

# The Possible Role of Mast Cells and VEGF in Peritumoural Oedema of Secretory Meningioma

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**Objective:** Secretory meningiomas constitute a relatively rare subtype of meningiomas and present often with massive peritumoural oedema. From our previous report, a high number of mast cells were demonstrable in this subtype of meningiomas. The present study aimed to obtain more information about mast cell derived proangiogenic factors and mediators as well as VEGF receptors in secretory meningioma. Additionally, the correlation of histological factors such as the presence of mast cells and the radiological evidence of surrounding tumour oedema was analysed.

**Material and Method:** Sixteen cases of secretory meningioma were examined. Relevant clinical information was obtained from the patient files. The peritumoural oedema was determined either by CT or MRI scans and graded as mild, moderate and severe. Immunohistochemical studies of histamine, substance P, serotonin, VEGF and VEGF receptors were performed. A double-blind quantitative evaluation of mast cells staining positively for VEGF in a comparison with total mast cells in secretory meningiomas was made by two histopathologists.

**Results:** There was no immunoreactivity against histamine or substance P within the tumour tissue or in mast cells. Fine granules of serotonin were demonstrated within the mast cells and a coarse granular expression of VEGF was found within the mast cells. Our preliminary data demonstrated that tumours with moderate to severe degree of peritumoural oedema usually contained more than 50% of VEGF-staining positive mast cells.

**Conclusion:** Secretory meningiomas are characterized by a significantly increased number of mast cells. VEGF and serotonin might be involved in the pathophysiological process of this vasogenic brain oedema. The preliminary data demonstrated the potential relation between the radiological evidence of increasing oedema and the high numbers of mast cell staining positively for VEGF.

**Keywords:** Mast cells, Peritumoural oedema, Secretory meningioma, Serotonin, VEGF

**J Med Assoc Thai 2016; 99 (Suppl. 3): S8-S15**

**Full text. e-Journal:** <http://www.jmatonline.com>

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Secretory meningioma is a relatively rare histological subtype of meningioma<sup>(1)</sup>, which first described by Cushing and Eisenhardt<sup>(2)</sup>. Secretory meningiomas are accompanied more often by massive peritumoural oedema compared to other meningiomas of similar location or size<sup>(3)</sup>. According to our group's previous studies, the other common features of secretory meningioma are immunohistochemically demonstrable high proportions of mast cells located in and around the pseudopsammoma bodies<sup>(4,5)</sup>. Mast

cells are not only critical players in inflammatory reactions, but they have also been shown to be important in angiogenesis<sup>(6)</sup>. Additionally, mast cells are a rich source of serotonin, substance P and several potent angiogenic factors, including vascular endothelial growth factor (VEGF)<sup>(6-9)</sup>. It is well established that VEGF is one of the principal regulators of angiogenesis as well as vasculogenesis in many tumours<sup>(10)</sup> and also in the brain<sup>(11,12)</sup>. VEGF correlates with vascular permeability causing peritumoural oedema in human meningiomas<sup>(12,13)</sup>.

Therefore, we examined the cases of secretory meningiomas diagnosed and/or treated in Department of Neurosurgery, Philipps University in order to provide more information on mast cell derived proangiogenic

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factors such as like VEGF and mediators (histamine, serotonin, substance P) as well as VEGF receptors in secretory meningioma. These immunohistochemical data were correlated with the radiological evidence of tumour oedema, so as to analyse the effects of mast cell derived substances on surrounding tumour oedema.

### Material and Method

Between January 1980 and January 2007, 18 cases of meningioma were diagnosed as secretory subtype at the Philipps University Hospital, Marburg. After approval was obtained from the institutional review board of Philipps University Hospital, the medical records of patients who were diagnosed as secretory meningioma were retrospectively reviewed. 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 mild, moderate and severe<sup>(14)</sup>. The surgical specimens were processed after fixation in 4% buffered formalin. Four-micrometer sections were cut from paraffin blocks. Sections were routinely stained with haematoxylin and eosin, periodic acid-Schiff without diastase, toluidine blue and immunohistochemistry. Only 16 cases were available for complete investigation of immunohistochemistry.

Immunohistochemistry was performed using the avidin-biotin complex method according to the manufacturer's instructions with primary antibodies to histamine (Chemicon International, monoclonal antibody), substance P (Chemicon International, polyclonal antibody), and serotonin (Chemicon International, polyclonal antibody; dilution 1: 100), in order to demonstrate mast cell mediator substances. Additionally, anti-VEGF (PromoCell, dilution 1: 200) and antibodies to its

receptor-1 (Oncogene, dilution 1: 2,000) and receptor-2 (Calbiochem, dilution 1: 2,000) were used to assess its presence and angiogenesis in this type of tumour. For mast cell analysis, anti-human CD 117 was used to label the transmembrane tyrosine kinase receptor CD117/c-kit (Dako, polyclonal antibody), located in the mast cells (see applied primary antibodies in Table 1). Negative control of each immunostaining included omission of the primary antibody.

To perform a double-blind quantitative evaluation of mast cells containing pro-angiogenic factor of VEGF in a comparison with mast cells in secretory meningiomas, specimen evaluation was performed by two histopathologists, who did not know the clinical data. CD117 marker (mast cell) and mast cells staining positively for VEGF were evaluated in a simple counting procedure. Positively stained mast cells (CD117 marker) or positively stained VEGF in mast cell located in ten regions of secretory meningioma sections were randomly counted with a single square microscopic counting ocular. Afterwards, mast cells with positive reaction against the VEGF were calculated and compared to the total mast cells.

### Statistical analysis

Descriptive statistics was performed using mean  $\pm$  SD or median and range. Incidences or proportions were analysed by using Chi-square tests. An unpaired non-parametric test (Mann-Whitney-U test) was used to compare VEGF expression between the two groups with and without oedema. The *p*-values less than 0.05 were considered statistically significant.

### Results

#### Clinical features

Tumour location, grade of oedema and the results of mast cell density are summarized in Table 2. Twelve patients were females and four were males. The

**Table 1.** Applied antibodies

Antibody	Specificity	Source
Monoclonal mouse anti-histamine	Histamine	Chemicon international
Polyclonal rabbit anti-substance P	Substance P	Chemicon international
Polyclonal rabbit anti-serotonin	Serotonin	Chemicon international
Polyclonal rabbit anti-human VEGF	"Total" Human VEGF	Promo cell
Polyclonal rabbit anti-human VEGF receptor-1	Human VEGF receptor 1	Oncogene
Polyclonal rabbit anti-human VEGF receptor-2/3	Human VEGF receptor 2/3	Calbiochem
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 the tumours and mast cell density

Case	Age	Gender	Location of tumour	Size (cm)	Oedema	Mast cell density %	VEGF positive mast cell %
1	49	F	Petroclivus	2.0	Without	0.35	100.0
2	53	F	Frontoparietal convexity	1.5	Without	1.05	85.0
3	75	F	Occipital convexity	3.0	Severe	0.46	65.2
4	62	F	Frontal basis	3.0	Severe	0.89	100.0
5	62	M	Lateral sphenoid wing	2.0	Mild	0.95	31.6
6	53	F	Parietal convexity	2.5	Without	1.62	15.4
7	66	F	Sphenoid wing	2.5	Moderate	0.16	100.0
8	49	M	Sphenoid wing	3.0	Mild	1.35	15.4
9	75	F	Frontal convexity	3.0	Severe	2.64	53.0
10	71	F	Frontal basis	2.5	Severe	1.33	75.0
11	61	F	Frontal convexity	3.0	Without	1.18	100.0
12	38	F	Temporal convexity	4.0	Severe	1.59	12.6
13	70	M	Temporal basis	3.0	Severe	0.60	88.2
14	44	F	Frontal convexity	3.5	Severe	2.70	100.0
15	67	M	Sphenoid wing	5.0	Moderate	1.10	100.0
16	77	F	Temporal convexity	2.5	Severe	0.70	19.4

common feature of the secretory meningiomas was the tendency to evoke brain oedema (Fig. 1A). Five convexity and five middle fossa meningiomas revealed a perifocal oedema. Eight cases (50%) presented with a severe oedema, two cases (12.5%) with a moderate oedema and two cases (12.5%) with a mild oedema, whereas oedema was absent in four cases (25%) (Fig. 1B).

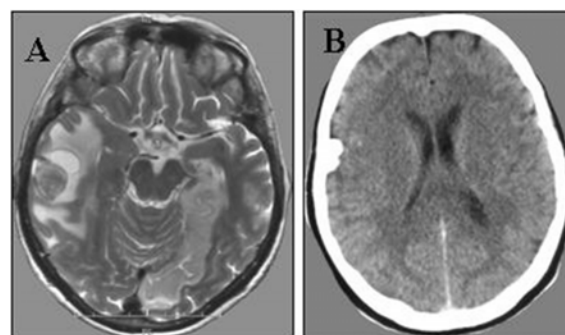
### Histology

All secretory meningiomas had the light microscopic appearance in accordance with the criteria of revised WHO classification of tumours of the central nervous system<sup>(15)</sup>. Each meningioma revealed an endotheliomatous growth pattern with the presence of moderate to abundant secretory globules of different sizes, staining intensely red with PAS and blue with toluidine blue. In all tumours of this type, more slightly basophilic mast cells could be detected. Throughout all specimens, a prominent spongy state was observed. These frequent vacuoles are considered as the oedematous formation within the tumours.

### Immunohistochemistry of secretory meningioma

#### 1) Mast cell immunohistochemistry

The presence of mast cells was assessed by immunohistochemistry using polyclonal rabbit anti human CD 117. The expression pattern of CD 117 in mast cells revealed a distinct appearance around the



**Fig. 1** Axial view of T2-weighted MRI reveals a well demarcated isointense temporal tumour with severe peritumoural oedema (A). Axial CT image shows a hyperdense tumour (calcification) without surrounding tumour oedema (patient 6) (B).

cytoplasmic membrane (Fig. 2A). No positive immunoreactivity was seen for histamine or substance P. Serotonin immunoreactivity was demonstrated regularly within the mast cells of the tumours. Its positive stain revealed fine granules within the mast cells (Fig. 2B).

#### 2) VEGF and VEGF-receptors

In contrast to the fine granular expression of serotonin, a coarse granular expression of VEGF was found within the mast cells (Fig. 2C). Positive immunoreactions against VEGF receptor 1 and receptor

2 were found and restricted to a few structures within these tumours. The clearest demonstration could be observed surrounding pseudopsammoma bodies (Fig. 2D, arrow). Since the immunological expression was minimal, a quantitative evaluation was omitted.

The quantitative evaluation of mast cells and mast cells with positive VEGF-staining granules is demonstrated in Table 2. Our preliminary data of clinical findings and results of mast cell immunohistochemistry showed a potential relationship between the high percentage of VEGF-staining positive mast cells and radiological evidence of oedema (Fig. 3). Tumours with a moderate to severe degree of peritumoural oedema (8/10 = 80%) usually revealed more than 50% of VEGF-staining positive mast cells (Fig. 3) compared to tumours with no or mild degree of peritumoural oedema (3/6 = 50%). This difference is not statistically significant ( $p = 0.210$ ) because of a small sample size.

## Discussion

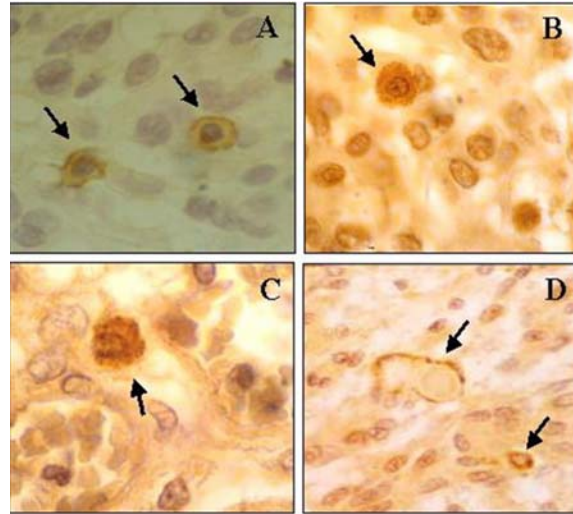
### *Incidence and clinical aspects*

Secretory meningiomas are rare tumours with a reported incidence of 1.2-4.4%<sup>(16-18)</sup>. The frequency of the secretory type among the meningiomas diagnosed in our institution is 1.1%<sup>(5)</sup>. However, other early reports quote a higher incidence of 8.1-9.3%<sup>(19,20)</sup>. A previous study revealed a female-to-male ratio of 10: 1 among patients with secretory meningioma<sup>(18)</sup>. In our present study, the female predominance was noticeable with the value of 3: 1 (12 females: 4 males), surpassing the 3: 2 ratio among patients with intracranial meningioma<sup>(21)</sup>.

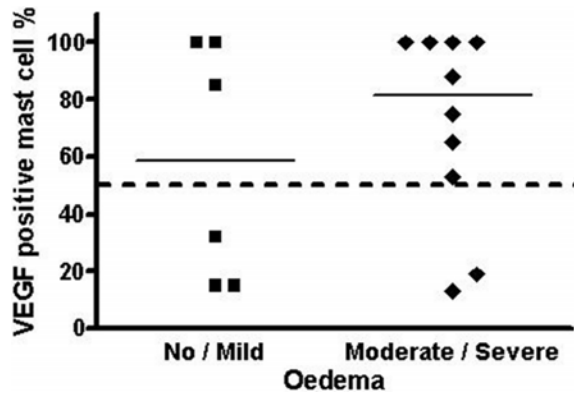
Many authors conclude that the higher incidence or the trend toward a high incidence of peritumoural oedema is associated with tumour volume<sup>(22-29)</sup>. Although all secretory meningiomas, except two (4 cm and 5 cm) of our series, were smaller than 3.5 cm, peritumoural oedema was observed in about three-quarters of the cases and two-thirds of this peritumoural oedema was classified as severe oedema. This is in agreement with early reports of a higher incidence of oedema in secretory meningiomas<sup>(3,18,30-32)</sup>.

### *Mast cells and mediator products*

In contrast to the report of Bo et al<sup>(33)</sup> about the role of mononuclear cells in meningiomas, we previously demonstrated that high mast cell numbers were a common feature in secretory meningiomas and these were found in and around pseudopsammoma bodies<sup>(4)</sup>. The number of mast cells in secretory



**Fig. 2** The expression of mast cells (CD117) is clearer near the cell membranes (original magnification x500) (A, arrows). The immunoreaction against serotonin reveals fine granules within the mast cell (original magnification x500) (B, arrow). Contrary to the positive stain appearance of serotonin, a coarse granular expression of antibody against VEGF is found within the mast cell (original magnification x500) (C, arrow). The immunological expression of VEGF receptor 2/3 is surrounding the secretory product (original magnification x250) (D, arrow).



**Fig. 3** Analysis of VEGF positive mast cells in percent and occurrence of peritumoural oedema of secretory meningiomas. Dotted line is the 50% cut-off level for VEGF positive mast cells. The difference is not statistically significant (Chi-square test  $p = 0.210$ ).

meningiomas was significantly increased compared with those cells in tissue of the control group (non-secretory meningiomas)<sup>(5)</sup>. Our data did not show any



positive staining for histamine or substance P, although in other samples positive staining was obtained indicating that the system worked (data not shown). We believe that this may be due to the long storage times and the storage conditions. We, therefore, cannot exclude any potential roles of histamine or substance P in pathological brain oedema. However, VEGF and serotonin seem to be involved in creating peritumoural oedema.

#### ***Peritumoural oedema and possible pathogenesis***

The exact pathogenesis of brain oedema associated with meningioma is not completely understood. In the previous literature, it was found that VEGF correlated with vascular permeability causing peritumoural oedema in human meningiomas<sup>(13)</sup>. Additionally, different pathogenic mechanisms may be involved in the up-regulation of VEGF in different meningiomas<sup>(12)</sup>, including placenta growth factor<sup>(34)</sup>. In secretory meningioma, we postulated that mast cells should be the important source of VEGF in this type of tumour<sup>(35)</sup> and VEGF as well as serotonin may have an important role of stimulating vascular leakage and inducing oedema formation. However, factors which may relate to the up-regulation of VEGF have to be further investigated because secretory meningioma is a slowly growing tumour with a rich blood supply. Therefore, this type of meningioma rarely faces the condition of hypoxia. Additionally, we agree that oedema formation in the intracranial meningioma is probably multifactorial<sup>(34)</sup>. Our present study demonstrated for the first time the high proportion (80%) of mast cells containing VEGF (>50%) and the development of moderate or severe peritumoural oedema. Three specimens, which demonstrated 85% to 100% of VEGF-staining mast cells, did not have the peritumoural oedema. One of these tumours was a small petroclival meningioma (Case 1) and the other was a calcified frontal convexity meningioma (Case 2). That no peritumoural oedema occurs in this petroclival case might be due to less white matter in the posterior fossa than in supratentorial brain tissue<sup>(36)</sup>. In the case with calcified lesion, the calcification might prevent the brain tissue from contacting with the VEGF. However, the explanation for the absence of peritumoural oedema in one of these three patients (Case 11) could not be provided.

#### **Conclusion**

Secretory meningiomas are often associated with a severe peritumoural oedema causing signs and

symptoms of raised intracranial pressure. Up to now, the initial step inducing peritumoural oedema is unknown. Mast cells are an important source of VEGF and serotonin in secretory meningioma. These mediators may be involved in the pathophysiological process of this vasogenic brain oedema. Our preliminary data indicate the potential relation between the radiological evidence of increasing oedema and the high numbers of mast cells staining positively for VEGF.

#### **What is already known on this topic?**

Secretory meningiomas are accompanied more often by massive peritumoural oedema compared to other meningiomas of similar location or size. According to our group's previous studies, the other common feature of secretory meningioma is a high proportion of mast cells.

#### **What this study adds?**

The authors examined the cases of secretory meningiomas in order to provide more information on mast cell derived proangiogenic factors as well as VEGF receptors in secretory meningioma. VEGF and serotonin seem to be involved in creating peritumoural oedema. Our present study demonstrated for the first time the high proportion (80%) of mast cells containing VEGF (>50%) and the development of moderate or severe peritumoural oedema. These immunohistochemical data were correlated with the radiological evidence of tumour oedema.

#### **Acknowledgement**

Wuttipong Tirakotai is a fellow of the Alexander-von-Humboldt Foundation, Bonn, Germany in the years 2005-2006. Prof. M. Ennis (Belfast) is acknowledged for her critical review of our paper.

#### **Potential conflicts of interest**

None.

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## บทบาทของ mast cell และ VEGF ภาวะ peritumoral oedema ใน secretory meningioma

วุฒิพงษ์ จิโรเมโท, ฮาสน์ ดีเคอร์ เมนเนล, สรัญญา พาพานิช, อูริช ชูเร, เฮลมุท เบอธาลันท์, อิลฮาน เชลิก

**วัตถุประสงค์:** secretory meningioma เป็นเนื้องอกชนิดที่พบไม่บ่อย และพบภาวะสมองบวมรอบก้อนเนื้องอกเป็นอย่างมาก (massive peritumoural oedema) จากการศึกษาก่อนหน้านี้พบการเพิ่มขึ้นของ mast cell จำนวนมากในเนื้องอกชนิดนี้ จุดมุ่งหมายการศึกษาคั้งนี้ คือ รายงานข้อมูลเพิ่มเติม บทบาท mast cell และสารสื่อกลางที่เกี่ยวข้องของรวมทั้ง VEGF receptors ใน secretory meningioma นอกจากนี้ยังวิเคราะห์ถึงความสัมพันธ์ ข้อมูลจากลักษณะทางกล้องจุลทรรศน์ เช่น mast cell ที่ปรากฏและผลทางด้านรังสีวิทยาของภาวะสมองบวมรอบเนื้องอก

**วัสดุและวิธีการ:** ศึกษาในผู้ป่วยจำนวน 16 ราย ข้อมูลผู้ป่วยได้รับจากรายงานการบันทึกเวชระเบียน การตรวจวินิจฉัยภาวะสมองบวมแบบ peritumoural ด้วยเครื่อง CT หรือ MRI scans และประเมินความรุนแรงของการบวมตั้งแต่ ระดับมีผลเล็กน้อย ปานกลาง และรุนแรง รวมถึงผลด้าน immunohistochemistry ของ ฮีสตามีน, substance P, ซีโรโทนิน, VEGF และ VEGF receptors โดยใช้วิธีวิเคราะห์แบบปิดสองด้าน (double-blind quantitative) เพื่อนับจำนวน mast cell ที่ย้อมติดสี VEGF และเทียบกับจำนวน mast cell ใน secretory meningioma โดยพยาธิแพทย์ 2 ท่าน

**ผลการศึกษา:** ผลที่ได้ไม่พบ immunoreactivity ของ histamine หรือ substance P ในเนื้อเยื่อเนื้องอกหรือใน mast cell แต่พบลักษณะการติดสีของซีโรโทนินใน mast cell ส่วนการติดสีของ VEGF ใน mast cell จะมีเนื้อที่หายจากการศึกษาข้อมูลเบื้องต้น เนื้องอกที่มีภาวะ peritumoural edema ระดับปานกลางถึงรุนแรงมีลักษณะ mast cell ที่ย้อมติดสี VEGF ใน mast cell มากกว่า 50% ของ VEGF

**สรุป:** เนื้องอก secretory meningioma มีจำนวน mast cell เพิ่มขึ้นนอกจากนี้ VEGF และซีโรโทนินใน mast cell อาจจะมีส่วนเกี่ยวข้องกับกระบวนการทางพยาธิวิทยาของ vasogenic brain oedema ดังนั้นข้อมูลเริ่มต้นที่ศึกษานี้แสดงความสัมพันธ์ผลทางรังสีวิทยาที่พบภาวะสมองบวม และจำนวนที่เพิ่มขึ้นของ mast cell ที่ย้อมติดสี VEGF

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