Peritumoral Brain Edema Associated with Meningioma

—Histological Study of the Tumor Margin and Surrounding Brain—

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Abstract

Thirty-nine cases of intracranial meningiomas were analyzed to identify factors causing brain edema. Edema was significantly correlated with tumor size and the destruction of the leptomeninges and cortex. Meningotheliomatous meningioma tended to have more peritumoral edema. There was no correlation between the presence of edema and location of the tumor or histological features including lymphocytic infiltration and the presence of glial fibrillary acidic protein-positive cells in the tumor tissue. Larger tumors destroy the leptomeninges and cerebral cortex, allowing direct transmission of humoral edema-promoting factor or edema fluid into the white matter, resulting in vasogenic edema.

Key words: brain edema, meningioma, computed tomography, glial fibrillary acidic protein, leukocyte common antigen

Introduction

Meningiomas are associated with brain edema at an incidence of 40–50%, despite their benign histology.^{19,29)} Many factors related to the development of brain edema have been studied such as tumor size, location, and histological features,^{8,14,23,28,30)} secretory activity of meningioma cells,^{7,22,25)} presence of sex hormone receptors,³⁾ and venous channel occlusion by the tumor.^{10,30)}

Recent reports have closely linked destruction of the brain cortical structure by the tumor and the development of edema.^{14,30)} However, the development of edema and signs of cortical damage were investigated by high-resolution computed tomography (CT), and no histological evidence of actual cortical damage was provided. We report our analysis of the histology of the marginal portion of the meningioma and the boundary between the tumor and brain tissue.

Materials and Methods

This study included 39 intracranial meningiomas excised between 1983 and 1990, and excluded multiple and recurrent meningiomas. Adequate CT scans were used to assess: 1) the tumor size (maximum diameter based on three-dimensional measurement), 2) location of tumor, and 3) presence or absence of peritumoral edema.

Tumor specimens were examined under a light microscope with HE and silver staining to classify the meningiomas according to the WHO classification. Immunohistochemical investigation used the peroxidase-antiperoxidase method with antibodies against glial fibrillary acidic protein (GFAP) and leukocyte common antigen (LCA) (DAKO, Copenhagen, Denmark) to identify lymphocytic infiltration and GFAP-positive cells in the marginal portion of the tumor.

The gross excised tumor surfaces were examined under a light microscope to identify the brain-tumor interface. Any interface between the tumor and brain tissue was examined histologically.

Results

There were six male and 33 female patients aged between 16 and 77 years (mean $\pm$ SD, 52.3 $\pm$ 13.2). Twenty-two cases (56%) demonstrated brain edema and 17 (44%) did not. Table 1 summarizes the results of the CT, histological, and immunohistological examinations.

Table 2 summarizes the measurements of tumor size and the presence of brain edema. There was a statistical correlation ($p < 0.01$, Kruskal and Wallis test), with larger tumors associated with peritumoral edema. However, in Cases 14 and 24, brain edema was absent despite the tumor exceeding 5.0 cm in diameter. No relationship was found between the location of the tumor and presence of brain edema

Table 1 Summary of 39 cases

Case No.	Age/Sex	Tumor location	Tumor size (cm)	Histological subtype	Brain edema	Lymphocytic infiltration	GFAP in tumor	Adhered brain tissue	Tumor-brain interface*
1	32/F	parasagittal	4.5	FIB	+	—	—	—	
2	52/F	parasagittal	2.5	FIB	—	—	—	—	
3	55/F	parasagittal	6.8	FIB	+	+	—	+	type I
4	72/M	parasagittal	5.0	MEN	+	—	—	+	type II
5	60/F	parasagittal	4.5	MEN	+	—	+	+	type II
6	55/F	parasagittal	4.3	TRA	+	+	+	+	type I
7	58/F	parasagittal	2.0	FIB	—	—	—	—	
8	25/F	falx	4.5	MEN	+	—	—	+	type I
9	54/F	convexity	4.0	MEN	+	—	—	—	
10	58/F	convexity	1.5	FIB	—	—	—	—	
11	41/F	convexity	6.3	MEN	+	+	—	+	type I
12	47/F	convexity	4.3	MEN	+	—	+	+	type I
13	48/F	convexity	7.3	MEN	+	—	+	+	type II
14	65/F	convexity	6.6	MEN	—	—	—	—	
15	77/F	convexity	5.0	MEN	+	+	+	+	type II
16	39/M	convexity	2.0	ANG	—	—	+	—	
17	72/F	sphenoid ridge	6.1	FIB	+	+	—	NE	
18	62/F	sphenoid ridge	5.0	MEN	+	—	—	—	
19	60/F	sphenoid ridge	5.0	MEN	+	—	—	—	
20	54/F	sphenoid ridge	5.3	MEN	+	—	—	NE	
21	75/F	sphenoid ridge	4.0	FIB	—	—	—	+	type I
22	48/M	sphenoid ridge	4.4	MEN	—	—	+	+	type I
23	49/F	middle fossa	5.0	MEN	—	—	—	NE	
24	16/F	middle fossa	5.5	HAP	—	—	—	—	
25	33/F	middle fossa	5.2	HAP	+	—	—	+	type I
26	62/F	middle fossa	1.5	FIB	—	—	—	—	
27	41/F	olfactory groove	3.5	MEN	+	+	—	—	
28	59/M	olfactory groove	4.0	MEN	+	—	+	+	type II
29	59/M	olfactory groove	5.5	MEN	+	—	+	+	type I
30	56/F	tuberculum sellae	3.5	MEN	—	—	—	—	
31	39/F	tuberculum sellae	2.5	TRA	—	—	—	—	
32	63/F	tuberculum sellae	5.0	MEN	—	—	—	—	
33	53/F	cerebellar convexity	4.3	FIB	—	—	—	—	
34	58/F	cerebellar convexity	3.3	FIB	+	+	—	—	
35	63/F	cerebellar convexity	4.0	FIB	—	—	—	—	
36	50/F	lateral ventricle	2.5	TRA	—	+	—	—	
37	54/F	lateral ventricle	7.5	TRA	+	—	+	—	
38	33/M	fourth ventricle	5.0	TRA	—	—	—	—	
39	42/F	cerebellopontine angle	3.9	TRA	+	—	—	—	

*Type I: relatively smooth plane, type II: interdigitated tumor invasion. ANG: angiomatous, FIB: fibrous, HAP: hemangiopericytic, MEN: meningotheliomatous, NE: not examined, TRA: transitional.

Table 2 Tumor size and associated brain edema

Edema	≤ 2.0	≤ 3.0	≤ 4.0	≤ 5.0	≤ 6.0	≤ 7.0	$7.0 <$
+	0	0	5	9	3	3	2
-	4	3	3	5	1	1	0

Table 3 Histological subtypes of meningioma and associated brain edema

Edema	MEN	FIB	TRA	ANG	HAP
+	14	4	3	0	1
-	5	7	3	1	1

Abbreviations, see Table 1.

(Table 1).

Table 3 shows the relationship between the histological subtypes of meningioma and presence of brain edema. Although there was no statistically significant correlation between any subtype and the presence of brain edema, the meningotheliomatous type tended to be associated with brain edema.

Seven (88%) of the eight cases with extensive lymphocytic infiltration into the marginal portion of the tumor had accompanying brain edema (Table 1). Lymphocytic infiltration appeared in the boundary between the tumor and brain (Fig. 1A) or in the tumor parenchyma as cell clusters (Fig. 1B), or scattered throughout the tumor. The correlation between lymphocytic infiltration and brain edema was not statistically significant.

The GFAP-positive cells within the tumor (Fig. 2) were probably astrocytes incorporated during growth. Ten cases were GFAP-positive within the tumor, but the relationship with brain edema was unclear (Table 1).

The tumor margin facing the brain tissue was identified in all cases except three with intracapsular removal (Table 1). In 14 cases (39%), brain tissue still adhered to the tumor. The histology of the interface could be classified into two types: a relatively smooth plane (type I) in nine cases and interdigitated tumor invasion of the brain (type II) in five. No intact arachnoid membrane between the tumor and brain tissue was present in either type, and thus no subarachnoid space.

Many type I cases demonstrated a connective tissue structure (so-called tumor capsule) (Fig. 3A). However, the thickness of this structure varied on the same tumor, and some type I cases had no connective tissue structure between the tumor parenchyma and brain tissue (Fig. 3B). In contrast, there

Fig. 1 Lymphocytic infiltration into the marginal portion of the meningioma. A: Extensive infiltration into the boundary between the tumor and brain tissue in Case 6. Immunoperoxidase stain for LCA, $\times 200$. B: Cluster of lymphocytes in the tumor tissue in Case 11. HE stain, $\times 400$.

Fig. 2 GFAP-positive cells in the tumor tissue in Case 5. Immunoperoxidase stain for GFAP, $\times 400$.

Fig. 3 Tumor-brain interface type I in Case 8. A: A connective tissue structure (so-called tumor capsule) is seen between the tumor and brain tissue. Arachnoid and pial membranes are not clearly identified. The brain tissue shows gliotic change with loss of neurons, edema, and cystic change. HE stain, $\times 200$. B: The tumor capsule is absent. Gliotic change is prominent in the brain tissue. Immunoperoxidase stain for GFAP, $\times 200$.

was absolutely no connective tissue between the tumor and brain tissue in any type II case. Tumors were more invasive than in type I, and interdigitation with the brain was seen (Fig. 4A, B). Clusters of tumor cells were scattered in the Virchow-Robin spaces or brain parenchyma (Fig. 4C). Some type II cases included brain tissue inside the tumor several millimeters from the surface (Fig. 4D). All type II cases were meningotheliomatous meningiomas. The adhered brain tissue showed gliotic change with loss of neurons, edema, and cystic change in both type I and II cases (Figs. 3 and 4A, B).

Twelve (86%) of the 14 cases with brain tissue adhesion showed peritumoral brain edema on CT scans. In contrast, only eight (36%) of the 22 cases without brain tissue adhesion had brain edema.

Brain tissue adhesion around the tumor margin and the development of peritumoral edema were significantly correlated ($p < 0.05$, Fisher test).

All tumors with adhered brain tissue were 4.0 cm or larger in diameter (Table 1). Intraoperatively, larger tumors were found to adhere more strongly to surrounding brain tissue, and dissection was more difficult. However, Case 14 with a large convexity meningioma exceeding 6.0 cm in diameter was exceptional, with loose adhesion and extremely easy dissection. After tumor removal, the brain surface was found to be completely covered with well-preserved arachnoid membrane, and the integrity of the cerebral cortex was preserved. In this case, no edema was present on CT scan (Fig. 5).

Discussion

Tumors located in the anterior parasagittal, frontal convexity,³⁰⁾ and frontobasal regions⁶⁾ are reported to induce edema more frequently than those in other locations. However, our study showed no relationship.

Histological studies show that transitional, meningotheliomatous,¹⁴⁾ angioblastic,^{8,28)} and malignant meningiomas²³⁾ cause edema more than other subtypes. Challa *et al.*⁸⁾ and Smith *et al.*²⁸⁾ found that edema was correlated with vascularity of meningioma, particularly in small tumors. No correlation has been reported between the development of edema and cellularity and mitosis in the tumor tissue.^{6,28)} Our study, like Gilbert *et al.*,¹³⁾ found no correlation between edema and histological type.

Only a few workers have investigated infiltrating lymphocytes in meningioma.^{2,24)} Lymphocytic infiltration reflects the host immunological reactions and may induce edema. However, we found no significant relationship between the lymphocytic infiltration and the development of peritumoral edema. GFAP-positive cells within the meningioma^{16,18)} indicate tumor invasiveness, but we found no correlation between the presence of GFAP-positive cells and edema.

Our study found a significant correlation between peritumoral edema and the tumor size. Compression is considered the fundamental factor in brain edema induced by meningioma.^{15,30)} Some authors have emphasized the importance of rapid tumor growth.^{8,23,28)} Animal experiments have revealed that extradural brain compression may induce vasogenic edema,^{17,26)} which will respond to steroids.³³⁾ However, brain edema associated with meningioma rarely responds to steroid therapy.¹⁵⁾ Epidural and chronic subdural hematomas may cause severe brain

Fig. 4 Tumor-brain interface type II in Cases 5 (A, C) and 13 (B, D). A, B: No connective tissue structure is present between the tumor and brain tissue. Loss of neurons, gliotic change, and cystic change are conspicuous. HE stain, A: $\times 40$, B: $\times 100$. C: Cluster of tumor cells in brain tissue. HE stain, $\times 200$. D: Brain tissue included in the tumor several millimeters from the surface. HE stain, $\times 40$.

Fig. 5 Case 14. *left*: Postcontrast CT scan shows a large tumor, exceeding 6.0 cm in diameter, but not inducing cerebral edema. *right*: Intraoperative photograph after tumor removal. Cerebral surface is completely covered with well-preserved arachnoid membrane. Cerebral cortex appears to be intact, without evidence of tumor invasion.

compression, but unlike meningioma rarely cause brain edema. Therefore, it is doubtful that brain edema develops from compression alone. In this study, two large tumors (>5.0 cm diameter) strongly compressed the brain without accompanying brain edema.

The origin of edema fluid in meningioma is unclear. Vasogenic edema might result from mechanical destruction of the blood-brain barrier (BBB) in the cortical vessels. Alternatively, humoral factors derived from the meningioma might destroy the BBB,^{1,10,11,28)} but there are no firm data. Go *et al.*¹⁴⁾ recently suggested that no or only slight BBB damage occurs in the edematous brain surrounding the meningioma. Brain edema in gliomas is caused by plasma leakage from tumor vessels with damaged BBB,³²⁾ possibly indicated on postcontrast CT scan by abnormal enhancement. However, the edematous white matter surrounding meningioma is very rarely enhanced, indicating little BBB damage in the white matter. Electron microscopy has found little evidence of BBB damage in the white matter with edema, only an increase in extracellular edema fluid.¹³⁾ In contrast, meningioma blood vessels demonstrate fenestrated endothelium, many pinocytotic vesicles, and punctate-type junctions,^{6,13,27)} indicating hyperpermeability of meningioma blood vessels. Some authors have emphasized the secretory activity of meningioma cells.^{7,22,25)} These findings suggest that the meningioma tissue may be the source of edema fluid.^{14,30,31)}

We also found a correlation between peritumoral edema and histological evidence of leptomeningeal and cortical destruction by the tumor. A small meningioma is separated from the brain cortex by the arachnoid membrane and pia mater, and can be easily dissected without brain damage. At this stage, brain edema is extremely rare. However, as tumor growth causes destruction of the arachnoid membrane and pia mater, the tumor finally contacts the brain cortex, with compression and adhesion causing cortical degeneration. Few studies have investigated the interface between the meningioma and the surrounding brain tissue.^{4,5,9,20,21)} Nakasu *et al.*^{20,21)} examined the interface in autopsy cases of meningioma without surgery. They found that meningioma frequently invades the brain despite the generally benign nature, destroying the leptomeninges and even cerebral cortex, and comes into direct contact with white matter. In our study, incidental attachment of brain tissue to the excised tumor may have occurred. However, histological examination of the interface revealed destruction of the leptomeninges and the brain cortex, and interdigitation of tissue in

many places. Therefore, incidental adhesion is unlikely because of technical factors. Such situations preclude accurate, flawless dissection of the tumor and brain.

Our hypothesis for the association of edema with destruction of the leptomeninges and cortex by meningioma is as follows. The arachnoid membrane is impermeable to fluid normally, while the pia mater is less permeable to macromolecular substances like protein in edema fluid.¹⁴⁾ The cerebral cortex is formed by dense networks of neuronal and glial processes and is thus quite resistant to the storage and spread of vasogenic edema fluid.^{12,14)} When the tumor is small, the intact leptomeninges and brain cortex prevent the easy spread of vasogenic edema fluid to the white matter. A larger tumor damages the leptomeninges and brain cortex and comes into direct contact with the white matter, allowing direct transmission of humoral edema-promoting factor or edema fluid into the white matter, resulting in vasogenic edema.

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