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Metachronous Double Pituitary Adenoma with Altered Transcriptional Factor Profile: A Case Report and Literature Review

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Abstract

Double pituitary adenomas (DPAs), especially metachronous DPAs, are extremely rare and there has been no report about DPAs with altered transcriptional factors. We describe the case of a 25-year-old man who presented with acromegaly 7 years after surgery for a non-functioning pituitary adenoma (NFPA). Before the initial surgery, endocrine evaluation confirmed NFPA or silent somatotroph pituitary adenoma (SPA) because of normal serum levels of insulin-like growth factor-1 (IGF-1) and insufficient suppression of growth hormone (GH) levels in the oral glucose tolerance test (OGTT). Immunohistochemistry of resected tissue obtained from gross total resection (GTR) with transsphenoidal surgery (TSS) was negative for follicle-stimulating hormone, luteinizing hormone, GH, and Pit-1 but positive for GATA3, which confirmed the gonadotroph pituitary adenoma (GPA) diagnosis. Seven years later, follow-up brain MRI revealed a 13.3 × 5.6 × 4.7 mm tumor within the sellar turcica. The endocrine evaluation confirmed acromegaly because of high serum levels of IGF-1 and insufficient suppression of GH levels upon OGTT. GTR with TSS was again performed, and immunohistochemistry was negative for GATA3 but positive for GH and Pit-1. Surprisingly, he showed altered transcription factor expressions between initial and recurrent surgery. Based on the overall clinical course and hormonal secretion findings, we speculated metachronous development of a DPA, i.e., SPA followed by GPA, wherein a few remaining cells of the SPA might have regrown after the initial surgery. We conducted a literature review of cases that documented altered hormone secretion at recurrence and emphasized the necessity of identifying a small adenoma when there is a discrepancy between pathological findings and hormone secretion tests.

Keywords: double pituitary adenoma, acromegaly, non-functioning pituitary adenoma, gonadotroph adenoma, somatotroph adenoma

Introduction

Pituitary adenomas are benign intracranial neoplasms that account for 14.7–16.9% of all intracranial tumors[1,2] and are classified as non-functioning pituitary adenomas (NFPAs) and functioning pituitary adenomas. The fourth edition of the World Health Organization (WHO) classification of tumors of endocrine organs, published in 2017, recommends introducing a more precise cell lineage-based classification of pituitary adenomas based on immunohistochemistry for transcription factors and secreted hormones.[3,4] Plurihormonal adenomas are defined as adenohypophyseal tumors that produce more than one hormone.

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They could either be monomorphous, i.e., consisting of a single cell type that produces two or more hormones, or polymorphous, i.e., composed of two or more different types of cells.[3] While some adenomas display immunoreactivity with two or more pituitary-specific transcription factors that do not always conform to cell lineage,[4] double pituitary adenomas (DPAs) are extremely rare and differ from plurihormonal adenomas. Specifically, in DPAs, each adenoma develops from a different cell type in the pituitary gland.[5–7] Here, we describe the case of a patient who was initially diagnosed with a gonadotroph pituitary adenoma (GPA) and underwent surgery. Subsequently, about 7 years later, he was diagnosed with a somatotroph pituitary adenoma (SPA) that was also surgically resected. There have been no reports of altered transcription factor expressions in pathological examination of primary and recurrent tumors. Immunopathological findings, including transcription factor staining and endocrinological profile of the resected GPA at the initial surgery, suggested the potential development of a metachronous DPA. We discuss this rare case along with a literature review.

Case Report

An 18-year-old male presented with bitemporal hemianopsia and headache. Upon admission to our facility, his body weight was 63.5 kg, height was 173.7 cm, and typical clinical features of acromegaly were absent. He had neither a family history of pituitary adenoma nor multiple endocrine neoplasias. Brain MRI demonstrated a large mass of approximately 21.5 × 22.9 × 18.1 mm within the sellar to upper sellar regions (Fig. 1a–1c) that was isointense with the gray matter and only weakly enhanced by gadolinium-based contrast. An endocrine evaluation revealed normal basal serum level and function of the anterior pituitary hormone (Table 1). The patient received a combination of thyrotropin-releasing hormone (TRH; 500 μg) and luteinizing hormone (LH)-releasing hormone (100 μg). He also underwent an insulin tolerance test (0.1 unit/kg), and the results indicated an NFPA.

Further, the 75 g oral glucose tolerance test (OGTT) showed insufficient suppression of growth hormone (GH) levels (Table 1), suggesting a GH-producing pituitary adenoma. Based on the above findings, the patient received an initial diagnosis of silent SPA or NFPA. He underwent transsphenoidal surgery (TSS) for gross total resection (GTR) of the tumor, including the pseudocapsule. Importantly, there was no cavernous sinus invasion. Pathological evaluation of the resected tissue showed that the tumor was composed of round to polygonal cells with nuclei showing moderate anisonucleosis and chromophobic

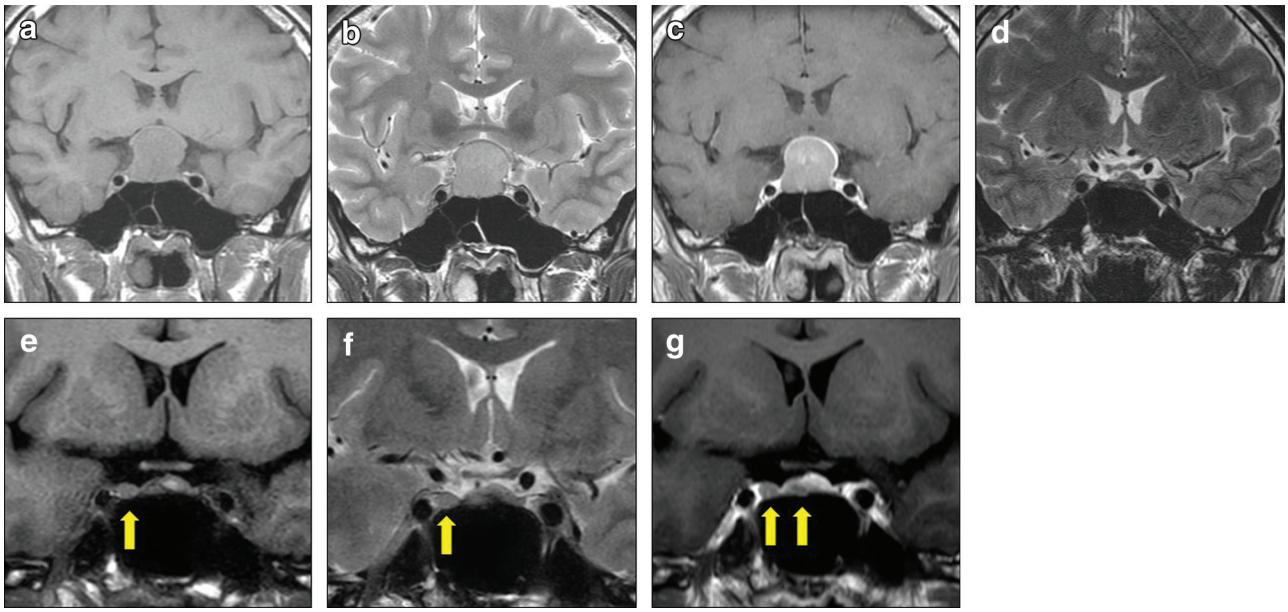

Fig. 1 (a)–(d) are MRIs of the sellar region at the age of 18. Coronal T1-weighted image (a), coronal T2-weighted image (b), and coronal contrast-enhanced T1-weighted image (c) show a homogenous lesion in the sellar to suprasellar region. Coronal T2-weighted image after initial TSS (d) confirms GTR of the tumor. (e)–(g) are MRIs of the sellar region at the age of 25. Coronal T1-weighted image (e), coronal T2-weighted image (f), and coronal contrast-enhanced T1-weighted image (g) show a small dumbbell-shaped homogenous lesion on the right side of the sellar region (arrow). GTR: gross total resection; TSS: transsphenoidal surgery.

Table 1 Hormone loading test results

	Before initial surgery		After initial surgery		Before secondary surgery		After secondary surgery		Reference range
	Base level		Base level		Base level		Base level		
FT3 (pg/ml)	2.6		1.4		3.2		3		2.3–4.0
FT4 (ng/dl)	1.2		3.2		1.4		1.7		1.1–1.8
Testosterone (ng/ml)	4.4		6		5.7		4.8		1.3–8.7
IGF-1 (ng/ml)	303		169		470		145		
SD score	–0.4		–1.8		3		–1.7		
TRH test	Base level	Peak level	Base level	Peak level	Base level	Peak level	Base level	Peak level	
TSH (μIU/ml)	3.47	12.4	3	12.4	1.3	9	1.73	12	0.5–5.0
PRL (ng/ml)	12.9	17.7	5	30.6	7.5	39.2	9.4	66.8	4.3–13.7
GH (ng/ml)	CT	CT	CT	CT	6.48	21.7	0.72	0.96	0–2.47
LHRH test	Base level	Peak level	Base level	Peak level	Base level	Peak level	Base level	Peak level	
LH (mIU/ml)	4.1	19.6	3.8	28	5.3	37.9	5.2	31.7	1.7–8.6
FSH (mIU/ml)	7.4	12.4	4.8	8.9	5	9.8	4.7	8.5	1.5–12.4
GH (ng/ml)	CT	CT	CT	CT	7.31	7.32	NM	NM	0–2.47
ITT	Base level	Peak level	Base level	Peak level	NP	NP	Base level	Peak level	
Cortisol (μg/dl)	10.7	20.7	8.4	18.2	NM	NM	8.6	15.5	6.2–18.0
ACTH (pg/ml)	43	NM	46.9	NM	NM	NM	20.2	112	7.2–63.3
GH (ng/ml)	3.11	5.02	4.74	6.05	NM	NM	2.87	11.7	0–2.47
OGTT	Base level	Nadir level	NP	NP	Base level	Nadir level	Base level	Nadir level	
GH (ng/ml)	2.3	1.5	NM	NM	6.6	5	1.2	0.2	0–2.47

TRH test, LHRH test, and insulin tolerance test were administered in combination before initial surgery. The peak level of adrenocorticotropic hormone was not measured before and after the initial surgery. TRH test and LHRH test were combined after the second surgery. ACTH: adrenocorticotropic hormone; CT: combination test with TRH, LHRH, and ITT; FSH: follicle-stimulating hormone; FT3: free triiodothyronine; FT4: free thyroxine; GH: growth hormone; IGF-1: insulin-like growth factor-1; ITT: insulin tolerance test; LH: luteinizing hormone; LHRH: luteinizing hormone-releasing hormone; NM: not measured, NP: not performed; OGTT: oral glucose tolerance test; PRL: prolactin; SD: standard deviation; TRH: thyrotropin-releasing hormone; TSH: thyroid-stimulating hormone.

cytoplasm. Immunohistochemistry was negative for adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), LH, prolactin (PRL), thyroid-stimulating hormone (TSH), GH, and Pit-1. However, it was positive for GATA3, with an MIB-1 label index of 2.4% maximum (Fig. 2a–2d). These histological findings confirmed the GPA diagnosis according to criteria listed in the recent WHO classification of tumors of endocrine organs.[3] He was discharged without sequelae 8 days after the surgery. At the 3 months after the surgery, an endocrine evaluation revealed normal levels of anterior pituitary function, and an MRI confirmed the GTR of the tumor (Fig. 1d). Both bitemporal hemianopsia and headache also improved.

Seven years later, a regular checkup revealed high serum levels of insulin-like growth factor-1 (IGF-1; 470 ng/ml, standard deviation score: +3.0). Brain MRI revealed a 13.3 × 5.6 × 4.7 mm dumbbell-shaped tumor to the right of the previous sellar lesion (Fig. 1e–1g). An OGTT (75 g) showed insufficient suppression of GH level, and a TRH stimulation

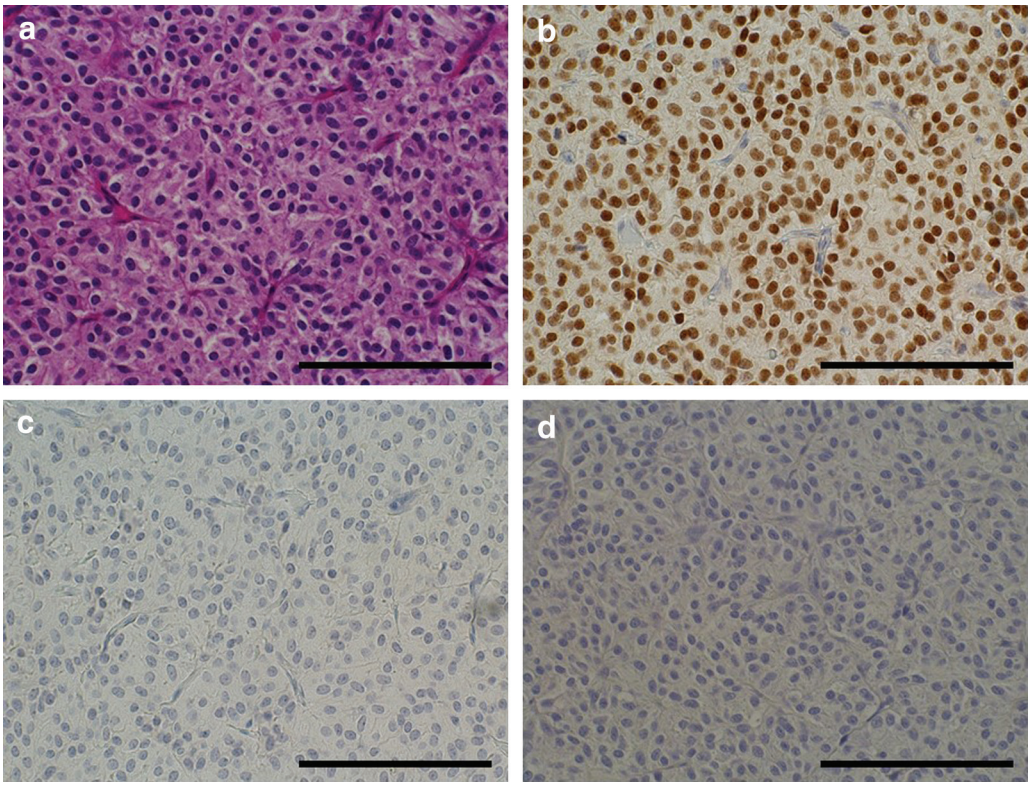

Fig. 2 Pathological findings during surgery for GPA. The specimen shows histological evidence of tumor cells that are round or polygonal, with nuclei showing moderate anisonucleosis and eosinophilic cytoplasm (a). Immunohistochemistry was positive for GATA3 (b) but negative for Pit-1 (c) and GH (d) (original magnification, ×400; bar, 50 μm). GH: growth hormone; GPA: gonadotroph pituitary adenoma.

test showed paradoxical GH response (Table 1), confirming a diagnosis of acromegaly with few typical clinical features. He underwent another TSS, and GTR was achieved. The left and the right sides of the dumbbell-shaped mass were yellowish and soft with continuity and no cavernous sinus invasion. Immunohistochemistry was negative for ACTH, FSH, LH, PRL, TSH, and GATA3 but positive for GH and Pit-1 with an MIB-1 label index of 2.0% maximum (Fig. 3a–3c). While these histological findings confirmed a diagnosis of SPA, postoperative endocrine examination revealed normal levels of anterior pituitary function and sufficient serum GH suppression upon 75 g OGTT (Table 1).

Discussion

Here, we describe an extremely rare case of two pituitary adenomas in the same patient but with a different profile of transcription factors, i.e., a GPA when he was 18 years old and an SPA when he was 25 years old. Typically, the transition from one tumor subtype to another is a very rare phenomenon. Recurrence is usually caused by residual tumor cells; therefore, very few reports have described such a transition from an NFPA to a hormonally active adenoma, or from a prolactinoma to a GH-producing pituitary adenoma, despite their common somato-mammotroph progenitor lineage.[8–13] In all previously reported cases except this, the transcription factor profile is expected to conform to the WHO classification (2017 edition).[3] To the best of our knowledge, no report has described hormone secretion changes due to altered transcription factor expression.

The reason of altered transcription factor between the initial surgery and the secondary surgery

In our case, GTR, including the pseudocapsule, was achieved during surgery for the GPA. This is the recommended approach as it increases the biochemical remission rate without heightening surgical risk.[14,15] Recurrence/persistence rates after TSS for pituitary adenomas are approximately 16–19%[16,17] but are reported to be 0.4% when the pseudocapsule is also resected during GTR.[18] Therefore, after 7 years, we speculated that the SPA was not a recurrence of the GPA but rather another compressed hidden tumor.

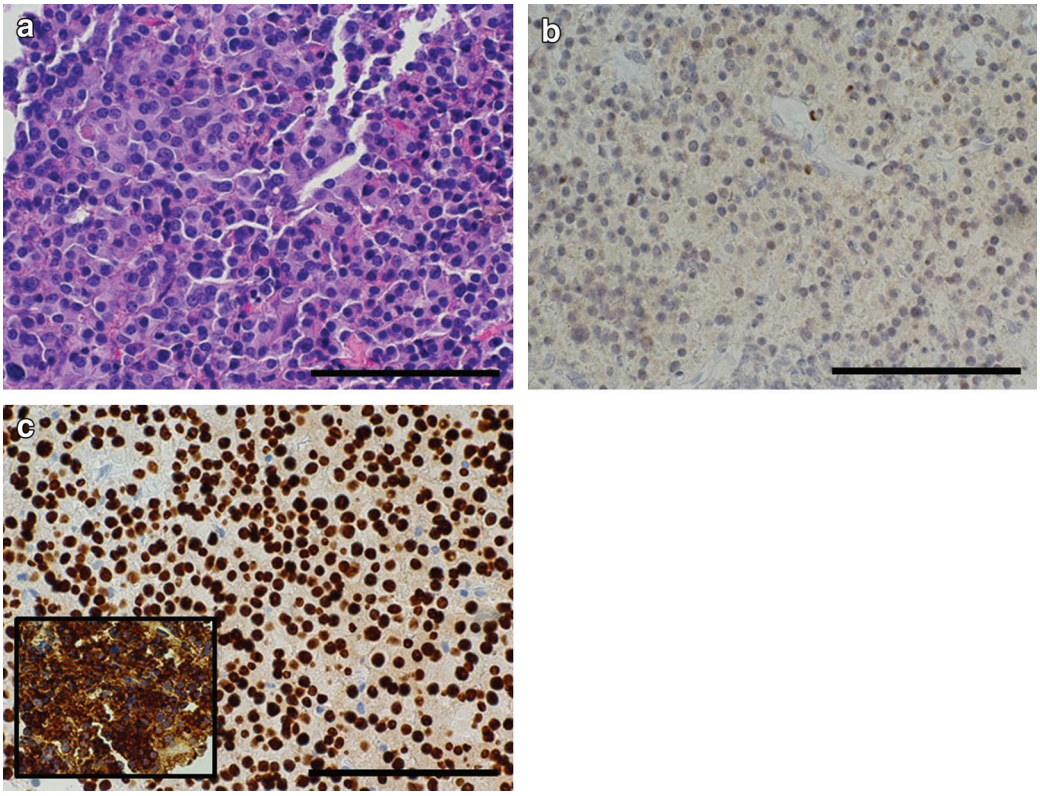

Fig. 3 Pathological findings after surgery for the SPA. The specimen shows histological evidence of tumor cells that are round or polygonal, with nuclei showing moderate anisonucleosis and scant chromophobic cytoplasm (a). Immunohistochemistry was negative for GATA3 (b) but positive for Pit-1 (c) and GH (c; bottom left) (original magnification, ×400; bar, 50 μm). GH: growth hormone; SPA: somatotroph pituitary adenoma.

Furthermore, it is also possible that the SPA was present when surgery for the GPA was performed but that the GPA had compressed it.

Additionally, the SPA's shape would become round or oval if it developed from normal pituitary tissue after surgery for the GPA. In contrast, the SPA developed adjacent to the cavernous sinus where there was no normal pituitary tissue after initial surgery for GPA. Insufficient depression in GH levels was observed upon OGTT before surgery for the GPA. These findings, along with normal serum levels of IGF-1 before GPA surgery, suggest the presence of a tiny but compressed SPA at the right side of the larger GPA. Thus, even though our patient had a double pituitary adenoma, i.e., SPA and GPA, only one large component was confirmed on preoperative MRI. This was probably because such a microadenoma might have been too small to be detected on MRI, given the other larger macroadenoma's mass effect. Nonetheless, we could not find any SPA component upon re-evaluation of the resected GPA tissue. Our case shows that identifying a small adenoma might be necessary when a discrepancy is observed between preoperative MRI and endocrinological findings. Alternatively, we might have been able to reach a diagnosis of DPA if the patient had been asked to undergo OGTT after surgery for the GPA.

Double pituitary adenomas

DPAs account for 0.5–2.6% of all pituitary adenomas, and most have been described as two components upon MRI,[5,6] incidentally identified during surgery or by pathological findings after surgery.[19,20] However, metachronous development has rarely been reported.[7] Iacovazzo et al. have described a DPA case wherein the patient developed Cushing's disease after cabergoline treatment for a PRL-producing adenoma. DPA was not identified on the initial MRI, and the patient was diagnosed with metachronous DPA because of the development of signs of Cushing's disease 1 year after cabergoline treatment.[7] Their case and our case underscore the importance of hormone tests in DPA diagnosis, but our case is unique in that both surgeries showed that the two tumors were different.

The genesis of pituitary adenomas is controversial and largely unclear, and it follows that the origins

of DPA are also uncertain. There are two pathogenetic hypotheses regarding DPA, namely, the multicentricity theory and the transdifferentiation theory. The multicentricity theory posits coincidental monoclonal expansion of two distinct genetically mutated pituitary cell types that could result in the development of synchronous adenomas[19] whose characteristic features include the presence of tumors with distinct pseudocapsules that are not immediately contiguous.[20] In contrast, the transdifferentiation theory postulates that cells of one already-present pituitary adenoma could transdifferentiate into another cell type, with different morphologic and phenotypic characteristics, including secretory features and local behavior.[19] However, X-chromosomal inactivation analysis has revealed that most pituitary adenomas, as with most tumors, derive from the clonal expansion of a single pituitary cell.[21] Therefore, further studies are needed to provide evidence for the transdifferentiation theory, and currently, the multicentricity theory might explain the occurrence of DPA.

Silent SPAs and acromegaly

SPAs are typically recognized by the presence of clinical features and high serum level of GH and IGF-1. Wade et al. retrospectively examined SPAs and found that 33.3% of SPAs patients did not have clinical symptoms and subclassified them into the "clinical silent" group. Moreover, they found a subgroup of SPAs who neither had clinical symptoms nor high serum level of IGF-1, and subclassified them into the "silent" group. The silent group was extremely rare, and the incidence was only 4.2%.[22] Physicians need to be aware that silent SPA may progress to acromegaly,[23,24] and SPAs have been reported to be a poorer prognosis group.[25] In fact, Sakharova et al reported that silent somatotroph adenomas represent an early stage in somatotrophic adenoma development.[23] The uniqueness of this case report is that in addition to being a metachronous DPA, it was also a silent SPA that developed acromegaly 7 years later, which could be detected early by regular measurement of IGF-1. Therefore, considering the possibility of silent SPAs, we would like to emphasize the importance of endocrinological study during long-term follow-up of non-surgical cases in NFPAs such as microadenomas. We further suggest for measuring the serum level of IGF-1 in all pituitary adenomas under observation. If physicians have any doubts about the diagnosis of NFPA, OGTT may give additional information for the diagnosis of SPA.

In summary, we describe a case of metachronous development of DPA, i.e., GPA followed by SPA. We speculate that this case might represent a scenario wherein a large GPA and a silent SPA had co-existed at the view point of altered transcription factor expressions in pathological examination of primary and recurrent tumors. The residual SPA became symptomatic 7 years after surgery for the GPA. A definitive diagnosis of DPA was difficult when based solely on MRI findings. As the endocrinological findings were suggestive of a SPA in the present case, we regret not considering the possibility of a DPA and undertaking a more careful observation of the space after tumor resection for the GPA. Thus, we would like to emphasize the importance of endocrinological findings in arriving at a silent DPA diagnosis.

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Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Akira Taguchi, Yasuyuki Kinoshita, Vishwa Jeet Amatya, and Fumiyuki Yamasaki. The first draft of the manuscript was written by Akira Taguchi. All authors read and approved the final manuscript.

Conflicts of Interest Disclosure

The authors declare that they have no conflicts of interest. Akira Taguchi, Yasuyuki Kinoshita, Atsushi Tominaga, and Fumiyuki Yamasaki have registered online self-reported COI disclosure statement Forms through the website for the Japan Neurosurgical Society members.

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