Contribution of sellar dura integrity to symptom manifestation in pituitary adenomas with intratumoral hemorrhage

Pituitary

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Response to Reviewers:	RRespond to reviewer's comments Manuscript Number: PITU-D-17-00049 Title: Contribution of sellar dura integrity to symptom manifestation in pituitary adenomas with intratumoral hemorrhage, Corresponding Author: Yasuhiko Hayashi, M.D., Ph.D. To the Editor We really appreciate for your cooperation about reviewing our manuscript carefully again. We are glad that you responded us with valuable comments. We sincerely request you to review our revised manuscript again and consider publication in Pituitary. Answers to reviewers' comments According to reviewer's suggestion, our classification was determined from the subjective viewpoints of patients. In group A, 20 patients (60.6%) had mild visual function disturbance, which was demonstrated on visual function examination. The proportion of hematoma volume within adenoma on preoperative MRI was significantly

	lower in both groups A (38.5 ± 24.6 %). The locations of hematoma inside adenoma were usually upper part, which meant had a contact with or close to the optic chiasm. However, the symptoms did not bother their daily living at all as reviewer commented. I apologized I did not mention the explanation about consciousness disturbance in patients in group C. Consciousness disturbance occurred in 3 patients in our study, and all of them were included only in group C (Page 13, line 1-3). We believe that their consciousness disturbance was caused by pituitary hormonal insufficiency (hypopituitarism), because their consciouness disturbance improved remarkably soon after administration of corticosteroid. In these patients, the tumors did not reach to the hypothalamus and no hydrocephalus was found on preoperative radiological evaluation (Page 13, line 3-6, and Page 22, line 9-12).

Clinical article

Contribution of sellar dura integrity to symptom manifestation in pituitary adenomas with intratumoral hemorrhage

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Abstract

Purpose Although hemorrhage within pituitary adenomas frequently exacerbates the symptoms, there are many grades of severity. Moreover, the contributing factors for symptom severity are still controversial.

Methods This retrospective study included 82 patients who underwent transsphenoidal surgery for pituitary adenomas with intratumoral hemorrhage. The grades of preoperative symptoms were classified into group A, asymptomatic or minor symptoms; group B, moderate symptoms sufficient for complain; and group C, severe symptoms disturbing daily life.

Results The hemorrhage volume within an adenoma was significantly higher in group C (92.6%) than in groups A (48.6%) and B (58.7%). Both headache and diplopia were dominant in group C, occurring in 72.2% and 27.8% of the patients, respectively. In group C, there was no significant difference in frequency between adenoma extensions into the sphenoid sinus (0%) and involvement of the cavernous sinus of Knosp grade 4 (0%), and extensions into the suprasellar region were not common (38.9%). The most distinctive feature was that “no extrasellar extension” was found

only in group C (41.2%), and “multidirectional extension” was not detected in this group (0%). Multiple regression analysis revealed that the most powerful determining factors were the high frequencies of intratumoral hemorrhage and lack of extrasellar and multidirectional extensions.

Conclusion Rapid volume expansion of a hematoma and lack of extension or unidirectional extension might lead to significant compression of the sellar and surrounding structures. Of note, the integrity of the sellar dura might contribute to the acute onset of symptom manifestations caused by hemorrhage in pituitary adenomas.

Introduction

The symptoms of pituitary adenomas, such as headache, visual function impairment, and pituitary function insufficiency, usually manifest as compression effects on the dura mater in the sella, the optic chiasm, and the pituitary gland (1-4). Intratumoral hemorrhages occur frequently and can exacerbate the symptoms of the adenoma, but there are many grades of severity (5,6). Asymptomatic hemorrhage or necrosis has been described in 14-22% of pituitary macroadenomas, while clinically significant pituitary apoplexy occurs in 0.6-9% (7). However, the contributing factors that determine the severity of symptoms in pituitary adenomas with intratumoral hemorrhage remain undefined.

Pituitary apoplexy has been known to be associated with the abrupt pathological changes in infarction, hemorrhage, or with co-occurrences of hemorrhage and infarction in pituitary adenomas, resulting in the sudden and fulminant expansion of the adenoma (5,7-10). Although the pathophysiology of pituitary apoplexy remains to be understood, various hypotheses have been proposed, such as occlusion of the vascular supply resulting from tumor growth, impaired blood supply resulting from

rapid growth, presence of abnormal vasculature, and other vasculopathic factors (6,11). Emergency surgery is required when there is deteriorating vision, sudden onset of blindness, or diminished level of consciousness. Early surgical removal of the adenoma within the first week from onset is recommended in cases with visual impairment (7). Transsphenoidal surgery (TSS) is generally accepted as the optimal surgical management, with concomitant rapid corticosteroid replacement (12-14).

In this study, we hypothesized that sudden enlargement of pituitary adenoma within the sella, or extension in the upward or lateral direction due to intratumoral hemorrhage, results in the compression of the sellar dura and/or neural structures. Therefore, we speculated that the sella and the surrounding structures possibly contribute to the elevation of intratumoral pressure in those pituitary adenomas with intratumoral hemorrhage. Hence, we examined the clinical and radiological characteristics of a series of 82 surgically treated patients at our institute.

Methods

Characteristics of study patients

This retrospective study included 82 patients with pituitary adenomas with intratumoral hemorrhage. The patients were selected based on magnetic resonance imaging (MRI) performed on 235 patients with pituitary adenomas who underwent TSS at Kanazawa University Hospital between 2006 and 2016. Lesions for which a previous TSS was performed were excluded. Patients were enrolled with the approval of the Institutional Review Board of Kanazawa University. Patient demographics, including age, sex, tumor histology, and symptoms were obtained from clinical records. This study consisted of 34 male and 48 female patients, with the age at diagnosis ranging from 15 to 88 years old (mean age, 52.0 ± 16.6 years). The diagnoses according to tumor histology were pituitary adenoma in all 82 patients (non-functioning in 67, and prolactin-secreting in 15). The symptoms observed were visual function disturbance in 49 patients (59.8%), headache in 27 patients (32.9%), symptoms derived from hypopituitarism (e.g., general malaise) in 13 patients (15.9%), diplopia in 7 patients (8.5%), and consciousness disturbance in 3 patients (3.7%) (Table 1).

Severity grades of symptoms caused by pituitary adenomas with intratumoral hemorrhage

Based on the severity of the preoperative symptoms caused by the pituitary adenomas with intratumoral hemorrhage, the patients were divided into the following three groups: A, asymptomatic or minor symptoms (33 patients); B, moderate symptoms enough to cause complaints (31 patients); and C, severe symptoms disturbing daily life (18 patients). The age at presentation, sex distribution, and tumor histology were compared among the groups (Table 1). A representative case from each group is shown (Figure 1-3).

Neuroradiological evaluation

In this study, intratumoral hemorrhages were confirmed using MRI by at least two neurosurgeons (Y.H., Y.S.) and a neuroradiologist (F.U.). The phases of the hematomas were determined based on the intensities of T1-weighted image (WI) and T2-WI by consensus of the three aforementioned authors (15,16). MRI was obtained using a Signa HDx 3T (GE Medical Systems, Milwaukee, WI). MRI was performed with both spin echo T1- and T2-weighted sequences. For T1-WI, the following were used:

repetition time, 550 ms; echo time, 11 ms; flip angle, 90°; field of view, 20 x 20 cm; matrix, 288 x 224; section thickness, 2.0 mm; and section gap 0.5 mm. Contrast enhancement with gadolinium administration in T1-WIs was examined for radiological diagnosis of the pituitary adenomas and the pituitary gland. For T2-WI, the following were used: repetition time, 2500-3500 ms; echo time, 98-104 ms; flip angle, 90°; field of view, 14 x 14 cm; matrix, 288 x 224 or 256 x 192; section thickness, 2.0-3.0 mm; and section gap, 0.5 mm. The integrity of the dura mater at the diaphragm sellae and the medial wall of the cavernous sinus were evaluated on T2-WIs or Fast Imaging Employing Steady State Acquisition (3,17). Tumor characteristics (maximum diameter, proportion of hematoma volume within adenoma, diameter of the diaphragmatic foramen, and extrasellar extensions) were also evaluated using MRI signal intensity on both T1- and T2-WI. The maximum diameter of the diaphragmatic foramen was measured on coronal sections including the pituitary stalk. The approximate volume of adenoma and hematoma was determined by multiplying their maximum height, width, and depth. Sphenoid sinus extension was defined as a downward extension of tumor with more than two-thirds of the height of the sphenoid sinus on the sagittal section of

MRI. Ossification of the sphenoid sinus was evaluated on the coronal and sagittal sections of the computed tomography (CT) scan (Table 2).

Endocrinological evaluation

An endocrinological study was performed preoperatively, which included the determination of the levels of plasma growth hormone, insulin-like growth factor-I, prolactin, adrenocorticotropic hormone, cortisol, thyroid-stimulating hormone, triiodothyronine, thyroxine, luteinizing hormone, and follicle-stimulating hormone. After TSS, corticotropin-releasing hormone, thyrotropin-releasing hormone, and luteinizing hormone-releasing hormone loading tests were performed for reserve capacity evaluation of each hormone tested preoperatively.

Statistical Analysis

The Mann-Whitney U-test was used to compare the ages of the patients at presentation, maximum diameter of the adenomas, proportions of hematoma inside the adenomas, and diaphragm defects among the groups. Post hoc analysis was used to compare sex distribution, tumor histology, rates of occurrence for each symptom, adenomas extensions, ossification of the sphenoid sinus as well as with or without

adenoma extensions, and grades of pituitary apoplexy grading system among the groups. A forward stepwise method was used to construct a multivariate logistic regression model to evaluate factors related to symptom manifestations in pituitary adenomas with intratumoral hemorrhage. These statistical analyses were performed using Microsoft Statview (ver. 5, SAS Institute Inc.). A p value of $< .05$ was considered as statistically significant.

Results

Comparisons of clinical features among groups of patients with pituitary adenomas

Among the 235 patients initially evaluated, intratumoral hemorrhages on MRI were detected in 82 patients (34.9%) before TSS. As described in the Methods section, these 82 patients were divided into three groups based on the severity of symptoms caused by pituitary adenomas with intratumoral hemorrhage. There were 33 patients (40.2%) in group A, 31 patients (37.8%) in group B, and 18 patients (22.0%) in group C. There was no significant statistical difference in age, sex distribution, and tumor histology among the three groups (Table 1).

Five patients (6.1%) in group A were asymptomatic regardless of the presence of intratumoral hemorrhage. The remaining 77 patients (93.9%) manifested at least one symptom. Out of the symptoms, visual function disturbance was predominant in groups A (20 patients, 60.6%) and B (25 patients, 80.6%) compared to group C (4 patients, 22.2%) ($p = 0.004$ respectively). In contrast, headache was more common in group C (13, 72.2%) than in groups A (8, 24.2%) and B (6, 19.4%) ($p < 0.001$). Similar to headache symptom, diplopia was more common in group C (5, 27.8%) than in

groups A (1, 3.0%) and B (1, 3.2%) (p = 0.004 respectively). Consciousness disturbance occurred only in 3 patients; however, all of them were in group C (16.7%) (p = 0.003). We considered the symptom was caused by hormonal insufficiency because of remarkable improvement soon after administration of corticosteroid. In addition, neither tumor compression to the hypothalamus nor hydrocephalus was found preoperatively. Symptoms derived from hypopituitarism were equally distributed in groups B (8, 25,8%) and C (5, 27.8%), although none existed in group A (p = 0.005 respectively, Table 1).

Comparisons of radiological features among groups of patients with pituitary adenomas

The size of pituitary adenomas with intratumoral hemorrhage was compared based on the maximum diameter on preoperative MRI among the three groups. The mean diameter in group C (21.6 ± 5.1 mm) was significantly smaller than that in groups A (29.5 ± 8.4 mm) and B (31.3 ± 9.1 mm) (p < 0.001 respectively). In contrast, the mean proportion of hematoma volume within adenoma on preoperative MRI was significantly higher in group C (91.2 ± 4.4 %) than in groups A (38.5 ± 24.6 %) and

B (53.8 ± 30.8 %) ($p < 0.001$ respectively, Table 2).

The extrasellar extensions of adenomas with intratumoral hemorrhage were compared in terms of extension into the suprasellar region, cavernous sinus, and sphenoid sinus on preoperative MRI. The frequency of extension into the suprasellar region was significantly lower in group C (7 patients, 38.9%) than in groups A (23 patients, 69.7%) and B (26 patients, 83.9%) ($p = 0.004$ respectively). In addition, the mean diameter of the diaphragm foramen was significantly narrower in group C (8.9 ± 2.9 mm) than in groups A (16.5 ± 5.4 mm) and B (17.4 ± 6.3 mm) ($p < 0.001$ respectively). These two results indicate that the suprasellar extension was inhibited by the narrow diaphragm defects in group C. Within group C, the mean diameter of the diaphragm foramen was significantly wider in patients with visual disturbance (14.4 ± 1.8 mm) than in those without visual disturbance (6.7 ± 2.1 mm, $p < 0.001$). The frequency of cavernous sinus extension was investigated separately based on Knosp grade 3 and 4. In Knosp grade 3, the frequency of the adenoma extension was not significantly different among the three groups (A, 7 patients, 21.2%; B, 5 patients, 16.1%; C, 5 patients, 27.8%; $p = 0.632$). Actually, intraoperative confirmation of the

extension into the cavernous sinus was not significantly different among the three groups (A, 2 patients, 28.6%; B, 2 patients, 40.0%; C, 5 patients, 40.0%). On the other hand, in Knosp grade 4, the frequency of adenoma extension was significantly lower in group C (0 patient, 0%) than in groups A (13 patients, 39.4%) and B (11 patients, 35.5%) ($p < 0.001$ respectively). All the patients identified as Knosp grade 4 radiologically were confirmed by examining the extension into the cavernous sinus intraoperatively.

All 5 patients who presented with diplopia in group C showed Knosp 3 extension. The frequency of sphenoid sinus extension was also significantly lower in group C (0 patients, 0%) than in groups A (15 patients, 45.5%) and B (17 patients, 54.8%) ($p < 0.001$, Table 2). All the patients identified with extension into the sphenoid sinus radiologically were confirmed by examining the extension intraoperatively.

Subsequently, the extrasellar extensions of the adenomas were also divided into three groups as follows: no extension, unidirectional extension, and multidirectional extension. Unidirectional extension means the adenomas exhibit an extrasellar extension in only one direction among the suprasellar region, cavernous sinus, and

sphenoid sinus. Multidirectional extension means the adenomas present extrasellar extensions in two or more directions among the suprasellar region, cavernous sinus, and sphenoid sinus. None of the patients in groups A and B presented “no extension”, although 7 patients (41.2%) in group C showed “no extension” ($p < 0.001$). Surprisingly, the symptoms of all the 7 patients with “no extension” in group C were severe headache only. Unidirectional extension was more frequent in group C (11 patients, 61.1%) than in groups A (11 patients, 33.3%) and B (12 patients, 38.7%); however, the difference did not reach statistical significance ($p = 0.149$). In contrast, none of the patients in group C revealed multi-directional extension. However, 18 patients in group A (54.5%) and 17 patients in group B (54.8%) revealed multidirectional extension, and the difference was statistically significant ($p < 0.001$ respectively) (Table 2).

In the surrounding structures, sphenoid sinus ossification, including the pre-sellar type and conchal type was examined using preoperative bone-window CT. However, no statistical difference was found among the three groups (A, 8 patients, 24.2%; B, 9 patients, 29.3%; C, 7 patients, 38.9%) ($p = 0.556$, Table 2).

Multiple regression analysis was performed both in comparisons of clinical and

radiological features among groups of patients with pituitary adenomas with intratumoral hemorrhage. In comparison of clinical features, visual function disturbance ($p = 0.015$) and headache ($p = 0.016$) were recognized as the most powerful determining factors on symptomatic manifestation of patients with pituitary adenomas with intratumoral hemorrhage. Subsequently, in comparison of radiological features, the high proportion of intratumoral hemorrhage ($p < 0.001$), and lack of extrasellar extension ($p = 0.012$) or multidirectional extension ($p = 0.012$) were found to have the biggest influence on the symptom manifestations (Table 2).

Discussion

Pituitary apoplexy typically occurs in pituitary macroadenomas; the majority of the cases are spontaneous, and numerous precipitating factors have been reported (9,11,18,19). The mechanism underlying the development of pituitary apoplexy has been proposed to be reduced blood flow in the pituitary gland, acute increase in blood flow in the gland, stimulation of the gland, and the anticoagulant state (7,19). The clinical presentation of pituitary apoplexy varies from a clinically relatively benign event to a catastrophic episode with severe neurological deficit, endocrine failure, or even death if untreated (5,11).

The clinical manifestations from a pathological point of view have been divided into three groups: 1) destruction or compression of the pituitary resulting in hypopituitarism, 2) sudden enlargement upward or laterally, resulting in the compression of neural structures, and 3) leaking of blood and necrotic tissue, resulting in meningism (10,20). The hemorrhages within pituitary adenomas rapidly expand the volume of the adenoma and severely raise the intrasellar pressure leading to the compression of the surrounding structures (6). Several patients required hormone replacement therapy for

hypopituitarism after the occurrence of an intratumoral hemorrhage (5,6,20).

Occurrence of hemorrhage within a pituitary adenoma does not always lead to severe symptoms, even if the hemorrhage is large enough to compress the surrounding structures. Therefore, previous reports delineated several grades of severity in those patients harboring a pituitary adenoma with intratumoral hemorrhage, although the factors contributing to the symptom severity remain to be determined (5-7). To elucidate the factors contributing to intratumoral hemorrhage-associated symptoms, we focused on the possible participation of structures surrounding the pituitary gland and the pituitary adenomas as the factors elevating intrasellar or intraadenoma pressure (21-24). When the integrity of the sellar dura mater is maintained, the intrasellar or intra-adenoma pressure is elevated after the occurrence of intratumoral hemorrhage (3,25). Regarding the landmarks of the surrounding structures in the sella, we took into account erosion or invasion of the medial wall of the cavernous sinus (Knosp grades 3 and 4) and the dura mater of the inferior aspect of the sellar floor, the size of diaphragm foramen, and ossification of the sphenoid sinus.

The maximum diameter of pituitary adenomas with intratumoral hemorrhage was significantly smaller in the patients in group C than in groups A and B. In contrast, the proportion of hemorrhage within the adenomas was significantly higher in the patients in group C, compared with both groups A and B. According to the results described above, we speculated that the rapid volume expansion upon the occurrence of intratumoral hemorrhage was one of the mechanisms causing severe symptom manifestation (10). Moreover, the extension of adenomas into the suprasellar region was significantly less frequent in the patients in group C than in groups A and B, with a significantly narrower diaphragm foramen in the patients in group C than in groups A and B. Likewise, the extension of adenomas into the cavernous sinus was significantly inhibited in the patients in group C relative to that in groups A and B. None of the patients in group C presented Knosp grade 4, although more than 30% of the patients in groups A and B did. Similarly, the extension of adenomas into the sphenoid sinus was significantly reduced in the patients in group C compared to that in groups A and B. None of the patients in group C presented extension into the sphenoid sinus, although more than 40% of the patients in groups A and B exhibited this extension. These

results revealed that the elevation of the intrasellar or intraadenoma pressure might be relieved partially by the extrasellar extension of the adenoma.

In addition, “no extrasellar extension” was observed in the patients in group C alone, and all of them presented with severe headache. In those cases, the integrity of the sellar dura was completely preserved, suggesting that the occurrence of hemorrhage within the adenomas caused a rapid elevation of the tension force on the sellar dura (3,21,23,26). In group C, all the patients who presented with visual function disturbance revealed unidirectional extension into the suprasellar region. Likewise, all the patients who presented with diplopia demonstrated unidirectional extension into the cavernous sinus. Hence, the unidirectional extension of adenomas might indicate that the integrity of the sellar dura in the other direction was maintained. Furthermore, the elevation of intraadenoma pressure was observed along the adenoma extension onto the surrounding structures, including the optic chiasm and the oculomotor and abducens nerves.

It was noteworthy that none of the patients in group C displayed a multidirectional extension of adenomas, which was recognized in more than 50% of patients in groups

A and B. These results strongly suggest that elevation of the intra-adenoma pressure was largely relieved by dispersing it into two or more directions.

The sella dura acts as a structural barrier, that is composed of a narrow foramen of the diaphragm sellae superiorly, an intact medial wall of the cavernous sinus laterally, and intact dura at the sella floor contacting with the sphenoid sinus inferiorly. From our results, we conclude that this integrity of the sella dura works conversely by increasing intrasellar pressure and causing rapid manifestation of symptoms when hemorrhage arises within pituitary adenomas. Therefore, the adenomas with intratumoral hemorrhage confined in the sellar dura might induce severe headache. In addition, this increasing intrasellar pressure also worked on the pituitary gland, leading to occurrence of consciousness disturbance, which was derived of pituitary insufficiency because of remarkable improvement soon after administration of corticosteroid. Furthermore, unidirectional extension of adenomas might convey much of the pressure along the extension on the surrounding structures, such as the optic chiasm superiorly and the cranial nerves in the cavernous sinus laterally.

Our grading of preoperative symptoms for pituitary adenomas with intratumoral

hemorrhage is based on the severity of symptoms caused by intratumoral hemorrhage. However, our grading scale is subjective, in that it relates to patients' complaints. Jho et al. proposed an objective scale for pituitary apoplexy evaluating the symptoms both clinically and radiographically with grading of 1: no symptoms, 2: endocrinopathy only, 3: headache, 4: ocular paresis, 5: visual acuity or field deficit, or consciousness disturbance (27). However, the severity of each symptom was not assessed, and the grading was only determined by the existence of each symptom. We assessed this grading system with our study cohort. The results were group A : 3.94 $\pm$ 1.48, B : 4.16 $\pm$ 0.74, C: 3.89 $\pm$ 0.84, and the statistical difference was not significant among three groups ($p = 0.122$). From the above, we determined that our grading scale produced different results from the previous objective scale for pituitary apoplexy. On the other hand, their results revealed that tumors with visual function disturbance had significantly larger diameters and those with headache had significantly smaller diameter. This result corresponded to our result that the mean diameters in groups A and B, in which their symptoms were predominantly visual function disturbance, were larger than those in group C, in which their symptoms were mainly headache.

There are some limitations in our study. First, this study was retrospective in design. Second, the total number of patients (82 patients) was too small to provide significant statistical power. This case series is also limited by the relatively long time frame in which the cases were collected. In addition, although we speculated that the elevation of the intrasellar pressure causes rapid manifestation of symptoms when hemorrhage arises within pituitary adenomas if the integrity of the sellar dura is maintained, but we did not perform actual measurement of the intrasellar pressure. Finally, our grading scale is still subjective, as described above.

It is clinically useful for pituitary neurosurgeons to consider this mechanism of symptom manifestation from the viewpoints of the anatomical structures surrounding the sellar turcica to determine the contribution of intratumoral hemorrhage to the symptoms and the best window of surgical removal of the pituitary adenomas.

Conflict of Interest

All authors have no conflict of interests.

List of Abbreviations

CT: computed tomography

MRI: magnetic resonance imaging

TSS: transsphenoidal surgery

WI: weighted image

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Figure Legends

Figure 1. A representative case of magnetic resonance imaging (MRI) in Group A. (A) T1-weighted image (WI) with contrast enhancement on a coronal section showing a pituitary adenoma with extension into the suprasellar region containing small hemorrhage and extension into the cavernous sinus surrounding the internal carotid artery completely (arrow). (B) T1–WI with contrast enhancement on a sagittal section showing adenoma extension into the sphenoid sinus (arrows). (C) T2-WI on a coronal section showing wide opening of the defect of the diaphragm sellae (17.4 mm, arrowheads) permitting the suprasellar extension with remarkable compression of the optic chiasm.

Figure 2. A representative case of MRI in Group B. (A) T1-WI with contrast enhancement on a coronal section showing a pituitary adenoma with large intratumoral hemorrhage with extension into the suprasellar region elevating the optic chiasm and extension toward the cavernous sinus (arrows). (B) T1-WI with contrast enhancement on a sagittal section showing adenoma with suprasellar extension (arrow). (C) T2-WI on a coronal section showing wide opening of the defect of the

diaphragm sellae (18.4 mm) allowing suprasellar extension with remarkable compression of the optic chiasm (arrowheads).

Figure 3. A representative case of MRI in Group C. (A) T1-WI with contrast enhancement on a coronal (A) and a sagittal (B) sections showing a pituitary adenoma with intratumoral hemorrhage localized only in the sella without extension into the suprasellar region and cavernous sinus (arrow). (C) T2-WI on a coronal section showing narrow opening of the defect of the diaphragm sellae (6.2mm) not allowing for the suprasellar extension.

Table Legends

Table 1. Comparisons of the clinical features among the groups of patients with pituitary adenomas with intratumoral hemorrhage

Table 2 . Comparisons of the radiological features among the groups of patients with pituitary adenomas with intratumoral hemorrhage

Figure 1

Yasuhiko Hayashi ↑

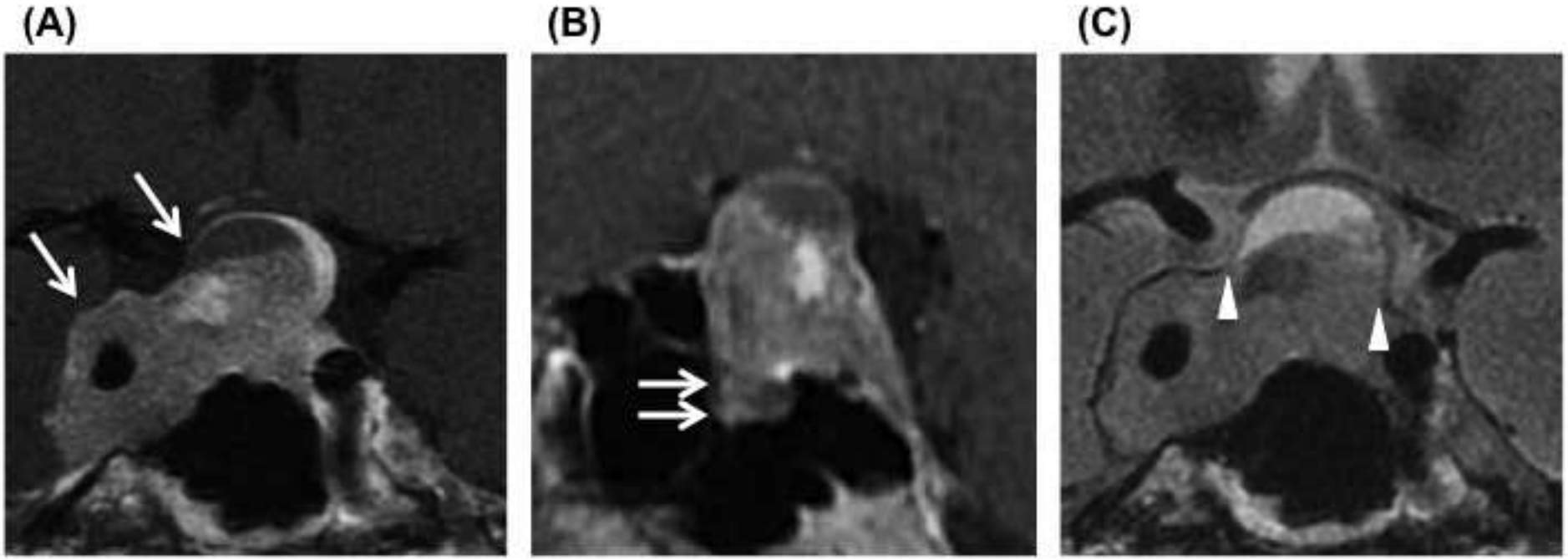

Figure 2

Yasuhiko Hayashi ↑

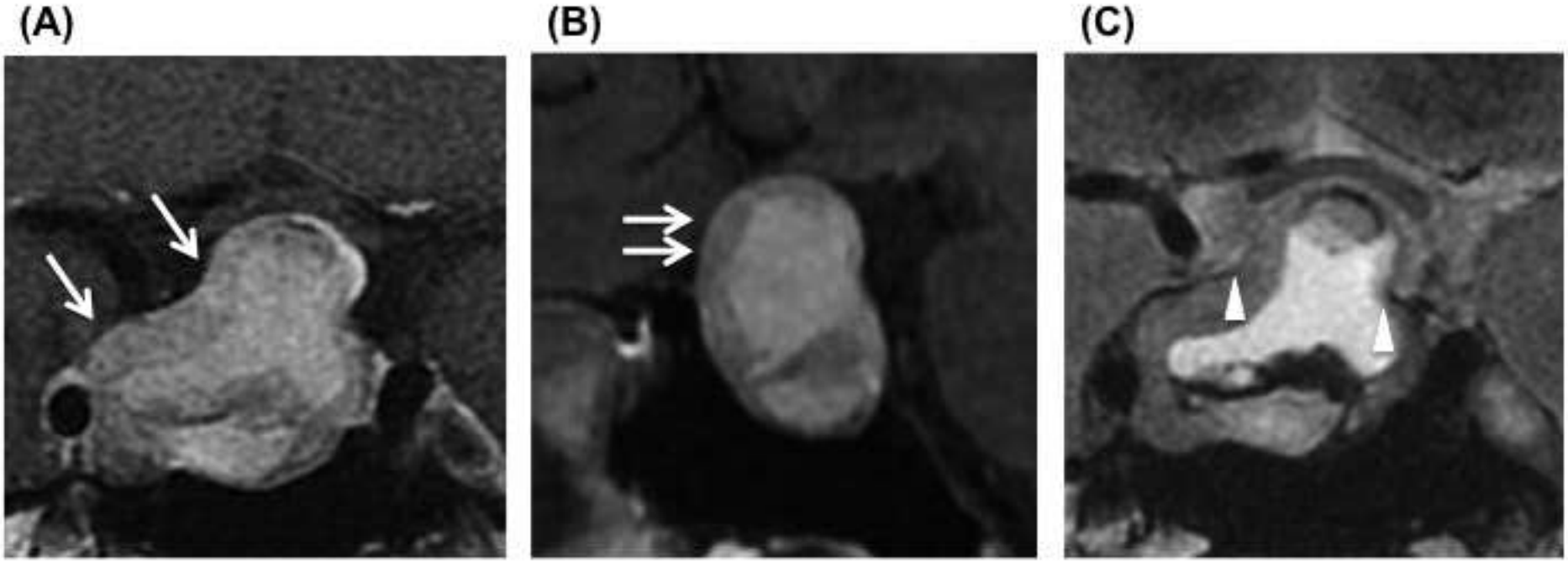

Figure 3

Yasuhiko Hayashi ↑

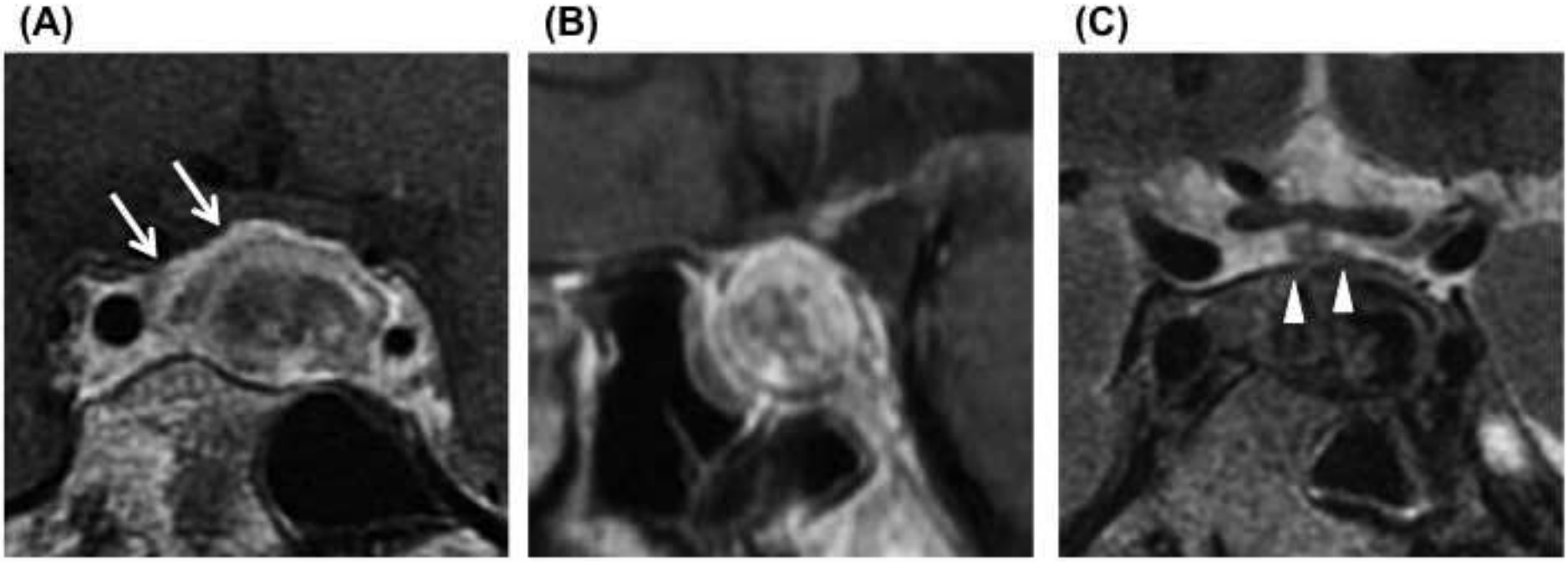

Table 1

Comparisons of the clinical features among the groups of patients with pituitary adenomas with intratumoral hemorrhage

		A	B	C	Total	p vales	
						univariate	multivariate
Number	**(%)**	33 (40.2)	31 (37.8)	18 (22.0)	82 (100)		
Age	**(yrs)**	55.2 ± 14.8	48.6 ± 16.6	51.7 ± 16.5	52.0 ± 16.6	0.29	
Sex	**(Men : Women)**	12:21	14:17	8:10	34:48	0.75	
Tumors	**NFA**	27	25	15	67	0.974	
	PRL	6	6	3	15		
Symptoms	**VD**	20 (60.6)	25 (80.6)	4 (22.2)	49 (59.8)	0.004 *	0.015 *
	HA	8 (24.2)	6 (19.4)	13 (72.2)	27 (32.9)	< 0.001 *	0.016 *
	DP	1 (3.0)	1 (3.2)	5 (27.8)	7 (8.5)	0.004 *	0.377
	CD	0 (0)	0 (0)	3 (16.7)	3 (3.7)	0.003 *	0.163
	HP	0 (0)	8 (25.8)	5 (27.8)	13 (15.9)	0.005 *	0.103
	Asymptomatic	5 (15.2)			5 (6.1)		

1: NFA; non-functioning pituitary adenoma, PRL; prolactin secreting pituitary adenoma, VD; visual function disturbance, HA; headache, DP; diplopia, CD; consciousness disturbance, HP; general symptoms due to hypopituitarism , 2: * $p < 0.01$

Table 2

Comparisons of the radiological features among the groups of patients with pituitary adenomas with intratumoral hemorrhage

		A	B	C	Total	p vales	
						univariate	multivariate
Number	**(%)**	33 (40.2)	31 (37.8)	18 (22.0)	82 (100)		
Size	**(mm)**	29.5 ± 8.4	31.3 ± 9.1	21.6 ± 5.1	28.4 ± 8.9	< 0.001 *	0.679
Hematoma	**(%)**	38.5 ± 24.6	53.8 ± 30.8	91.2 ± 4.4	55.9 ± 31.5	< 0.001 *	< 0.001 *
Diaphragma Defect	**(mm)**	16.5 ± 5.4	17.4 ± 6.3	8.9 ± 2.9	15.2 ± 6.3	< 0.001 *	0.416
Extrasellar Extension (number, %)							
Suprasellar region		23 (69.7)	26 (83.9)	7 (38.9)	54 (65.9)	0.004 *	0.394
Cavernous sinus	**Knosp 3**	7 (21.2)	5 (16.1)	5 (27.8)	17 (20.7)	0.632	
	Knosp 4	13 (39.4)	11 (36.5)	0 (0)	24 (29.3)	< 0.001 *	0.423
Sphenoid sinus		15 (45.5)	17 (54.8)	0 (0)	32 (39.0)	< 0.001 *	0.079
w/o extension		0 (0)	0 (0)	7 (41.2)	7 (8.5%)	< 0.001 *	0.012 *
w/ extension	**unidirection**	11 (33.3)	12 (38.7)	11 (61.1)	34 (41.5)	0.149	
	multidirections	18 (54.5)	17 (54.8)	0 (0)	35 (42.6)	< 0.001 *	0.012 *
SS ossification	**(%)**	8 (24.2)	9 (29.3)	7 (38.9)	24 (29.3)	0.556	

1: Size means averaged maximum diameter of adenoma, 2: Hematoma means the averaged volume proportion of hematoma in adenoma, 3: * $p < 0.01$

Respond to Reviewer's Comments