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Clinical Article

A Study about Peritumoral Brain Edema in Meningiomas using Angiographic Pattern and MIB-1

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Objective : Peritumoral brain edema(PTBE) accounts for approximately 60% of meningiomas. It has not been identified why vasogenic edema, frequently shown in intra-axial tumors is also developed in extra-axial tumor such as meningiomas. Therefore, the authors assess the peritumoral brain edema of meningiomas with a focus on the angiographic pattern and expression of MIB-1 to clarify their correlation.

Methods : A total 32 cases of meningioma was studied. The authors attempted to identify 1) the location of PTBE and the edema index (EI), 2) the location and dominancy of pial supply compared with meningeal supply, 3) the biological activity of meningiomas indicated by the MIB-1 LI (labeling index), 4) their interaction.

Results : No PTBE was observed in the meningiomas without pial arterial supplement from internal carotid artery (ICA) and vertebral artery (VA). The PTBE of meningiomas with pial supply was developed intensely along the pial arterial supplement, and increased statistically in proportion to the extent of pial supply from ICA or VA rather than meningeal supply. Also, the MIB-1 LI in meningiomas tended to be larger in the tumors of the larger EI and the dominancy of pial supply.

Conclusion : A strong correlation is found between the extent of PTBE in meningiomas and the dominancy of pial supply. The MIB-1 LI also tend to be associated with the PTBE. Therefore, the MIB-1 LI in benign meningiomas may represent not only the proliferative potential of the tumor, but also the biological activity like angiogenesis.

KEY WORDS : Meningioma · Brain edema · Blood supply · MIB-1 antibody.

Introduction

Meningiomas are generally benign tumors that do not invade into surrounding cerebral parenchyma. But they may or may not accompany with peritumoral brain edema (PTBE) of which size varies to great extent : up to several times as large as the tumor. Vasogenic brain edema can be generated by the effusion of plasma into the white mater in a case of the impairment of blood-brain barrier. It is a specific finding of intra-axial tumor. However, it is well known that extra-axial meningiomas are also accompanied by vasogenic edema[6]. The degree of PTBE in intra-axial tumors such as a glioma is associated with the degree of the tumor's histologic malignancy. However, many causative factors for the development of PTBE in meningiomas have been suggested. These factors include size and location of the tumor, growth potential, angiographic pattern, histology and degree of differentiation, secteretory activity, hormonal receptor, and proliferation potential[7,21,26,27]. Recently angiographic patterns of feeding vessels and biological activities of meningiomas became the focuses of duscussion as primary factors for the development of PTBE[2,11,12,16,21,29]. Rather than simply using morphological or histopathological classification, most researchers gradually try to determine the biological activities of tumors using the proliferative potential marker such as labeling index(LI) of Ki-67, MIB-1, and proliferating cell nuclear antigen(PCNA). Also they try to determine the dominancy of the blood supply between pial supply from internal carotid artery(ICA) or vertebral artery (VA) and meningeal supply from external carotid artery(ECA). But, many studies above mentioned, were not fully covered in a single study. In the present study, the authors tried to identify causative factors for the development of PTBE in meningimas using brain MRI, brain CT, angiography, and the immunohistochemical method such as MIB-1 LI in a same group of study.

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Materials and Methods

Materials

We examined 32 patients (8 male, 24 female) with an average of 53 years (26-79 years) who had undergone operations for

meningiomas at the department of neurosurgery in our institute between 1994 and 1999. Tumors were classified according to the WHO classification of meningiomas[14]; 12 meningotheliomatous, 9 fibroblastic, 7 transitional, 2 angiomatous, 1 psammomatous, and 1 atypical.

Radiologic evaluation

All 32 tumors were assessed by preoperative imaging study including brain MRI and CT. The maximal AP (a) and lateral (b) diameters of tumor and PTBE volume were measured on axial images, and the sagittal (c) diameters on sagittal images or the numbers of axial images multiplied by the slice thickness were measured. Total volumes of the tumor and PTBE were estimated by using the ellipsoid formula, which was $4/3 \times \pi$ (a/2)(b/2)(c/2). Edema index (EI) was determined by the ratio of the total volume of tumor and PTBE to the volume of tumor. The diameters of PTBE were measured in high signal intensity area on T2-weighted image or the low-density area on CT scans. Therefore, when there was no PTBE, the EI is 1.0. The pial branch of ICA or VA and the meningeal branch of ECA were assessed in 23 cases using Seldinger's method. After the respective ICA, VA and ECA angiogram, they were compared each other at the phase of maximal staining. The extent of dominancy was graded according to the pial blush criteria by Bitzer, et al[2]: grade I as no pial supply; grade II as pial supply smaller than dural supply; grade III as pial supply equal to dural supply; grade IV as pial supply greater than dural supply; and grade V as no dural supply. After discovering the pial branch and comparing the pial blush with the location of edema, the patterns of edema were classified by the spatial relation scale[2] from 0 to 4: scale 0 as edema present but distant from pial arterial supply; scale 1 as some edema adjacent to pial arterial supply; scale 2 as edema surrounding the tumor in a regular fashion; scale 3 as maximum amount of edema adjacent to pial blush; and scale 4 as edema only adjacent to pial blush.

Immunohistochemistry

The 25 samples were fixed by formalin and embedded into paraffin, and xylene was applied to remove the paraffin. They were hydrated in distilled water after the treatment of ethanol step by step. In order to inhibit intrinsic peroxidase, the 25 samples were treated in methanol with 3% H_2O_2 solution for 30 minutes. And then, they were put in the citric acid (PH 6.0) solution and processed by microwave for 20 minutes. MIB-1 (monoclonal antibody, Dako Co., Denmark) was diluted by 1:100 and was used as primary antibody. After the application of primary antibody, secondary antibody (Dako Co., Denmark) and peroxidase conjugates of streptavidin-HRP (Zymed Co., U.S.A.) were applied to the samples, they were incubated at room temperature for 30 to 60 minutes. Next, AEC was applied for 10 minutes, and then they were counterstained with Mayer's hematoxylin wet mounting. The samples were observed under light microscopy after all these sequential processes. The MIB-1 LI were determined by counting at least 1000 tumor nuclei in three to five randomly selected high cellular area at high power fields ($\times 400$). The positive reaction was determined by definite intranuclear location of red brown granules. The MIB-1 LI was determined by the fraction of the positive cells.

Statistical analysis

Statistical analysis was performed using Wilcoxon rank sum test, and Kruskal-Wallis test (SPSS 11.0 English version, U.S.A.). P values less than 0.05 were determined to be statistically significant.

Results

The mean volume of meningiomas was 34.10cm^3 (range; 1.77-188.40cm^3) and that of the PTBE including the tumor mass was 79.9cm^3 (range; 1.77-279.66cm^3). The EI ranged from 1.0 (no PTBE) to 11.25, which means that the PTBE was more than 10 times as large as the tumor volume, and the mean EI was 2.36. The tumors with PTBE were found in 17 cases (53.1%). The mean volume of meningiomas without PTBE (15 cases) was 20.63cm^3 and with PTBE (17 cases) was 45.99cm^3. This finding supports notion that the size of meningioma was positively related with the size of PTBE. But, in 8 cases of

Table 1. Results of mean EI and mean MIB-1 LI according to locations of meningiomas except atypical meningioma (number of cases in brackets)

Location	EI	MIB-1 LI
Supratentorial	2.58(26)	3.44(20)
Convexity	3.13(10)	3.13(9)
Sphenoid and sellar	2.69(11)	3.84(9)
Parasagittal	1.23(5)	1.10(2)
Infratentorial or tentorial	1.00(5)	0.68(4)

Table 2. Results of mean EI and mean MIB-1 LI according to histological subtypes of meningiomas (number of cases of brackets)

Histological subtypes of meningiomas	EI	MIB-1 LI
Meningotheliomatous	2.04(12)	2.45(8)
Fibrous	1.50(9)	1.38(6)
Transitional	2.93(7)	5.46(7)
Angiomatous	6.22(2)	2.60(2)
Psammomatous	1.00(1)	0.20(1)
Atypical	3.56(1)	30.10(1)

moderate to severe grade PTBE (EI ≥ 2.5) of which average tumor volume was 27.74cm³, there was no statistically significant difference between tumor size and EI (P = 0.445). The mean of MIB-1 LI was 4.06 (range; 0.1-30.1). The mean MIB-1 LI without any PTBE (11 cases) was 0.96, whereas the mean MIB-1 LI with moderate to severe PTBE (EI ≥ 2.5; 8 cases) was 6.48 and they were significantly different (P < 0.001). This finding implicates that the MIB-1 LI is higher in cases with higher EI than in those with no PTBE. Similarly, none of the 9 cases whose MIB-1 LI was below 1.5 did not have any PTBE (EI = 1.0), and the other 7 cases whose MIB-1 LI was above 3.0 have large PTBE (EI = 3.53). The EI for the former 9 cases was significantly different from that for the later 7 cases (P < 0.001). This finding indicates that the EI is higher in cases with higher MIB-1 LI than in those with lower MIB-1 LI. The EI and MIB-1 LI were compared to each other (Table 1) after the tumors were classified by their location. Even though there was no statistical significance, the EI and MIB-1 LI for convexity, sphenoid ridge, and sellar meningiomas were relatively higher than those for parasagittal meningiomas. Also, the EI (P = 0.023) and MIB-1 LI (P = 0.020) for supratentorial meningiomas were significantly higher than those for tentorial and infratentorial meningiomas. The authors evaluated EI and MIB-1 LI according to the histological classification of meningioma (Table 2). The EI was relatively higher in meningotheliomatous and transitional meningiomas than in fibrous meningiomas. Although there were only a few cases, the EI and MIB-1 LI for the angiomatous and atypical meningiomas were also high. Similarly, the MIB-1 LI for fibrous meningiomas were relatively low (1.38) compared to those for meningotheliomatous and transitional meningiomas. The MIB-1 LI for the atypical meningioma was high (30.1). The authors classified meningiomas according to their vascular supplement patterns. According to this classification, none of the meningiomas fell on grade V, which has no dural supply. The EI increased significantly in proportion to the grade of pial blush criteria (P < 0.001, Kruskal-Wallis test).

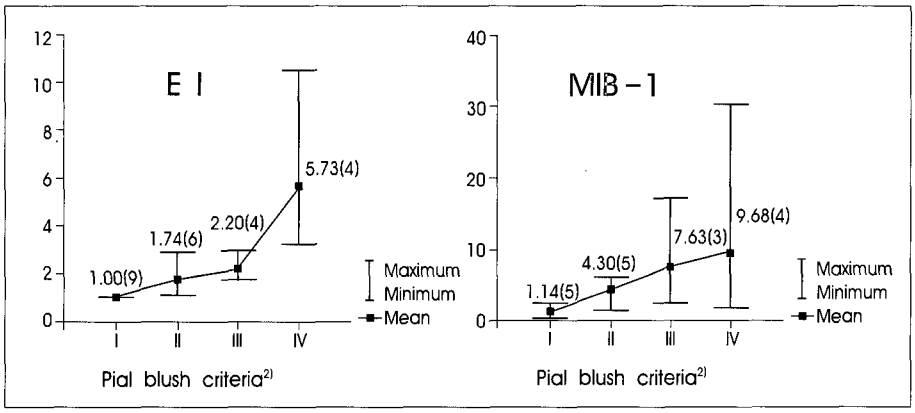

Fig. 1. Graph depicting the significant associations between mean EI and pial blush criteria[2], and between mean MIB-1 LI and pial blush criteria[2] (number of cases in brackets).

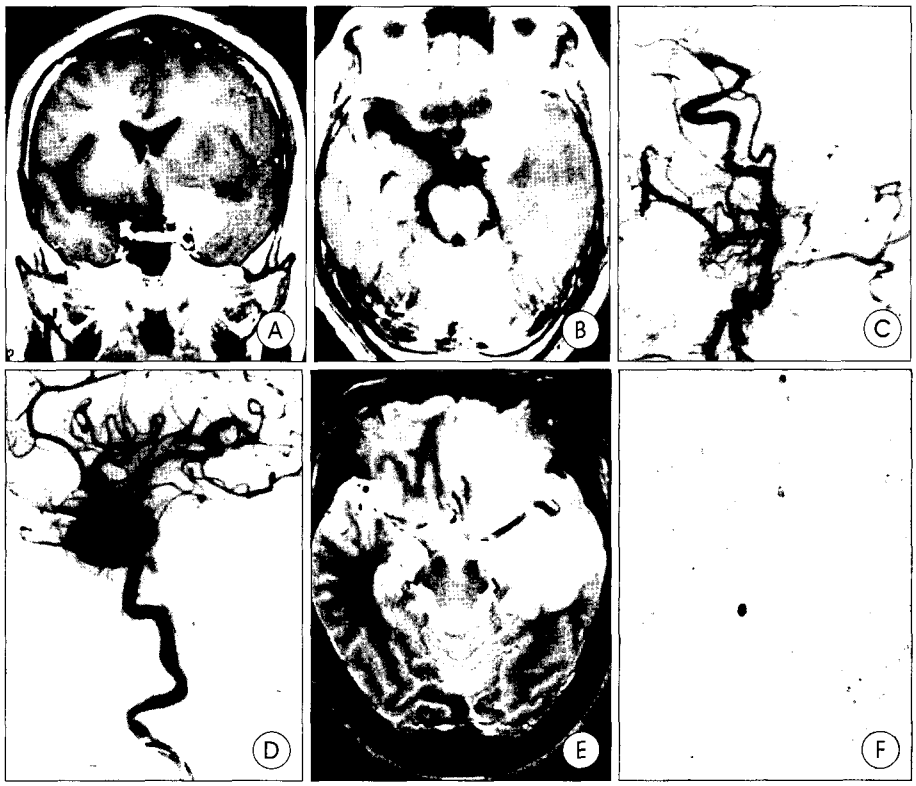

Fig. 2. A case of small angioblastic meningioma with the large peritumoral brain edema. Enhanced T1-weighted image demonstrates a left small (tumor size : 16.11cm³) sphenoid ridge meningioma (A,B). A small rate of meningeal supply from ECA is presented (C). The tumor supply is guaranteed mainly via pial arteries from ICA (D). T2-weighted image demonstrates the massive peritumoral brain edema in frontal and temporal region (E). MIB-1 positive labeling cells (×400), MIB-1 LI : 2.4 (F). This tumor's indices are EI : 10.56, pial blush criteria : IV, spatial relation scale : 3.

The mean EI was high (5.73) in grade IV (4 cases), which pial supply was greater than dural supply. There was no PTBE in any cases of grade I (9 cases), which there was no pial supply. Also, since the result for assessing the MIB-1 LI according to the pial blush criteria was determined to be statistically significant, it would be strongly suggested that the MIB-1 LI increased more in proportion to the grade of pial blush criteria ($P = 0.051$, Kruskal-Wallis test) (Fig. 1). While the mean MIB-1 LI was high (9.68) in 4 cases of grade IV including atypical meningioma, which pial supply was greater than dural supply, it was low (1.14) in 5 cases of grade I, which there was no pial supply. The author compared the location of pial branch with that of PTBE in 14 cases.

There was no case of scale 0 and 1, which were defined as the entire or most edema far from pial supply. The mean EI was 3.07 in 6 cases of scale 2, which edema was developed surrounding the tumor in a regular fashion, and 3.85 in 5 cases of scale 3, which the maximum amount of edema was developed adjacent to pial blush. The mean EI tended to be high when the location of PTBE was associated with the distribution of pial branch, but there was no statistical significance. In 3 cases of scale 4, However, the mean EI was measured to be low (1.50). Even though the above 3 cases had the somewhat low EI (1.14-1.88), the volume of tumor and PTBE were already 58.09cm^3 to 279.66cm^3. Therefore, there could have been a possibility that the PTBE was found at the early stage of the edema formation because of the early development of neurologic deficit associated with mass effect.

Discussion

PTBE has been found in 60% of meningiomas[3]. In this study, although the average volume of tumor accompanied with PTBE was larger than that with no PTBE, the relationship between the tumor volume and the extent of PTBE could not be determined. A number of studies reported that the PTBE was developed more commonly in frontal or sphenoid ridge than in parietal or occipital regions. The PTBE tended to be especially smaller in infratentorial region than in supratentorial region. That might be explained in that there are small amounts of white mater where vasogenic edema is mainly developed and the PTBE could be found at the early stage of its formation due to the early sign of increased intracranial pressure (IICP)[12,26].

This study found that the PTBE in convexity, sphenoid ridge, sellar, and parasellar regions was larger than that in parasagittal region, and the mean EI (2.58) in supratentorial region was statistically higher than mean EI (1.00) of 5 cases in tentorial and infratentorial region. The development of pial branch in supratentorial meningiomas was more common than in other meningiomas. Although meningioma is a benign, extra-axial, and slow growing tumor, which is separated from the parenchyma by the arachnoid and the pia, it has been proved by electron microscopy that the pattern of PTBE is similar to the vasogenic edema which is the characteristics of the intraaxial tumors[6]. Other hypotheses[9,21,29] that have been suggested such as peritumoral ischemia due to mass effect, the macrophage infiltration, and physiologic venous congestion, have not been

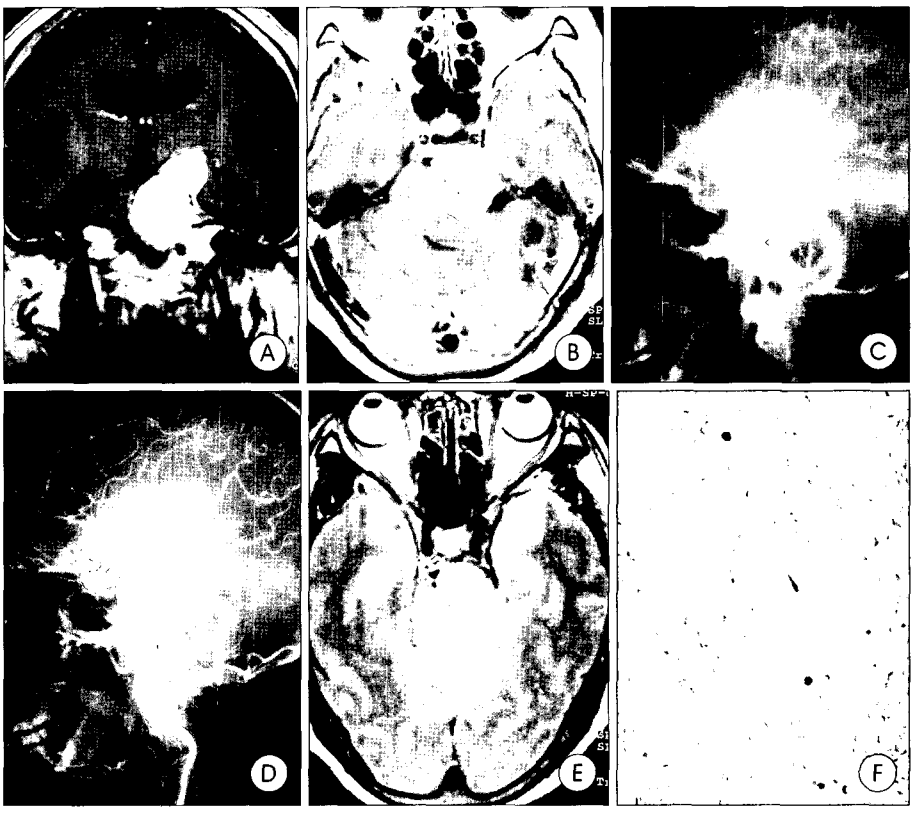

Fig. 3. A case of clinoid meningioma with minimal peritumoral brain edema. Enhanced T1-weighted image demonstrates a left moderate sized (tumor size : 35.19cm^3) clinoid meningioma (A,B). The tumor supply is guaranteed mainly via meningeal arteries from ECA (C). A small rate of pial supply from ICA is also presented in posterior portion of the tumor (D). T2-weighted image demonstrates the minimal peritumoral brain edema in posterior portion of the tumor (E). MIB-1 positive labeling cells (×400), MIB-1 LI : 1.5 (F). This tumor's indices are EI : 1.15, pial blush criteria : II, spatial relation scale : 3.

enough to explain the pathophysiology for the development of PTBE in meningioma. Since Inamura et al.[12] suggested the development of pial branch to meningioma from intrinsic cerebral artery such as ICA or VA is the cause of PTBE, vascular supplement pattern and vascular endothelial growth factor (VEGF) have been focuses of researches to find the main causative factors responsible for the development of PTBE. The authors could not find PTBE in 3 cases in which the volumes of tumor were larger than 45cm^3 with no pial supply. However, the PTBE was found in 3 cases in which the volumes of tumor were smaller than 15cm^3 with pial supply.

Therefore, the volume of tumor does not appear to affect the growth of pial branch. In a case report[1], where a histopathologically identified meningioma simultaneously invaded bilateral frontal lobe, the PTBE was developed in only one side which had arterial supply from the ICA. This case reported the same findings shown in our study. In the operative field of meningioma accompanied with vasogenic finger-like edema, it was reported that many vessels went through tumor-parenchymal interspace and the cerebral cortex in the area with serious PTBE[24]. In our study, there was no case in which the PTBE was not accompanied with pial arterial supply (scale 0 and 1). The authors confirmed that the PTBE developed intensively around the tumor surface where pial vessels were distributed, and the volume of PTBE became larger as the location of PTBE was closer to the distribution of pial branch. It has been known that the most important pathophysiology for the development of the PTBE in meningioma was invasion and adhesion of peritumoral parenchyma and destruction of arachnoid by the development of pial branch[10,28].

The Angiogenic factor such as VEGF stimulates peritumoral vascular endothelial cell, and thus, the growing of pial arteries. The pial arteries destroy arachnoid for the physiologic barrier, and perforate into the cerebral cortex across subarachnoid space as tumor-parenchymal interspace. And then vascular permea-bility increased. Finally the PTBE was developed by accelerating the transport of prostaglandin E2, leukotriene, and macromolecules like macrophage[17,22,25,27]. In our study, this was confirmed by observing that 1) there was no PTBE in all cases with no pial supply, and 2) the size of PTBE was significantly related with the degree of pial supply (Fig. 2, 3). In addition to the angiogenic factor such as the VEGF, another hypothesis was also suggested that the imbalance of matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) related to the destruction of cell basement membrane and connective tissue would play a fundamental role in tumor invasion and angiogenesis such as the development of pial vessels[13]. Some studies reported, however, that the VEGF expression was not associated with the development of PTBE when there was no pial supply[8,23,30]. Therefore, it is suggested that future studies focus on investigating the pathophysiologic features of the development of pial vessels.

The MIB-1 antibody, using the recombinant part of Ki-67 antibody, has been widely used to measure

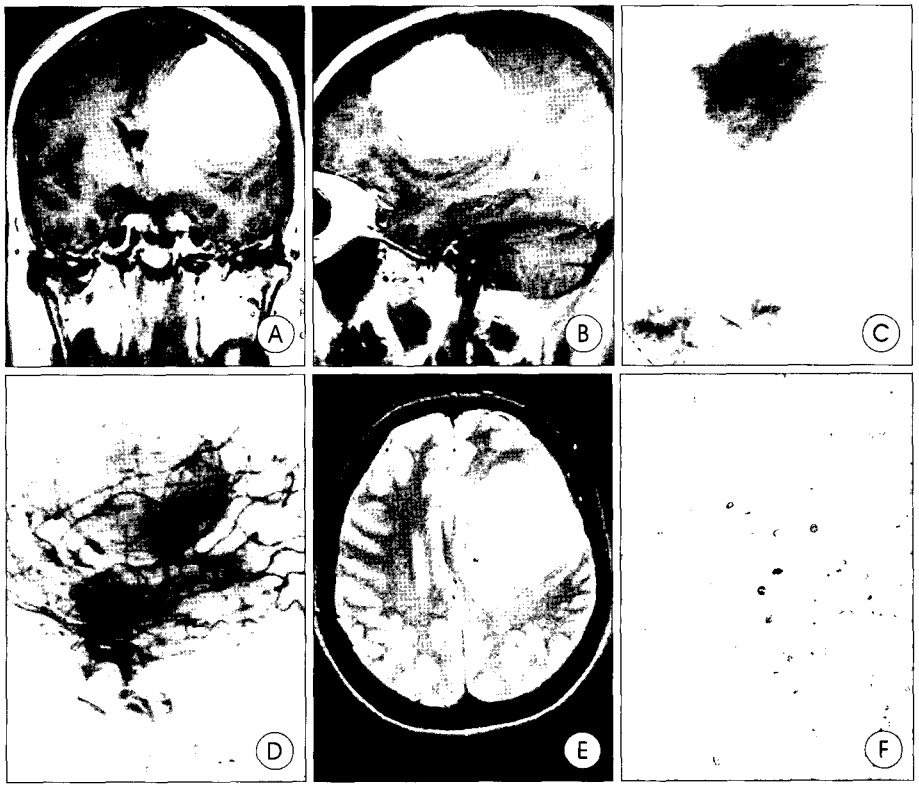

Fig. 4. A case of large convexity meningioma with minimal peritumoral brain edema. Enhanced T1-weighted image demonstrates a left large (tumor size : 109.27cm^3) convexity meningioma (A,B). The tumor supply is guaranteed mainly via meningeal arteries from ECA (C). A small rate of pial supply from ICA is also presented in posteromedial portion of the tumor (D). T2-weighted image demonstrates the minimal peritumoral brain edema in posteromedial portion of the tumor (E). MIB-1 positive labeling cells(×400), MIB-1 LI : 7.1 (F). This tumor's indices are EI : 1.14, pial blush criteria : II, spatial relation scale : 4. This case demonstrates high MIB-1 LI in spite of low EI, therefore, it would be associated with a potency of malignant transformation.

the proliferative potential of a tumor[4]. The MIB-1 LI has been generally used as the index for degree of malignancy because it increases in atypical and malignant meningioma[11,15,16,18,19]. The PTBE of intra-axial tumors such as a glioma is associated with the proliferative potential of the tumor. However, in meningioma, the relationship between the PTBE and proliferative potential of the tumor is still under question. The authors evaluated the relationship between the biological activity measured by MIB-1 and the development of PTBE by the pial vessels.

There has been no consensus on the relationship between the PTBE and MIB-1 LI in meningioma[11,18-20]. However, it has been reported that the development of PTBE in meningioma does not have any relationship with the degree of histological malignancy of the tumor[16]. In this study, there were significant differences in the development of PTBE and the MIB-1 LI among benign meningiomas. The higher MIB-1 LI had higher EI, and vice versa. This finding supports the previous finding by Ide et al.[11]. Also MIB-1 LI increased more in proportion to the dominancy of pial supply and this result had statistical significance. Therefore, the correlation between pial supply and MIB-1 LI could be strongly suggested.

In 3 cases, in which the MIB-1 LI showed relatively high in spite of low EI, the EI versus MIB-1 LI were 3.56:30.1, 1.14:7.1, and 1.80:17.3. In other cases, the mean EI and MIB-1 LI were 2.14:1.69. Therefore, when the MIB-1 LI is high and not associated with the EI, and the tumor is not histologically malignant as in the 3 cases presented, the possibility of malignant transformation of the tumor could be high (Fig. 4). It is not desirable to determine the malignancy of a meningioma based on the MIB-1 LI when there is no histological evidence of malignancy. In addition, it is not reasonable to relate the degree of PTBE with the degree of malignancy of the tumor. Instead, the difference in the PTBE among benign meningiomas needs to be interpreted as the difference in the biological activities of the tumors. In this regard, in benign meningiomas, it appears that the MIB-1 LI represents not only the malignancy or the proliferative potential of the tumor but also the biological activity of the tumor such as the peritumoral angiogenesis.

It has been reported that there is some bias in the measurement of MIB-1 LI among different researchers[5]. In this study, the MIB-1 LI differed in each slices from different region of the same tumor, hence, it is argued that different portions in the same tumor may have a different level of biological activities. Therefore, it is suggested that MIB-1 LI can be used as a useful diagnostic aid for the malignancy or biological activity of the tumor, but cannot be used as decisive diagnostic measure.

Conclusion

Our study demonstrates the relation between the PTBE in associated with vascular supplement patterns and the biological activity of meningioma observed by MIB-1 LI. The conclusion is as follows.

First, no PTBE was found in meningioma with no pial supply. Since the development of PTBE is significantly associated with the development of pial arteries from ICA or VA ($P < 0.001$), it can be concluded that the development of PTBE is larger as the pial supply is more dominant to the meningeal supply.

Second, the immunohistochemical analysis for the proliferative potential of meningiomas using MIB-1 LI has been one of the ways to assess the degree of tumor malignancy. In addition, since the MIB-1 LI is significantly associated with the development of pial arteries, it also can be concluded that MIB-1 LI represents the biological activity like angiogenesis as well as the proliferative potential of meningiomas.

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