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

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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

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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-
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. 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/m². 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 (99mTc-MIBI) scintigraphy revealed significant uptake in the anterior mediastinal tumor (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 68Ga-labeled 1,4,7,10-tetraazacyclododecane-Ν,Ν',Ν'',Ν'''-tetracetic acid-d-Phe3,-Tyr1-octreotide positron emission tomography / CT (DOTATOC-PET / CT) and 18F-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 leucocytes 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-
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 131I-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 T2-weighted imaging, as well as a significant uptake in this tumor in the distal region of the pancreas (3.21; Fig. 3c). DOTATOC-PET/CT similarly showed significant uptake in this tumor in the distal region of the pancreas (SUVmax =24.6; Fig. 3d). No evidence of duodenal tumors present in the body and tail of the pancreas 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.

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

| Complete blood count | Reference ranges | Hormone |
|----------------------|------------------|---------|
| WBC (×10^3/μL)       | 5,990            | TSH (IU/mL) | 2.13 | 0.54-4.26 |
| RBC (×10^6/μL)       | 380              | Free T4 (ng/dL) | 0.78 | 0.71-1.52 |
| Hb (g/dL)            | 10.6             | ACTH (pg/mL) | 8.0 | 7.2-63.3 |
| Hematocrit (%)       | 32.4             | Cortisol (μg/dL) | 12.0 | 4.0-18.3 |
| Platelet (×10^3/μL)  | 21.9             | LH (mL/μL) | 7.2 | 5.7-64.3 |
| Sodium (mEq/L)       | 143              | FSH (mIU/mL) | 24.0 | <157.8 |
| Chloride (mEq/L)     | 3.6              | Estradiol (pg/mL) | 2.75 | 6.0-37.0 |
| Potassium (mEq/L)    | 3.6              | PRL (ng/mL) | 452.0 | 6.1-26.1 |
| Creatinine (mg/dL)   | 105              | GH (ng/mL) | 174 | 77-212 |
| Calcium (mg/dL)      | 8.8              | IGF-1 (ng/mL) | 550 | 0-200 |
| Phosphorus (mg/dL)   | 5.7              | Glucagon (pg/mL) | 1310 | 70-174 |
| HbA1c (%)            | 5.3              | Plasma renin activity | 3.0 | 3.2-9 |
| Plasma total AA (nmol/L/mL) | 1,864.8 | Midnight Cortisol (μg/dL) | 29.3 |
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| Plasma total AA (nmol/L/mL) | 1,864.8 | Midnight Cortisol (μg/dL) | 29.3 |

**Blood Chemistry**

- ALB (g/dL) 3.4 3.7-5.2
- AST (IU/L) 8 10-40
- ALT (IU/L) 11 4-44
- ALP (IU/L) 341 104-338
- BUN (mg/dL) 33.2 8-22
- Creatinine (mg/dL) 6.13 0.61-1.04
- Sodium (mEq/L) 143 135-147
- Chloride (mEq/L) 105 98-110
- Calcium (mg/dL) 8.8 8.2-10.0
- Phosphorus (mg/dL) 5.7 2.5-4.5

**Complete blood count**

- WBC (×10^9/L) 5,990 3,500-9,400
- RBC (×10^6/μL) 380 420-570
- Hb (g/dL) 10.6 13-17.5
- Hematocrit (%) 32.4 40-52
- Platelet (×10^3/μL) 21.9 15-35

**Hormone**

- TSH (IU/mL) 2.13 0.54-4.26
- Free T4 (ng/dL) 0.78 0.71-1.52
- ACTH (pg/mL) 8.0 7.2-63.3
- Cortisol (μg/dL) 12.0 4.0-18.3
- LH (mL/μL) 7.2 5.7-64.3
- FSH (mIU/mL) 24.0 <157.8
- Estradiol (pg/mL) 2.75 6.0-37.0
- PRL (ng/mL) 452.0 6.1-26.1
- GH (ng/mL) 174 77-212
- IGF-1 (ng/mL) 550 0-200
- Glucagon (pg/mL) 1310 70-174
- Plasma renin activity (ng/mL/hr) 3.0 3.2-9
- Aldosterone (pg/mL) 287 29.9-159
- Intact-PTH (pg/mL) 110 10-65
- Midnight Cortisol (μg/dL) 29.3

**Table 1.** Laboratory Results of the Present Case at the Referral.
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 hyperglucagoneemia 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 gastrin and plasma glucagon, a gastrinoma of the pancreas was confirmed as glucagonomas. While the immunochemical studies demonstrated positive staining for glucagon (Fig. 4d), a neuroendocrine tumor observed in the distal pancreas (Fig. 4f), the microscopic findings were consistent with neuroendocrine tumors, and immunochemical studies demonstrated spotty positive staining for glucagon (Fig. 4g). 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

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. 4g). 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).
was 15 years. During this interval, she developed end-stage renal failure and multiglandular hyperplasia and that of MEN1 between the diagnosis of early-onset primary hyperparathyroidism was the case in the present patient in whom the interval of MEN1. The diagnosis of MEN1 is often delayed (3, 4), also rarely described (11). Renal failure, and endocrine evaluations of GEPNETs are 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-
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).

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