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Histopathological findings in the peritumoral edema area of human glioma

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Summary. Peritumoral brain edema (PTBE) is considered to be one of the main biological behaviors of brain glioma. However, the histopathological features of PTBE remain imprecisely defined. We analyzed the histopathological characteristics in the PTBE area of 22 cases of glioma. Microscopically, the pre-existing basic structure in the edema area was still preserved but there were varying degrees of loose tissue. The main components of the edema tissue were scattered invasive tumor cells, reactive cells, and various blood vessel patterns. Invasive tumor cell density was significantly higher in high-grade glioma than in low-grade glioma, and the density was significantly higher in the area near compared to the area far from the glioma. The Ki-67 proliferative index of the invasive tumor cells was higher in high-grade glioma than in low-grade glioma, but the index was not different in the area near compared to the area far from the glioma. The microvessel pattern in PTBE was primarily branching capillary. The microvessel densities (MVDs) of $CD34^+$ and $CD105^+$ were higher in high-grade glioma and the area near the glioma than in low-grade glioma and the area far from the glioma. Compared to $CD34^+$, the MVD of $CD105^+$ exhibited a more significant downward trend in terms of distance from the glioma. The most obvious types of reactive cells were reactive astrocytes and activated microglia. The reactive astrocytes were positive for nestin. The activated microglia emerged in the area near the glioma in most cases and in the area far from the glioma in more than half of the cases. In addition, several cases displayed focal collections of small lymphocytes around small blood vessels and tumor cells arranged around a neuronal cell, and a limited number of cases displayed giant dysmorphic neurons in an edematous cortex. Our data indicate that PTBE is a consequence of tissue reconstruction resulting from tumor cell invasion and is an appropriate niche for the growth and spread of glioma cells.

Key words: Peritumoral edema, Glioma, Histopathology, Immunohistochemistry

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Introduction

Peritumoral brain edema (PTBE) is considered to be one of the main biological behaviors of brain glioma. PTBE serves as a suitable niche (trophic niche) for the invasion of neoplastic glial cells (Lin, 2013) and is significantly associated with the clinical outcome of glioma. Recent studies have confirmed that the presence of PTBE on preoperative magnetic resonance imaging (MRI) is an independent unfavorable prognostic factor (Pope et al., 2005; Schoenegger et al., 2009). PTBE has been shown to exhibit negative effects on the cognitive functions of patients with glioma (Talacchi et al., 2011). In addition, the evaluation of PTBE can offer a valuable reference for the delineation of radiotherapy clinical

target volumes for glioblastoma (Chang et al., 2007). However, even though integrative cancer therapies have been improved, basic questions about drug resistance, tumor spread and the role of normal tissue remain unanswered (Bourzac, 2014).

With regard to brain glioma, peritumoral edema is a consequence of the interaction of tumor cell spread and the role of normal tissue. Thus, clinical manifestations, imaging features, formation mechanisms and the effect of PTBE therapy are important topics in the field of brain tumor research. One previous study showed that the development of peritumoral edema in brain neoplasm is associated with tumor type, tumor size and various molecular pathways (Stummer, 2007). Additionally, the histological characteristics of glioma-induced edema are considered to result from pathological tissue remodeling regulated by the interaction with nutrients in the tumor microenvironment (Yang et al., 2011). However, the histopathological features of PTBE remain imprecisely defined. In this study, we analyzed the histopathological characteristics of areas of glioma-induced PTBE.

Materials and methods

Twenty-two cases of glioma were identified from case files of our institution's surgical pathology department. The glioma masses, including the tumor body and peritumoral edema tissue, were resected. The selected patients had no medical history of brain tumor or surgical therapy and did not receive radiotherapy or chemotherapy preoperatively. Out of the 22 patients, 13 were male and 9 were female. Age at diagnosis ranged from 31 to 72 years, with a median age of 57 years. In total, 7 cases were classified as low-grade glioma (WHO grade II, diffuse astrocytoma), and 15 cases were classified as high-grade glioma consisting of anaplastic astrocytoma (WHO grade III, 5 cases) and glioblastoma (WHO grade IV, 10 cases). Using MRI scans, PTBE was classified as being near the glioma (≤1 cm) and far from the glioma (>1 cm). Eighteen cases, including 4 low-grade and 14 high-grade gliomas, contained edema in the area far from the glioma. Thirteen cases, including 6 low-grade and 7 high-grade gliomas, contained a cortical edema area, which was identified through the distribution of neurons and neuropil background.

According to the preoperative assessments conducted by the neurosurgeon, the prospective candidate cases of gliomas included a severe peritumoral edema band (diameter >2 cm) that did not contain an important functional area, such as a language or motor center, and could be massively excised. Peritumoral edema was determined by regions of hyperintense on a T2-weighted fluid-attenuated inversion recovery (FLAIR) image signal and hypointense on a T1-weighted image without enhancement surrounding the tumor. The excised massive tissue was marked by the neurosurgeon with an orientation tag and sent for pathological examination. The pathologist made a cut to produce a 0.3-cm thick slab perpendicular to the pia surface of the resected specimen (Fig. 1c). Based on gross observations and neuroimaging, the pathologist marked the zones of the tumor body and edema area, measured and classified the edema tissue as being near the glioma (distance from the tumor margin ≤1 cm) or far from the glioma (distance from the tumor margin >1 cm), and cut along the boundary to divide the tissue into two sections. These tissues were processed into formalin-fixed and paraffin-embedded specimens. Next, 4 μm sections were made and stained with hematoxylin-eosin, and immunoreactions were performed using EnVision (Dako A/S, Glostrup, Denmark) and double staining methods. The primary antibodies (listed in Table 1) included CD34 (1:200 dilution), CD105 (1:100 dilution), GFAP (1:200 dilution), CD68 (1:200 dilution) and KI-67 (1:100 dilution) from Dako, and Nestin (1:100 dilution) from Abcam (Abcam Inc., Cambridge, MA).

Invasive tumor cell density, the Ki-67 index and microvessel density (MVD) in the edema were evaluated. Invasive tumor cell density was defined as the average number of tumor cells detected in five high-power views. The Ki-67 index was scored according to the percentage of positively stained nuclei of tumor cells. To determine the MVD, edema tissue sections stained with CD34 and CD105 antibodies were examined using a Nikon 80i bright-field microscope (Nikon, Tokyo, Japan). The images were captured with a digital camera (Nikon DS-Fi2, Japan) under 200× magnification. For each edema tissue section, 2 "hot spot" fields of view, or areas with high densities of positively stained vessels, were evaluated. MVD was defined based on the number of positively stained vessels per high-power field of view. MVD was

Table 1. Antibodies used for the immunohistochemical examination.

Antibody	Producer	Species	Dilution	Cellular localization	Positive cells	Main biological function in this study
CD34	Dako	Monoclonal Mouse anti-human	1:200	Membrane	Endothelial	Mark all types of vessels
CD105	Dako	Monoclonal Mouse anti-human	1:200	Membrane	Endothelial	Mark neovascularization
GFAP	Dako	Monoclonal Mouse anti-human	1:200	Membrane Cytoplasm	Astrocytes	Mark reactive astrocytes
Nestin	Abcam	Monoclonal Mouse anti-human	1:100	Cytoplasm	Neural stem cells	Mark reactive astrocytes, part of tumor cells
CD68	Dako	Monoclonal Mouse anti-human	1:200	Cytoplasm	Microglia	Mark reactive microglia and macrophage
Ki-67	Dako	Monoclonal Mouse anti-human	1:100	Nucleus	Tumor cells	Mark proliferating index of tumor cells

calculated using a free image processing and analyzing program, Image Tool 3.00 (UTHSCSA; San Antonio, TX).

Statistical calculations were performed using SPSS (Statistical Package for the Social Sciences) 19.0 software (SPSS Inc.; Chicago, IL). The data are reported as the means, standard errors and ranges. One-way analysis of variance (ANOVA) was used to evaluate differences between the near and far groups and among different tumor grades. All statistical tests were two-sided, and P values of less than 0.05 were considered to be statistically significant.

Results

Pre-existing basic structures were preserved in the field of edema tissue with a clear boundary of gray and white matter and a wet tender cut surface (Fig. 1c). Microscopically, the edema area where the pre-existing basic structure was still preserved showed varying degrees of loose tissue, depending on the water content (Fig. 2a). Occasional axonal swelling was also observed. The main components of the edema tissue were invasive tumor cells and reactive cells, such as reactive astrocytes and microglia, and various blood vessel patterns, including tumor angiogenesis and pre-existing capillaries. The glioma grades exhibited different distributions of cells and vascular patterns (Table 2).

Distribution of tumor cells and microvessels

Tumor cells were observed in the edema area, especially in the near area adjacent to the tumor body. All cases of glioma contained varying numbers of invasive tumor cells in the PTBE area. Invasive tumor cell density was significantly higher in high-grade glioma than in low-grade glioma (F=28.990, p=0.000), and the density was significantly higher in the area near the glioma compared to the area far from the glioma (grade II, p=0.001; grade III, p=0.005; grade IV, p=0.000). The Ki-67 proliferative index of the invasive tumor cells was higher in high-grade glioma than in low-grade glioma (F=220.060, p=0.000), but the index was

Table 2. Distribution of cellular composition and microvessel patterns in peritumoral edematous tissues.

Histological feature	Area near the glioma		Area far from the glioma	
	Low-grade	High-grade	Low-grade	High-grade
Invasive tumor cells	7/7	15/15	4/4	14/14
Reactive cells				
Astrocytes	5/7	13/15	1/4	7/14
Pilocytic astrocytes	1/7	2/15	0/4	0/14
Microglia	6/7	15/15	3/4	12/14
Perivascular lymphocytes	1/7	2/15	0	0
Neuronal changes of cortex				
Dysmorphic neurons	2/6	2/7	0	0
Neurofibrillary tangles	1/6	0/7	0	0
Vessels				
Branching capillaries	7/7	15/15	4/4	14/14
Microvessel with endothelial proliferation	0/7	8/15	0/4	1/14

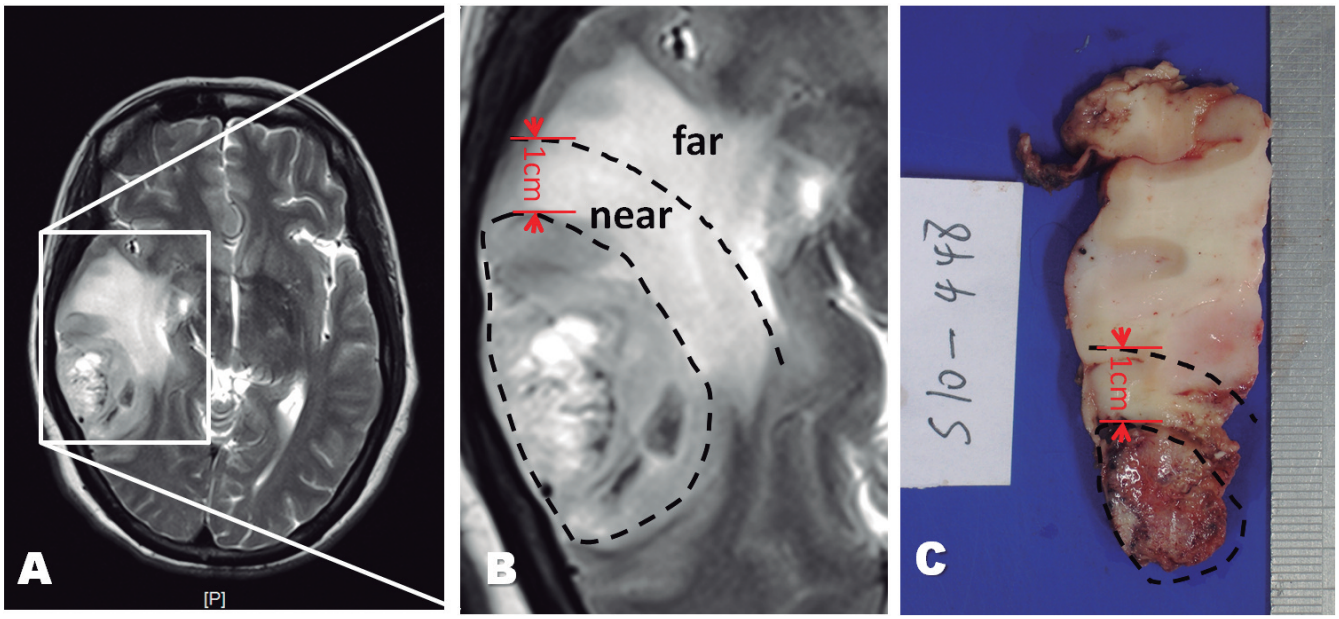

Fig. 1. The magnetic resonance imaging (MRI) scan showed peritumoral edema, which was an unenhanced T1-weighted hypointense, T2-weighted hyperintense image **(A).** Using MRI-scans, PTBE was classified as being near the glioma (≤1 cm) and far from the glioma (>1 cm) **(B).** Grossly, the primary basic structures were preserved in the field of the edema tissue with a clear boundary of the gray and white matter and a wet tender cut surface **(C)**.

not different in the area near the glioma compared to the area far from the glioma.

The microvascular pattern in PTBE was primarily branching morphology (Fig. 2b). Microvessels with proliferative endothelial cells were observed in the area near the glioma in 8 cases (8/22, 36.4%), including 7 cases of high-grade glioma (7/15, 46.7%) and one case of diffuse astrocytoma (1/7, 14.3%). Most of the proliferating microvessels were garland-like (Fig. 2c), and one case exhibited microvascular proliferation with the formation of glomerular capillary loops (Fig. 2d). In all cases, the endothelial cells were immunopositive for CD34, and some cases co-expressed CD105, especially in the area near the glioma (Fig. 3a-d). The MVDs of

Table 3. Raw data for invasive tumor cell density, Ki-67 index, and MVDs of $CD34^+$ and $CD105^+$ in each sample.

Case	Grade	Near				Far			
		Invasive cell density	Ki-67 index	$CD34^+$ -MVD	$CD105^+$ -MVD	Invasive cell density	Ki-67 index	$CD34^+$ MVD	$CD105^+$ MVD
1	II	21.3	5.3	32	29	9.2	3.5	21	10
2	II	28.1	3.2	31	25	/	/	/	/
3	II	19.5	6.1	25	25	/	/	/	/
4	II	15.2	2	17	14	8.3	1.5	14	3
5	II	26.6	1.5	29	27	13.9	1.7	34	9
6	II	25.8	4.4	34	33	11.1	2.1	25	12
7	II	22.7	2.7	24	24	/	/	/	/
8	III	27.6	13.6	45	43	12.3	8.3	31	8
9	III	39.3	17.4	41	32	/	/	/	/
10	III	35.2	13.2	36	34	20.3	19.2	27	13
11	III	34.2	8.3	38	33	15.8	10.3	19	21
12	III	42.1	26.9	51	53	28.1	25.3	29	10
13	IV	37.9	59.5	57	49	13.7	40.7	39	11
14	IV	44.1	77.8	68	60	12.5	80.9	35	8
15	IV	39.8	63.2	52	56	31.3	58.1	31	23
16	IV	42.2	61.9	49	51	22.4	50.9	23	15
17	IV	32.6	80.3	55	43	29.6	77.5	37	10
18	IV	47.2	72.7	59	52	14.8	81.6	41	6
19	IV	41.4	69.7	61	55	25.1	42.7	36	20
20	IV	37.7	75.4	56	61	22.7	67.8	39	16
21	IV	45.5	54.4	73	66	17.4	60.5	41	9
22	IV	51.2	68.1	71	63	23.5	80.7	44	10

Table 4. The comparison of mean invasive tumor cell density, Ki-67 index, and MVDs of $CD34^+$ and $CD105^+$ among tumor grades and near vs. far edema regions.

Index	Grade	Near (mean±SD)	Far (mean±SD)	F value	P value
Invasive cell density	II	22.74±4.52	10.63±2.48	23.891	0.001
	III	35.68±5.52	19.13±6.82	16.297	0.005
	IV	41.96±5.35	21.3±6.53	59.909	0.000
F value		28.990	4.539		
P value		0.000	0.029		
Ki-67 index	II	3.60±1.72	2.20±0.90	2.227	0.170
	III	15.88±6.96	15.78±7.92	0.000	0.984
	IV	68.30±8.47	64.14±15.94	0.532	0.475
F value		220.060	42.054		
P value		0.000	0.000		
$CD34^+$ MVD	II	27.43±5.86	23.50±8.35	0.853	0.380
	III	42.20±5.97	26.50±5.26	16.981	0.004
	IV	60.10±8.10	36.60±6.00	54.302	0.000
F value		45.220	7.496		
P value		0.000	0.006		
$CD105^+$ MVD	II	25.29±5.85	8.50±3.87	25.775	0.001
	III	39.00±8.97	13.00±5.72	25.037	0.002
	IV	55.60±7.06	12.80±5.51	228.346	0.000
F value		37.480	1.065		
P value		0.000	0.369		

$CD34^+$ and $CD105^+$ were higher in high-grade glioma and the area near the glioma than in low-grade glioma and the area far from the glioma. Compared to $CD34^+$, the MVD of $CD105^+$ exhibited a more significant downward trend in terms of distance from the glioma. A relatively high density of invasive cells was observed around the microvessel with proliferative endothelial cells (Fig. 2d). The results are summarized in Tables 3 and 4.

Reactive cell populations

Many types of reactive cells were present in the peritumoral edema area. One of the most obvious cell types was reactive astrocytes with abundant eosinophilic cytoplasm and the absence of nuclear atypia and mitosis (Fig. 4a,b), which were immunopositive for nestin (Fig. 4c). These reactive astrocytes were present in the area near the glioma in nearly all of the cases (18/22, 81.8%) and in the area far from the glioma in more than half of the cases (8/14, 57.1%). GFAP was overexpressed in the reactive astrocytes, and Ki-67-positive neoplastic glial cells were intimately mixed in the edema area (Fig. 4d). In addition, the focal proliferation of reactive pilocytic cells was observed in 3 cases (3/22, 13.6%). An additional reactive cell type was activated microglia, which was observed in the area near the glioma in all but one case (21/22, 95.5%) and in the area far from the glioma in most cases (15/18, 83.3%). The activated microglia showed rod-like and foamy cells (Fig. 5a) and were immunoreactive for CD68 (Fig. 5b). Additionally, a rare feature involving focal collections of small

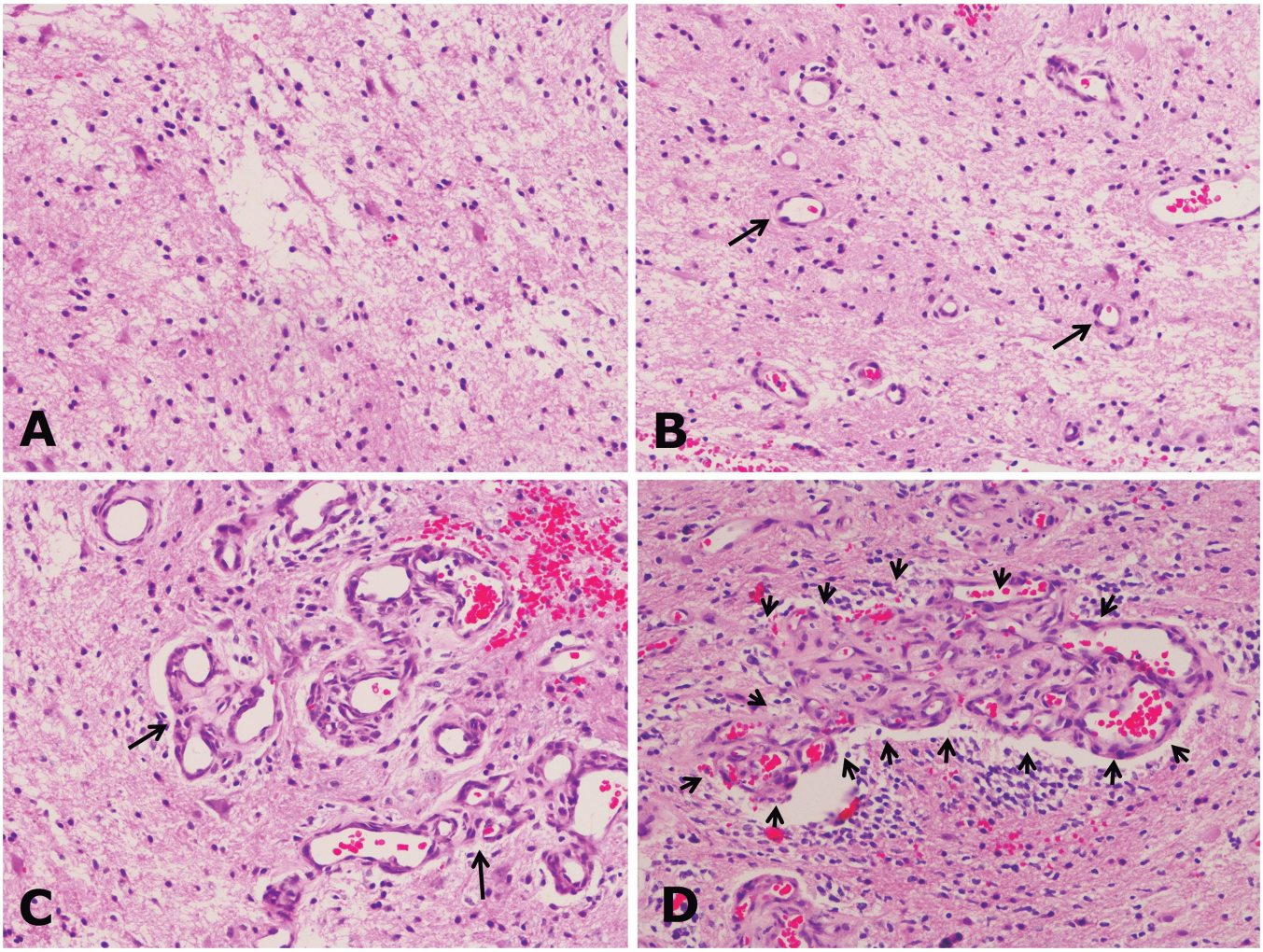

Fig. 2. The edema fields showed different degrees of loose tissue based on the water content **(A).** The primary microvessel pattern in PTBE was branching capillary (**B**, arrows). Microvessels with proliferative endothelial cells were observed in the area near the glioma. The majority of the microvessels were garland-like vessels (**C**, arrows), and one vessel displayed glomerular microvascular proliferation (**D**, arrowhead) (HE). Scattered invasive tumor cells were observed in the edema area of all cases, and the invasive cell density was relatively high around the microvessel with proliferative endothelial cells **(D)**. x 200

lymphocytes around small blood vessels was observed in the area near the glioma in 3 cases (3/22, 13.6%) (Fig. 5c).

Histopathological features in the area of cortical edema

Cortical edema was found in 13 of 22 cases. Histologically, the neuronal distribution was generally normal with various amounts of neuron loss and red neurons. Scattered tumor cells infiltrated the area of cortical edema, and some tumor cells were arranged around a neuronal cell to form "satellitosis." Similar to the edema area of the white matter, the area of cortical edema contained abundant reactive astrocytes and activated microglia. In addition, 4 cases (4/13, 30.8%) displayed giant dysmorphic neurons in the edematous cortex (Fig. 5d). Neurofibrillary tangles were observed in one case of diffuse astrocytoma.

Discussion

Glioma-related brain edema is a common condition, especially in peritumoral brain edema. Researchers have shown that PTBE promotes neoplastic glial cell invasion (Lin et al., 2010), and the degree of PTBE is closely associated with the recurrence and prognosis of glioma (Liu et al., 2013; Spanberger et al., 2013). A recent study suggested that the histological characteristics of PTBE are the pathologic consequence of the reconstructed trophic linkage within the tumor microenvironment (Yang et al., 2011). In this study, we found that the pre-existing basic structure was still preserved, but distinctive histopathological features also emerged, including scattered invasive tumor cells, various types of reactive cells, and various microvessel patterns. In particular, in the area near the glioma, the tumor cells displayed high proliferating activity, suggesting that

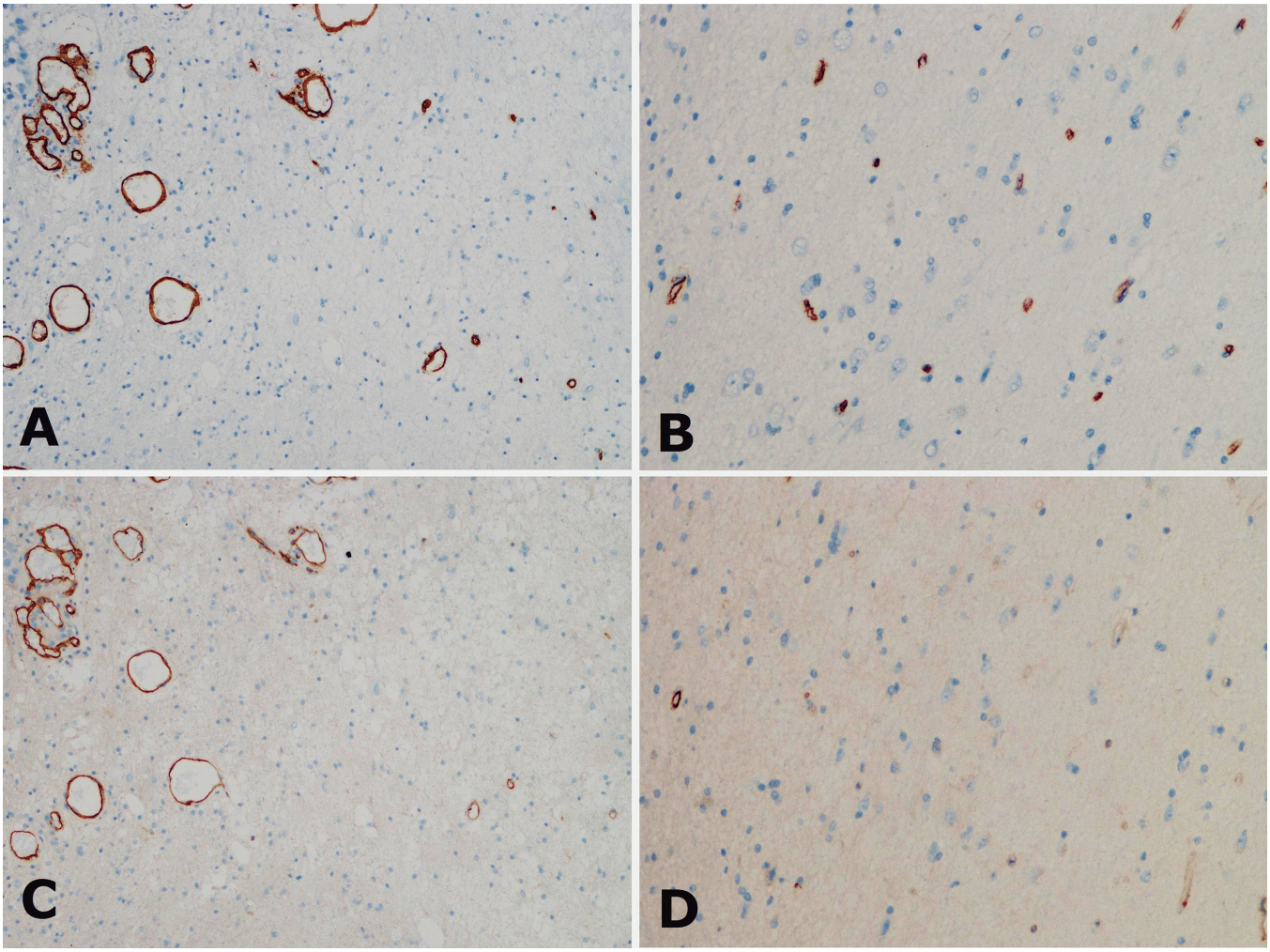

Fig. 3. All blood vessel patterns were positive for CD34 (**A,** near area; **B,** far area) and some of the patterns, especially in the area near the glioma, showed neoplastic angiogenesis and co-expressed CD105 (**C**, near area; **D,** far area**; A** and **C, B** and **D** are in the same area) (EnVision, DAB). x 100

these cells may have a strong invasive ability that allows them to promote the development of glioma.

These findings indicate that PTBE may be a forefront to the spread of glioma cells in the surrounding brain tissue (Engelhorn et al., 2009). The most common type of blood vessel in the present study was branching capillary. Microvessels with proliferative endothelial cells primarily involved garland-like vessels and occasionally involved glomerular capillary loops; these microvessels were observed in the area near the high-grade glioma. Studies have demonstrated that the anti-CD105 antibody is immunoreactive in neoplastic neovascularization but not in the normal vessels of the brain tissue (Behrem et al., 2005). In the present study, CD105 was expressed in some microvessels in PTBE, especially in the area near the glioma, which indicates that angiogenesis is present in the edematous tissue. The increased permeability of angiogenesis may be an important factor in the formation of edema. The overexpression of CD105 in peritumoral tissue has been correlated with a poor prognosis of glioblastoma (Sica et al., 2011). Therefore, removing as much of the edematous tissue around the tumor as possible may reduce the incidence of recurrence and improve the prognosis in glioma patients. Additionally, the edema area is also a key post-operative radiotherapy field.

The histological appearance of PTBE, including tumor cell invasion and various blood vessel patterns, may have an important guiding role in the diagnosis of glioma, especially in the use of stereotactic biopsy or intra-operative frozen diagnosis. For instance, if biopsy material from a patient with glioma showed edematous tissue under microscopy, the surgeons would know to obtain additional diagnostic tissue. If the biopsy showed

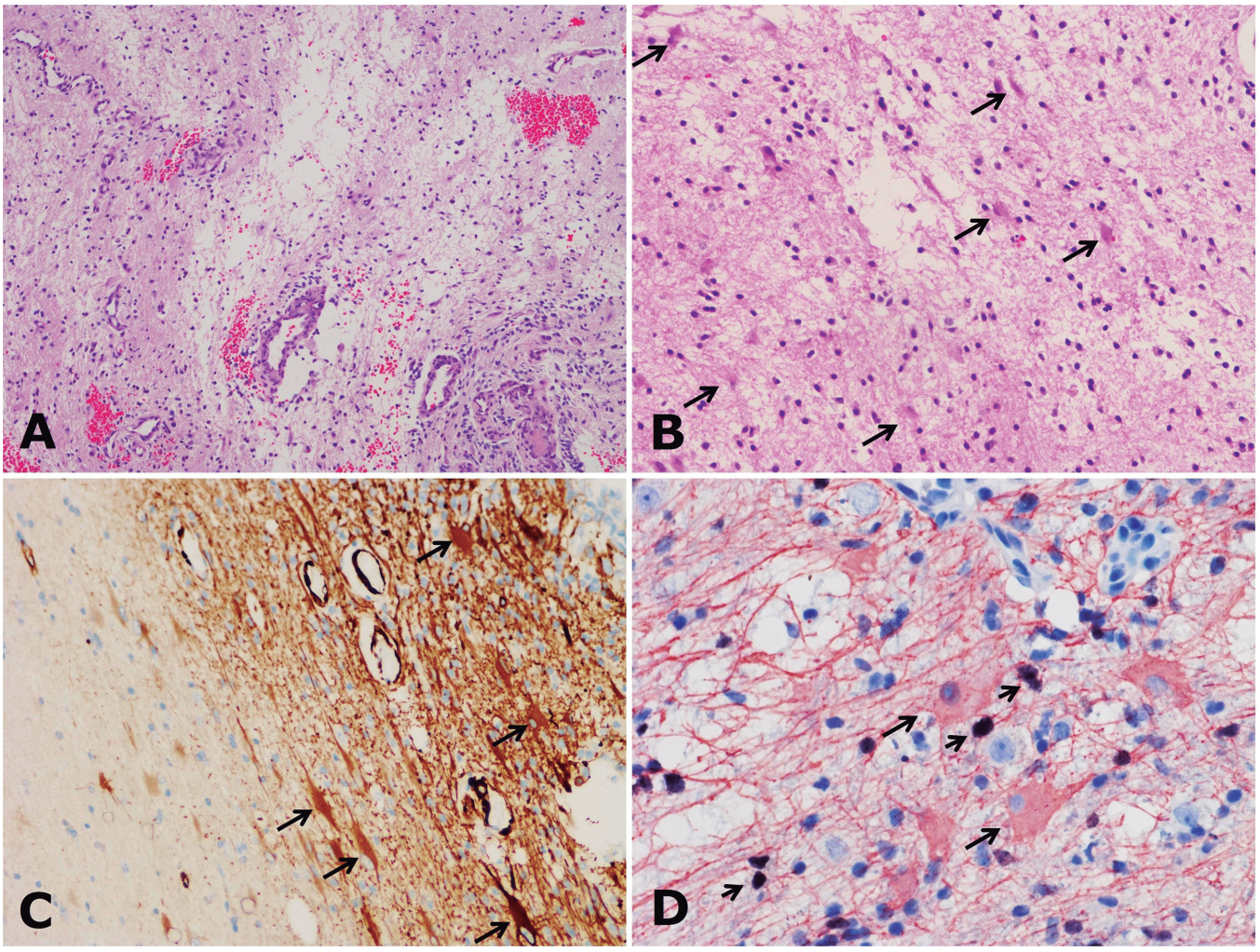

Fig. 4. One of the most obvious reactive cell types was reactive astrocytes (**A; B,** arrows), which were immune-positive for nestin (**C**, EnVision, DAB, arrows). The reactive astrocytes, which overexpressed GFAP, and Ki-67-positive neoplastic glial cells, were intimately mixed in the edema area (**D**, double staining; tumor cells are shown by arrowheads and astrocytes are shown by arrows). A, x 100; B, C, x 200; D, x 400

edematous tissue containing garland-like and glomerular microvessels, the surgeons would know to obtain more effective tissue for an accurate diagnosis. The immunophenotyping pattern can be useful in ambiguous cases that cannot be sufficiently defined as tumors. Specifically, the increasing of $CD105^{+}$-MVD may indicate that a case is likely to be a tumor lesion, which suggests the need for a re-biopsy.

A previous study demonstrated that brain edema is associated with reactive cells (reactive astrocytes and activated microglia) within the edematous tissue (Engelhorn et al., 2009). In the present study, we found that most reactive cells were astrocytes, and these cells were found in the majority of cases. In normal brain tissue, astrocytes have been shown to regulate the balance of intra- and extra-cellular water. However, in malignant glioma, reactive astrocytes lose this regulating function by secreting neurotoxic compounds, and they subsequently promote the formation of PTBE (Savaskan et al., 2008). A limited number of cases have shown focal encephalomalacia in the white matter with partial glial scar formation, which may be a secondary reaction to edema-induced injury. Activated microglia is another common type of reactive cell (Engelhorn et al., 2009). Studies have found that the presence of activated microglia is an important factor for promoting tumor growth and angiogenesis in glioma (Nishie et al., 1999; Farber et al., 2008) and the formation of brain edema (Badie et al., 2003). PTBE primarily occurs in the white matter, but a small amount of edema occurs in the cortex, especially in cases in which the tumor mass infiltrates or is near the cortex. Cortical edema

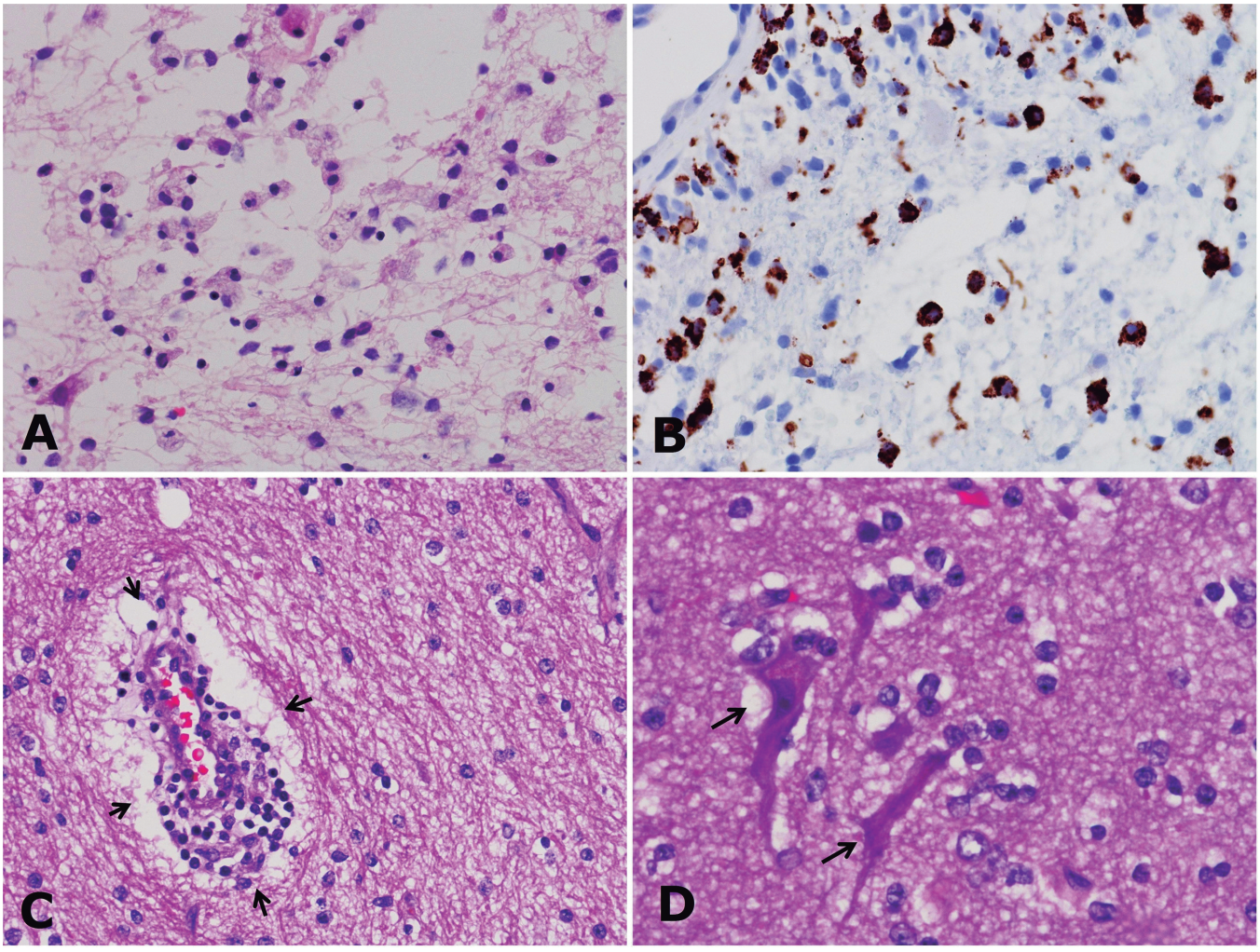

Fig. 5. An additional reactive cell type was activated microglia. Activated microglia were present in the area near the glioma in nearly all cases, displayed rod-like and foamy cells **(A)**, and were immunoreactive for CD68 **(B)**. An additional rare feature was the focal collection of small lymphocytes around a small blood vessel (**C**, arrows). The cortical edema area displayed abundant reactive astrocytes and activated microglia that were similar to the edema area of white matter. In addition, a limited number of cases displayed giant dysmorphic neurons in the edematous cortex (**D**, arrows). A-C, x 400; D, x 600

contributes to an increase in tissue pressure and changes in vascular permeability, leading to ischemia and hypoxia of the cortical neurons. This results in the degeneration, apoptosis and loss of neuronal cells. In the present study, we found that a limited number of cortical neuronal cells showed dysmorphologic or neurofibrillary changes, but the mechanism of these changes remains unclear. However, these dysmorphologic neurons may be one of the main causes contributing to seizures, which are a symptom in patients with glioma (Shamji et al., 2009). The remaining edema tissue that contains abnormal neuronal cells may be the histological basis of cortex-associated lesions, such as epilepsy.

In summary, PTBE in human brain glioma shows many histopathological features, including invasive tumor cells, various types of reactive cells, and angiogenesis with different immunophenotypes. PTBE is a consequence of tissue reconstruction resulting from tumor cell invasion and is an appropriate niche for the growth and spread of glioma cells.

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Conflicts of interest The authors declare that they have no conflicts of interest.

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