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ORIGINAL

Duodenal adenocarcinoma with neuroendocrine features in a patient with acromegaly and thyroid papillary adenocarcinoma: a unique combination of endocrine neoplasia

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Abstract. A 67-year-old woman with familial clustering of thyroid papillary adenocarcinoma was diagnosed with acromegaly due to pituitary macroadenoma. She had multiple skin vegetations, but had no parathyroid and pancreas diseases. Before transsphenoidal surgery, she was further diagnosed as having a duodenal tumor and multiple hypervascular liver nodules. Biopsy specimens from the duodenal tumor and liver nodules were diagnosed histologically as moderately differentiated adenocarcinoma. Immunohistochemically, the tumor cells were positive for chromogranin, synaptophysin and somatostatin receptor 2a, suggestive for neuroendocrine features. After surgery, the patient was not in biochemical remission, and octreotide treatment was initiated. The duodenal cancer was treated with chemotherapy (neoadjuvant cisplatin and S-1). After 24 months, the patient's insulin-like growth factor I level had been normalized, and her liver tumors had not progressed macroscopically. This is a rare case of acromegaly associated with multiple endocrine tumors, not being categorized as conventional multiple endocrine neoplasia. Octreotide treatment might have had beneficial effects on our patient's duodenal adenocarcinoma and liver metastases, both directly *via* SSTR2a and indirectly *via* GH suppression, thereby contributing to their slow progression.

Key words: Acromegaly, Duodenal cancer, Neuroendocrine features, Multiple endocrine tumors, Octreotide

ACROMEGALY is associated with an increased risk of developing malignant tumors, particularly colorectal cancer, and possibly other cancers including breast, prostate, thyroid, and hematopoietic cancers [1-3]. Indeed, epidemiologic studies have shown wide variation in cancer-related morbidity and mortality in acromegaly [4]. Insulin-like growth factor I (IGF-I) plays a critical role in the development of malignant tumors [5-7]. In addition, growth hormone (GH) exerts mitogenic and anti-apoptotic effects on many tissues *via* the GH receptor, which is expressed in a variety of tumor tissues, including colorectal and breast cancers [8, 9]. Several epidemiologic studies have shown that duodenal carcinoma rarely occurs in acromegaly [10, 11].

We report a rare case of the coexistence of acromegaly and multiple tumors, including duodenal adenocarcinoma with neuroendocrine features and papillary adenocarcinoma of the thyroid with familial history. This patient had multiple neuroendocrine neoplasms affecting the pituitary gland, thyroid gland, and duodenum, which are not typically seen in conventional multiple endocrine neoplasia (MEN).

Case Report

A 67-year-old postmenopausal woman was referred to our hospital by an endocrinologist because of acromegalic face, macroglossia, and recurrent history of colon polypectomy. She and other four women of her six siblings had undergone thyroidectomies due to thyroid papillary adenocarcinoma, not medullary carcinoma, without familial clustering of polyposis of the

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Table 1 Laboratory data on admission

WBC	6610 /μL	Na	145 mEq/L	CEA	<2.0 ng/mL
RBC	482×10^4 /μL	K	3.5 mEq/L	CA19-9	53 U/mL
Hemoglobin	14.2 g/dL	Cl	103 mEq/L	GH	10.9 ng/mL
Hematocrit	46.2 %	Calcium	9.2 mg/dL	IGF-I	480 ng/mL
Platelets	26.9×10^4 /μL	IP	4.5 mg/dL	PRL	83.6 ng/mL
		BUN	10 mg/dL	ACTH	26.6 pg/mL
AST	19 IU/L	Creatinine	0.4 mg/dL	Cortisol	13.3 μg/dL
ALT	18 IU/L	T-Chol	202 mg/dL	TSH	5.74 μU/mL
γGTP	16 IU/L	TG	81 mg/dL	FT_4	1.49 ng/dL
ALP	221 IU/L	HDL-Chol	62 mg/dL	FT_3	3.14 pg/mL
LDH	229 IU/L	TP	7 g/dL	FSH	26.8 mIU/mL
T-bil	0.6 mg/dL	CRP	0.1 mg/dL	LH	10.5 mIU/mL
CK	209 IU/L	PG	100 mg/dL	PTH	48.1 pg/mL
Amylase	74 IU/L	HbA_{1c}	5.1 %	Gastrin	180 pg/mL
				VIP	44 pg/mL
				Serotonin	0.05 μg/mL

WBC, white blood cell; RBC, red blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γGTP, γ-glutamyltransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; T-bil, total bilirubin; CK, creatine kinase; Na, sodium; K, potassium; Cl, chloride; IP, inorganic phosphorus; BUN, blood urea nitrogen; T-Chol, total cholesterol; TG, triglycerides; HDL-Chol, high density lipoprotein cholesterol; TP, total protein; CRP, C-reactive protein; PG, plasma glucose; HbA1c, glycated hemoglobin; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; GH, growth hormone; IGF-I, insulin like growth factor-1; PRL, prolactin; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; FT_4, free thyroxine; FT_3, free triiodothyronine; FSH, follicle stimulating hormone; LH, luteinizing hormone; PTH, parathyroid hormone; VIP vasoactive intestinal polypeptide

colon or other tumor in her siblings. Her family members and doctor-in-charge never noticed acromegalic features at least at age of 59. On admission, the patient's blood pressure was 150/98 mmHg. She had typical acromegalic features, such as macroglossia, thick lips, and thickening of her hands and feet. She had multiple skin vegetations, but had no parathyroid and pancreas diseases. Her serum levels of GH and IGF-I were found to be elevated (10.93 ng/mL (normal range: <2.1 ng/mL) and 480 ng/mL (normal range: 37-150 ng/mL), respectively) (Table 1). The nadir GH level after an oral glucose tolerance test (OGTT) was also high (11.06 ng/mL; Table 2). Brain magnetic resonance imaging (MRI) with gadolinium enhancement revealed a pituitary macroadenoma (14 mm in diameter). Based on these physical, endocrine, and imaging data, the patient was diagnosed with a GH-producing pituitary macroadenoma.

Table 2 Oral glucose tolerance test (75 g)

Time (min)	0	30	60	120
Glucose (mg/dL)	100	142	172	145
IRI (μU/mL)	7.5	41.9	45.2	44.7
GH (ng/mL)	11.18	11.06	12.18	12.26

IRI, immunoreactive insulin; GH, growth hormone

Before transsphenoidal surgery for the pituitary adenoma, gastrointestinal fiberscope analysis revealed a duodenal tumor (30 mm in diameter; Fig. 1A-a) and whole-body computed tomography revealed multiple hypervascular liver nodules (up to 40 mm in diameter; Fig. 1B-a). Biopsy specimens from the duodenal tumor (Fig. 1A-b) and liver nodules (Fig. 1B-b) were diagnosed histologically with moderately differentiated adenocarcinoma. Unfortunately, primary duodenal tumor specimen was not enough in volume for further immunohistochemical analyses, we performed immunohistochemical staining for somatostatin receptor 2a (SSTR2a), gastrin, vasoactive intestinal polypeptide (VIP) and serotonin only in the metastatic liver tumor. Immunohistochemically, the tumor cells were positive for chromogranin (Fig. 1A-c, 1B-c), synaptophysin (Fig. 1A-d, 1B-d) and SSTR2a (Fig. 1B-e). The circumferential membranous SSTR2a reactivity was observed in more than 50% of tumor cells, which corresponds to score 3 according to scoring system proposed by Volante [12]. However, the tumor cells were negative for gastrin, VIP and serotonin (Fig. 1B-f, g and h). On the basis of the histological findings, the

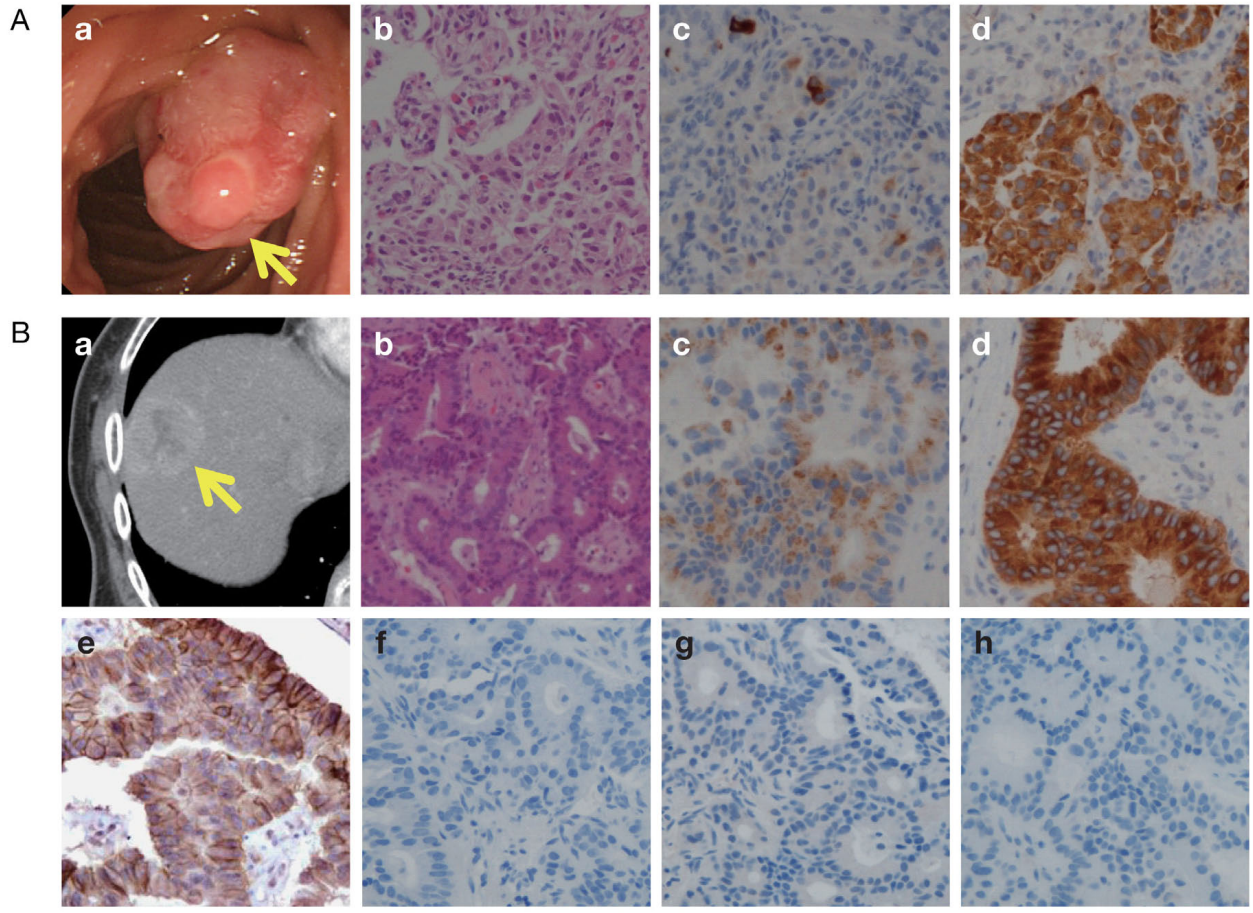

Fig. 1 Diagnostic imaging and histopathology of duodenal and liver tumors
A a. Gastrointestinal fiberscope analysis of a duodenal tumor (arrow); b. hematoxylin & eosin staining (original magnification ×200); c. immunohistochemical staining for chromogranin (original magnification ×200); d. immunohistochemical staining for synaptophysin (original magnification ×200). B a. Computed tomography analysis of a liver tumor (arrow); b. hematoxylin & eosin staining (original magnification ×200); c. immunohistochemical staining for chromogranin (original magnification ×200); d. immunohistochemical staining for synaptophysin (original magnification ×200); e. immunohistochemical staining for somatostatin receptor 2a (original magnification ×200); f. immunohistochemical staining for gastrin (original magnification ×200); g. immunohistochemical staining for VIP (original magnification ×200); h. immunohistochemical staining for serotonin (original magnification ×200). Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded specimens of resected tumor samples by the avidin-biotin-peroxidase complex (ABC) method using an auto-staining machine (Ventana Benchmark HX System; Ventana Medical System, Tucson, AZ, USA), according to the manufacturer's protocols. Antibodies used in this study were a rabbit monoclonal antibody against human synaptophysin (1:75 dilution; Thermo Scientific, Yokohama, Kanagawa, Japan), a rabbit monoclonal antibody against human chromogranin (1:100 dilution; Thermo Scientific, Yokohama, Kanagawa, Japan), a rabbit polyclonal antibody against human somatostatin receptor 2a (1:1000 dilution; Gramsch Laboratories, Schwabhausen, Germany), a rabbit polyclonal antibody against human gastrin (1:300 dilution; DAKO, Denmark A/S, Glostrup, Denmark), a rabbit polyclonal antibody against human VIP (1:100 dilution; Novocastra, San Ramon, CA, USA) and a mouse monoclonal antibody against human serotonin (1:50 dilution; DAKO, Denmark A/S, Glostrup, Denmark).

patient was diagnosed as having adenocarcinoma with neuroendocrine features. Her tumors did not fulfill the diagnostic criteria for neuroendocrine tumors, carcinoid or gastrointestinal hormone producing tumors. Thus, we diagnosed duodenal adenocarcinoma with multiple liver metastases with neuroendocrine features. The patient was negative for *MEN1* gene mutations.

Transsphenoidal surgery was performed for the GH-producing pituitary macroadenoma. Postoperatively, basal GH levels remained >1 ng/mL, and the plasma GH level did not fall below 1 ng/mL (GH nadir: 1.85 ng/mL) after an OGTT. Long-acting repeatable (LAR) octreotide treatment was initiated. The duodenal adenocarcinoma with multiple liver metastases was not

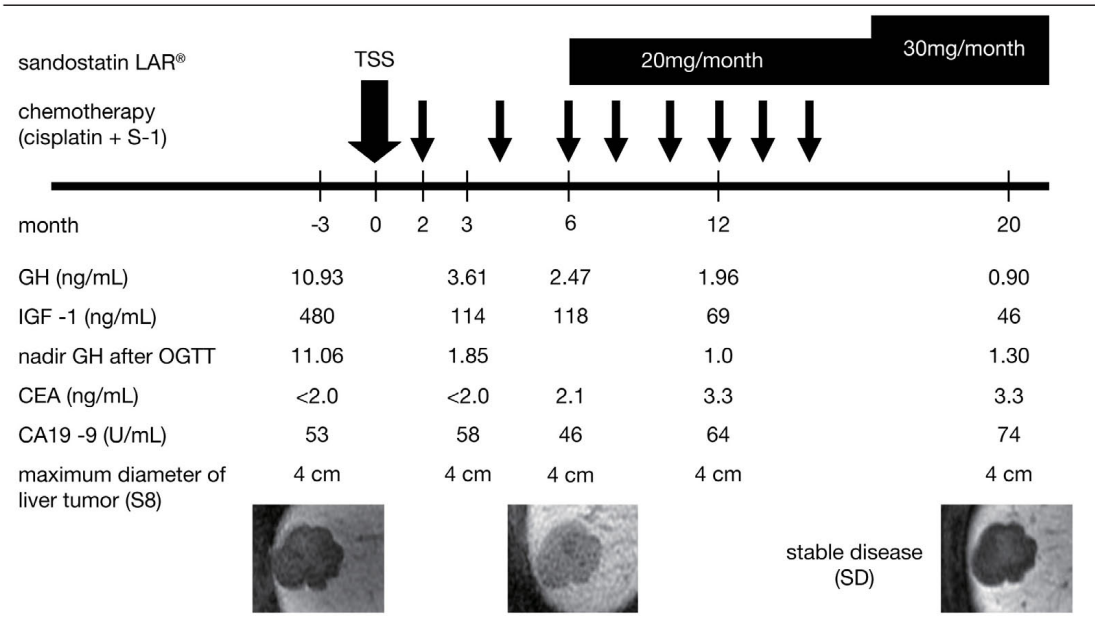

Fig. 2 Clinical course
TSS, transsphenoidal surgery; S8, segment 8 of the liver

treated surgically, but chemotherapy (neoadjuvant cisplatin (CDDP) and S-1) was administered at 2 months. After 24 months, the patient's IGF-I level was normalized (46 ng/mL), the liver tumors had not progressed macroscopically, and the tumor response was classified as stable according to the Response Evaluation Criteria in Solid Tumors (RECIST) (Fig. 2).

Discussion

To the best of our knowledge, this is the first reported case of acromegaly complicated by multiple tumors, including duodenal and thyroid adenocarcinomas. Ectopic growth hormone-releasing hormone (GHRH) secretion by a neuroendocrine tumor [13-15] seems unlikely to have been the cause of acromegaly in our patient because pituitary MRI and histological findings revealed a pituitary macroadenoma, rather than a hyperplasia.

Primary adenocarcinoma of the duodenum is rare, accounting for less than 0.5% of all gastrointestinal tract malignant neoplasms and up to 45% of small bowel cancers [16-20]. Generally, the prognosis in duodenal adenocarcinoma is poor, and early surgery is required for long-term survival [21-24]. No effective therapy has been established for inoperable duodenal adenocarcinoma. In a recent large retrospective study, 80 patients with small bowel adenocarcinoma received chemotherapy regimen with or without 5-fluorouracil and platinum agent; the response rate was 41% and progression-free survival was 8.7 months [25]. Our patient has survived for more than 24 months without progression of the primary and metastatic lesions, despite not undergoing surgical resection. Several possible reasons may explain this outcome. First, the duodenal adenocarcinoma might have been predominantly a neuroendocrine tumor of low malignancy potential, rather than a common adenocarcinoma. Second, the octreotide treatment may have had a direct beneficial effect on the duodenal carcinoma *via* SSTR2a and an indirect effect *via* the suppression of GH release from the GH-producing pituitary adenoma. Indeed, immunohistochemical SSTR2a status is correlated with response to treatment with octreotide [12]. Third, chemotherapy (CDDP and S-1) might have had a beneficial effect for suppression of inoperable duodenal adenocarcinoma. However, given the response rate and efficacy of chemotherapy reported [26], contribution of chemotherapy to tumor suppression may be quite partial compared with that of octreotide.

Our patient suffered tumors in multiple endocrine organs: GH-producing pituitary adenoma, papillary adenocarcinoma of the thyroid with family history, and duodenal adenocarcinoma with neuroendocrine

features. Some reports indicate association between acromegaly and papillary carcinoma of the thyroid [27]. In our patients, causal association between acromegaly and papillary carcinoma seems less likely because the patient was diagnosed with thyroid papillary carcinoma 8 years before she was diagnosed with acromegaly at age of 67. However, we cannot completely rule out the possibility of their association. These tumors are not typically seen in conventional MEN. MEN type 1 (MEN1) is diagnosed by the presence of at least two of the three main MEN1-related endocrine tumors (parathyroid adenomas, entero-pancreatic endocrine tumors, and pituitary tumors) [28]. Primary hyperparathyroidism is the most precocious and frequent clinical presentation of MEN1, with a prevalence of 100% at age of 50 [29], and *MEN1* gene mutations are identified in approximately 80-90% of familial cases [28]. Considering high prevalence of hyperparathyroidism and other involved organs in MEN1, our case was not diagnosed with conventional MEN1 because she presented with only one of the three main MEN1-related endocrine tumors (pituitary adenoma) and was negative for *MEN1* mutations. Because our case has not produced a clinical picture similar to known MEN and there was no apparent familial clustering of tumors except papillary thyroid carcinoma, we did not perform genetic testing except for *MEN1* gene mutation. MEN1 has a heterogeneous nature and causes any combination of more than 20 endocrine and non-endocrine lesions [28]. Indeed, a new type of MEN has been reported as Carney complex, an autosomal dominant condition comprising myxomas of the heart and skin, hyperpigmentation of the skin, and endocrine overactivity [30]. Our case had a unique combination of endocrine neoplasia, including acromegaly, thyroid papillary carcinoma, duodenal adenocarcinoma with neuroendocrine features and multiple skin vegetations, but had no parathyroid and pancreas diseases. Causative gene mutations of genetic diseases have not yet been revealed fully. For instance almost 80% of causal gene mutations of maturity-onset diabetes of the young (MODY) is still unknown [31]. Similarly, many causative gene mutations of familial tumor syndrome including MEN are thought to be unknown [32]. Also, the penetrance of the causal gene and disease onset may be variable depending on the mode of hereditary and gene expression, respectively. Possible multiple endocrine neoplasia might be variable in combination of the involved organs depending on the responsible genes. Therefore, in order to categorize a novel form of MEN in future, it is important to accumulate clinical information, the genome and the involved tissues of various cases with unique combination of involved organs. Such registration will lead to future linkage analyses for identifying responsible gene.

In summary, we have presented a rare case of acromegaly associated with multiple tumors (GH-producing pituitary adenoma, thyroid papillary adenocarcinoma with familial clustering, and duodenal adenocarcinoma with neuroendocrine features). Octreotide treatment might have had beneficial effects on our patient's duodenal adenocarcinoma and liver metastases, both directly *via* SSTR2a and indirectly *via* GH suppression, thereby contributing to their slow progression.

References

1. Ma J, Pollak MN, Giovannucci E (1999) Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. *J Natl Cancer Inst* 91: 620-625.
2. Giovannucci E, Pollak MN, Platz EA (2000) A prospective study of plasma insulin-like growth factor-1 and binding protein-3 and risk of colorectal neoplasia in women. *Cancer Epidemiol Biomarkers Prev* 9: 345-349.
3. Hankinson SE, Willett WC, Colditz GA (1998) Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. *Lancet* 351: 1393-1396.
4. Wu X, Liu F, Yao X (2007) Growth hormone receptor expression is up-regulated during tumorigenesis of human colorectal cancer. *J Surg Res* 143: 294-299.
5. Gebre-Medhin M, Kindblom LG, Wennbo H (2001) Growth hormone receptor is expressed in human breast cancer. *Am J Pathol* 158: 1217-1222.
6. Jenkins PJ (2006) Cancers associated with acromegaly. *Neuroendocrinology* 83: 218-223.
7. Popovic V, Damjanovic S, Micic D (1998) Increased incidence of neoplasia in patients with pituitary adenomas. *Clin Endocrinol (Oxf)* 49: 441-445.
8. Kurimoto M, Fukuda I, Hizuka N (2008) The prevalence of benign and malignant tumors in patients with acromegaly at a single institute. *Endocr J* 55: 67-71.
9. Loeper S, Ezzat S (2008) Acromegaly: re-thinking the cancer risk. *Rev Endocr Metab Disord* 9: 41-58.
10. Orme SM, McNally RJ, Cartwright RA (1998) Mortality and cancer incidence in acromegaly: a retrospec-

tive cohort study. United Kingdom Acromegaly Study Group. *J Clin Endocrinol Metab* 83: 2730-2734.
11. Ron E, Gridley G, Hrubec Z (1991) Acromegaly and gastrointestinal cancer. *Cancer* 68: 1673-1677.
12. Volante M, Brizzi MP, Faggiano A (2007) Somatostatin receptor type 2A immunohistochemistry in neuroendocrine tumors: a proposal of scoring system correlated with somatostatin receptor scintigraphy. *Mod Pathol* 20: 1172-1182.
13. Zatelli MC, Maffei P, Piccin D (2005) Somatostatin analogs in vitro effects in a growth hormone releasing hormone-secreting bronchial carcinoids. *J Clin Endocrinol Metab* 90: 2104-2109.
14. Faglia G, Arosio M, Bazzoni N (1992) Ectopic acromegaly. *Endocrinol Metab Clin North Am* 21: 575-595.
15. Biermasz NR, Smit JWA, Pereira AM (2007) Acromegaly caused by growth hormone-releasing hormone-producing tumors: long-term observational studies in three patients. *Pituitary* 10: 237-249.
16. Alwmark A, Andersson A, Lasson A (1980) Primary carcinoma of the duodenum. *Ann Surg* 191: 13-18.
17. Cortese AF, Cornell GN (1972) Carcinoma of the duodenum. *Cancer* 29: 1010-1015.
18. Spira IA, Ghazi A, Wolff WI (1977) Primary adenocarcinoma of the duodenum. *Cancer* 39: 1721-1726.
19. van Ooijen B, Kalsbeek HL (1988) Carcinoma of the duodenum. *Surg Gynecol Obstet* 166: 343-347.
20. Barnes G Jr, Romero L, Hess KR (1994) Primary adenocarcinoma of the duodenum:management and survival in 67 patients. *Ann Surg Oncol* 1: 73-78.
21. Joesting DR, Beart RW Jr, van Heerden JA, Weiland LH (1981) Improving survival in adenocarcinoma of the duodenum. *Am J Surg* 141: 228-231.
22. Rose DM, Hochwald SN, Klimstra DS (1996) Primary duodenal adenocarcinoma: a ten-year experience with 79 patients. *J Am Coll Surg* 183: 89-96.
23. Scott-Coombes DM, Williamson RCN (1994) Surgical treatment of primary duodenal carcinoma: a personal series. *Br J Surg* 81: 1472-1474.
24. Sohn TA, Lillemoe KD, Cameron JL (1998) Adenocarcinoma of the duodenum:factors influencing long-term survival. *J Gastrointest Surg* 2: 79-87.
25. Overman MJ, Kopetz S, Wen S (2008) Chemotherapy with 5-fluorouracil and a platinum compound improves outcomes in metastatic small bowel adenocarcinoma. *Cancer* 113: 2038-2045.
26. Kang SM, Murata A, Tendou M (2009) A case report of primary duodenal adenocarcinoma with marked lymph node metastases responding to chemotherapy with S-1 plus CDDP combination. *Jpn J Cancer Chemother* 36: 1569-1571 (In Japanese).
27. Patrizia T, Maria RA, Claudia S (2005) High prevalence of differentiated thyroid carcinoma in acromegaly. *Clin Endocrinol* 63: 161-167.
28. Brandi ML, Gagel RF, Angeli A (2001) Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 86: 5658-5671.
29. Brandi ML, Marx SJ, Aurbach GD (1987) Familial multiple endocrine neoplasia type I: a new look at pathophysiology. *Endocr Rev* 8: 391-405.
30. Carney J, Gordon H, Carpenter P (1985) The complex of myxomas, spotty pigmentation, and endocrine overactivity. *Medicine* 64: 270-283.
31. Horikawa Y, Miyake K, Kazuki Y, et al (2008) Replication of genome-wide association studies of type 2 diabetes susceptibility in Japan. *JCEM* 93: 3136-3141.
32. Georgitsi M (2010) MEN-4 and other multiple endocrine neoplasias due to cyclin-dependent kinase inhibitors ($p27^{Kip1}$ and $p18^{INK4C}$) mutations. *Best Pract Res Clin Endocrinol Metab* 24: 425-437.