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Secretory meningioma: immunohistochemical findings and evaluation of mast cell infiltration

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Abstract Secretory meningiomas constitute a relatively rare subtype of meningiomas, accounting for only 1.1% at our institution, with a 6:1 predominance of female patients. This study aimed to obtain more information about the immunohistochemical characteristics of this histological entity, and to analyse the effects of histological factors such as the presence of mast cells on the radiological evidence of surrounding tumour oedema that frequently occurred in this subtype of meningioma. Fourteen cases of secretory meningioma were examined. Relevant clinical information was obtained from the patient files. Peritumoural oedema was determined either by CT or MRI scans and graded as small, moderate and severe. In order to perform the quantitative evaluation of mast cells in secretory meningiomas in a comparison with other meningiomas, 14 non-secretory meningiomas were randomly selected and used as a control group. The immunohistochemical staining of carcinoembryonic antigen was positive within the secretory droplets and the cells surrounding them in all cases. Ki 67 (MIB 1) proliferative index mean values were 2.4%, indicating low expression in all secretory meningiomas. Moreover, from our statistical analysis, there is no clear-cut pattern of various types of cytokeratins emerging in secretory meningiomas. The secretory meningiomas were characterized by a significantly increased number of mast

cells as compared with non-secretory meningiomas of different grades. As the present clinical findings and laboratory results could not confirm a correlation between mast cell density and radiological evidence of oedema, further studies of mediators are warranted.

Keywords Cytokeratin · Immunohistochemistry · Mast cell · Pericytic proliferation · Secretory meningioma

Introduction

Secretory meningioma is a subtype of meningioma characterized by unique epithelial differentiation with glandular lumina containing secretory globules (hyaline bodies). This histological subtype was first described by Cushing and Eisenhardt [15]. Subsequently, Kepes and other authors described these hyaline bodies as pseudopsammoma bodies [8, 19, 24, 25, 27, 28]. In 1986, Alguacil-Garcia investigated the secretory features of these meningiomas and proposed the term “secretory meningioma” [1].

The secretory subtype of meningiomas is relatively rare, with only a limited number of cases reported up to 2003 [14]. Although immunohistochemical and electron microscopic studies demonstrated the epithelial differentiation features of secretory meningioma [1, 9, 18, 19, 25, 32, 40, 46, 48], the types of cytokeratin and mast cell numbers have never been investigated. According to our group's previous studies, the other common feature of secretory meningioma is a high proportion of mast cells, immunohistochemically demonstrable in and around the pseudopsammoma bodies [20]. Therefore, we examined 14 cases of secretory meningiomas diagnosed and/or treated in our institution from 1980 to 2004 in order to provide more information on the histological characters of this tumour. This study also aimed to analyse the effects of histological factors (the presence of mast cells as well as pericytic proliferation) on radiological evidence of surrounding tumour oedema, which occurred more frequently in this subtype of meningioma.

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Materials and methods

Between January 1980 and February 2004, 1310 cases of meningioma were diagnosed and/or operated on at the Philipps University Hospital, Marburg. Fourteen cases (1.1%) were diagnosed as secretory meningioma. Relevant clinical information was obtained from the patient files. The peritumoural oedema was determined either by computerized tomography (CT) or magnetic resonance imaging (MRI) scans, and graded as small, moderate and severe [9]. The surgical specimens were processed after fixation in 4% buffered formalin. Sections (4 µm) were cut from paraffin blocks. Sections were routinely stained with haematoxylin and eosin, periodic acid-Schiff without diastase, toluidine blue and other immunohistochemical antibodies.

Immunohistochemistry was performed using the avidin-biotin complex method according to the manufacturer's instructions with primary antibodies to epithelial membrane antigen (EMA) (monoclonal; DAKO, Hamburg, Germany), carcinoembryonic antigen (CEA) (polyclonal; DAKO), Ki-67 (MIB-1, monoclonal; Dianova, Hamburg, Germany), pancytokeratins (CK MNF 116), cytokeratin 5/6, cytokeratin 7, cytokeratin 8 and cytokeratin 20. Additionally, pericytic proliferation was demonstrated using SM-actin staining. For mast cell analysis, anti-human CD 117 was used to label the transmembrane tyrosine kinase receptor CD117/c-kit, located in the mast cells (see applied primary antibodies in Table 1).

In order to perform quantitative evaluation of mast cells in secretory meningiomas in a comparison with other meningiomas, 14 non-secretory meningiomas were randomly selected and used as a control group. The control group of meningiomas comprised mostly endotheliomatous types, but included one malignant and one angiomatous meningioma. CD 117 marker was evaluated in a simple counting procedure. Positively stained mast cells located in five regions of secretory meningioma slice and

control tumour slice were randomly counted with a single square microscopic counting ocular.

Statistics Descriptive and explorative statistics was performed. Data are presented as mean±SD or median and range. Both the number of the whole cell content in the field and the number of mast cells were evaluated and calculated. For statistical evaluation, the non-parametric Mann-Whitney *U*-test was used. A *P*-value <0.05 was considered significant.

Results

Clinical feature

Tumour location, grade of oedema and the results of mast cell density are summarized in Table 2. Twelve patients were female and two were male. The common feature of the secretory meningiomas was the tendency to evoke brain oedema (Fig. 1). Five convexity and four middle fossa meningiomas revealed perifocal oedema. Six cases (43%) presented with a grade 3 oedema, one case (7%) with a grade 2 oedema and two cases (14%) with a grade 1 oedema, whereas oedema was absent in five cases (36%).

Histology

All secretory meningiomas had light microscopic appearance in accordance with the criteria of revised WHO classification of tumours of the central nervous system [31]. Each meningioma revealed an endotheliomatous growth pattern with the presence of moderate to abundant secretory globules of different sizes, staining intensely red with PAS (Fig. 2a) and blue with toluidine (Fig. 2b).

Table 1 Applied antibodies

Antibody	Specificity	Source
Monoclonal mouse anti-human cytokeratin, Clone MNF 16	Cytokeratin 5,6,8,17 and probably 19	Dako
Monoclonal mouse anti-human cytokeratin 5/6	Cytokeratin 5, cytokeratin 6	Dako
Monoclonal mouse anti-human cytokeratin 7	Cytokeratin 7	Dako
Monoclonal mouse anti-human cytokeratin 8	Cytokeratin 8	Dako
Monoclonal mouse anti-human cytokeratin 20	Cytokeratin 20	Dako
Monoclonal mouse anti-human epithelial membrane antigen	Epithelial membrane antigen	Dako A/S
Rabbit anti-human Ki-67	Ki-67	Dako A/S
Mouse monoclonal antibody CEA	Carcinoembryonic antigen	Dako A/S
Mouse monoclonal antibody SM actin	Pericytic proliferation	Progen
Polyclonal rabbit anti-human CD 117, c-kit	Transmembrane tyrosine kinase receptor CD117/c-kit, located in mast cells	Dako

Table 2 Clinical details of tumours and mast cell density

Case	Age	Gender	Location of tumour	Size	Oedema	Mast cell density %
1 GM	49	F	Petroclivus	2.0 cm	Without	0.35
2 BM	53	F	Frontoparietal convexity	1.5 cm	Without	1.05
3 HA	37	F	Frontotemporal convexity	2.0 cm	Without	2.12
4 HE	75	F	Occipital convexity	3.0 cm	Severe	0.46
5 BW	62	F	Frontal basis	3.0 cm	Severe	0.89
6 BI	62	M	Lateral sphenoid wing	2.0 cm	Mild	0.95
7 AS	53	F	Parietal convexity	2.5 cm	Without	1.62
8 PH	47	F	Sphenoid wing	2.0 cm	Severe	1.10
9 OI	66	F	Sphenoid wing	2.5 cm	Moderate	0.16
10 AS	49	M	Sphenoid wing	3.0 cm	Mild	1.35
11 KL	75	F	Frontal convexity	3.0 cm	Severe	2.64
12 WM	71	F	Frontal basis	2.5 cm	Severe	1.33
13 ZE	61	F	Frontal convexity	3.0 cm	Without	1.18
14 SS	38	F	Temporal convexity	4.0 cm	Severe	1.59

In all tumours of this type, obviously more slightly basophilic mast cells could be detected. Regressive changes and transition into other subgroups of meningioma were noticed at random. Throughout all specimens, a prominent spongy state was observed. These frequent vacuoles are considered as oedema formation within the tumours.

Immunohistochemistry of secretory meningioma

Cytokeratin

Pancytokeratins were strongly expressed in the surrounding of the secretory droplets in almost all tumour specimens (11/13) (Fig. 3a). One patient's specimen was excluded from this analysis because the tissue was unavailable. However, expression varied in strength from one specimen to the others. The immunoreactivity of different cytokeratins is shown in Table 3. The expression of CK 5/6, which represents squamous differentiation, was found in six cases (Fig. 3b), whereas markers of mucosal epithelial cells (CK 7, CK 8) were found in seven and four tumours

(Fig. 3c,d), respectively; some expressed both CK7 and CK8. Cytokeratin 20 was absent in all specimens.

CEA, vimentin, epithelial membrane antigen, MIB-1

CEA was expressed within the secretory droplets and the cells surrounding them in all cases (Fig. 4a). Generally, the membrane and the cytoplasm of tumour cells were positive for EMA and vimentin. Positive vimentin staining was seen in clusters of focally arranged cells, whereas EMA

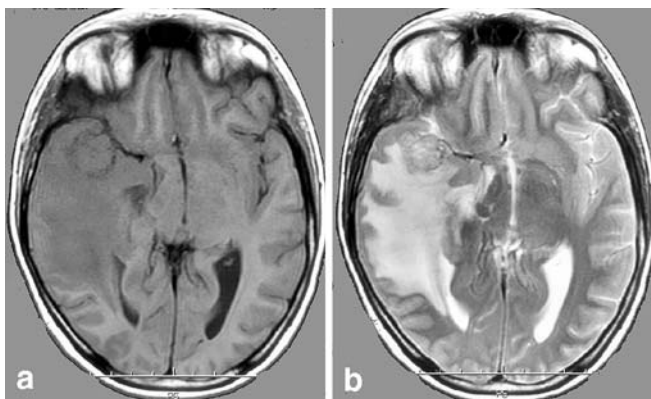


Fig. 1 **a** Axial view of T1-weighted MRI reveals a well demarcated isointense temporal tumour. **b** T2-weighted axial image showing a hyperintense area surrounding the tumour consistent with severe peritumoral oedema

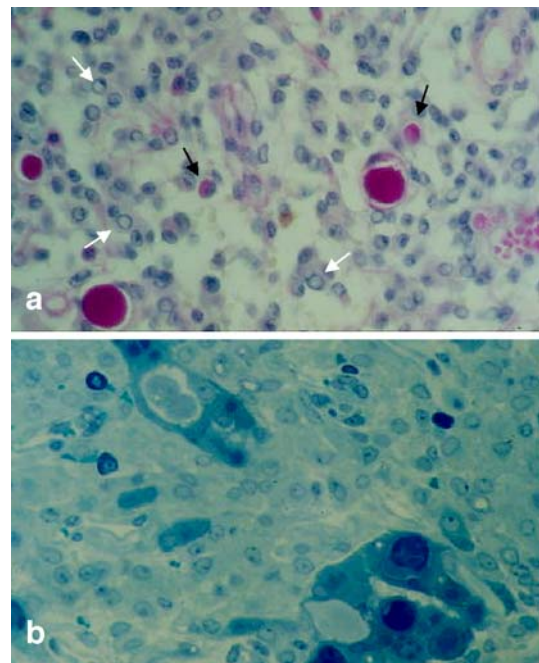
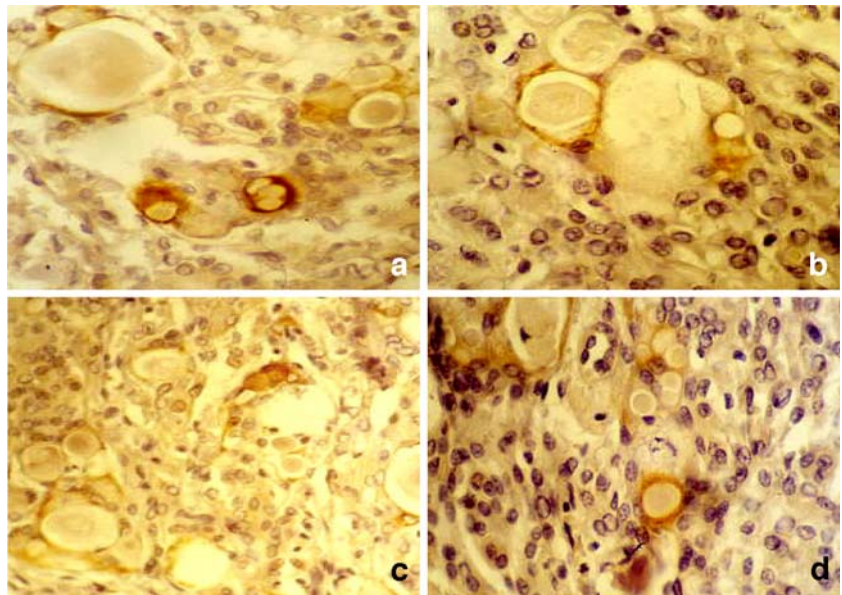


Fig. 2 **a** Secretory meningioma with secretory products that stain vividly with the periodic acid-Schiff (PAS, original magnification $\times 500$). Mast cells locating in the vicinity of these secretory products are observed (black arrows). Note: typical meningioma cells demonstrate the nuclear indentations (white arrows). **b** Toluidine stain-positive hyaline inclusions are shown. Mast cells also reveal deep blue reactions in their granules (original magnification $\times 1000$)

Fig. 3 **a** Pancytokeratin expression is demonstrated in the cells surrounding the secretory droplets (original magnification $\times 500$). **b** In some tumours, the epithelial marker CK5 or CK6 are expressed in these secreting cells (original magnification $\times 500$). **c** CK7 is present in the same manner surrounding those pseudopsammoma bodies (original magnification $\times 250$). **d** CK8 expresses in few secreting cells (original magnification $\times 500$). CK cytokeratin



was found both in the focally distributed tumour cells and the tumour cells surrounding secretory globules. The EMA expression was almost identical to the expression of pancytokeratin in cells those lay around the secretory product. Ki 67 (MIB 1) proliferative index mean values were 2.4%, indicating low expression in all secretory meningiomas.

Mast cell immunohistochemistry

The presence of mast cells was assessed by immunohistochemistry using polyclonal rabbit anti-human CD 117 (Fig. 4b). The quantitative evaluation of mast cells in secretory meningioma in comparison with other non-selected meningiomas of different cell types is demonstrated in Fig. 5.

Although the general cellular densities of control meningiomas were significantly higher than corresponding values of secretory meningioma (mean 310 (range 186 –

496) versus 207 (range 132–340) cells per 0.0575 mm^2 ; $P=0.001$, Mann-Whitney *U*-test), the secretory meningioma had significantly more mast cells (mean 2.43 (range 0.020–5.60) versus 0.27 (range 0,0–2.0) cells per 0.0575 mm^2 ; $P=0.0001$, Mann-Whitney *U*-test).

Sm-actin marker for pericytic proliferation

A remarkable pericytic proliferation within the vessel walls was observed in 12/13 cases (92%) (Fig. 4c). Sm-actin immunoreactivity was found in perivascular pericytes located adjacent to the capillary endothelial cells. Sm-actin content gradually decreased with increasing distance from the lumen of vessel. This expression pattern was confirmed by electron microscopic findings (data not shown). The vascular endothelial proliferation rim is regularly surrounded by a zone of spongy holes representing perivascular oedema (Fig. 4d).

Table 3 Cytokeratins (nta no tissue available)

Case	Age	CK-MNF	CK-5/6	CK-7	CK-8	CK-20	Oedema
1 GM	49	–	–	–	–	–	Without
2 BM	53	+	–	+	+	–	Without
3 HA	37	+	+	–	–	–	Without
4 HE	75	+	–	–	–	–	Severe
5 BW	62	+	+	+	–	–	Severe
6 BI	62	+	+	+	–	–	Mild
7 AS	53	+	–	–	–	–	Without
8 PH	47	nta	nta	nta	nta	nta	Severe
9 OI	66	+	+	+	+	–	Moderate
10 AS	49	+	–	+	+	–	Mild
11 KL	75	+	–	+	+	–	Severe
12 WM	71	+	+	–	–	–	Severe
13 ZE	61	–	–	–	–	–	Without
14 SS	38	+	+	+	–	–	Severe

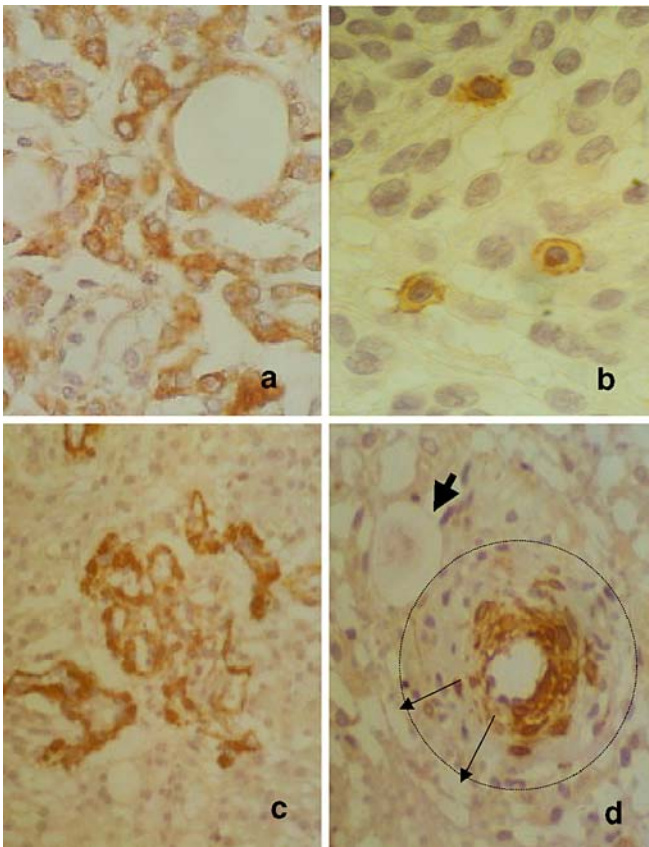


Fig. 4 **a** Vimentin expression is found in tumour cells with rather clonal expression. Both diffusely scattered tumour cells and those surrounding the secretory product are stained (original magnification $\times 500$). **b** With CD 117, mast cells are detected. Expression is clearer near the cell membrane (original magnification $\times 500$). **c** SM-actin demonstrates vascular proliferation (original magnification $\times 250$). **d** Only the center of pericytic proliferation reacts with SM-actin. Cells that form the periphery of the proliferation zone (*dotted line*) obviously lose smooth muscle differentiation. *Thin arrows* point to the surrounding oedema. The *thick arrow* points to a secretory droplet (original magnification $\times 250$)

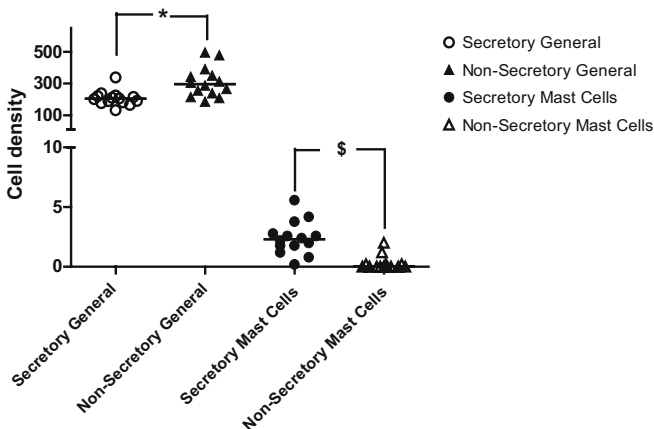


Fig. 5 The quantitative evaluation of mast cells in secretory meningioma in comparison with non-selected meningiomas of different cell type is revealed. In the control group, the general cellular density was significantly higher than corresponding values in the secretory meningioma group. However, secretory meningiomas have significantly more numbers of mast cells than control meningiomas

Discussion

Incidence and clinical aspects

Secretory meningiomas are rare tumours with a reported incidence of 1.2–4.4% [19, 37, 40]; however, other early reports quote higher incidences of 8.1–9.3% [1, 42]. The frequency of the secretory type among the meningiomas diagnosed in our institution is 1.1%. A previous study revealed a female-to-male ratio of 10:1 among patients with secretory meningioma [40]. In our study, the female predominance was noticeable with the value of 6:1 (12 females: 2 males), surpassing the 3:2 ratio among patients with intracranial meningioma [10]. Although a variable presence of both progesterone and oestrogen receptors has been reported by several authors [12, 17, 34, 40], the pathophysiological function and molecular role of sex hormones with regard to pathogenesis of meningioma remains unknown.

Many authors conclude that the higher incidence or the trend toward a high incidence of peritumoral oedema is associated with tumour volume [3, 4, 6, 7, 21, 30, 33, 49]. Although all secretory meningiomas except one (4 cm) of our series were smaller than 4 cm, peritumoral oedema was observed in about two-thirds of cases and two-thirds of cases with this peritumoral oedema were classified as severe oedema. This is in agreement with early reports of a higher incidence of oedema in secretory meningiomas [13, 23, 35, 40, 46].

Immunohistochemistry

It is well recognized that meningioma can develop multiple mesenchymal differentiation (fibroblastic, transitional, meningoendothelial, etc.) and meningioma with hyaline inclusions is thought to represent the focal epithelial differentiation of meningoendothelial cells [1, 36, 47]. Additionally, epithelial differentiation can be easily demonstrated via staining of cytokeratin [40]. Although positive staining with cytokeratin or pancytokeratin in the inclusions and in the cytoplasm of cells surrounding secretory meningiomas has been reported [1, 18, 40, 46], we have not found data focusing on the types of cytokeratin. From our study of cytokeratins, the secretory meningiomas may express markers of squamous or columnar epithelia, or even both. This could indicate a progressive undirected process of differentiation. Moreover, from our statistical analysis there is no clear-cut pattern of various types of cytokeratins emerging in secretory meningioma (Table 3).

Histological similarity of secretory meningioma and other carcinoma

Intracellular and extracellular lumina with prominent microvilli surrounding hyaline inclusion in both meningiomas [19, 25] and other carcinomas [2, 44] was shown using ultrastructural studies. These findings indicate the associ-

ation between epithelial and secretory differentiation. Light microscopic findings of similar cytoplasmic hyaline inclusions have been also reported in carcinomas of the breast, lung, colon and liver [2, 16]. Our immunohistochemical study demonstrated CEA and EMA expressed in epithelial cells and inclusions of secretory meningiomas. The strong positivity for CEA and EMA in cells forming intracellular lumina and duct-like structures support the epithelial secretory nature of these benign meningiomas and malignant tumour cells [1, 11, 26, 43].

Although these malignant tumours and secretory meningiomas are very different in terms of progression, some morphological aspects and immunohistochemical features of intracellular hyaline bodies are similar suggesting a similar pathogenesis of these structures in both benign and malignant tumours. Additionally, both secretory meningioma and intracerebral metastatic carcinoma are associated with severe brain oedema.

Mast cells and pericytic proliferation

According to the report of Bo et al., mononuclear cell infiltrates in meningiomas are mainly composed of T-cells and macrophages, indicating an immune system surveillance and response to the tumour cells, with mast cells found only in nine out of 32 tumours [5].

In contrast to the above finding, we previously demonstrated that high mast cell numbers are a common feature in secretory meningiomas and these were found in and around pseudopsammoma bodies [20]. After investigating the mast cell density in secretory meningiomas and the control group (non-secretory meningiomas), the number of mast cells in secretory meningiomas was significantly increased compared with those cells in tissues of the control group (Fig. 5). Mast cell derived mediators, e.g. histamine, may play an important role in creating pathological brain oedema. Further studies of mediators are required to clarify the correlation between the presence of mast cells and the development of oedema, although our preliminary data of clinical findings and results from the laboratory did not clarify the relation between mast cell density and radiological evidence of oedema.

Pericytic proliferation is another component that aids diagnosis of secretory meningioma [1, 8, 13, 18, 40]. Pericytic proliferation was observed in 83% of cases in a recent study [14]. In our study, a high ratio (92%) of pericytic proliferation was also observed using sm-actin staining. We agree that this histological feature is a helpful finding in the diagnosis of secretory meningiomas, especially with cases where secretory inclusions are not prominent [14]. However, an unusual vascular pericytic proliferation as a cause of peritumoral cerebral oedema is still a matter of debate [13, 37, 40].

Peritumoral oedema and possible pathogenesis

A noteworthy finding of secretory meningioma is that they are accompanied more often by massive peritumoral oedema than other meningiomas of similar location or size [23]. However, the exact pathogenesis of meningioma-associated brain oedema is not completely understood. Controversies in the literature concerning the correlation between the degree of peritumoral oedema in intracranial meningiomas and tumor size, location, or histological subtype have been reported [9, 40]. According to the venous compression theory, the incidence of oedema would be higher in meningioma located at the frontal or sphenoidal region. In our study, 13 secretory meningiomas are less than 4 cm and ten of them are located at either the frontal convexity or the sphenoid ridge. Thus, venous compression might have some influence on peritumoral oedematous formation. The other possible mechanisms seem related to the secretion of vascular mediating substances such as vascular endothelial growth factor (VEGF) [29, 38, 39] or other modulating factors regulating its secretion [45]. Particularly in secretory meningioma, which demonstrate a higher number of mast cells than other subtype of meningioma, other mast cell mediators (e.g. histamine, serotonin) or VEGF might play a significant role in oedematous formation. Further research should be conducted in order to demonstrate the possible relation of secretion of mast cell mediators or VEGF and oedematous process. Additionally, we agree that oedematous formation in the intracranial meningioma is probably multifactorial [9, 22].

Conclusion

Secretory meningiomas are often associated with severe peritumoral oedema, causing signs and symptoms of increased intracranial pressure. So far, the initial step inducing peritumoral oedema has not been demonstrated. Many histological findings such as increased numbers of mast cells, pseudopsammoma bodies, CEA, and pericytic proliferation might be involved in the pathophysiological process of this vasogenic brain oedema. Demonstration of mediators in the tumour tissue might define the role of mast cells and provide more information about the nature of this particular type of meningioma.

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