Table 3 The pathological classification based on endoscopic findings in patients with acromegaly in this study

(a) Pathology

Pathological findings	Total (n = 57)
No neoplasms	14 (24.5)
Hyperplastic polyps	22 (38.6)
Adenomas	18 (31.6)
Adenocarcinomas	3 (5.3)

(b) A comparison with irritable bowel syndrome [16]

Pathological findings	Total (n = 2,323)	*P* value
No neoplasms	2,009 (90.6)	<0.0001
Hyperplastic polyps	223 (6.7)	<0.0001
Adenomas	84 (2.5)	<0.0001
Adenocarcinomas	7 (0.2)	<0.0001

Pathological findings	Odds ratio (95 % CI)
Hyperplastic polyps	4.0 (2.9, 5.1)
Adenomas	8.7 (6.0, 11.4)
Adenocarcinomas	17.5 (5.2, 29.8)

(c) Age distribution

Age (year)	Prevalence
<40	7/12 (58.3)
40–49	12/16 (75.0)
50–59	12/14 (85.7)
60<	12/15 (80.0)

(d) Number and site distribution of hyperplastic polyps and adenomas

	Hyperplastic polyps (n = 14)	Adenomas (n = 11)
Single	3 (21.4)	4 (36.4)
Multiple	11 (78.6)	7 (63.6)

Site distribution	Hyperplastic polyps	Adenomas
Cecum	0 (0)	1 (4.8)
Ascending colon	3 (15.0)	5 (23.8)
Transverse colon	2 (10.0)	3 (14.3)
Sigmoid colon	4 (20.0)	7 (33.3)
Descending colon	0 (0)	3 (14.3)
Rectum	11 (55.0)	2 (9.5)

(e) Colon diverticulum

Prevalence of colon diverticulum
6/28 (21.4)

Number of diverticulum	Number of case
3	1 (16.7)
2	1 (16.7)
1	4 (66.7)

Location of diverticulum	Number of case
Ascending colon	6 (66.7)
Sigmoid colon	2 (22.2)
Descending colon	1 (11.1)

Numbers in brackets show percentage. (b) Asian patients with irritable bowel syndrome in the previous report [16] were compared with the patients in this study. *P* values show the results of the χ^2 statistics with Yate's correction test. Odds ratio was described with 95 % confidence interval

diverticulum was detected predominantly in the ascending colon (66.7 %).

We next compared the profile of colorectal neoplasms with those reported in previous studies on acromegaly (Caucasian in Italy, n = 235 [11] and Caucasian in U.K., n = 115 [18]; Fig. 1a). The prevalence of colorectal neoplasms in our study (74.1 %) was significantly higher than that in the previous studies ($P < 0.0005$ [11] and $P < 0.01$ [18]). Of the patients with acromegaly, 38.6 % of patients in our study had hyperplastic polyps compared to 19.1 and 32.2 % of patients with acromegaly in the previous studies. The prevalence of adenomas was 26.3 % in our study compared to 23.4 and 19.1 % in the previous studies. Further, adenocarcinoma was diagnosed in 5.3 % of patients in our study compared to 4.3 and 2.6 % of patients in the previous studies. Thus, the prevalence of hyperplastic polyps was significantly higher in our study than in the Italian study. Next, we compared the prevalence of adenomas and adenocarcinomas between the acromegalic patients in our study and historical Japanese control subjects who were asymptomatic at colonoscopy [19] (Fig. 1b). Patients were excluded who reported symptoms of disease of the lower gastrointestinal tract, including visible rectal bleeding, recent change in bowel habits, and lower abdominal pain, from the analysis [19]. The combined prevalence of adenomas and adenocarcinomas in our patients aged <40, 40–49, 50–59, and ≥60 years were 16.7, 37.5, 50.0, and 40.0 %, respectively. There was no difference in any age band between patients with acromegaly and the asymptomatic control subjects, with prevalence showing a tendency to increase in patients with acromegaly in their 40 and 50 s (Fig. 1b).

Adenocarcinomas

We compared the prevalence of adenocarcinomas in patients with acromegaly in our study with that among historical Japanese control subjects, who were recruited using similar inclusion criteria, as previously described [20] (Table 4). With regard to background characteristics, age did not differ significantly between the two groups ($P = 0.0890$), whereas the proportion of male individuals

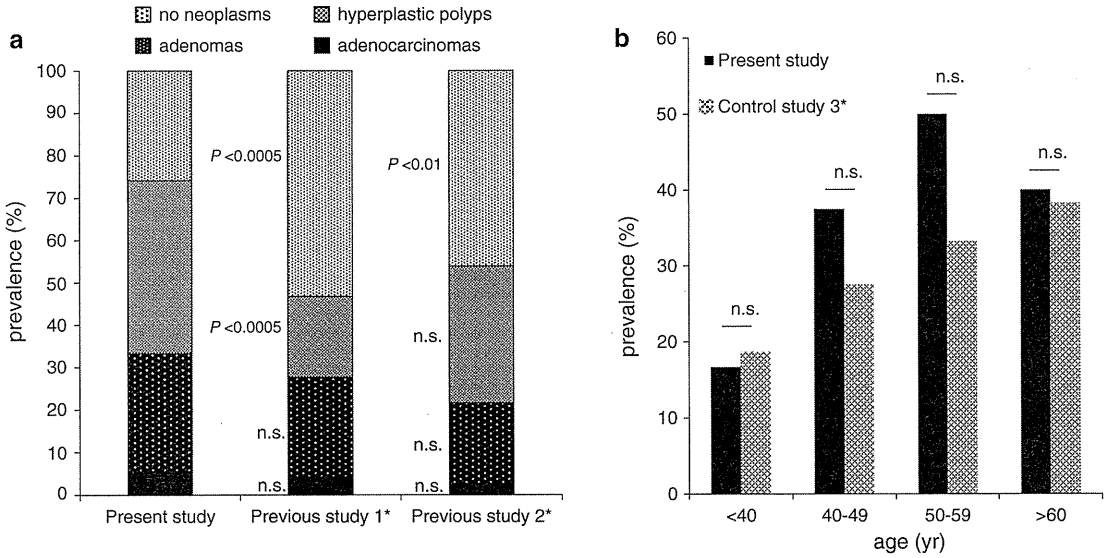

Fig. 1 Comparison with the previous reports in prevalence of colorectal neoplasms by histological classification (**a**). The prevalence of adenomas and adenocarcinomas by age was compared with the previous report (**b**). *P* values show the results of the Fisher's exact test versus present study. 1*: Ref. [11], 2*: Ref. [18], 3*: Ref. [19]

Table 4 Prevalence of colon cancer in acromegaly versus control

	Acromegaly	Control[a]	*P* value
No. of patients with colon cancer	3	79	
No. of patients who performed colonoscopy	57	21,805	
Prevalence of male (%)	42.1	72.0	<0.0001
Age (mean ± SD, year)	50.3 ± 12.9	48.2 ± 9.3	0.089
Prevalence of colon cancer (%)	5.3	0.4	<0.0001
Odds ratio (95 % CI)	14.5 (5.8,23.3)		

Asymptomatic Japanese control subjects in the previous report [20] were compared with the patients with acromegaly. *P* values show the results of the χ^2 statistics with Yate's correction test. a: Ref. [20]

was significantly higher in the control subjects than in the patients with acromegaly ($P < 0.0001$). Male sex and advanced age have been reported to be associated with a higher prevalence of colorectal adenocarcinomas [21]. Although acromegaly group showed a female predominance and tendency of higher age, we found that the prevalence of adenocarcinomas in the patients with acromegaly was significantly higher (14.5-fold higher) than that in the asymptomatic control subjects ($P < 0.0001$).

Differences in characteristics between patients according to the type of colorectal neoplasm

We further compared endocrinological and metabolic parameters between patients with acromegaly in this study according to the type of colon neoplasm (Table 5; Fig. 2). Basal GH and IGF-I levels, glycated hemoglobin levels, HOMA-IR, and HOMA-β did not differ significantly between these patient groups (Table 5), nor did the serum IGF-I SD score (Fig. 2a). However, the GH AUC was significantly higher in patients with adenocarcinomas than in those with no colonic lesion or those with hyperplastic polyps (Fig. 2b).

Discussion

In this study, we found that the prevalence of colorectal neoplasms, especially colorectal adenocarcinomas was significantly higher in Japanese patients with acromegaly than in historical control subjects. Furthermore, the presence of colorectal neoplasms was associated with disease duration, and the GH AUC was higher in patients with adenocarcinomas than in those with no colonic lesion or those with hyperplastic polyps. Recently, Tanimoto et al. [6] reported that the prevalence of colorectal neoplasms showed an age-dependent increase, a finding that corresponds with our data. Another study also revealed a high prevalence of colorectal adenocarcinomas (11.4 %) in Japanese patients with acromegaly [7]. Taken together, it is consistent that the prevalence of colorectal neoplasms is increased in Japanese patients with acromegaly as reported in Caucasian patients [4, 11, 18, 22].

Our study was limited by the relatively small number of patients and the fact that the control individuals were historical subjects. Only three patients had colorectal adenocarcinomas,

Table 5 The profile among patients with each type of colon neoplasms

	No neoplasms	Hyperplastic polyps	Adenomas	Adenocarcinomas	*P* value
No. of patients (%)	14 (24.5 %)	22 (38.6 %)	18 (31.6 %)	3 (5.3 %)	
No. of males/females	6/8	9/13	8/10	1/2	
Age (year)	47.1 ± 15.2	49.7 ± 1.9	52.7 ± 11.4	54.3 ± 12.5	0.56
Disease duration (years)	6.4 ± 5.2	10.2 ± 7.1	12.9 ± 10.4	10.0 ± 7.0	0.08
BMI (kg/m^2)	26.6 ± 6.0	24.5 ± 3.9	25.4 ± 3.8	24.4 ± 1.8	0.85
Basal GH levels (ng/mL)	18.4 ± 17.1	27.8 ± 36.0	37.1 ± 37.2	34.6 ± 11.0	0.14
Nadir GH levels after oral glucose (ng/mL)	13.2 ± 9.4	22.9 ± 32.2	24.2 ± 27.0	32.6 ± 11.0	0.15
IGF-I levels (ng/mL)	852.5 ± 426.4	745.6 ± 300.9	752 ± 331.6	770.6 ± 347.5	0.91
HbA1c (%)	5.6 ± 0.9	6.0 ± 1.9	7.0 ± 3.0	5.5 ± 0.6	0.33
Fasting glucose level (mg/dL)	92.6 ± 19.2	98.9 ± 17.6	135.9 ± 91.0	85.7 ± 6.4	0.06
Fasting insulin level (mU/mL)	11.3 ± 7.7	12.9 ± 16.3	8.8 ± 5.1	5.7 ± 4.6	0.59
HOMA-R index	2.6 ± 1.7	3.5 ± 6.2	2.6 ± 1.5	1.2 ± 1.1	0.48
HOMA-β index	183.1 ± 151.2	140.2 ± 123.0	91.3 ± 72.7	81.9 ± 43.4	0.27
Insulinogenic index	1.1 ± 1.6	0.9 ± 0.08	0.8 ± 1.0	0.6 ± 0.3	0.69

Data are shown as mean ± SD. *P* values show the results of the Kruskal–Wallis test

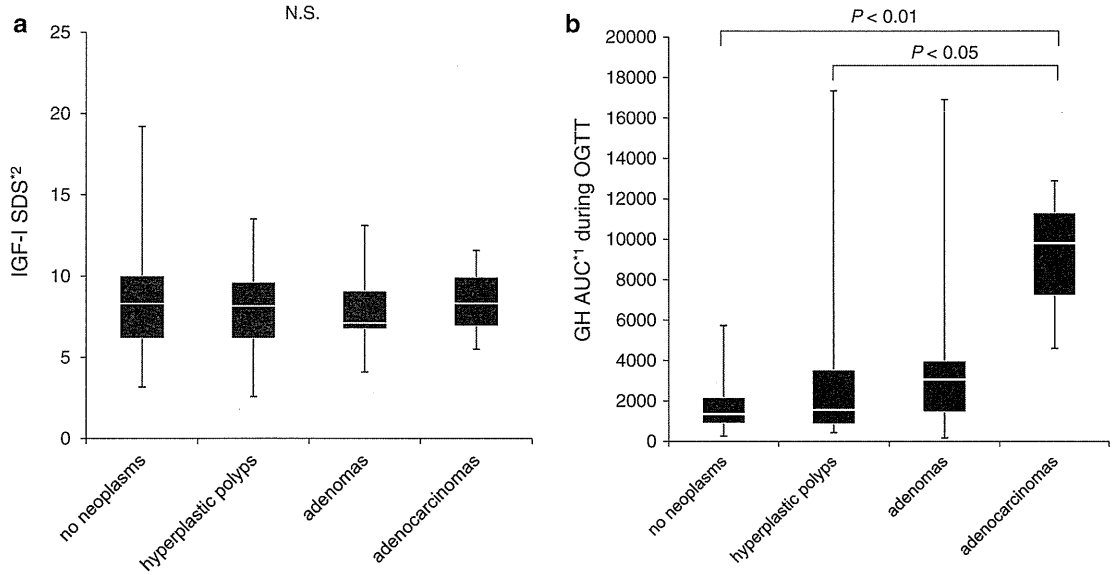

Fig. 2 Serum IGF-I SD score (**a**) and GH AUC during OGTT (**b**) in patients with each type of colorectal neoplasms. On the *left* of individual values in different groups are shown the 25th–75th percentiles. *P* values show the results of the Kruskal–Wallis test, followed by the Dunn's test for multiple comparisons. *1. *AUC* area under the curve, *2. *SDS* standard deviation score

and therefore, the possibility of this being a coincidence cannot be excluded. In addition, because this study is rather small study, expected variables as IGF-I levels and random GH levels might not attain statistical significance. Further, this was a retrospective analysis, and therefore, exclusion of a selection bias is difficult. Nevertheless, the association between the GH AUC and the increased risk of colorectal adenocarcinomas provides a new dimension to the complication of colorectal neoplasms in patients with acromegaly.

To evaluate the prevalence of colorectal neoplasms, we compared with several historical control subjects. The comparison with Chinese patients with IBS, which is a common functional but not organic bowel disease, demonstrated that the prevalence of hyperplastic polyps, adenomas, and adenocarcinomas was significantly higher in patients with acromegaly. The odds ratios for hyperplastic polyps, adenomas, and adenocarcinomas were 4.0, 8.7, and 17.5, respectively, suggesting an increased prevalence of colonic neoplasms in acromegaly compared with IBS. Screening colonoscopy surveys including healthy individuals have shown that the prevalence of hyperplastic polyps varies 9–34 % [23] and that the rate was 10.2–11.5 % in

Japanese subjects [24], suggesting that risk of hyperplastic polyps was increased. The comparison with patients with acromegaly in the previous reports showed that the prevalence of hyperplastic polyps was higher in our patients than in Italian patients with acromegaly. Although precise reason for the increased prevalence of hyperplastic polyps in this study in unknown, this may be attributable to racial differences, including dietary habits.

Hyperplastic polyps are considered to be benign, with no malignant potential. Histologically, they are characterized by elongated and branched crypts with epithelial hyperplasia in the proliferative zone and by the slow migration of colonic maturing cells upward along the crypt [25]. Acromegalic patients show accelerated colonic mucosal proliferation compared to normal individuals [26, 27], which may contribute to the increased prevalence of hyperplastic polyps. Recently, hyperplastic polyps are classified as one of serrated lesion [28]. In particular, serrated polyp, which is typically large lesion (>10 mm) and located in the right side has recognized as lesions with malignant potential developing to cancer by molecular mechanisms of *k-ras* or *BRAF* mutation and microsatellite instability in a different pathway from the adenomas [28–30]. In this aspect, the increased prevalence of hyperplastic polyps in acromegaly suggests the need for caution. It is also important that most of polyps and adenomas were multiple in this study.

The site distribution of hyperplastic polyps observed mostly in rectum was in line with the previous reports [8, 18]. The prevalence of colon diverticulum was comparable with general population in the previous reports [17]. In contrast, there has been reported that the prevalence of colon diverticulum is increased in patients with acromegaly (37 %, odds ratio 3.6) [17]. This discrepancy may be explained by a racial difference or limited number of the patients in this study. With regard to the prevalence of adenomas and adenocarcinomas, while we detected a significant increase in the prevalence of adenocarcinoma in our patients with acromegaly compared with the Japanese historical control subjects (Table 4), there were no significant differences in the prevalence of adenomas and adenocarcinomas by age-band between two groups (Fig. 1b). This discrepancy may be explained by a couple of points. One possibility is that the effect of GH/IGF-I excess is different on the development of adenoma and adenocarcinoma, therefore the effect on adenocarcinoma was masked. The other possibility is simply because of a small number of the patients; we could actually observe a substantial increase in the prevalence of adenomas and adenocarcinomas in the age between 40 and 59 in patients with acromegaly, although there were no statistical differences.

Oral glucose tolerance test has been used as the gold standard diagnostic test for acromegaly and can be used to assess the autonomous and excessive secretion of GH. In this study, the basal or nadir GH concentration during OGTT did not differ among patients according to the type of colorectal neoplasm; however, intriguingly, the GH AUC was significantly higher in patients with adenocarcinomas than in those with no colonic lesion or those with hyperplastic polyps. Furthermore, the GH AUC tended to increase with the malignant potential of colorectal neoplasms, suggesting that the degree of excess GH secretion may be associated with the developmental sequence of epithelium–adenoma–carcinoma [31]. However, we did not observe any differences in serum IGF-I levels among patients according to the type of colorectal neoplasm or between patients with colorectal neoplasms and those without these neoplasms, which was in agreement with previous findings [10, 11, 18]. Generally, IGF-I action is well known to play a pivotal role in tumor cell proliferation, survival, growth, and treatment sensitivity in many malignant diseases, including colon cancer [32]. A meta-analysis of 19 epidemiological studies of normal populations including 5,155 cases and 9,420 controls showed an association between a high IGF-I level within the normal range and the risk of colorectal cancer [33]. A possible explanation for our and previous finding is the existence of a threshold serum IGF-I level that promotes colon cancer, and the levels in patients with acromegaly may exceed this threshold level.

Recent research has highlighted the involvement of not only IGF-I signaling but also GH signaling itself in colon tumorigenesis. Signal transducer and activator of transcription-5 (STAT5) protein, which is activated by GH, has been shown to play an important role in tumor progression through the stimulation of cell proliferation and prevention of apoptosis. STAT5 activation is involved in the development of prostate cancer, breast cancer, and leukemia [34–36]. Colorectal adenocarcinomas show higher levels of STAT5b expression than normal colonic mucosa, and the expression levels are associated with the TNM stage [37]. Furthermore, STAT5 phosphorylation has frequently been observed in colon adenocarcinomas and is associated with a poor prognosis [38]. Suppressor of cytokine signaling-2 (SOCS2) is a key molecule downstream of GH signaling, well known as a negative regulator of STAT5 [39]. A cross between SOCS2-knockout and bovine GH-transgenic mice results in a development of mice with hyperplastic mucosa and polyps [40]. Intriguingly, the d3GHR polymorphism, which enhances GH signaling, was associated with an increased odds ratio of adenomatous polyps without increasing serum IGF-I level compared to wild-type GHR in patients with acromegaly, also suggesting the significance of GH signaling in humans [41]. These data suggest the importance of GH signaling in the development of colon polyps and adenocarcinomas, independent of IGF-I signaling.

In conclusion, an increase in the GH AUC may be useful in predicting the presence of colorectal adenocarcinomas in patients with acromegaly, although further studies with large numbers of patients are warranted to validate our results.

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Conflict of interest The authors declare that they have no conflict of interest.

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A diagnostic pitfall in IgG4-related hypophysitis: infiltration of IgG4-positive cells in the pituitary of granulomatosis with polyangiitis

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Abstract
Introduction Immunoglobulin (Ig) G4-related hypophysitis is an emerging clinical entity, which is characterized by an elevated serum IgG4 concentration and infiltration of IgG4-positive plasma cells in the pituitary. Although some criteria for its diagnosis have been proposed, they have not been fully established. In particular, differential diagnosis from secondary chronic inflammation including granulomatosis with polyangiitis (GPA) is difficult in some cases. We describe central diabetes insipidus with pituitary swelling exhibiting infiltration of IgG4-positive cells.
Patient A 43-year-old woman in the remission stage of GPA presented with sudden-onset polyuria and polydipsia. Pituitary magnetic resonance imaging revealed swelling of the anterior and posterior pituitary and stalk, with heterogeneous gadolinium enhancement and disappearance of the high signal intensity of the posterior pituitary. Evaluation of biochemical markers for GPA suggested that the disease activity was well-controlled. Endocrinological examination revealed the presence of central diabetes insipidus and growth hormone deficiency. Pituitary biopsy specimen showed IgG4-positive cells, with a 43 % $IgG4^+/IgG^+$ ratio, which met the criteria for IgG4-related hypophysitis. However, substantial infiltration of polymorphonuclear neutrophils with giant cells was also noted, resulting in a final diagnosis of pituitary involvement of GPA.
Conclusion These results suggest that pituitary involvement of GPA should be taken into account for the differential diagnosis of IgG4-related hypophysitis.

Keywords Granulomatosis with polyangiitis · IgG4-related hypophysitis · IgG4-related disease · Hypophysitis

Introduction

In recent years, immunoglobulin G4 (IgG4)-related hypophysitis has emerged as a novel clinical entity, and as a part of systemic IgG4-related disease (RD) [1]. Although it has traditionally been considered a rare condition, it has recently been reported that IgG4-related hypophysitis is noted in 30 % of hypophysitis cases and 4 % of all cases of hypopituitarism and/or diabetes insipidus (DI), suggesting that its prevalence may have been underestimated [2]. In the literature, IgG4-related hypophysitis cases were frequent in middle-aged and elderly men. Hypopituitarism was observed in 83 % and DI was observed in 72 %. Fifty-nine percent cases presented with both hypopituitarism and DI [2]. Glucocorticoid administration reduced serum IgG4 levels and shrank pituitary mass and the stalk thickening; however, the pituitary functions were not generally improved [1, 2]. Recently, Leporati et al. [3] proposed diagnostic criteria for IgG4-related hypophysitis. These criteria strengthened the importance of pituitary biopsy for IgG4

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immunostaining as a means for the definitive diagnosis of IgG4-related hypophysitis. When IgG4-related hypophysitis is suspected, IgG4-RD involvement in other tissues such as autoimmune pancreatitis, retroperitoneal fibrosis, orbital pseudotumor, and Riedel's thyroiditis as well as elevation of the serum IgG4 concentration, strongly suggest the diagnosis of IgG4-related hypophysitis. However, several cases of IgG4-related hypophysitis with involvement of the pituitary alone, without any other lesions, have also been reported [2, 4, 5]. Moreover, several cases have been diagnosed by pituitary biopsy specimen only, in the absence of elevation in serum IgG4 concentrations because of the corticosteroid administration [2, 4]; and in these cases, it is especially important to perform a careful differential diagnosis.

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA; also known as Wegener's granulomatosis), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (also known as Churg-Strauss syndrome), and single-organ AAV (for example, renal-limited AAV) [6]. The main histological characteristics of GPA are necrotizing vasculitis and irregular basophilic parenchymal necrosis with associated palisading granuloma [7]. In addition, neutrophilic microabscesses and fibrosis are commonly found with mixed inflammatory infiltrate composed of polymorphonuclear neutrophils, lymphocytes, plasma cells, multinucleated giant cells, and macrophages frequently observed [3, 8]. GPA typically involves the classical combination of the ELK triad, namely the ear, nose, throat (E), lungs (L) and kidney (L); but may also affect the joints, skin, eyes, and virtually any other tissue or organ including the pituitary gland. Although it is a rare condition, GPA is an important differential diagnosis of hypopituitarism and/or DI with pituitary swelling [9]. Generally, proteinase 3 (PR3)-ANCA is considered a useful serological marker for GPA, while myeloperoxidase (MPO)-ANCA is utilized as a marker for MPA [10]. However, MPO-ANCA is also reportedly detected in approximately 5–10 % of all GPA patients. Interestingly, several cases of GPA have been reported to show IgG4-positive plasma cells in various tissues, including in the nasal mucosa, lung, orbital tissue, kidney, dura, pleura, and eyelid, as part of the inflammatory background [11, 12].

Several conditions need to be excluded before the diagnosis of IgG4-RD can be made. For example, patients with cancer, infection, autoimmune and allergic diseases, and ANCA-associated vasculitis may also exhibit an elevation of the serum IgG4 concentrations [13]. In addition, an infiltration of IgG4-positive cells in the pituitary specimens is occasionally observed in various conditions associated with secondary chronic inflammation, such as pituitary adenoma, Rathke's cleft cyst, craniopharyngioma, and pituitary invasion of malignant lymphoma [14].

Herein, we report a case involving a patient with pituitary swelling and central DI, who exhibited a substantial infiltration of IgG4-positive cells in the pituitary, and in whom the final diagnosis was involvement of GPA in the pituitary.

Case report

A 34-year-old woman initially attended a hospital because of chronic sinusitis, chronic otitis media, and auditory disturbance. At the age of 38 years, she developed general fatigue, appetite loss, low-grade fever, nasal stiffness, gait disturbance, and blood-stained sputum. Physical examination at this time revealed saddle nose and eschar in the nasal cavity. Magnetic resonance imaging (MRI) and computed tomography showed thickened mucosa of the nasal sinus and multiple small nodular lesions in the lung, respectively (Fig. 1a, b). Serology revealed positive MPO-ANCA (156 EU; normal range <20 EU), while PR3-ANCA was negative, and the C-reactive protein (CRP) was elevated. No abnormalities were noted upon urine examination. Histological analysis of the nasal mucosa revealed a mixed inflammatory infiltrate composed of polymorphonuclear neutrophils, lymphocytes, plasma cells, and macrophages, which was comparable with the diagnosis of GPA (Fig. 2, left). The involved organs, clinical course, and the results of the serological and histological analyses met the diagnosis of GPA [15] and Watt's algorithm [16], and the patient was commenced on cyclophosphamide and prednisolone therapy (Fig. 3). However, because the responses of her serological markers, serum MPO-ANCA and CRP levels, became refractory to the therapy after 1 year, cyclophosphamide was changed to azathioprine, after which the clinical symptoms resolved and the serological markers improved. After 3 years of continuous remission, azathioprine was tapered and eventually stopped, with 5 mg of prednisolone administered as the maintenance therapy. However, at the age of 43 years, she developed sudden-onset polydipsia and polyuria, and her urine volume increased to 6000–9000 mL/day; accordingly, she was referred to our division for the diagnosis of DI (Fig. 3).

Upon admission, biochemical examination revealed that serum MPO-ANCA was undetectable and that her serum CRP level was within the normal range, suggesting that the remission of GPA had been maintained (Table 1; Fig. 3). Generally, the specificity of these markers is very high and they are used not only for diagnosis but also for the assessment of disease control [11]. The serum levels of chorionic gonadotropin, soluble interleukin-2 receptor, adenosine deaminase, and alpha-fetoprotein were measured and were all within the normal range, excluding a

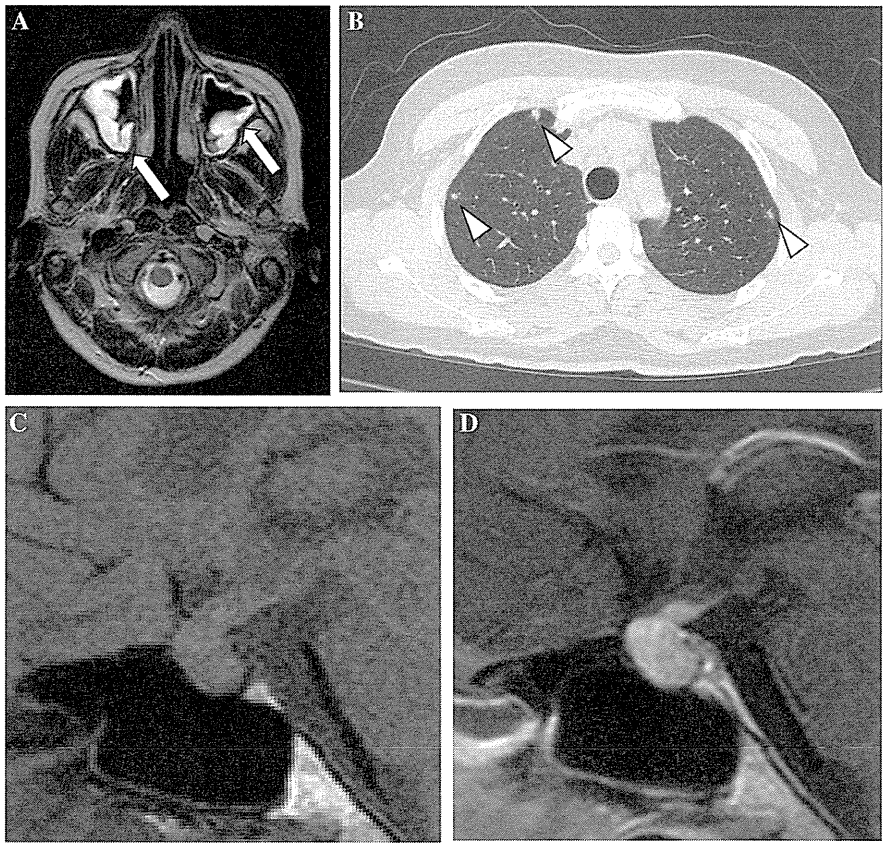

Fig. 1 Imaging findings. **a** T2-weighted brain magnetic resonance imaging (MRI). *Arrows indicate* thickening nasal sinus mucosa. **b** Chest computed tomography (CT). *Arrow heads indicate* alveolar hemorrhage. **c** Plain and **d** gadolinium-enhanced T1-weighted sagittal pituitary MRI

differential diagnosis of germ cell tumor, malignant lymphoma, or tuberculosis. The normal serum osmolality but low urine osmolality, unresponsiveness of arginine vasopressin secretion to the elevation of serum osmolality during the hypertonic saline test, and response of urine osmolality to 1-desamino-8-D-arginine vasopressin (DDAVP) confirmed the diagnosis of central DI (Table 1). The insulin tolerance test revealed a deficiency in growth hormone (GH) secretion (Table 1). Moreover, a decreased response of cortisol to insulin hypoglycemia was noted and it was considered as a secondary adrenal insufficiency due to long-term administration of prednisolone. TSH and FT4 values showed no TSH deficiency. She had regular menstruation cycle (Table 1). MRI revealed enlargement of the whole pituitary, including the stalk, with heterogeneous gadolinium enhancement and a disappearance of the high signal intensity of the posterior pituitary (Fig. 1c, d). Based on these findings, the patient was diagnosed with central DI and adult GH deficiency, and was treated with DDAVP.

Although it has been previously reported that GPA may involve the pituitary [9], the present patient's GPA was in remission at the time, and the MRI results suggested several possibilities, including hypophysitis, granuloma, and infection, especially tuberculosis. We decided to perform pituitary biopsy because the accurate diagnosis was crucial to ensure prompt and appropriate treatment depending on the diagnosis. Upon receiving written informed consent from the patient, pituitary biopsy was performed. Histological analysis of the pituitary revealed infiltration of lymphocytes and polymorphonuclear neutrophils with giant cells (Fig. 2, right). Intriguingly, immunohistochemical analysis showed a substantial infiltration of IgG4-positive cells (37 cells/high power field) with an $IgG4^+/IgG^+$ ratio of 43 %, which met the criteria for IgG4-related hypophysitis (Fig. 2, right). Furthermore, we also analyzed the nasal mucosa, and immunostaining of IgG4 and IgG revealed similar results as observed in the pituitary. The result of IgG4 immunostaining suggested the diagnosis of IgG4-related hypophysitis; however, the presence of neutrophils and giant cells indicated the final diagnosis of pituitary involvement of GPA because these features were one of the specific characteristics of GPA [17].

Discussion

Approximately 20 % of all GPA patients reportedly show central nervous system involvement, which most commonly presents as cranial neuropathies [18]. On the other hand, pituitary involvement is rare, and has been

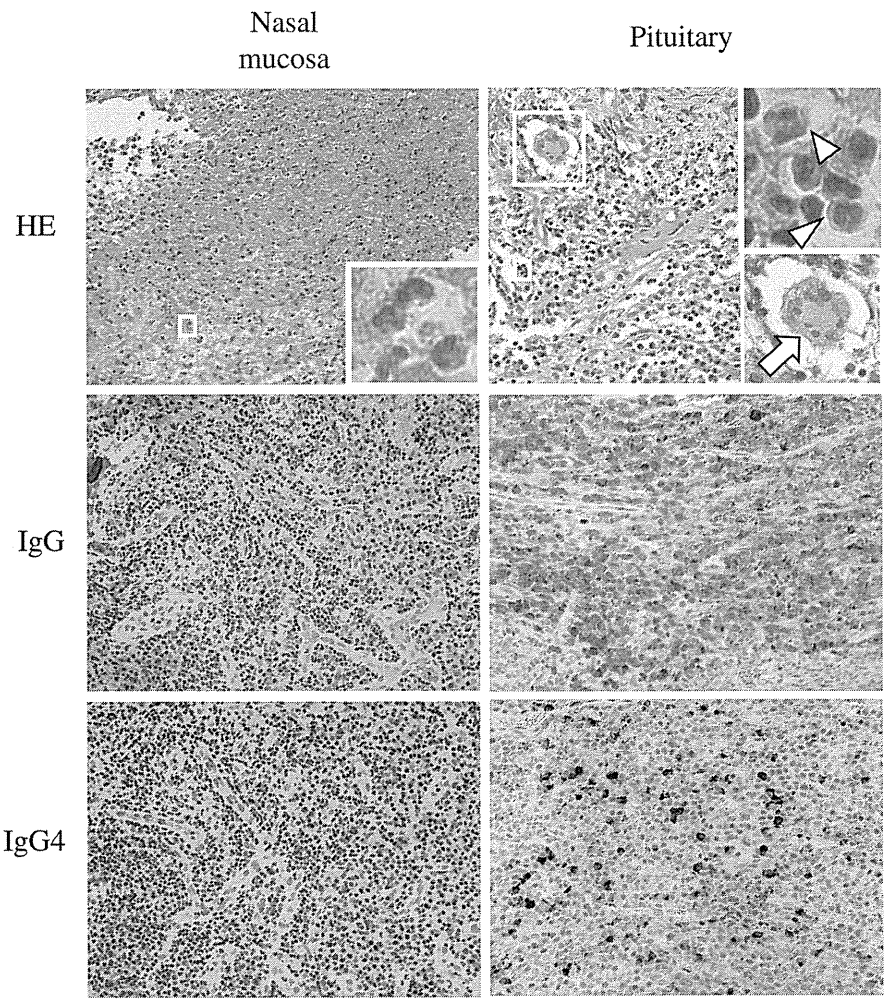

Fig. 2 Histopathological analyses. Hematoxylin and eosin (HE) staining and immunohistochemical analysis of immunoglobulin (Ig) G and IgG4 are shown (original magnification, ×400). *Left panel* nasal mucosa, *right panel* pituitary. *Arrow head* and *arrow indicate* a neutrophil and giant cell in the pituitary, respectively

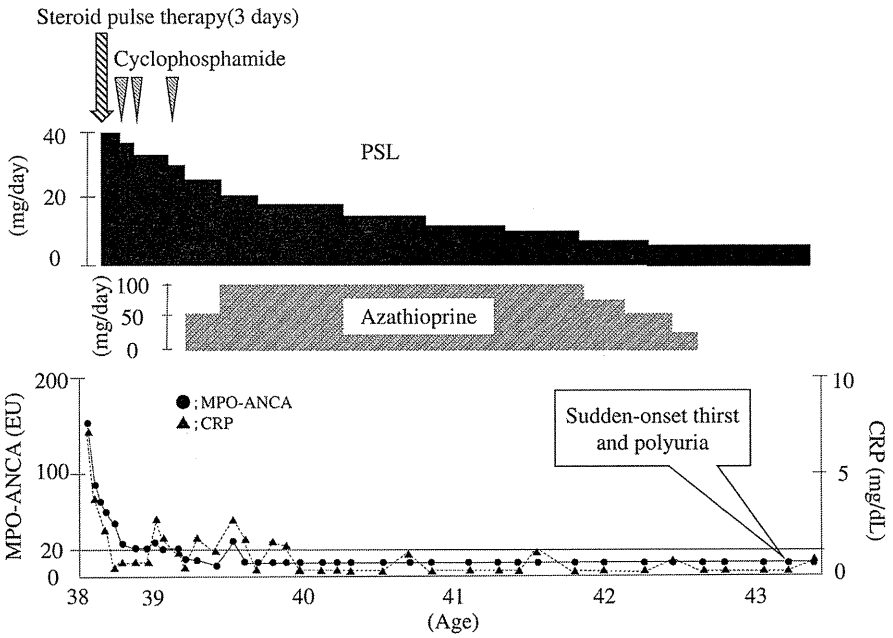

Fig. 3 Clinical course of the patient

Table 1 Laboratory data

		Reference range
Laboratory data		
Serum Na	139 mEq/L	135–145
K	4.0 mEq/L	3.5–4.8
Cl	103 mEq/L	98–108
Ca	9.4 mg/dL	8.5–10.2
P	2.9 mg/dL	2.3–4.3
Serum osmolality	279 mOsm/kg	276–292
Urine osmolality	47 mOsm/kg	100–1300
IgG	1521 mg/dL	880–1800
IgG4	56 mg/dL	4–108
CRP	0.28 mg/dL	0–0.3
MPO-ANCA	Undetectable level	<20
Endocrinological data		
GH	0.1 ng/mL	
IGF-1	87 ng/mL	
IGF-1 SDS	−2.2	
TSH	3.0 μIU/mL	
FT4	0.95 ng/dl	
LH	2.9 mIU/mL	
FSH	7.3 mIU/mL	
E2	52 pg/mL	
PRL	61.9 ng/mL	
ACTH	65.1 pg/mL	
Cortisol	11.2 μg/dL	
AVP	2.7 pg/mL	

Responses of GH, ACTH, and cortisol to intravenous injection of insulin (0.1 U/kg)

	0 min	30 min	60 min	90 min	120 min
GH (ng/mL)	0.1	0.5	2.3	0.7	0.3
ACTH (pg/mL)	23.4	93.5	88.9	45.8	50.0
Cortisol (μg/dL)	5.0	5.1	12.8	8.4	7.9

DDAVP test		Hypertonic saline test		
	Urine osmotic pressure (mOsm/kg)		Serum Na (mEq/L)	AVP (pg/mL)
Before	156	Before	140	Undetectable
After administration	583	After administration	153	Undetectable

AVP arginine vasopressin, *IgG* immunoglobulin G, *CRP* C-reactive protein, *MPO-ANCA* Anti-myeloperoxidase anti-neutrophil cytoplasmic antibodies, *GH* Growth hormone, *ACTH* Adrenocorticotropic hormone, *TSH* thyroid-stimulating hormone, *PRL* prolactin, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *DDAVP* 1-desamino-8-D-arginine vasopressin

documented in less than 1 % of all patients with GPA [9, 18, 19]. Ahlström et al. reported the first case of central DI caused by GPA in 1953 [20]. Yong et al. reviewed 23 case reports published between 1966 and 2006 [9], and Kapoor et al. [21] reported on eight patients with pituitary involvement out of a total of 637 patients with GPA. To our knowledge, there have been 48 cases (11 men and 37 women) of GPA with pituitary involvement including our present case (Table 2) [8, 9, 18, 20–50]. The mean age of the onset of pituitary involvement was 40.5 ± 14.1 years.

Fifty-six percent of the patients showed a late manifestation of pituitary involvement; however, most of the cases exhibited serologically positive ANCA (Table 2) [9]. When the systemic activity is high, it is generally not difficult to assess the involvement of GPA in the pituitary. However, in patients with remission, the diagnosis is not

Table 2 Reported cases of GPA with pituitary involvement in the literature

Case no.	Author	Sex	Age at onset pituitary involvement	Type of elevated ANCA	Hypopituitarism	DI	Reference
1	Bando	F	43	MPO	AF	AF	Present case
2	Sampei	M	52	MPO	–	AF	23
3	Kapoor	F	67	All but one tested positive for ANCA reacting with PR3	AF	–	21
4		F	48		AF	AF	
5		F	28		AF	AF	
6		M	55		AF	–	
7		M	35		AF	AF	
8		M	54		AF	–	
9		M	68		AF	AF	
10		F	28		–	AF	
11	Al-Fakhouri	F	33	PR3	AF	AF	24
12		F	61	PR3	AF	AF	
13	Huges	F	30	MPO	AF	AF	25
14	Pereira	F	48	Not described	AF	–	26
15	Slabu	F	30	Negative	AF	–	27
16	Kara	F	16	c-ANCA	AF	AF	28
17	Santoro	F	53	c-ANCA	AF	AF	29
18	Tenorio Jimenez	F	38	c-ANCA	AF	AF	30
19	Barlas	F	37	c-ANCA	–	AF	31
20	Xue	F	63	PR3	–	AF	32
21	McIntyre	F	22	c-ANCA	AF	AF	33
22	Thiryayi	F	21	c-ANCA	–	–	34
23	Yong	M	33	PR3	AF	AF	9
24	Spísek	M	29	c-ANCA	AF	AF	35
25	Seror	F	50	PR3	–	AF	36
26		F	41	PR3	–	AF	
27		M	57	PR3	–	AF	
28	Dutta	F	37	c-ANCA	–	AF	37
29		F	40	c-ANCA	–	AF	
30	Düzgün	F	47	PR3	–	AF	38
31	Tao	F	19	PR3	AF	AF	39
32	Garovic	F	47	c-ANCA	AF	AF	40
33	Tappouni	F	57	PR3	ND	ND	41
34	Goyal	F	48	c-ANCA	AF	AF	22
35	Woywodt	M	30	Not described	ND	ND	8
36	Hajj-Ali	F	21	Not described	–	AF	42
37	Katzman	F	41	c-ANCA	–	AF	43
38		F	18	c-ANCA	–	AF	
39	Miesen	M	45	PR3	–	AF	44
40	Bertken	F	36	Absent	AF	AF	45
41	Czarnecki	F	34	Not described	–	AF	46
42	Roberts	F	71	Positive	AF	AF	47
43		F	28	Positive	AF	AF	
44	Rosete	F	51	Not described	–	AF	18
45	Lohr	F	19	Not described	AF	–	48
46	Hurst	F	47	Not described	–	AF	49

Table 2 continued

Case no.	Author	Sex	Age at onset pituitary involvement	Type of elevated ANCA	Hypopituitarism	DI	Reference
47	Haynes	M	25	Not described	–	AF	50
48	Ahlström	F	41	Not described	–	AF	20

ANCA anti-neutrophil cytoplasmic antibody, *DI* diabetes insipidus, *AF* affected function, *ND* not described

straightforward. Difficult decisions regarding the treatment are sometimes required, as the treatment options differ completely depending on the diagnosis. In particular, in cases of involvement of GPA, it is necessary to consider whether to strengthen the immunosuppressive therapy, whereas if infections such as tuberculosis are associated with the immunocompromised status, anti-infective therapy should be considered. In the present case, the final diagnosis was involvement of GPA made by pituitary biopsy irrespective of systemic remission, and we were able to observe the patient carefully with a maintenance dose of glucocorticoid while administering replacement therapy of DDAVP.

Pituitary involvement in GPA often manifests as central DI and partial disruption of the anterior pituitary axis. In the literature, the percentage of hypopituitarism, DI, and hypopituitarism + DI are 13, 41, and 43 %, respectively in GPA (Table 2). A recent study reported that isolated pituitary hormone deficiency without DI is uncommon [19], which is compatible with our case. Although isolated GH deficiency with DI was observed in our case, there is a possibility that the GH secretion was affected by the long-term steroid therapy. Similar to our case, Goyal et al. [22] reported on a patient who developed central DI and central hypothyroidism with a status of well-controlled systemic GPA; however, pituitary biopsy was not performed in their study. The patient was treated with steroids, and the sellar mass with suprasellar extension nearly completely resolved without an improvement of DI [22]. Moreover, in a previous report, 86 % of patients with hypopituitarism and/or DI with GPA showed enlargement of the pituitary and/or infundibulum or intrasellar mass, and were treated with steroids, cyclophosphamide, azathioprine, infliximab, and/or methotrexate [9]. Despite treatment of GPA, only 17 % of the GPA cases reportedly recovered fully in their pituitary function [9], although the DI resolved at a higher rate of 67 % [19]. Although most of the cases develop pituitary involvement during general GPA symptoms, in a rare case of GPA, DI preceded other manifestations of GPA [23]. Onset of DI during the remission status in our case might suggests the exacerbation of the GPA, therefore, we are carefully observing the patient and we have continued oral prednisolone therapy in the same dose (Fig. 3). The majority of IgG4-related hypophysitis cases were observed in middle-aged and elderly men [1, 2]. On the other hand, female patients are predominant in the cases of pituitary involvement of GPA and, there was a wide range of age distribution (Table 2). These different clinical characteristics in the age and gender are useful for the differential diagnosis of IgG4-related hypophysitis and GPA with pituitary involvement.

On histologic examination, some biopsy specimens from GPA patients may mimic those of IgG4-RD, owing to the fact that the inflammatory background in GPA contains numerous plasma cells and is accompanied by dense fibrosis areas and/or obliterated blood vessels [51, 52]. Increased IgG4-positive cells and $IgG4^+/IgG^+$ ratios have also been reported for both PR3- and MPO-ANCA positive GPA [12]. In the study, 18.6 % of biopsy specimens of GPA-affected organs and tissues, including the nasal mucosa, lung, orbital tissue, kidney, dura, pleura, and eyelid, revealed increased IgG4-positive cells (>30/high-power field and >40 % $IgG4^+/IgG^+$ ratio) [12]. The IgG4-positive cells and $IgG4^+/IgG^+$ ratio in these cases ranged from 37 to 139/high-power field and from 44 to 83 %, respectively [12]. Importantly, these results met the criteria for IgG4-RD including the hypophysitis [3, 53]. GPA may also presents as a mass lesion in various tissues. In particular, the lung and kidney are common organs involved both in IgG4-RD and GPA [8, 51]. Additionally, hypertrophic pachymeningitis with infiltration of IgG4-positive cells can develop both in IgG4-RD and GPA [12, 54]. Furthermore, steroid therapy is commonly used for the treatment in GPA, which frequently decreases the serum IgG4 levels in IgG4-RD, and this can also lead to confusion. In the present case, the serum IgG4 levels were normal; however, as a result of the steroid therapy for GPA, it was considered that the IgG4 levels may have been normalized. Thus, our results suggest that GPA is one of the important differential diagnosis of IgG4-related hypophysitis even when the results of the histological analysis are compatible with IgG4-related hypophysitis.

The clinical characteristics of MPO-ANCA positive GPA have not been fully clarified, owing to the rarity of this condition as compared with PR3-ANCA positive GPA. It has been reported that MPO-ANCA positive GPA exhibits less organ involvement than PR3-ANCA positive GPA. In particular, the kidneys, eyes, and peripheral nervous system tend to be less frequently involved in MPO-ANCA positive GPA patients [55]. Regarding the pituitary, our case is the third case of MPO-ANCA positive GPA

with pituitary involvement [23, 25] (Table 2). In one report, the MPO-ANCA positive GPA primarily involving pituitary was refractory to both steroids and immunosuppressants; and, intriguingly, IgG4-positive cells were observed in the pituitary, although they were relatively few [25]. It is possible that these therapies affected the number of IgG4-positive cells in the pituitary.

Generally, an increase in serum IgG4 levels represents the presence of a large amount of antigens, and is considered a marker of chronic antigen exposure [56]. It has been reported that the ANCAs in patients with GPA predominantly belong to the IgG1 and IgG4 subclasses [57]. Although it cannot be ruled out that the infiltration of IgG4-positive cells in GPA is a nonspecific inflammatory reaction, the IgG4 subclass of MPO-ANCA, similarly to PR3-ANCA, can activate the neutrophils through co-ligation of the MPO antigen and FcγRIIa/IIIb receptors expressed on neutrophils, and thus it may play a role in the pathogenesis of GPA [58, 59]. In terms of IgG4-RD, it remains unclarified whether IgG4 itself plays a pathogenic role in its development [51]. IgG4-RD is considered as chronic inflammation and fibrosis caused by autoimmune reactions [51], suggesting a presence of common pathways in the development of these disease.

In conclusion, the findings of the present case suggest that the possibility of GPA should be taken into account in cases with infiltration of IgG4-positive cells in pituitary biopsy specimens, especially in cases with normal serum IgG4 levels.

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Conflict of interest The authors declare that they have no conflict of interest.

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Median-lower normal levels of serum thyroxine are associated with low triiodothyronine levels and body temperature in patients with central hypothyroidism

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Abstract

Objective: Although it has been recommended that serum free thyroxine (FT_4) levels should be targeted to middle-upper normal levels during levothyroxine (L-T_4) replacement therapy in patients with central hypothyroidism (CeH), the rationale has not been clarified.

Methods: A retrospective single-center study enrolled 116 patients with hypothyroidism (CeH, $n=32$; total thyroidectomy (Tx), $n=22$; primary hypothyroidism (PH), $n=33$; and control benign thyroid nodule (C), $n=29$). The patients had received L-T_4 therapy at the Kobe University Hospital between 2003 and 2013. They were stratified according to serum FT_4 level (≥ 1.10 or <1.10 ng/dl), and body temperature (BT), serum free triiodothyronine (FT_3) levels, FT_3/FT_4 ratio, and lipid profiles were compared. The effect of GH replacement therapy on thyroid function was also analyzed.

Results: FT_3 levels and FT_3/FT_4 ratios were significantly lower in patients with CeH than in patients with PH ($P<0.05$) or C ($P<0.05$). In patients with FT_4 <1.10 ng/dl, BT was significantly lower in patients with CeH ($P=0.002$) and Tx ($P=0.005$) than in patients with PH, whereas no differences were found in patients with $FT_4 \geq 1.10$ ng/dl. In patients with CeH, FT_3 levels were higher in those with GH replacement therapy ($P=0.018$).

Conclusion: In CeH, patients with median-lower normal levels of serum FT_4 exhibited lower serum FT_3 levels and lower BT. These results support the target levels of serum FT_4 as middle-upper normal levels during L-T_4 replacement therapy in patients with CeH.

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Introduction

Central hypothyroidism (CeH) is caused by various hypothalamic–pituitary diseases and frequently combined with other deficiencies of pituitary hormones such as adrenocorticotropic hormone (ACTH), growth hormone (GH), and gonadotropins (Gn). The administration of levothyroxine (L-T_4) is standard therapy not only for patients with primary hypothyroidism (PH) but also for patients with CeH. However, despite L-T_4 replacement therapy, it has been reported that some of the patients still complain of symptoms related with hypothyroidism and

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impaired quality of life (QOL) (1, 2, 3). Generally, serum thyroid-stimulating hormone (TSH) level is used as a marker for dose adjustment of L-T_4 replacement therapy (4, 5, 6). However, in patients with CeH, TSH secretion does not often accurately reflect the changes in serum free thyroxine (FT_4) levels. In patients with CeH, it has been recommended that serum FT_4 levels should be targeted within the middle to upper limit of the reference range during L-T_4 replacement therapy (7, 8). However, little evidence supports the rationale for these target FT_4 levels (9).

The replacement therapy of other pituitary hormones may affect the free triiodothyronine (FT_3)/FT_4 ratio in patients with CeH associated with hypopituitarism. GH replacement therapy promotes peripheral T_4 to T_3 conversion (10, 11), whereas high-dose glucocorticoid replacement therapy inhibits deiodinase activity (12, 13), indicating that the status of replacement therapy is also important in determining the FT_3/FT_4 ratio. Recently, it has been reported that serum FT_3 levels to FT_4 levels ratio (FT_3/FT_4 ratio) is lower in patients with CeH than in control subjects (C) (14). In addition, patients who underwent total thyroidectomy (Tx) exhibited relatively lower FT_3 levels compared with FT_4 levels (15, 16). These results suggest that T_3 secretion from the thyroid gland plays an important role in the regulation of serum FT_3 levels.

To clarify the optimal levels of serum FT_4 during L-T_4 replacement therapy in patients with CeH, we assessed serum FT_3 levels and FT_3/FT_4 ratio, and the physiological effects of thyroid hormones such as BMI, heart rate (HR), body temperature (BT), and the parameters of lipid metabolism (17) and compared these with those in patients with Tx and PH.

Subjects and methods

Subjects and design

This was a retrospective observational single-center study involving 116 consecutive patients with hypothyroidism (36 men and 80 women; mean age, 56.1±17.4 years) who had been treated with L-T_4 replacement therapy at Kobe University Hospital between 2003 and 2013. These four groups were stratified (FT_4 ≥1.10, or <1.10 ng/dl) according to the median value (1.10 ng/dl) of the normal range of serum FT_4 levels (0.70–1.48 ng/dl) (FT_4 ≥1.10 ng/dl group: CeH, n=12; Tx, n=14; PH, n=19; and C, n=17; FT_4 <1.10 ng/dl group: CeH, n=20; Tx, n=8; PH, n=14; and C, n=12). The following parameters were compared between these groups; BMI, systolic blood pressure (sBP), diastolic blood pressure (dBP), HR, BT, serum FT_3 level, FT_3/FT_4 ratio, and lipid profiles (total cholesterol (T-Chol), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), and triglycerides (TG)). All BT measurements were performed at 10 a.m. in the hospital during hospitalization by using an axillary digital thermometer in a single evaluation (Topnic ET-16, TOP Corporation, Tokyo, Japan). In the CeH group, patients who showed organic hypothalamic damage by tumor invasion or treatment including surgery and/or radiotherapy were excluded. In the Tx group, patients with TSH levels <0.4 μiu/ml who had received suppression therapy were excluded as previously described (15). Control subjects were recruited from among patients with nonfunctioning benign thyroid nodules (<20 mm diameter), whose TSH levels were within the reference range (0.35–4.94 μiu/ml). Most of the patients in the CeH group had panhypopituitarism as etiology, including GH deficiency (GHD) caused by various pituitary injuries, and some patients received GH replacement therapy. The status of pituitary function, the number of patients who had received pituitary hormone replacement therapy and etiology of CeH, including CeH subgroups, were summarized in Table 1. The hypothalamic–pituitary–thyroid axis, hypothalamic–pituitary–adrenal axis, and hypothalamic–pituitary–gonadal axis were evaluated as previously described (18). For the diagnosis of GHD, each patient was subjected to an insulin tolerance test or GH-releasing peptide 2 test. All of the patients in this study were studied after informed consent.

Biochemical assays

Serum FT_4, FT_3, and TSH levels were measured by using chemiluminescent immunoassay (ARCHITECT; CLIA, Abbott Japan). The reference ranges were 0.70–1.48 ng/dl for FT_4, 1.71–3.71 pg/ml for FT_3, and 0.35–4.94 μiu/ml for TSH. The intra- and inter-assay coefficients of variation (CV) were 2.79–4.23% and 2.78–4.11% for FT_4, 2.29–2.49% and 2.81–4.20% for FT_3, 1.52–2.65% and 4.16–4.71% for TSH respectively. Serum T-Chol, LDL-C, HDL-C, and TG levels were measured by using enzymes or the direct method (Kyowa Medex, Tokyo, Japan). The reference ranges were 146–219 mg/dl for T-Chol, 0–139.99 mg/dl for LDL-C, 40–60 mg/dl for HDL-C, and 28–149 mg/dl for TG. The intra- and inter-assay CV were 0.64–0.65 and 1.16–1.72% for T-Chol, 0.60–0.63 and 1.72–1.76% for LDL-C, 0.42–0.43 and 1.43–1.79% for HDL-C, 0.47–0.51 and 1.32–1.51% for TG respectively.

Table 1 Status of pituitary function and etiology of CeH. Number of patients who had received pituitary hormone replacement therapy. Among the patients with CeH, 81.3% exhibited GHD and 26.9% had GH replacement therapy.

		FT_4		GH replacement	
	Total	≥1.10	<1.10	(−)	(+)
Pituitary insufficiencies					
TSH	32 (32)	12 (12)	20 (20)	25 (25)	7 (7)
GH	26 (7)	10 (3)	16 (4)	19 (0)	7 (7)
FSH/LH	25 (5)	9 (2)	16 (3)	21 (2)	4 (3)
ACTH	28 (27)	9 (9)	19 (18)	23 (22)	5 (5)
ADH	11 (10)	5 (5)	6 (5)	8 (7)	3 (3)
Etiology					
Lymphocytic hypophysitis	6	3	3	5	1
Rathke's cleft cyst	4	0	4	4	0
Pituitary adenoma	3	1	2	3	0
Sheehan's syndrome	2	1	1	1	1
Craniopharyngioma	2	0	2	1	1
Empty sella	2	2	0	0	2
Germinoma	1	0	1	1	0
Other	12	5	7	10	2

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Statistical analysis

All data were expressed as mean±S.D. values. Comparisons between the two groups were performed by using Student's *t*-test. The χ^2 test was used to analyze differences between categorical variables. A multiple linear regression analysis was used to evaluate the following independent valuables associated with BT: serum FT_4, FT_3, and TSH levels, FT_3/FT_4 ratio, age, BMI, the dose of L-T_4 replacement therapy, and the dose of L-T_4 per kilogram of body weight. The stepwise method entered the predictors sequentially. The tested factors including serum FT_4 and FT_3 levels, and FT_3/FT_4 ratio were followed by a variance inflation factor analysis. Comparisons between more than two groups were performed by using the ANOVA, followed by Bonferroni's multiple comparison test between each of the two groups. P values <0.05 were considered as statistically significant. Data were analyzed by using the SPSS Software package (Dr SPSS II for Windows, Nankodo Co., Ltd, Japan).

Results

Clinical characteristics, clinical parameters, and L-T_4 doses

The clinical characteristics of the patients in the four groups are described in Table 2. No significant differences were found in age, sex distribution, blood pressure (BP), HR, and BT between the groups. BMI was higher in patients with CeH than in those with PH or C (CeH; 26.5±7.6 vs PH; 23.0±5.9 kg/m^2; $P=0.045$, CeH; 26.5±7.6 vs C; 21.6±3.9 kg/m^2; $P=0.003$) respectively. Serum T-Chol, LDL-C, HDL-C, and TG levels were comparable between the groups (Table 2).

The dose of L-T_4 replacement therapy was greater in patients with Tx than in those with CeH or PH (Tx; 108.0±24.9 vs CeH; 68.9±32.0 μg/day; $P<0.001$, Tx; 108.0±24.9 vs PH; 40.9±43.7 μg/day; $P<0.001$). The dose in patients with CeH was greater than in those with PH (CeH; 68.9±32.0 vs PH; 40.9±43.7 μg/day; $P=0.004$). The dose of L-T_4 per kilogram of body weight showed similar results (Tx; 1.9±0.6 vs CeH; 1.1±0.6 μg/day per kg; $P<0.001$, Tx; 1.9±0.6 vs PH; 0.7±0.6 μg/day per kg; $P<0.001$, CeH; 1.1±0.6 vs PH; 0.7±0.6 μg/day per kg; $P=0.023$; Table 2).

Serum FT_3 levels and FT_3/FT_4 ratios

Serum FT_4, FT_3, and TSH levels, and FT_3/FT_4 ratios were compared between the four groups. Serum FT_4 levels were comparable between patients with CeH, PH, and C (CeH; 1.04±0.25 vs PH; 1.15±0.20 ng/dl; $P=0.306$, CeH; 1.04±0.25 vs C; 1.13±0.15 ng/dl; $P=0.612$, PH; 1.15±0.20 vs C; 1.13±0.15 ng/dl; $P=1.000$; Fig. 1A). In contrast, serum FT_3 levels were lower in patients with CeH than in those with Tx, PH, or C (CeH; 2.08±0.51 vs Tx; 2.55±0.51 pg/ml; $P=0.007$, vs PH; 2.78±0.40 pg/ml; $P<0.001$, vs C; 2.80±0.43 pg/ml; $P<0.001$; Fig. 1B). In addition, the mean FT_3/FT_4 ratios were significantly lower in patients

Table 2 Comparison of clinical characteristics between four groups. Data are expressed as mean±S.D.

	CeH	Tx	PH	C	*P* value[a]
Age (y)	54.5±19.3	56.9±15.3	53.9±16.9	62.8±13.9	0.09
Gender (male/female)	10/22	9/13	6/27	11/18	0.70
BMI (kg/m^2)	26.5±7.6*,†	23.8±4.2	23.0±5.9*	21.6±3.9†	0.004
sBP (mmHg)	118.8±20.4	127.7±20.6	125.9±19.2	125.7±21.6	0.27
dBP (mmHg)	69.9±13.2	72.1±11.3	72.2±9.6	66.8±9.5	0.21
HR (bpm)	72.9±13.0	71.2±9.7	74.6±11.8	73.9±12.8	0.79
BT (°C)	36.0±0.7	35.9±0.7	36.3±0.4	36.0±0.8	0.22
T-Chol (mg/dl)	216.6±53.2	226.3±38.0	194.0±49.4	194.9±47.5	0.06
LDL-C (mg/dl)	127.6±37.9	138.2±26.1	112.4±42.5	112.9±39.6	0.14
HDL-C (mg/l)	58.0±20.0	66.0±13.5	62.0±17.1	60.1±24.7	0.64
TG (mg/dl)	140.0±77.3	135.8±72.6	130.1±63.9	152.5±113.0	0.49
L-T_4 dose (μg/day)	68.9±32.0†,‡	108.0±24.9‡	40.9±43.7†	–	<0.001
L-T_4 dose (μg/day/kg) (per body weight)	1.1±0.6*,‡	1.9±0.6 ‡	0.7±0.6*	–	<0.001

$^{*}P<0.05$, $^{\dagger}P<0.01$, $^{\ddagger}P<0.001$.
[a]*P* values are for the comparisons between all groups by ANOVA, except for sex distribution (χ^2 test), followed by Bonferroni's multiple comparison test between each of the two groups.

with CeH than in those with PH, whereas no difference was found between patients with CeH and Tx (CeH; 2.10±0.67 vs PH; 2.49±0.52; $P=0.045$, vs Tx; 2.12±0.44; $P=1.002$; Fig. 1C).

In patients with CeH and PH, the remaining function of TSH secretion from the pituitary, and the T_3 and/or T_4 secretion from the thyroid, which may affect the FT_3/FT_4 ratio, had to be considered. Therefore, the subjects were stratified according to L-T_4 dose per kilogram of body weight (≥1.0 or <1.0 μg/day per kg), and the serum thyroid hormone levels were compared between the groups. The serum FT_4 levels were comparable between patients with CeH and PH, whereas the serum FT_3 levels were lower in patients with CeH than in those with PH, both in the L-T_4 ≥1.0 and L-T_4 <1.0 μg/day per kg groups (data not shown).

Association between serum thyroid hormone levels and clinical parameters

Next, we analyzed the association between serum thyroid hormone levels and clinical parameters such as HR and BT, which are regulated by thyroid hormone action. In the multiple linear regression analysis, no significant association was observed between the serum thyroid hormone levels and HR (data not shown). Serum FT_3 value was an independent factor associated with BT ($\beta=1.051$, 95% CI 0.012 to 2.089, $P=0.045$; Table 3). However, no significant association was observed between serum FT_4 levels and BT ($\beta=-2.027$, 95% CI −4.146 to 0.093, $P=0.07$; Table 3).

Therefore, we stratified the subjects according to the median value of the normal range of serum FT_4 levels (≥1.10 or <1.10 ng/dl), and analyzed the association between serum thyroid hormone levels and BT. Clinical characteristics are summarized in Table 4. The dose of L-T_4 was greater in patients with Tx than in those with CeH or PH, both in the FT_4 ≥1.10 and FT_4 <1.10 ng/dl groups. Intriguingly, in the FT_4 <1.10 ng/dl group, patients with CeH and Tx exhibited lower BT than those with PH (CeH;

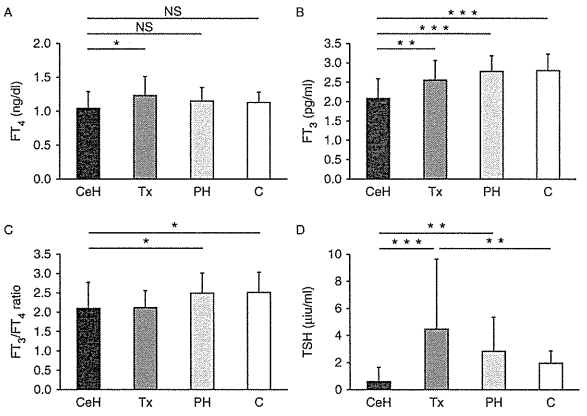

Figure 1
Serum FT_4 (A) and FT_3 (B) levels, FT_3/FT_4 ratios (C), and serum TSH levels (D) between four groups. Serum FT_4 levels were comparable between patients with CeH, PH, and C. Serum FT_3 levels were lower in patients with CeH than in those with Tx, PH, and C. FT_3/FT_4 ratios were lower in patients with CeH than in those with PH, whereas no difference was found between patients with CeH and Tx. Data are expressed as mean±S.D. *P* values are for the comparisons between all groups by ANOVA, followed by Bonferroni's multiple comparison test between each of the two groups. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, NS, not significant.

Table 3 Associations between BT and serum thyroid hormone levels by multiple linear regression analysis. Serum FT_3 level was independently associated with BT. However, there was no significant association between serum FT_4 level and BT.

	β (95% CI)	P value
FT_4	−2.027 (−4.146 to 0.093)	0.07
FT_3	1.051 (0.012 to 2.089)	0.045
FT_3/FT_4 ratio	−1.021 (−2.086 to 0.037)	0.06
TSH	0.004 (−0.034 to 0.047)	0.89
Age	−0.001 (−0.009 to 0.008)	0.77
BMI	0.019 (−0.009 to 0.049)	0.19
L-T_4 dose	−0.004 (−0.013 to 0.008)	0.37
L-T_4 dose (per body weight)	0.107 (−0.473 to 0.683)	0.74

35.9±0.5 vs PH; 36.4±0.3 °C; P=0.002, Tx; 35.8±0.4 vs PH; 36.4±0.3 °C; P=0.005; Table 4), whereas no significant differences were found in the $FT_4 \geq 1.10$ ng/dl group (CeH; 36.0±0.7 vs PH; 36.3±0.5 °C, Tx; 36.0±0.8 vs PH; 36.3±0.5°C; Table 4). These results suggest that the activity of the thyroid hormone is not sufficient in patients with CeH, whose serum FT_4 levels were lower than the median value of the normal range.

We next analyzed whether the decreased BT in patients with CeH was associated with serum FT_3 levels. As shown in Fig. 2, in the FT_4 <1.10 ng/dl group, patients with CeH and Tx exhibited lower serum FT_3 levels and FT_3/FT_4 ratios than those with PH (FT_3 levels; CeH; 2.18±0.56 vs PH; 2.76±0.35 pg/ml; P=0.001, Tx; 2.26±0.53 vs PH; 2.76±0.35 pg/ml; P=0.041; Fig. 2A) (FT_3/FT_4 ratios; CeH; 2.41±0.64 vs PH; 2.87±0.41; P=0.040, Tx; 2.39±0.54 vs PH; 2.87±0.41; P=0.039; Fig. 2B). In contrast, in the $FT_4 \geq 1.10$ ng/dl group, no significant differences in serum FT_3 levels and FT_3/FT_4 ratios were observed between these groups (FT_3 levels; CeH; 2.48±0.46 vs PH; 2.82±0.47 pg/ml, Tx; 2.71±0.44 vs PH; 2.82±0.47 pg/ml; Fig. 2C) (FT_3/FT_4 ratios; CeH; 1.85±0.36 vs PH; 2.20±0.45, Tx; 1.97±0.29 vs PH; 2.20±0.45; Fig. 2D). Taken together, these data suggest that lower BT in patients with CeH is associated with relatively lower serum FT_3 levels.

CeH patients with GH replacement therapy

To clarify the effect of GH replacement therapy on the pituitary–thyroid axis, serum FT_4 and FT_3 levels, and the dose of L-T_4 in CeH patients with GH replacement therapy (GH (+)) or without (GH (−)) were compared. In the GH (+) group, serum FT_3 levels were significantly higher than those in the GH (−) group (GH (−); 2.01±0.53 vs GH (+); 2.48±0.42 pg/ml; P=0.018; Fig. 3A). In contrast, no significant difference in serum FT_4 levels was found between the groups (GH (−); 1.04±0.26 vs GH (+); 1.13±0.26 ng/dl; P=0.150; Fig. 3B). Furthermore, the dose of L-T_4 tended to be higher in the GH (+) group than in the GH (−) group (GH (−); 69.4±26.5 vs GH (+); 80.9±36.0 μg/day; P=0.075; Fig. 3C).

We also analyzed the influence of obesity, menopause, and other pituitary hormone deficiency on BT or serum thyroid hormone levels in CeH. We stratified the CeH subjects according to BMI (BMI ≥25 kg/m^2: n=15; BMI <25 kg/m^2: n=17), the presence or absence of menopause (menopause (−): n=14; menopause (+): n=18), ACTH deficiency (ACTH deficiency (−): n=4; ACTH deficiency (+): n=28), and hypogonadism (hypogonadism (−): n=7; hypogonadism (+): n=25), and compared the following parameters between these groups: BT, serum FT_4 and FT_3 levels, FT_3/FT_4 ratios, the dose of L-T_4 replacement therapy, and the dose of L-T_4 per kilogram of body weight (Table 5). However, no significant differences were observed between these groups.

Discussion

In this study, we demonstrated that patients with CeH, who exhibited median-lower normal levels of serum FT_4, revealed low BT with relatively low serum FT_3 levels. Although serum FT_4 levels have been recommended to target within the middle to upper limit of the reference range in patients with CeH, few evidences have been shown to support the rationale of this target. Considering that a low BT represents a state of hypothyroid (17), the relatively lower serum FT_3 levels with decreased BT in the present study suggest that median-lower normal levels of serum FT_4 are not sufficient to maintain normal thyroid hormone action in patients with CeH. We also compared serum FT_3 levels or FT_3/FT_4 ratios in four different etiologies of hypothyroidism including patients with CeH, Tx, PH, and C simultaneously, and showed that serum FT_3 levels were lower in patients with CeH compared with the other three groups.

Physiologically, serum T_4 is secreted by the thyroid grand (~100%), and serum T_3 is derived from both the thyroid gland (20%) and extra-thyroidal tissues, where T_4 is converted to T_3 (80%) (19). Meanwhile, owing to the lack of TSH stimulation, T_3 produced by the thyroid gland will decrease in patients with CeH, resulting in lower serum FT_3 levels.

Several factors can affect serum FT_3 and FT_4 levels, and the FT_3/FT_4 ratio in patients with CeH, including other pituitary hormone deficiency, hormone replacement