Dural Invasion and Proliferative Potential of Pituitary Adenomas

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Abstract

The relationship between invasiveness and proliferative potential was studied in 31 cases of pituitary adenomas. The invasiveness was determined by histological examination of sellar floor dura resected during transsphenoidal surgery. The proliferative potential of adenoma specimens was examined immunohistochemically using monoclonal antibody (MIB-1). There were 11 adenomas with histologically verified dural invasion out of 31 cases. These adenomas had a higher MIB-1-positive ratio than adenomas without dural invasion ($p < 0.05$). Pituitary adenomas with a high proliferative potential tend to be invasive.

Key words: dura mater, neoplasm invasiveness, pituitary neoplasm, proliferative cell nuclear antigen

Introduction

Invasive pituitary adenomas were previously thought to be rare.³⁾ However, more recent studies have found that invasion of pituitary adenomas into the cavernous sinus is not uncommon and invasion into the dura of the pituitary fossa is frequent.¹⁵⁾ Histological studies of surgical specimens of pituitary adenomas have verified that dural invasion is common.^{7,9,14)}

Magnetic resonance (MR) imaging has been used in many studies on the clinical diagnosis of invasion into the cavernous sinus, but the criteria still remain controversial.^{4,8,11,13)} We previously reported a positive relationship between MR imaging of cavernous sinus invasion and histologically verified dural invasion of the sellar floor.¹⁾

Here, we report the relationship between histologically verified dural invasion and the proliferative potential of pituitary adenomas.

Materials and Methods

Thirty-one specimens of pituitary adenomas and dura from the sellar floor were resected by transsphenoidal surgery at Asahikawa Medical College Hospital between March 1986 and June 1994. Classification of the adenomas was based on endocrine

analysis (Table 1). The height and width of each adenoma was measured on coronal MR images with gadolinium-diethylenetriaminepenta-acetic acid administration. The size of the adenomas was conveniently represented by multiplying the height by the width.

Specimens of pituitary adenomas and pieces of the sellar floor dura about 4 mm² were embedded in paraffin after formalin fixation. After 4- μ m thick sections were prepared, the dura was stained with HE. The presence of a mass of adenoma cells in the dura was judged as a positive invasion of the pituitary adenoma (Fig. 1). The proliferative potential of the adenomas was estimated by an immunohistochemical method: unstained slides were prepared from paraffin-embedded samples, and antigen retrieval of adenoma tissue was performed by microwave irradiation.¹⁶⁾ The slide was stained using a monoclonal antibody (MIB-1; Immunotech S.A., Marseille, France). The cells were counted in nonhemorrhagic and less vascular areas containing more than 1000 cells, and the MIB-1-positive ratio was calculated (Fig. 2).

Results

Adenoma invasion into the dura was present in 11 of the 31 cases (Table 1). The MIB-1-positive ratio ranged from 0.58 to 3.72 (mean $\pm$ SD 1.80 $\pm$ 0.85) in the 11 adenomas with invasion, and 0.26 to 2.02

Table 1 Details of pituitary adenoma cases

Case No.	Age/ Sex	Type of adenoma	Extent of adenoma			Dural invasion*	MIB-1-positive ratio
			H (mm)	W (mm)	Size (H × W, mm ²)		
1	44/F	PRL	29	17	493	—	2.02
2	49/M	GH	12	15	180	—	0.81
3	34/F	ACTH	13	10	130	—	1.10
4	39/F	GH	28	17	476	—	0.81
5	64/M	non	33	20	660	—	0.26
6	49/F	non	27	25	675	—	0.38
7	59/F	non	44	26	1144	—	0.52
8	44/M	non	48	26	1248	—	0.65
9	46/F	PRL	30	25	750	—	0.70
10	35/M	GH	15	19	285	—	0.69
11	35/F	PRL	11	7	77	—	0.49
12	29/F	PRL	9	9	81	—	0.96
13	51/M	non	37	20	740	—	0.39
14	44/M	PRL	28	13	364	—	0.57
15	60/F	FSH	26	21	546	—	0.90
16	54/M	ACTH	22	25	550	—	0.69
17	20/F	ACTH	9	12	108	—	0.39
18	18/F	PRL	18	17	306	—	1.27
19	78/M	non	31	20	620	—	0.36
20	50/F	non	9	17	153	—	0.65
21	28/M	PRL	40	21	840	+	2.02
22	68/F	FSH	29	22	638	+	1.35
23	67/M	PRL	27	20	540	+	1.21
24	45/F	non	23	15	345	+	3.72
25	28/F	GH	25	20	500	+	2.03
26	69/M	non	39	18	702	+	1.80
27	29/M	non	35	27	945	+	1.62
28	57/F	PRL	30	32	960	+	0.58
29	49/F	non	30	26	780	+	2.42
30	59/M	PRL	31	33	1023	+	2.17
31	59/F	non	21	46	966	+	0.93

*Histologically verified dural invasion. ACTH: adrenocorticotrophic hormone-secreting adenoma, FSH: follicle-stimulating hormone-secreting adenoma, GH: growth hormone-secreting adenoma, H: vertical length of adenomas on MR images, non: non-secreting adenoma, PRL: prolactin-secreting adenoma, W: width of adenomas in the sella turcica on Gd-DTPA-enhanced coronal MR images.

(0.73 ± 0.40) in the 20 adenomas without invasion. The difference in MIB-1-positive ratio between these two groups was statistically significant ($p < 0.01$) (Table 2). There was no significant difference in the height of adenomas between these two groups. However, the width and size were significantly different ($p < 0.05$) (Table 2).

Discussion

There is no agreement on the definition of "invasive adenoma" among the many reports on the invasive nature of pituitary adenomas. We previously showed a positive relationship between MR imaging findings

and histologically verified invasion into the sellar floor dura by adenoma cells,¹⁾ and therefore defined an "invasive (pituitary) adenoma" as a histologically verified adenoma invading the sellar floor dura in this study.

An investigation of cavernous sinus invasion based on operative findings in 365 cases showed that the overall rate of invasion into the cavernous sinus was 35%, and that macroadenomas tended to invade more frequently than microadenomas.¹²⁾ Microscopic examination of surgical specimens has shown that dural invasion of pituitary adenomas occurs in about 64–85% of cases.^{7,9,14)} However, the conclusions of these studies disagree. Selman *et al.*¹⁴⁾ reported the

Fig. 1 Case 21. Photomicrograph revealing invasion of the dura by adenoma cells (arrow). The eroded sellar floor bone is in the upper field. HE stain, $\times 40$.

Fig. 2 Case 21. Photomicrograph showing the MIB-1-positive cells easily distinguished from negative cells. MIB-1 immunostain, $\times 200$.

rate of dural invasion was higher in large adenomas than in smaller adenomas. In contrast, Knosp *et al.*⁷⁾ concluded that invasion was not related to the size of the adenomas. Our study found that the height of the adenomas was not significantly related to the dural invasion or MIB-1-positive ratio, but the width and size were significantly related. This may be due to the mode of extension of the adenoma in addition to the tumor proliferative activity. Presumably intrasellar growth due to a tough diaphragm is related to lateral extension and invasion of the dura and cavernous sinus, indicating that invasiveness of adenoma is multifactorial. In our study the occurrence of dural invasion was less frequent than reported in other studies, possibly due to differences in the histological diagnosis of invasion. Our diagnosis of invasion was based on the presence of an apparent adenoma cell island in the dura. Scattered cells along the dural fibers was not considered as invasion, because the diagnosis of these cells as adenoma cells is uncertain due to the size and appearance of the nuclei, or scanty cytoplasm.

There are few reports on the proliferative potential of pituitary adenomas.^{10,17)} Two investigations of the proliferative potential of pituitary adenomas with invasion into the sellar floor dura with histological verification, using Ki-67 antibody for the evaluation of the growth fraction, demonstrated that invasive adenomas had higher values than noninvasive adenomas.^{6,9)} Kitz *et al.*⁶⁾ only counted Ki-67-positive cells in areas where the positive cells were concentrated, which may be the reason why their proliferation rate (1.56) was slightly higher than that (0.97) reported by Landolt *et al.*⁹⁾

Our study used MIB-1, which reacts to the Ki-67 nuclear antigen appearing in cell proliferation, so is equivalent to Ki-67 antibody.⁵⁾ However, the MIB-1 is superior to Ki-67 antibody because it can be applied to paraffin-embedded samples, whereas only frozen sections can be used for Ki-67, and positive cells are easy to determine. Proliferative cell nuclear antigen (PCNA) is another antibody which can be used to count proliferative cells using paraffin-embed-

Table 2 Analysis of adenomas with vs. without invasion

	No. of cases	MIB-1-positive ratio	H (mm)	W (mm)	Size (H $\times$ W, mm ²)
Without invasion	20	0.73 $\pm$ 0.40	23.95 $\pm$ 5.93	18.05 $\pm$ 4.23	479.30 $\pm$ 334.97
With invasion	11	1.80 $\pm$ 0.85**	30.00 $\pm$ 9.21	25.45 $\pm$ 8.08*	749.00 $\pm$ 223.11*

Growth rate, height, width, and size are shown as mean $\pm$ SD. * $p < 0.05$, ** $p < 0.01$: statistically significant difference between the groups.

ded samples, but the stained nuclei are variable in density.²⁾ Therefore, the ratio of positive cells by PCNA tends to vary between studies. MIB-1 is therefore superior to PCNA for the recognition of proliferating cells.

Our study showed a clear relationship between dural invasion and proliferative potential of pituitary adenomas, although there were a few exceptions. Invasiveness and the width and size dimensions of pituitary adenomas were significantly related, but the height was not. Further investigation on the proliferative potential and other factors related to the invasive nature of pituitary adenomas is needed.

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