REVIEW

Pancreatic GHRHomas in Patients with or without Multiple Endocrine Neoplasia Type 1 (MEN 1) : An Analysis of 36 Reported Cases

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Abstract : Pancreatic GHRHomas (pGHRHomas) with acromegaly have unique conditions, harboring the existence of multiple endocrine neoplasia type 1 (MEN 1). Moreover, pituitary lesions are affected by both protracted ectopic GHRH and loss of menin function. Of significance is the clarification of clinicopathological aspects of pGHRHomas in patients with or without MEN 1. From 1977-2016, thirty-six patients with pGHRHomas were reported. Twenty-two out of 36 patients (61%) had pGHRHomas with MEN 1 and 14 patients did not. The former had a tendency of male predominance, benign tumor behavior and fewer metastasis rather than the latter. The latter is a single pGHRHoma accompanied by pituitary enlargement with somatotroph hyperplasia (hyperplasia) caused by protracted ectopic GHRH. Nine patients with MEN 1 underwent transsphenoidal surgery (TSS). The hyperplasia associated with various pituitary adenomas (PAs) including three GH-related adenomas was observed in seven subjects (32%). In these patients, the resection of their pGHRHomas was feasible. Furthermore, all patients with acromegaly due to pGHRHomas without MEN 1 had non-TSS, whereas approximately 70% of those with MEN 1 had unnecessary TSS. The association with hyperplasia and various PAs suggested that formation of the three GH-related adenomas may be induced by the foundations of MEN 1 gene mutations. J. Med. Invest. 71 : 1-8, February, 2024

Keywords **:** *pancreatic GHRHoma, MEN 1, acromegaly, somatotroph hyperplasia, GH adenoma formation*

INTRODUCTION

Neuroendocrine neoplasms (NENs) secreting growth hormone (GH)-releasing hormone (GHRH) are referred to as GHRHomas (1, 2) and result in acromegaly that arises from NENs of the lung (50%), pancreas (35%), small intestine (7%) and others (8%). These GHRHomas are diagnosed by the elevation of circulating GHRH concentrations. Since 1977, approximately one hundred patients with acromegaly due to GHRHomas were reported (3), wherein pancreatic (p) GHRHomas were observed in thirty-six patients, harboring the existence of multiple endocrine neoplasia type 1 (MEN 1) syndrome. Recently, a collective understanding of MEN 1 has advanced : MEN 1 is an autosomal dominant disorder due to MEN 1 gene mutations and subsequent tumor formation in the parathyroids, pancreas and anterior pituitary (2). In 1988, the MEN 1 gene was observed as a tumor suppresser gene, located on chromosome11q13 closely linked to the skeletal muscle glycogen phosphorylase (PYGM) locus (4). In 1997, the MEN 1 gene was identified by positional cloning, and encoded a 610-amino acid protein referred to as "menin" (5, 6). Consequently, pituitary GHRH-related lesions are affected by both protracted ectopic GHRH and menin loss of function (the two factors). Of particular interest it is whether these characteristics may play a role in GH adenoma formation. Thus, the clarification of the clinical and pathological aspects of pGHRHomas in patients with or without MEN 1, especially those with pituitary lesions, is investigated in this article.

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PATIENTS AND METHODS

A search for the cases of pGHRHomas in the literature was performed using PubMed, Google Scholar, and Journal of Health Care and Society (in Japanese). The 36 reported patients with pGHRHomas were collected from 1977 to 2016. Statistical analysis was performed using the statistical software of JMP Pro 17 (SAS Institute Tokyo Japan). Comparisons of frequencies were performed by the Peason X^2 test or with Fisher exact test. Medians comparison was realized by Willcoxson's two-sample test. A P value < 0.05 was considered as statistically significance.

CLINICAL AND PATHOLOGICAL ASPECTS OF PGHRHOMAS IN PATIENTS WITH OR WITHOUT MEN 1

In 1982, GHRH was isolated simultaneously by two groups, of whom Guillemin R, *et al*. (7) identified GHRH-44, -40, and -37 amino acids from the pancreatic tumor of a male patient with acromegaly in the presence of MEN 1. Another GHRH-40 was characterized by Rivier J, *et al*. (8) from the pancreatic tumor of a female patient with acromegaly without MEN 1. Thirty-six cases with similar patients including the above two cases were reported in the English literature. All patients with pGHRHomas (cases 1-36) are listed in Tables 1 and 2 ; of whom 22 patients (61%) had pGHRHomas with MEN 1 and the remaining 14 patients were those without MEN 1. Although the clinical classification of pGHRHomas in patients with MEN 1 or in those patients without is cautious due to unconfirmed information, the association with hyperparathyroidism (HPT) and/or histological pituitary adenomas (PAs) indicates the presence of MEN 1. Four patients were non-acromegalic, two of them (cases 13 and 19) underwent laparotomy such that they did not proceed to development of features of acromegaly (9, 10) and the others were

Table 1. Pancreatic GHRHomas in patients with MEN 1

No	Age/Sex Authors References	Reported	GHRH (ng/mL)	HPT	Histology of PNENs	Elevation of PRL	Pituitary imaging	TSS	Pituitary histology	Outcome after laparotomy	Comments
1[a]	39/F Aida M, *et al.* 12, 35	1977	Tumor tissue 0.6 μg/g	Yes	Carcinoid like (approx. 10 cm)	Yes	Enlarged	Yes	Chromo-phobe adonoma	Remission	
2	55/M Sassolas G, *et al.* 7, 37, 38	1983	50	Yes	Well-differentiated thymic tumor (25 cm)	Yes	Enlarged	No	At autopsy ; a diffused micro-nodular hyperplasia	Remission	Isolation of GHRH-44, -40, -37 amino acid
3	25/F Wilson DM, *et al.* 39, 40	1984	5.6	Yes	Islet cell carcinoma H-M (NA)	No	Non-homo-genous mass	No	No	Progress of acromegaly	ZES
4	58/F Ch'ng JLC, *et al.* 41, 42	1985	11.5	Yes	APUD-oma H-M (NA)	NA	Enlarged	No	No	Inoperable (biopsy)	ZES
5	30/F Asa SL. *et al.* 11	1987	1.03	Yes	NET (4.5 cm)	Yes	A tumor	No	No		Non-acromegalic Prolactinoma treated with DA
6[a]	36/M Sano T, *et al.* 14, 15	1987	0.299	Yes	NET (6.5 cm)	No	Enlarged (a tumor like)	Yes	GH adenoma+ Null cell adenoma	Partial remission	LOH of PYGM locus in P-triad
7	28/F Ramsay JA, *et al.* 43	1988	0.52	Yes	WDET (NA)	Yes	Enlarged	No	No	Remission	
8[a]	42/M Price DE, *et al.* 44	1992	3.0	Yes	NET (NA)	Yes	Enlarged	No	No	Died 5 weeks after laparotomy	
9[a]	36/M Bertherat J, *et al.* 45	1994	5.9	Yes	NET (5 cm)	Yes	Invasive pituitary tumor	Yes	Gonado-troph adenoma+ hyperplasia	Remission	
10[a]	51/M Liu SW, *et al.* 46	1996	3.8	Yes	NET (5 cm)	NA	Asym-metry	Yes	Hyper-plasia	Remission	
11	27/M Suga K, *et al.* 36	2002	GHRH-positive cells	Yes	NET (7 cm)	Yes	A tumor	Yes	Chromo-phobe adenoma	Remission	
12	50/M Biermasz NR, *et al.* 47	2007	3.8	Yes	NET (4 cm)	NA	No ab-normality	Yes	Hyper-plasia	Remission	
13[a]	31/M Sugihara H, *et al.* 9	2007	0.861	Yes	WDET (2.2 cm)	Yes	Enlarged	No	No	Shrinkage of pituitary enlarge-ment	Non-acromegalic
14[a]	46/F Weiss DE, *et al.* 22	2011	2.6	Yes	NET (6.2 cm)	Yes	Seller mass	Yes	PRL-ACTH adenoma+ null cell adenoma+ hyperplasia	Remission	c.152_160 dell19, ex2
15[a]	35/F Garby L, *et al.* 10	2012	2.6	Yes	WDET (8 cm)	Yes	Macro-adenoma	No	No	Remission	c.1325 delG, ex9
16	34/F Garby L, *et al.* 10	2012	0.512	Yes	WDEC H-M (4.5 cm)	Yes	Macro-adenoma	Yes	Hyper-plasia+ PRL-GH adenoma		c.1650inC, ex10

No	Age/Sex Authors References	Reported	GHRH (ng/mL)	HPT	Histology of PNENs	Elevation of PRL	Pituitary imaging	TSS	Pituitary histology	Outcome after laparotomy	Comments
17	47/M Garby L, *et al.* 10	2012	0.721	Yes	NA H, P-M (1.3 cm)	Yes	Macro-adenoma	Yes	Hyper-plasia+ PRL-GH adenoma	Death due to ileal carcinoma	
18	67/M Garby L, *et al.* 10	2012	0.545	Yes	NA H, P-M (4.3 cm)	NA	Normal	No	No	Stability of tumoral disease	c.1607 delA, ex10
19[a]	37/M Garby L, *et al.* 10	2012	0.27	Yes	WDET (5 cm)	NA	Micro-cystic lesion	No	No		Non-acromegalic c.1325delG, ex9
20	17/M Garby L, *et al.* 10	2012	0.534	No	WDEC (7 cm)	Yes	Macro-adenoma	No	No	Stable	Prolactin-oma treated with DA
21[a]	36/M Saleem TFM. *et al.* 48	2012	4.8	Yes	NET (6.2 cm)	Yes	Enlarged	No	No	Remission	
22[a]	18/M Sala E, *et al.* 24	2013	0.06	Yes	NET (1.5 cm)	No	Enlarged	No	No	Remission	c.207delC ; p. P69PtsX 118

[a] Familial MEN 1 ; GHRH, growth hormone-releasing hormone ; HPT, hyperparathyroidism ; PNENs, pancreatic neuroendocrine neoplasms ; PRL, prolactin ; TSS, transsphenoidal surgery ; NA, not available ; H, liver ; P, pulmonary ; M, metastasis or metastases ; ZES, Zollinger-Ellison syndrome ; NET, neuroendocrine tumor ; WDET, well-differentiated endocrine tumor ; WDEC, well-differentiated endocrine carcinoma ; hyperplasia, somatotroph hyperplasia ; DA, dopamine agonists ; LOH, loss of heterozygosity ; PYGM, skeletal muscle glycogen phosphorylase ; P-triad, parathyroids, pancreas and pituitary.

prolactinoma (case 5) (11) and ectopic ACTH syndrome (case 26) (12, 13).

MOLECULAR AND GENETIC ASPECTS OF PGHRHOMAS IN PATIENTS WITH MEN 1

In a series of 22 patients with pGHRHomas accompanied by MEN 1, a fact of significance is that the loss of heterozygosity (LOH) of the PYGM locus on chromosome 11_q 13 in the P-triad (parathyroids, pancreas and pituitary) including a pGHRHoma, was demonstrated in humans (case 6) (14, 15). This suggests that the mechanism of tumor formation was explained by Knudson's "two-hits" hypothesis (16, 17) and the LOH led to tumorigenesis of specific organs (P-triad). In 2001, Crabtree JS, *et al.* (18) reported that heterozygous *Men 1* mutant mice developed pancreatic islet tumors and parathyroid adenomas as early as nine months, involving the tumorigenesis of the pituitary and the adrenal cortex by 12 months, which was confirmed by Bertolino P, *et al.* (19). The DNA testing of MEN 1 gene mutations disclosed that generally a comparison of the clinical features in patients and their families with the same mutations revealed an absence of a phenotype-genotype correlation (20, 21), whereas two patients (cases 15 and 19) with pGHRHomas in the same family having MEN 1 mutations (c.1325 del G, ex9) were extremely rare (10). Pancreatic neuroendocrine tumors (PNETs) with MEN 1 gene mutations of exon 2, which was demonstrated in case 14 (c.152_160del 119, ex2) (22), had malignant behavior, noted on long time follow up (23).

DISTINCTION OF CLINICOPATHOLOGICAL ASPECTS IN PATIENTS WITH PGHRHOMAS BETWEEN THE PRESENCE OF MEN 1 AND THE ABSENCE OF MEN 1

As displayed in Table 3, a female predominance ($P = 0.0043$) in patients accompanied by pGHRHomas without MEN 1 was observed, whereas a moderate increase of frequency in males with MEN 1 was demonstrated. The circulating GHRH concentration of pGHRHomas in patients with MEN 1 was 1.815 ng/mL (median, range 0.06-50 ng/mL) and 1.123 ng/mL (median, range 0.293-38.9 ng/mL) in those without MEN 1, wherein no significant difference was observed as well as in terms of age. The lowest GHRH concentration of 60.14 pg/mL (normal value, 9.4±5 pg/mL) was detected in case 22 (24) ; however, the evaluation of this GHRH amount in comparison with other data is difficult due to a different GHRH assay system. A marked difference of plasma GHRH concentrations of the same sample as measured by different GHRH assays was observed : e.g., 270 pg/mL by N-terminus and midportion assay with the preparation of plasma extract using an acid-acetone and petroleum ether method (recovery rate, 59%) (25) vs. 999 pg/mL by N-terminus assay using a hydrophobic Sep-Pac C_{18} and methanol method (recovery rate, 83%) (26). Importantly, observations from a French series of 21 cases, where circulating GHRH was measured by the same assay system, showed no correlation between GHRH concentrations in GHRHomas and tumor localization, size or extension. Furthermore, a threshold of GHRH concentration of 0.250 ng/mL (normal value, <0.03) was identified for diagnosing extracranial GHRHomas (10). The tumor size of pGHRHomas in patients with MEN 1 was 5.0 cm (median, range 1.3-25 cm)

Table 2. Pancreatic GHRHomas in patients without MEN 1

No	Age/Sex Authors References	Reported	GHRH (ng/mL)	Histology of PNENs	Elevation of PRL	Pituitary imaging	TSS	Pituitary histology	Outcome after laparotomy	Comments
23	30/F Caplan RH, *et al.* 49, 50	1978	NA	Islet cell tumor (10 cm)	NA	Asym-metry	No	No	Remission	GHRH bioactivity in tumor extract
24	21/F Thorner MO, *et al.* 8, 27	1982	NA	Islet cell tumor (5 cm)	Yes	Enlarged	Yes	Hyperplasia	Remission	Isolation of GHRH-40
25	54/F Seager W, *et al.* 28, 29	1986	1.1	Islet cell tumor (10 cm)	Yes	A pituitary tumor	Yes	NA	Remission	
26	41/F Sasaki A, *et al.* 12, 13	1987	9.9	NEC H, Pe-M (NA)	No	NA	No	No	Inoperable	Non-acromegalic, Ectopic ACTH syndrome
27	52/F Genka S, *et al.* 30, 31	1995	1.145	NEC (Islet cell carcinoma) (16.5 cm)	NA	Enlarged	Pituitary biopsy	Hyper-plasia+ metastatic GHRH-producing tumor	Death of cachexia due to metastases	
28	48/M Kawa S, *et al.* 51	1997	38.94	NEC (8.5 cm)	Yes	Enlarged	No	No	Remission	
29	60/F Minif Feki M, *et al.* 52	2011	0.604	NET (10 cm)	Yes	Empty sella	No	No	Remission	
30	29/F Garby L, *et al.* 10	2012	0.293	NA (6 cm)	NA	No abnor-mality	No	No	Remission	
31	14/M Garby L, *et al.* 10	2012	0.376	WDEC H, Pe-M (NA)	Yes	Macro-adenoma	Yes	Hyperplasia	Remission after a hepatic recurrence	
32	27/F Garby L, *et al.* 10	2012	0.548	WDEC H-M (7 cm)	NA	Enlarged	No	No	Remission	
33	36/F Garby L, *et al.* 10	2012	1.614	WDEC H, P, S-M (NA)	NA	Enlarged	No	No	Slowly progressive tumoral disease	
34	59/F Garby L, *et al.* 10	2012	0.35	WDEC H-M (4 cm)	NA	Enlarged	No	No	Progressive tumoral disease	
35	34/F Garby L, *et al.* 10	2012	1.297	WDEC H, A-M (1.0 cm)	Yes	Normal	No	No	Stability of tumoral disease	
36	57/F Zornitzki T, *et al.* 53	2016	1.273	NET (6 cm)	No	Enlarged	No	No	Remission	

GHRH, growth hormone-releasing hormone ; PNENs, pancreatic neuroendocrine neoplasms ; PRL, prolactin ; TSS, transsphenoidal surgery ; NA, not available ; H, liver ; P, pulmonary ; M, metastasis or metastases ; NET, neuroendocrine tumor ; WDET, well-differentiated endocrine tumor ; WDEC, well-differentiated endocrine carcinoma ; hyperplasia, somatotroph hyperplasia ; NEC, neuroendocrine carcinoma ; Pe, peritoneal ; S, spleen ; A, adrenal gland.

and was 7.0 cm (median, range 1.0-16.5 cm) in those patients without MEN 1, showing no significance. Pancreatic neuroendocrine neoplasms (PNENs) consist of PNETs and pancreatic neuroendocrine carcinomas (PNECs). The PNETs, including well-differentiated endocrine tumors (WDETs), islet cell tumors, carcinoid tumors, and amine precursor uptake and decarboxylation cell tumors (APUDomas) with no distant metastasis, have a tendency towards benign behavior. On the contrary, PNECs including well-differentiated endocrine carcinomas (WDECs), islet cell carcinomas, carcinoid tumors and APUDomas with distant metastasis, have a tendency towards malignant behavior. The ratio of PNETs to PNECs in patients with MEN 1 was 16 : 6 vs. 6 : 8 in those without MEN 1 ($P = 0.0731$), and the ratio of non-metastasis to distant metastasis in the former was 17 : 5 vs. 7 : 7 in the latter ($P = 0.0906$), suggesting that the patients accompanied by pGHRHomas with MEN 1 have a tendency more towards benign behavior and fewer metastasis rather than that in those patients without MEN 1. It is important that the series of 14 patients without MEN 1 represent a considerable effort to clinicians in the diagnostic work up because of ectopic acromegaly or ectopic GHRH syndrome with pituitary enlargement (71%) caused by a single PNEN, suggesting like a MEN 1 syndrome (Table 4). The proper diagnosis and treatment require at least a routine chest X-ray and abdominal ultrasonography for all patients with acromegaly in facilities with no method of measurement of circulating GHRH.

PITUITARY LESIONS DUE TO PGHRHOMAS IN PATIENTS WITHOUT MEN 1

As shown Table 4, in a series of 14 patients with pGHRHomas but without MEN 1, three patients underwent transsphenoidal surgery (TSS). In 1982, Thorner MO, *et al*. (27) firstly reported that somatotroph hyperplasia (hyperplasia) caused by protracted ectopic GHRH secretion from a pancreatic tumor was observed in the pituitary lesion of an acromegalic female patient without MEN 1 (case 24). One of two patients with TSS (case 31) had hyperplasia (10), and the other (case 25) was histologically "unknown" whose acromegalic features were clinically "in remission" after laparotomy, suggesting the presence of hyperplasia in her pituitary lesion (28, 29). Six out of 14 patients (43%) after laparotomy without TSS were in remission of acromegaly. An elevation of prolactin (PRL) was present in six patients (43%) with no prolactinoma. The resection of their pGHRHomas was feasible. Thus, all acromegalic patients accompanied by pGHRHomas without MEN 1 have non-TSS. Although PNECs were occasionally associated with distant metastases, a female acromegalic patient (case 27) with distant metastases including her pituitary lesion which consisted of hyperplasia and a metastatic GHRH producing tumor, was a rare clinical condition (30, 31).

CHARACTERISTICS OF PITUITARY LESIONS DUE TO PGHRHOMAS IN PATIENTS WITH MEN 1

In series of 22 patients accompanied by pGHRHomas with MEN 1, nine of them (41%) underwent TSS before laparotomy except one with partial remission (case 6). Two patients had hyperplasia, whereas the remaining seven patients (32%) had an association with hyperplasia and PAs. Six patients (27%) after laparotomy without TSS were in remission of acromegaly or in shrinkage of pituitary enlargement. An elevation of PRL was present in 14 patients (64%), three of whom (cases 5, 14 and 20) were clinical and histological prolactinomas (10, 11, 22) (Table 4). Thus, an approximately 70% of the patients accompanied by

Table 3. Clinical aspects of pancreatic GHRHomas in patients with or without MEN 1

	Total patients (n)	F : M ratio	Age (year), median (range)	GHRH (ng/mL), median (range)	Tumor size (cm), median (range)	PNETs : PNECs ratio	Non-M : distant M ratio
pGHRHomas with MEN 1	22	8 : 14	36.5 (17-67)	1.815 (0.06-50)	5.0 (1.3-25)	16 : 6	17 : 5
pGHRHomas without MEN 1	14	12 : 2	34.5 (14-60)	1.123 (0.293-38.9)	7.0 (1.0-16.5)	6 : 8	7 : 7
P value		$P=0.0043$[a]	$P=0.7331$[b]	$P=0.6827$[b]	$P=0.2413$[b]	$P=0.0731$[a]	$P=0.0906$[a]

MEN 1, multiple endocrine neoplasia type 1 ; F, female ; M, male ; GHRH, growth hormone-releasing hormone ; PNETs, pancreatic neuroendocrine tumors ; PNECs, pancreatic neuroendocrine carcinomas ; M, metastasis or metastases ; pGHRHomas, pancreatic GHRHomas. A P value < 0.05 is significant level.
[a] Estimated by Fisher's exact test or X^2 test.
[b] Estimated by Wilcoxon's two-samples test.

Table 4. Pituitary imaging, pituitary surgery, hyperplasia, pituitary adenomas and prolactinomas in patients with or without MEN 1

	Pituitary enlargement	TSS	Hyperplasia	Hyperplasia associated with PAs	Remission after laparotomy[a]	Elevation of PRL	Clinical and histological prolactinomas
pGHRHomas with MEN 1 (n = 22)	19 (86%)	9 (41%)	2	7 (32%)	6 (27%)	14 (64%)	3[b] (14%)
pGHRHomas without MEN 1 (n = 14)	10 (71%)	3 (21%)	2[c]	0	6 (43%)	6 (43%)	0

Hyperplasia, somatotroph hyperplasia ; MEN 1, multiple endocrine neoplasia type 1 ; TSS, transsphenoidal surgery ; PAs, pituitary adenomas ; PRL, prolactin. [a] Did not undergo TSS. [b] Including cases 5, 14 and 20. [c] One of three patients with TSS was histologically unknown.

Table 5. Pathological aspects of the pituitary adenomas associated with somatotroph hyperplasia in seven patients with transsphenoidal surgery

Types of PAs	GH-related adenomas[a] (n)		Non-GH-related adenomas (n)	
Pathological aspects	GH adenoma	(1)	Chromophobe adenoma [b]	(2)
	PRL-GH adenoma	(2)	Null cell adenoma [c]	(2)
			Gonadotroph adenoma	(1)
			PRL-ACTH adenoma [d]	(1)

PAs, pituitary adenomas ; GH, growth hormone ; n, number of cases ; PRL, prolactin ; ACTH, adrenocorticotropic hormone.
[a] Referenced by Trouillas J, *et al*. (32).
[b] Suspicion of null cell adenoma (cases 1 and 11).
[c] Multiple adenomas (cases 6 and 14).
[d] Prolactinoma (case 14).

pGHRHomas with MEN 1 were treated with unnecessary TSS. According to the classification of PAs by Trouillas J, *et al*. (32), the pathological aspects of the PAs in seven patients who underwent TSS were as follows (Table 5) : 1) GH-related adenomas, including a GH adenoma and two PRL-GH adenomas were identified in three patients, and 2) other various PAs (non-GH-related adenomas), including two chromophobe adenomas (suspected null cell adenomas), two null cell adenomas with multiple adenomas in two patients (cases 6 and 14), a gonadotroph adenoma, and a PRL-adrenocorticotrophic hormone (ACTH) adenoma were observed.

CONSIDERATION OF "GH ADENOMA FORMATION" ACCOMPANIED BY GHRHOMAS

In 2006, Nasr C, *et al*. (33) described a female acromegalic patient with a pulmonary GHRHoma accompanied by distant metastases, wherein her pituitary lesion co-existed with a metastatic GHRH producing tumor, hyperplasia, and "focal neoplastic transformation". In this case, the GH adenoma formation may have been induced by the paracrine effect of GHRH secretion that was firstly demonstrated in humans as well as in animal experiments ; in 1992, Asa SL, *et al*. (34) demonstrated that GHRH transgenic mice induced hyperplasia and formed GH adenomas. On the contrary, pituitary lesions related to pGHRHomas in patients with MEN 1 were affected by the two factors. In addition, the details of the histological features of six patients were as follows : Firstly, the pituitary lesion (case 14) showed a PRL-ACTH adenoma, a null cell adenoma, and an association with hyperplasia detected in the adjacent pituitary gland (22). Secondly, two patients with acromegaly (cases 1 and 11) with similar clinical courses underwent TSS before laparotomy revealed chromophobe adenomas in both pituitary lesions. Despite the successful resection of the chromophobe adenomas, the elevation of GH and acromegalic features continued and these abnormalities disappeared after laparotomy, suggesting that hyperplasia coexisted with a chromophobe adenoma in the adjacent pituitary gland as well (12, 35, 36). Thirdly, the pituitary lesion (case 16) demonstrated an intimate association with a 1-mm PRL-GH adenoma accompanied by hyperplasia (10, 32). Fourthly, a patient (case 6) who underwent TSS six years after laparotomy had a GH adenoma, a null cell adenoma, and an association with non-tumorous residual fragments with a rich area of GH-positive cells bearing the normal architecture of the reticulin system, suggesting that the hyperplasia was histologically reversible for six years at least (15). Finally, at autopsy, the pituitary lesion (case 2) which was affected by the two factors (7, 37, 38) showed a diffused and micronodular hyperplasia with "no true adenoma" (32). These observations and the association with hyperplasia and various PAs in patients accompanied by pGHRHomas with MEN 1 suggested that formation of the three GH-related adenomas may have been induced by the foundations of MEN 1 gene disorders, such as LOH and menin inactivation, rather than by protracted ectopic GHRH.

CONCLUSION

The patients accompanied by pGHRHomas with MEN 1 had a tendency of male predominance, benign tumor behavior and fewer distant metastasis rather than those patients without MEN 1. The latter with hyperplasia required no TSS. On the contrary, seven out of 22 patients (32%) with pGHRHomas and MEN 1 had hyperplasia associated with PAs, indicating approximately 70% of them were unnecessary TSS. Pituitary lesions related to pGHRHomas in patients with MEN 1 had the association of hyperplasia and various PAs, suggesting that formation of the three GH-related adenomas may have been induced by the foundations of MEN 1 gene mutations.

CONFLICT OF INTEREST

The author declares there is no conflict of interest.

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ADDENDUM

Of particular importance was that the 5th World Health Organization (WHO) classification (2021) renamed PAs as pituitary neuroendocrine tumors (PitNETs) and changed their behavior code from "0" to "3". However, this article uses the term PAs as before, since it reviews studies from 1977 to 2016.

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