467 in exon 10 of the *MEN1* gene. Her brother died of a thymic neoplasm at 44 years of age; however, no detailed clinical information regarding this case was available. The patient's family history was otherwise unremarkable.

The patient's current medications included furosemide (20 mg/day), 1α-hydroxyvitamin D3 (0.25 μg/day), mosapride citrate hydrate (10 mg/day), precipitated calcium carbonate (1,000 mg/day), lanthanum carbonate hydrate (500 mg/day), and rebamipide (300 mg/day). The patient was 156.4 cm tall and weighed 61.2 kg. Her body mass index (BMI) was 25.0 kg/m^2. The patient did not complain of weight loss, diarrhea, black stool, erythema, or tetany. A physical examination revealed galactorrhea and the absence of a Cushingoid appearance. The findings on laboratory testing revealed normocalcemia (corrected serum calcium level, 9.4 mg/dL) with an elevated serum intact PTH level of 1,080 pg/mL measured using an electrochemiluminescence immunoassay (Mitsubishi Chemicals, Tokyo, Japan). 99 m technetium-sestamibi (^{99m}Tc-MIBI) scintigraphy revealed significant uptake in the anterior mediastinal tumor and right superior parathyroid gland (Fig. 1a). Cervicothoracic computed tomography (CT) demonstrated a well-circumscribed anterior mediastinal mass 13 mm in diameter (Fig. 1b). This lesion was isointense on T1- and T2-weighted magnetic resonance imaging (MRI; Fig. 1c). Mild uptake was observed in the mediastinal tumor on ^{68}Ga-labeled 1,4,7,10-tetraazacyclododecane-*N,N´,N'',N''*-tetraacetic acid-d-Phe^{1}-Tyr^{3}-octreotide positron emission tomography / CT (DOTATOC-PET / CT) and ^{18}F-fluorodeoxyglucose PET/CT (FDG-PET/CT). Exons 2 through 10 of the *MEN1* gene were amplified by a polymerase chain reaction using genomic DNA extracted from leukocytes after obtaining written informed consent from the patient, revealing the same deletion mutation (c.1400delC) in the *MEN1* gene as observed in the patient's mother (Fig. 2).

We subsequently performed clinical screening of other endocrine organs in light of the diagnosis of MEN1. Consequently, a pituitary mass, suggestive of a microadenoma, was detected by dynamic contrast-enhanced MRI. The serum prolactin levels were consistently high, despite the pa-

Intern Med 56: 1375-1381, 2017 DOI: 10.2169/internalmedicine.56.7230

Table 1. Laboratory Results of the Present Case at the Referral.

Complete blood count		Reference ranges	***Hormone***		
WBC (/µL)	5,980	3,500-9,400	TSH (IU/mL)	2.13	0.54-4.26
RBC (×10⁴/µL)	308	420-570	Free T4 (ng/dL)	0.78	0.71-1.52
Hb (g/dL)	10.6	13-17.5	ACTH (pg/mL)	8.0	7.2-63.3
Hematocrit (%)	32.4	40-52	Cortisol (µg/dL)	12.0	4.0-18.3
Platelet (×10⁴/ µL)	21.9	15-35	LH (mIU/mL)	7.2	5.7-64.3
Blood Chemistry			FSH (mIU/mL)	24.0	< 157.8
ALB (g/dL)	3.4	3.7-5.2	Estradiol (pg/mL)	2.75	6.0-37.0
AST (IU/L)	8	10-40	PRL (ng/mL)	452.0	6.1-26.1
ALT (IU/L)	11	4-44	GH (ng/mL)	0.37	0-2.47
ALP (IU/L)	341	104-338	IGF-1 (ng/mL)	174	77-212
BUN (mg/dL)	33.2	8-22	Gastrin (pg/mL)	550	0–200
Creatinine (mg/dL)	6.13	0.61-1.04	Glucagon (pg/mL)	1310	70–174
Sodium (mEq/L)	143	135-147	Plasma renin activity (ng/mL•hr)	3.0	0.3-2.9
Potassium (mEq/L)	3.6	3.5-5.0	Aldosterone (pg/mL)	287	29.9-159
Chloride (mEq/L)	105	98-110	Intact-PTH (pg/mL)	1080	10–65
Calcium (mg/dL)	8.8	8.2–10.0	Midnight Cortisol (µg/dL)	29.3	
Phosphorus (mg/dL)	5.7	2.5-4.5	***1mg overnight dexamethasone suppression test***		
			Cortisol (µg/dL)	6.7	
HbA1c (%)	5.3	4.7–6.2	***8mg overnight dexamethasone suppression test***		
Plasma total AA (nmoL/mL)	1,864.8	2,068.2–3,510.3	Cortisol (µg/dL)	17.7	

RBC: Red blood cell count, ALB: serum albumin, AST: aspartate aminotranferase, ALT: alanine aminotranferase, ALP: alkaline phosphatase, BUN: blood urea nitrogen, HbA1c: hemoglobin A1c, Total AA: total amino acid, TSH: thyroid stimulating hormone, free T4: free total thyroxine, ACTH: adrenocorticotropic hormone, LH: lutenizing hormone, FSH: follicle stimulation hormone, PRL: prolactin, GH: growth hormone, IGF-1: insulin-like growth factor 1, intact-PTH: intact parathyroid hormone

tient's chronic renal failure (Table 1). The prolactin response to thyrotropin-releasing hormone was found to be blunted, prompting a diagnosis of prolactinoma. Furthermore, abdominal CT and MRI revealed bilateral adrenocortical multinodular enlargement, with equivalent uptake on ^{131}I-adosterol scintigraphy. The endocrine findings were consistent with a diagnosis of subclinical Cushing's syndrome (Table 1).

In addition, abdominal dynamic CT revealed a ring-enhancing tumor in the distal region of the pancreas (Fig. 3a). The tumor showed a low signal intensity on T2-weighted MRI (Fig. 3b) and a high signal intensity on diffusion-weighted imaging, as well as a significant uptake on FDG-PET/CT (standardized uptake value [SUV]max = 3.21; Fig. 3c). DOTATOC-PET/CT similarly showed significant uptake in this tumor in the distal region of the pancreas (SUVmax =21.5) and a separate tumor in the body of the pancreas (SUVmax =24.6; Fig. 3d). No evidence of duodenum, liver, or lymph node tumors were observed using any imaging modality, although upper gastrointestinal endoscopy revealed multiple erosions and raised submucosal nodules in the duodenum. The fasting blood samples had elevated levels of serum gastrin (550 pg/mL; normal range, 0-200 pg/mL) as measured by a radioimmunoassay using the polyethylene glycol technique (SRL Inc., Tokyo, Japan) and plasma glucagon (1,310 pg/mL; normal range, 70-174 pg/mL) as measured using a double antibody radioimmunoassay (RIA; SRL Inc.), and decreased total plasma amino acid levels (1,864.8 nmoL/mL; normal range, 2,068.2-3,510.3 nmoL/mL) as measured via liquid chromatography-mass spectrometry (SRL Inc.). The results of a gastrin stimulation test after a calcium infusion were positive (serum gastrin: baseline, 560 pg/mL; 4 minutes after calcium infusion, 720 pg/mL), although the glucagon response was negative. Selective arterial calcium injection (SACI) testing was also performed, in accordance with previously reported methods (9, 10). A significant selective increase in gastrin from a baseline level of 640 pg/mL to a peak level of 2,000 pg/mL at 30 s after stimulation was observed in the gastroduodenal artery (GDA) but not in the superior mesenteric or splenic arteries. Endoscopic ultrasonography (EUS) revealed another tumor 13 mm in diameter while moving from the pancreatic head to the body. All three tumors were found to be gastrin-negative and glucagon-positive on an immunohistochemical analysis of the samples obtained from EUS-guided fine needle aspiration (EUS-FNA) cytology.

Because of the clinical possibility of gastrinoma, we performed total pancreatectomy with duodenum and right adrenal gland resection following mediastinal tumor resection. Although pancreaticoduodenectomy and enucleation of the tumors present in the body and tail of the pancreas were recommended in consideration of the patient's quality of life, the patient and her family ultimately requested total pancreatectomy. After performing mediastinal tumor resection, the serum intact PTH level decreased to 512 pg/mL.

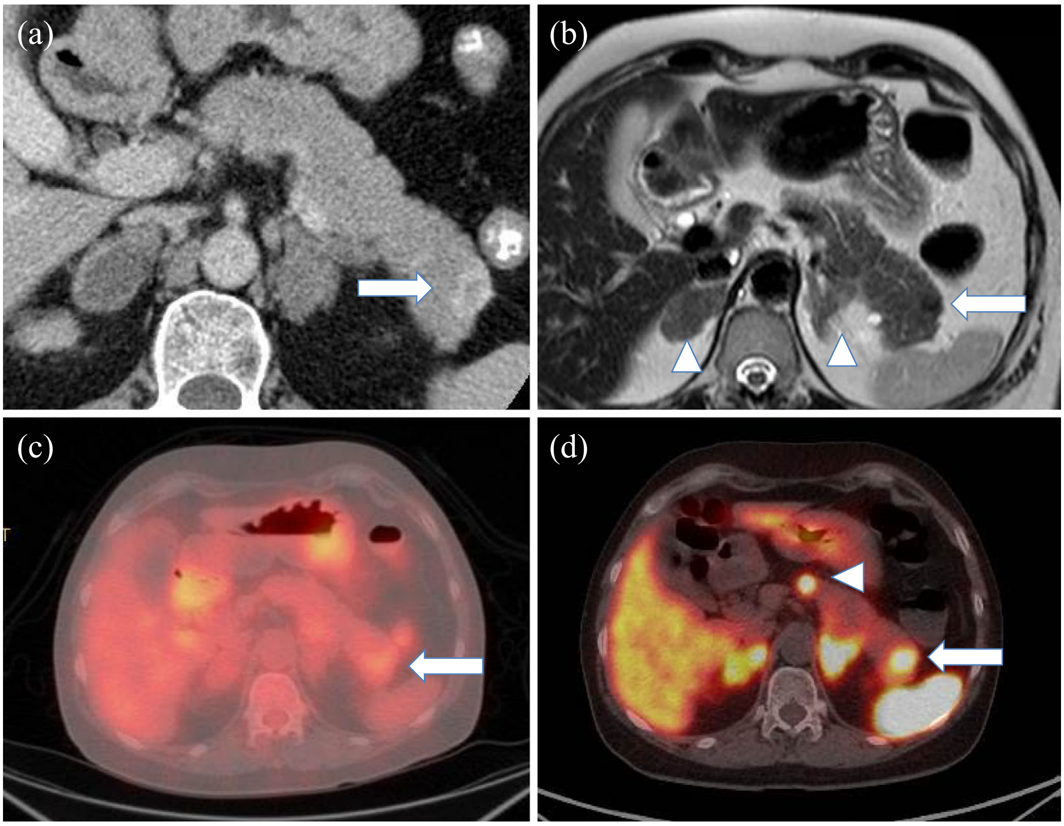

Figure 3. **(a) Abdominal dynamic CT demonstrating a gradually ring-enhancing tumor in the distal region of the pancreas. (b) T2-weighted MRI demonstrating a low-signal-intensity pancreatic tumor (shown with an arrow) and enlarged adrenal glands (shown with arrow heads). (c) ^{18}F-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) demonstrating a significant tumoral uptake. (d) ^{68}Ga-labeled 1,4,7,10-tetraazacyclododecane-*N*,*N'*,*N''*,*N'''*-tetraacetic acid-d-Phe^1-Tyr^3-octreotide PET/CT (DOTATOC-PET/CT) demonstrating significant uptake by the tumor in the pancreatic distal region and a separate tumor in the pancreatic body (shown with an arrow head).**

The findings on a pathological examination of the resected mediastinal tumor and right adrenal gland were consistent with ectopic parathyroid hyperplasia and macronodular adrenal hyperplasia, respectively. In addition, the pathological examination revealed numerous small tumors, measuring less than 5 mm in diameter, throughout the pancreas, but no duodenal tumors. A tumor 5 mm diameter was also observed in the pancreatic head in addition to the tumors detected preoperatively (Fig. 4a).

Concerning the tumor in the pancreatic head (Fig. 4b), immunochemical studies demonstrated positive staining for chromogranin A (Fig. 4c) and diffuse positive staining for glucagon (Fig. 4d). Concerning the tumors in the body and distal pancreas (Fig. 4f), the microscopic findings were consistent with neuroendocrine tumors, and immunochemical studies demonstrated spotty positive staining for glucagon (Fig. 4 g). Therefore, these tumors were pathologically confirmed as glucagonomas. While the immunochemical studies showed that none of the pancreatic tumors expressed gastrin (Fig. 4e and h), a neuroendocrine tumor observed in the peripancreatic lymph node (Fig. 4i) was found to be positive for gastrin in an immunohistochemical analysis (Fig. 4j and k).

The Ki-67 proliferative indices of all tumors were less than 1%. The patient's pathological staging was determined as T1bN1M0 (stage III) and T2N1M0 (stage III b), according to the AJCC/UICC and European neuroendocrine tumor society tumor node metastasis (TNM) staging system, respectively. After surgery, the plasma glucagon and serum gastrin concentrations decreased (Table 2), and the results of gastrin stimulation testing after calcium infusion were negative (serum gastrin: baseline, 26 pg/mL; 4 minutes after calcium infusion, 80 pg/mL).

Discussion

We herein report the case of a patient who was clinically diagnosed with MEN1 due to the presence of primary hyperparathyroidism, pancreatic NETs (pNETs), and a prolactinoma. The patient was also found to have hypergastrinemia and hyperglucagonemia with end-stage renal failure as a result of a 15-year history of primary hyperparathyroidism. Although the renal function is known to affect serum levels of gastrin and plasma glucagon, a gastrinoma of the

Intern Med 56: 1375-1381, 2017 DOI: 10.2169/internalmedicine.56.7230

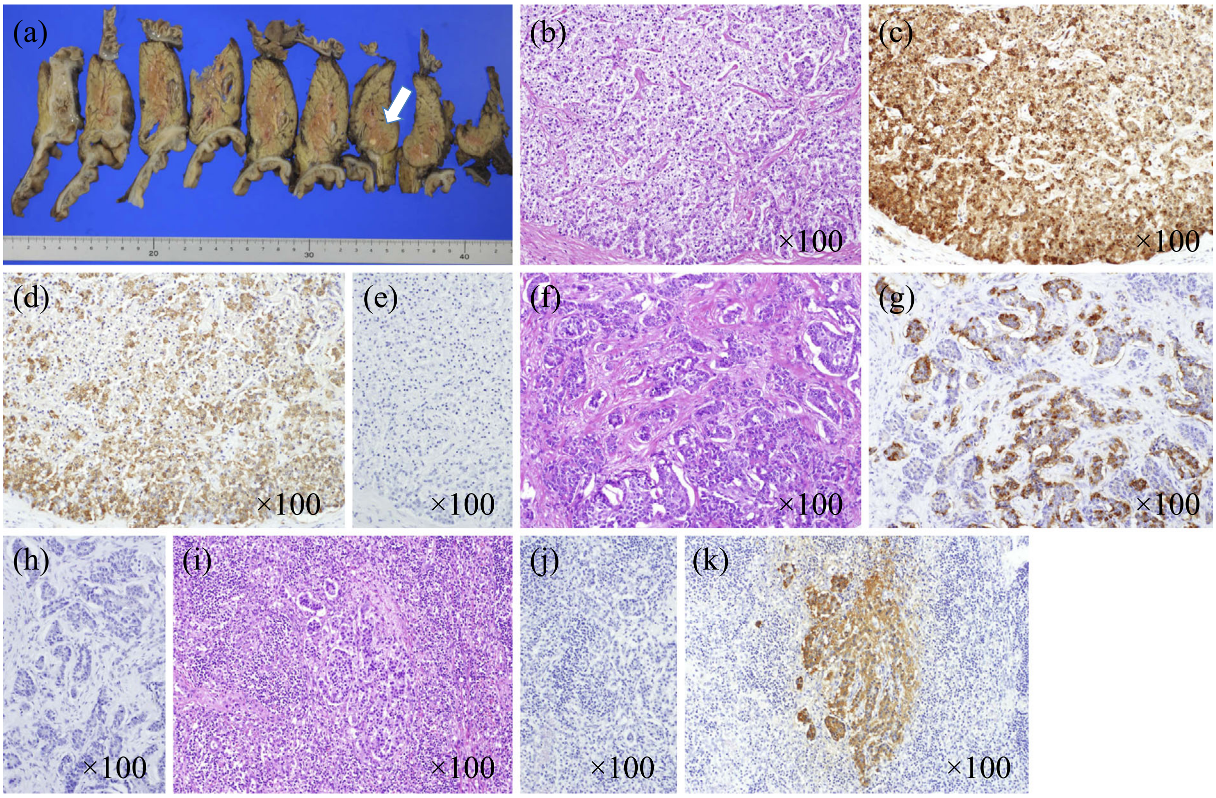

Figure 4. Pathological examinations confirmed the tumors in the pancreatic head and distal region as glucagonomas. Tumor in the pancreatic head: (a) macroscopic findings (arrow), (b) Hematoxylin and Eosin (H&E) staining, (c) positive chromogranin A staining on an immunohistochemical analysis, (d) diffusely positive glucagon staining on an immunohistochemical analysis, and (e) absence of gastrin staining on an immunohistochemical analysis. Tumor in the pancreatic body: (f) H&E staining, (g) punctate expression of glucagon on an immunohistochemical analysis, and (h) absence of gastrin staining on an immunohistochemical analysis. A pathological examination confirmed the presence of a gastrinoma in a peripancreatic lymph node. (i) H&E staining, (j) absence of glucagon staining on an immunohistochemical analysis, and (k) diffusely positive gastrin staining on an immunohistochemical analysis.

peripancreatic lymph node and pancreatic glucagonomas were revealed by pathological examinations. Few reports have so far been published regarding MEN1 in patients with renal failure, and endocrine evaluations of GEPNETs are also rarely described (11).

MEN1 germline mutation testing has demonstrated substantial utility in the diagnosis of MEN1 and should be offered to index patients with MEN1 and their relatives (1, 2). Heterozygous germline mutations of the *MEN1* gene have been identified in approximately 90% of all MEN1 patients. In the present study, a direct sequence analysis revealed a deletion mutation at codon 467 in exon 10 of the *MEN1* gene. To our knowledge, this mutation has not been previously reported (12) or registered in the Human Gene Mutation Database (HGMD®).

Our case demonstrated the importance of early diagnosis of MEN1. The diagnosis of MEN1 is often delayed (3, 4), as was the case in the present patient in whom the interval between the diagnosis of early-onset primary hyperparathyroidism with multiglandular hyperplasia and that of MEN1 was 15 years. During this interval, she developed end-stage renal failure that was most likely due to recurrent primary hyperparathyroidism. A previous study reported that urolithiasis-related renal complications in MEN1-associated primary hyperparathyroidism were more frequent and progressive than sporadic complications (13). Supernumerary and/or ectopic parathyroid glands are common in MEN1 cases, as observed in the present case (14). In addition, total parathyroidectomy with autotransplantation or subtotal parathyroidectomy should be recommended in MEN1 cases (1). The characteristic symptoms of MEN1 should not be overlooked, and its diagnosis should always be considered as a differential diagnosis due to the potential effects of MEN1 on the renal function and its implications for diagnostic and therapeutic strategies for primary hyperparathyroidism. As a final note, residual parathyroidectomy should be considered in the present case in the near future.

Endocrine evaluation of pNETs is clinically important. As previously reported, more than one type of functional pNET (e.g. gastrinoma and glucagonoma) may be observed in patients with MEN1, as in the present case (15). Hypergastrinemia in patients with renal failure is a well-known clini-

Table 2. Laboratory Results before and after the Pancreatectomy.

	- Day1	Day3	Day7	Reference ranges
Gastrin (pg/mL)	420	350	94	0–200
Glucagon (pg/mL) (RIA)	914	156	192	70–174
Glucagon (pg/mL) (sandwich ELISA)	247.1	26.8	-	9.2-44.8

RIA: radioimmunoassay, ELISA: enzyme-linked immunosorbent assay
Glucagon RIA and sandwich ELISA measured by SRL Inc., Tokyo, Japan.

cal phenomenon, as gastrin metabolism by the kidney is decreased under such conditions (7). In contrast, gastrinoma is the most common GEPNET in patients with MEN1 and is often observed in the duodenum or pancreatic head and can be clinically aggressive (16). In the present case, both systemic calcium infusions and SACI testing for gastrinoma were positive. Although the sensitivities and specificities of these tests are reported to be reasonably high, their utility has rarely been examined in cases of renal failure (10, 17, 18).

Unfortunately, we were unable to monitor the gastric pH in the present case. As previously reported, gastric pH monitoring may be useful and is recommended for the diagnosis of gastrinoma (19). Furthermore, the possibility of occult microscopic tumors in the resected specimen remained in the present case, although no evidence of gastrin-expressing tumors was observed in either the duodenum or pancreas. However, a primary gastrinoma may just not have been detected in our case, although primary lymph node gastrinomas have been previously reported (20). We did confirm a decrease in the serum levels of gastrin postoperatively (Table 2), indicating complete excision of the gastrinomas. Careful follow-up should be performed to detect the presence of non-resected and/or recurrent gastrinomas.

Hyperglucagonemia is common in renal failure patients, as the kidneys play a major role in endopeptidase-induced glucagon metabolism (21). The levels of glucagon therefore increase under conditions of renal failure, and a plasma glucagon level of over 1,000 pg/mL (8) and SACI have proven useful in diagnosing glucagonoma (9). However, the traditional glucagon RIA can also detect peptides with the same C-terminal amino acids as intact glucagon (21, 22). In the present case, the plasma glucagon level prior to pancreatectomy was greater than 1,000 pg/mL as measured using the traditional RIA; however, the plasma glucagon level was also relatively high when measured using a sandwich enzyme-linked immunosorbent assay (ELISA), which has been shown to have greater specificity in detecting intact pancreatic glucagon (21) (Table 1, 2). However, SACI testing was negative in the present case. These results suggest that the measurement of the plasma glucagon level using either the traditional RIA or a sandwich ELISA has substantial utility in the diagnosis of glucagonoma, even in patients with renal failure. However, we were unable to clarify the superiority of the traditional RIA or the sandwich ELISA for measuring the plasma glucagon level in the present study, since a direct comparison between these two assays in renal failure cases has not been validated.

Regarding the relationship between bilateral macronodular adrenal hyperplasia and MEN1, adrenal cortical tumors are recognized in almost 40% of MEN1 patients (1, 2). Although bilateral macronodular adrenal hyperplasia including ACTH-independent macronodular adrenal hyperplasia (AIMAH) is rare in MEN1 cases (23), a previous report showed that pNETs were present in all of the the MEN1 patients with adrenal involvements (24). The present case might also suggest a close relationship between the development of pNETs and adrenal lesions in MEN1 (23).

In summary, we herein reported a case of MEN1 with a novel deletion mutation at codon 467 of the *MEN1* gene. Hyperglucagonemia and hypergastrinemia with renal failure were observed in the present case, in addition to positive gastrin responses on systemic calcium infusion and SACI testing. A pathological examination demonstrated the presence of multiple glucagonomas and a lymph node gastrinoma. The findings in the present case highlight the importance of the early diagnosis of MEN1 and the utility of systemic calcium infusion and SACI testing in diagnosing gastrinoma, even in patients with renal failure.

The authors state that they have no Conflict of Interest (COI).

References

1. Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab **97**: 2990-3011, 2012.
2. Sakurai A, Suzuki S, Kosugi S, et al. Multiple endocrine neoplasia type 1 in Japan: establishment and analysis of a multicentre database. Clin Endocrinol (Oxf) **76**: 533-539, 2012.
3. Yamazaki M, Suzuki S, Kosugi S, et al. Delay in the diagnosis of multiple endocrine neoplasia type 1: typical symptoms are frequently overlooked. Endocr J **59**: 797-807, 2012.
4. Murakami T, Usui T, Nakajima A, et al. A novel missense mutation of the MEN1 gene in a patient with multiple endocrine neoplasia type 1 with glucagonoma and obesity. Intern Med **54**: 2475-2481, 2015.
5. Jamilloux Y, Favier J, Pertuit M, et al. A MEN1 syndrome with a paraganglioma. Eur J Hum Genet **22**: 283-285, 2014.
6. Soga J, Yakuwa Y. Glucagonoma/diabetico-dermatogenic syndrome (DDS): a statistical evaluation of 407 reported cases. J Hepatobiliary Pancreat Surg **5**: 312-319, 1998.
7. Arnold R. Diagnosis and differential diagnosis of hypergastrinemia. Wien Klin Wochenschr **119**: 564-569, 2007.
8. Chastain MA. The glucagonoma syndrome: a review of its features and discussion of new perspectives. Am J Med Sci **321**: 306-320, 2001.
9. Okauchi Y, Nammo T, Iwahashi H, et al. Glucagonoma diagnosed by arterial stimulation and venous sampling (ASVS). Intern Med **48**: 1025-1030, 2009.
10. Turner JJ, Wren AM, Jackson JE, Thakker RV, Meeran K. Localization of gastrinomas by selective intra-arterial calcium injection.

Clin Endocrinol (Oxf) **57**: 821-825, 2002.

11. Suzuki H, Katoh T, Sakuma Y, et al. Multiple endocrine neoplasia type 1 in end-stage renal failure. Clin Exp Nephrol **8**: 380-383, 2004.

12. Lemos MC, Thakker RV. Multiple endocrine neoplasia type 1 (MEN1): analysis of 1336 mutations reported in the first decade following identification of the gene. Hum Mutat **29**: 22-32, 2008.

13. Lourenço DM Jr, Coutinho FL, Toledo RA, Montenegro FL, Correia-Deur JE, Toledo SP. Early-onset, progressive, frequent, extensive, and severe bone mineral and renal complications in multiple endocrine neoplasia type 1-associated primary hyperparathyroidism. J Bone Miner Res **25**: 2382-2391, 2010.

14. d'Alessandro AF, Montenegro FL, Brandão LG, Lourenço DM Jr, Toledo Sde A, Cordeiro AC. Supernumerary parathyroid glands in hyperparathyroidism associated with multiple endocrine neoplasia type 1. Rev Assoc Med Bras **58**: 323-327, 2012.

15. Le Bodic MF, Heymann MF, Lecomte M, et al. Immunohistochemical study of 100 pancreatic tumors in 28 patients with multiple endocrine neoplasia, type I. Am J Surg Pathol **20**: 1378-1384, 1996.

16. Gibril F, Schumann M, Pace A, Jensen RT. Multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome: a prospective study of 107 cases and comparison with 1009 cases from the literature. Medicine **83**: 43-83, 2004.

17. Imamura M. Recent standardization of treatment strategy for pancreatic neuroendocrine tumors. World J Gastroenterol **16**: 4519-4525, 2010.

18. Wada M, Komoto I, Doi R, Imamura M. Intravenous calcium injection test is a novel complementary procedure in differential diagnosis for gastrinoma. World J Surg **26**: 1291-1296, 2002.

19. Roy PK, Venzon DJ, Feigenbaum KM, et al. Gastric secretion in Zollinger-Ellison syndrome. Correlation with clinical expression, tumor extent and role in diagnosis--a prospective NIH study of 235 patients and a review of 984 cases in the literature. Medicine (Baltimore) **80**: 189-222, 2001.

20. Harper S, Carroll RW, Frilling A, Wickremesekera SK, Bann S. Primary lymph node gastrinoma: 2 cases and a review of the literature. J Gastrointest Surg **19**: 651-655, 2015.

21. Inagaki T, Kushida A, Matsuo T, Kusunoki Y, Miyagawa J, Namba M. Basic and clinical evaluation of ELISA assay kit for pancreatic glucagon. Jpn J Med Pharm Sci **72**: 491-497, 2015 (in Japanese, Abstract in English).

22. Kuku SF, Jaspan JB, Emmanouel DS, Zeidler A, Katz AI, Rubenstein AH. Heterogeneity of plasma glucagon. Circulating components in normal subjects and patients with chronic renal failure. J Clin Invest **58**: 742-750, 1976.

23. Yoshida M, Hiroi M, Imai T, et al. A case of ACTH-independent macronodular adrenal hyperplasia associated with multiple endocrine neoplasia type 1. Endocr J **58**: 269-277, 2011.

24. Skogseid B, Larsson C, Lindgren PG, et al. Clinical and genetic features of adrenocortical lesions in multiple endocrine neoplasia type 1. J Clin Endocrinol Metab **75**: 76-81, 1992.