Virchows Arch (2000) 436:131–137

ORIGINAL ARTICLE

Jean-François Mosnier · Anne Gentil Perret
Jean-Yves Scoazec · Jacques Brunon

Expression of β2 integrins and macrophage-associated antigens in meningeal tumours

Received: 14 April 1999 / Accepted: 15 July 1999

Abstract This study assessed the expression of leukocyte integrins and macrophage-associated antigens in meningiomas. Fourteen benign meningiomas, ten atypical/anaplastic meningiomas, two hemangiopericytomas and one solitary fibrous tumour (SFT) were included. Frozen sections were immunostained using antibodies directed against leukocyte integrins, CD68, CD14, CD2, CD1a, DRC1 and CD34. Their expression was evaluated semi-quantitatively. Ki67 positive cells were counted. Arachnoid membranes served as controls. Arachnoid cells expressed the β2-integrin subunit and KP1. Beta2 was detected in the tumour cells of 14 meningiomas. In nine cases, this was associated with an α-integrin subunit. There was no statistical difference in the expression of β2 between benign and atypical/anaplastic meningiomas. KP1 was constantly expressed by the tumour cells of meningiomas. It was not expressed by other meningeal tumours. CD34 was detected in the fibrous meningiomas, hemangiopericytomas and the SFT. In each tumour, macrophages were more numerous than T lymphocytes. There was no statistical difference in the density of macrophages and T lymphocytes between the benign and atypical/anaplastic meningiomas. There was no correlation between the Ki67 proliferation index and macrophage infiltration. Meningiomas, through the expression of leukocyte antigens, have a very particular phenotype. The expression of β2 integrins could play a role in the attraction of immunocompetent cells in the stroma of meningiomas.

J.-F. Mosnier (✉) · A. Gentil Perret
Service d'Anatomie Pathologique, Hôpital de Bellevue,
Boulevard Pasteur, F-42023 Saint-Etienne cedex 2, France
e-mail: jean.francois.mosnier@wanadoo.fr
Tel.: +33-4-77427734
Fax: +33-4-77420916

J. Brunon
Service de Neurochirurgie, Hôpital de Bellevue, Saint-Etienne, France

J.-Y. Scoazec
Service d'Anatomie Pathologique, Hôpital Edouard Herriot, Lyon, France

Key words Adhesion molecule · Integrins · Meningiomas · Macrophages · Immunohistochemistry

Introduction

Integrins are expressed as heterodimers in which one of at least 14 α subunits is noncovalently associated with one of at least 8 β subunits to form a functional receptor [14]. The β2-integrin family is known as the leukocyte integrins because their expression is believed to be limited to white blood cells. This family is composed of lymphocyte function antigen (LFA)-1 (αLβ2), Mac-1(αMβ2) and p150,95 (αXβ2). LFA-1 is one of the most important adhesion molecules contributing to cell–cell adhesion between lymphocyte–lymphocyte, lymphocyte–macrophage, or leukocyte–vascular endothelial cell during immune response or inflammation. Mac-1 and p150,95 are particularly important in adhesion of myeloid cells to other cells and to ligands that become insoluble during activation of the complement and clotting cascades [29].

Arachnoid cells have been described as positive for the β2-integrin family using immunohistochemistry [25]. We were therefore prompted to analyse the expression of leukocyte integrins and macrophage-associated antigens in meningiomas thought to be derived from arachnoid cells. Meningiomas are frequently central nervous system tumours and raise several histogenetic and prognostic problems. The histogenetic borderline between meningiomas and other meningeal tumours, such as hemangiopericytomas and solitary fibrous tumours, is still not well defined. Meningiomas exhibit a wide spectrum of histological patterns, ranging in aspect from principally fibroblastic to predominantly epithelioid [3, 18, 19], coexisting with phenotypic characteristics consistent with either mesenchymal or epithelial differentiation [1, 30]. It has also been reported that meningothelial cells have the ability to endocytose some exogenous particles, such as polyvinylpyrrolidone [6]. This raises the question of whether meningothelial cells, like macro-

phages, have the capacity for phagocytosis. Therefore, it appears that the exact histogenesis of the various types of tumour cells identifiable in meningiomas has not been definitely assessed.

Although meningiomas are considered as benign tumours, almost 15% of them are recurrent, while metastases are exceedingly rare [3]. Histologically, lymphocytes, monocytes and macrophages appear as a major component of the meningioma stroma. They occur in variable numbers. The factors regulating their attraction is currently unknown. Leukocyte infiltration might be of biological significance when using histological evaluation to predict meningioma outcome [2, 28]. The single most important factor in the clinical outcome of meningiomas is probably the localisation and resectability of the tumour [18]. However, some histological findings have been associated with a higher risk of recurrences [15, 16, 21]: invasion of the underlying brain tissue, a high degree of cellularity and cytological features of malignancy, including aneuploidy, mitotic figures, large prominent nucleoli and the presence of necrotic areas [5, 7, 9, 22].

The aim of this study was therefore to determine the potential value of β2 integrins and macrophage-associated antigens as cell lineage, diagnostic and prognostic markers in meningiomas and to assess their functional role. For this purpose, we designed an immunohistochemical study to analyse the pattern of expression of the β2 integrins in (a) the tumour cells of a series of meningiomas representative of the various histological subtypes of this group of tumours and (b) the immunocompetent cells constituting the stroma of meningiomas.

Material and methods

Patients

Twenty-seven patients with meningeal tumours were included in the study. There were 17 women and 10 men. Their age ranged from 25 years to 72 years (mean 54.9 years). The tumours removed for diagnostic purposes were systematically divided into two parts. The first part was processed for routine histological examination. The remainder was immediately snap-frozen in liquid nitrogen for immunohistochemical study. The tumours included 24 meningiomas, 1 solitary fibrous tumour and 2 hemangiopericytomas. The three latter tumours were included in the work as recurrent meningeal tumours following meningiomas from 6 years to 20 years after the initial removal. To compare the expression of the different markers assessed in normal arachnoid tissue, normal dura mater and meningeal tumours, three samples of dura mater and arachnoid tissue were taken during autopsies performed within 6 h post-mortem.

Histological study

For histological examination, tissues were fixed in 10% neutral buffered formalin. Three-micron thick sections were stained with hematoxylin–eosin–safran. Meningiomas were classified using standard histological criteria [19], as follows. Fibrous meningiomas are composed of interlacing bundles of long narrow spindle cells, with some degree of whorl formation and possible psammoma bodies. Meningothelial meningiomas are characterised by sheets of polygonal tumour cells, with connective tissue fibres confined to the vascularised trabeculae that intersect the tumour dividing it into lobules of variable sizes and shapes. Transitional meningiomas were characterised by the formation of whorls, in which the cells are closely wrapped around each other, with a small blood vessel or psammoma body sometimes forming the core of the whorls. The psammomatous meningiomas represent a variant of transitional meningioma. They result from the hyalinisation and subsequent calcification of the cellular whorls. Secretory meningiomas represent another variant of transitional meningioma. These are characterised by the presence of foci of glandular metaplasia and eosinophilic hyaline inclusions.

The following histopathological features were recorded for each case of meningioma to evaluate its histological prognosis index: mitotic activity; small cell formation (high nuclear to cytoplasmic ratio), macronucleoli, sheeting (patternless architecture), hypercellularity and areas of tumour cell necrosis. The tumours were classified into three groups: benign, atypical and anaplastic meningiomas. Atypical and anaplastic meningiomas were classified following the definition of the World Health Organization [19]. Invasion of dura, bone and brain were systematically assessed. However, invasion alone was not sufficient to qualify a tumour as atypical or anaplastic. Hemangiopericytomas were considered as sarcomas [19].

Immunohistochemical study

Serial sections from frozen tissue blocks were cut and stained using a three-step immunoperoxidase technique as described by Mason and Sammons [23] performed on serial sections using specific primary monoclonal antibodies directed against: αL-integrin subunit (clone MHM24, dilution 1:100; Dako, Glostrup, Denmark), αM-integrin subunit (clone Leu-15, dilution 1:25; Beckton Dickinson, Mountain View, Calif.), αX-integrin subunit (clone KB90, dilution 1:25; Dako), β2-integrin subunit (clone 7E4, dilution 1:50; Immunotech, Marseille, France), CD68 macrophages (clone KP1, dilution 1:50; clone EBM11, dilution 1:20; and clone HAM56, dilution 1:1; all from Dako), CD14 monocytes (clone TUK 14, dilution 1:10; Dako), CD2 T lymphocytes (clone MT910, dilution 1:100; Dako), CD1a interdigitating dendritic cells (clone Leu-1, dilution 1:100; Beckton Dickinson), follicular dendritic cells (clone DRC-1, dilution 1:25; Dako), CD34 progenitor cells (clone BIRMA-K3, dilution 1:10; Dako) and the formalin-resistant epitope of Ki 67 (clone Mib-1, dilution 1:50; Immunotech).

Five-micron thick cryostat sections were dried overnight at room temperature and fixed for 10 min in cold acetone before use. After rehydration in Tris buffer, tissue sections were incubated for 40 min with primary monoclonal antibodies diluted in Tris buffer. Sections were then sequentially incubated for 30 min with peroxidase-labelled species-specific anti-immunoglobulin antibodies. Peroxidase-labelled rabbit anti-mouse immunoglobulin (Dako) and swine anti-rabbit immunoglobulin (Dako) were diluted 1:20 in Tris buffer. The colour reaction product was developed using the Graham and Karnovsky method [13]. Peroxidase activity was revealed using 3.3'- diaminobenzidine (Sigma Chemical Co, St Louis, Mo.). A light counter-coloration was obtained by staining the section with Harris' hematoxylin for 60 s. Negative controls were set up for each immunostaining procedure omitting the primary antibody.

Given the results obtained from the frozen tissue, sections from paraffin-wax-embedded blocks were then cut and stained using the same three-step immunoperoxidase technique with the KP1 monoclonal antibody but without the retrieval antigen technique.

Semi-quantitative analysis

The expression levels of αM-, αX-, αL-, β2-integrin subunits, KP1, EBM11, HAM56 and CD34 on tumour cells and macrophages were evaluated using a semi-quantitative grading system based on a four-point scale representing the proportion of positive cells in each case. For tumour cells, the grades were defined as

follows: 0, no staining; 1+, staining of <10% of tumour cells; 2+, staining of 10–50% of tumour cells; and 3+, staining of >50% of tumour cells. For macrophages, the grades were defined as follows: 0, no staining; 1+, slight infiltration; 2+, moderate infiltration; and 3+, heavy infiltration. The macrophages filling the necrotic areas were not included in this evaluation. The labelling index for Ki-67 was expressed as a percentage and determined from the number of positive-staining nuclei per 1000 tumour cells. Only nuclear staining was accepted as being positive. Several fields with the highest labelling were chosen for evaluation. Statistical analysis was performed using Spearman's correlation tests and Student's *t*-tests. $P<0.05$ was considered to be statistically significant.

Results

Histological results

The primary meningeal tumours included 4 fibrous meningiomas, 3 transitional meningiomas, 12 meningothelial meningiomas, 3 secretory meningiomas, 1 oncocytic meningioma [27], 1 microcystic meningioma, 1 meningeal solitary fibrous tumour and 2 hemangiopericytomas. A psammomatous pattern was observed in two transitional meningiomas. Tumours were classified as atypical meningiomas in nine cases and as anaplastic (malignant) meningiomas in three. The three anaplastic meningiomas showed the histological patterns of meningothelial meningiomas. Ten meningiomas showed invasion of the adjacent tissues: six tumours had invaded the brain parenchyma and six had invaded the bone, muscles or skin. The hemangiopericytomas were recurrent tumours.

Immunohistochemical results

The main quantitative data of this study are summarised in Table 1.

Arachnoid membrane and dura mater

Normal arachnoid cells expressed the β2-integrin subunit (Fig. 1). The superficial leptomeningeal cells were more intensely immunostained for the β2-integrin subunit than the leptomeningeal cells of the inner zone. They did not express αL- or αX-integrin subunits. All these cells, whatever their location in the arachnoid membrane, strongly expressed KP1 (Fig. 2). CD34 was only expressed by endothelial cells lining the vessels of the arachnoid membrane. In normal dura mater, only rare stellate cells were immunolabelled for αM- and β2-integrin subunits scattered between collagen fibres. These cells were also immunostained for KP1. Numerous spindle cells intermingled with collagen fibres were CD34 positive. The fibrous tissue also showed slight immunostaining for CD34.

Table 1 Main data of the meningeal tumours included in the study. *SFT* solitary fibrous tumour; *HPC* hemangiopericytoma

No.	Histological type	Grade	Mib-1	β2 integrin (Tumour cells)	EBM11 (Stroma)	CD14 Stroma)	CD2 (Stroma)
1	Meningothelial	1	2.9	1	3	3	2
2	Meningothelial	1	1.9	0	1	2	1
3	Meningothelial	1	3.8	0	1	1	1
4	Secretory	1	–	0	3	2	2
5	Fibrous	1	3.8	3	3	3	2
6	Fibrous	1	1.6	2	-	3	2
7	Meningothelial	1	2.6	0	2	1	1
8	Secretory	1	0.6	1	–	2	1
9	Fibrous	1	2.8	1	2	2	1
10	Transitional	1	1.5	2	3	3	2
11	Meningothelial	1	0.4	0	1	1	1
12	Secretory	1	2.5	0	–	1	3
13	Oncocytic	1	2.8	0	3	3	2
14	Meningothelial	1	2.7	3	3	3	–
Mean			2.5	0.92	2.2	2.1	1.6
15	Meningothelial	2	4.8	1	1	1	1
16	Fibrous	2	–	2	–	2	–
17	Transitional	2	–	1	3	3	1
18	Microcystic	2	11.2	0	3	3	2
19	Meningothelial	2	9.0	0	2	1	1
20	Transitional	2	10.2	2	3	2	1
21	Meningothelial	2	10.5	1	1	1	1
22	Anaplastic	3	17	0	–	2	2
23	Anaplastic	3	9.6	1	2	2	1
24	Anaplastic	3	8.4	1	–	3	3
Mean			10	0.9	2.1	2.0	1.4
25	SFT	2	–	0	2	1	1
26	HPC/anaplastic	4	–	0	–	–	1
27	HPC	4	6.2	0	–	3	3

Tumour cells of meningeal tumours

The β2-integrin subunit was detected within the tumour cells in 14 of the 24 meningiomas studied (58%): 6 of the 12 meningothelial meningiomas, all of the 4 fibrous meningiomas (Fig. 3), all of the 3 transitional meningiomas and 1 of the 3 secretory meningiomas. There was no statistical difference in the β2-integrin subunit expression by the tumour cells when considering either benign meningiomas versus atypical and anaplastic meningiomas or meningiomas associated with bone, muscle and brain invasion and those meningiomas without invasion. The hemangiopericytomas and the solitary fibrous tumour did not express the β2-integrin subunit. The immunodetection of the β2-integrin subunit in the tumour cells was associated with that of the αM-integrin subunit in seven meningiomas, αL-integrin subunit in five meningiomas and αX-integrin subunit in four meningiomas. The β2-integrin subunit was associated with the expression of more than one integrin subunit in five meningiomas. In the five remaining cases, no α-integrin subunit was associated with the expression of the β2 integrin.

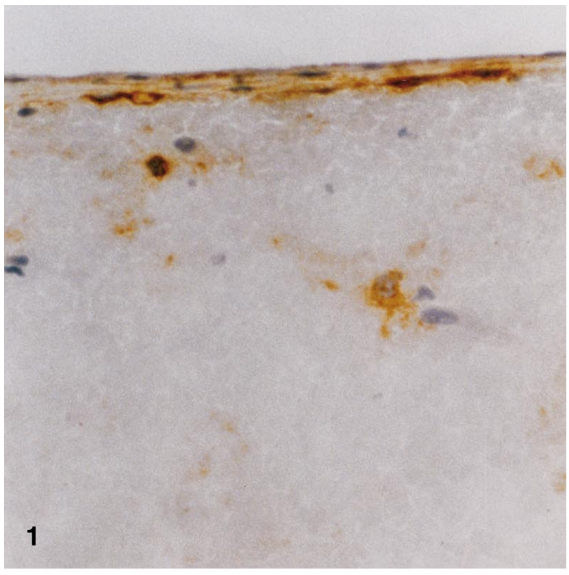
KP1 was expressed by all of the 24 meningiomas studied (100%). In most cases, the cytoplasm of nearly all the tumour cells was strongly immunolabelled (Fig. 4). One of the two hemangiopericytomas was also immunostained for KP1. The solitary fibrous tumour was KP1 negative. CD68 antigens other than KP1 were also expressed by the tumour cells of some meningiomas. EBM11 was detected within the cytoplasm of tumour cells in 6 of the 21 meningeal tumours studied (28%). There were two fibrous meningiomas, one transitional meningioma, one microcystic meningioma and one secretory meningioma. HAM56 was detected within the cytoplasm of tumour cells in 5 of the 18 meningeal tumours studied (27%): three meningothelial meningiomas, one fibrous meningioma and the solitary fibrous tumour. CD14 was detected within the tumour cell cytoplasm of only 4 of the 27 meningeal tumours (15%): two meningothelial meningiomas, one secretory meningioma and one hemangiopericytoma. Finally, the tumour cells of the 11 meningeal tumours expressed at least two macrophage-associated antigens. One tumour expressed all the macrophage-associated antigens studied; this was a recurrent atypical meningothelial meningioma. No tumour cell from a meningioma was immunolabelled for CD1a and DRC-1. CD34 was expressed by four meningeal tumours (15%): two fibrous meningiomas, the KP1-negative hemangiopericytoma and the solitary fibrous tumour. All the tumour cells from one hemangiopericytoma and the solitary fibrous tumour strongly expressed CD34, whereas only about 30% of spindle tumour cells of fibrous meningiomas expressed this antigen. Ki-67 labelling ranged from 0.4% to 17.0% (mean 5.38%, median 3.35%) in whole meningiomas. There was a significant correlation between Ki-67 proliferation index and the histological grade of meningiomas (Spearman's correlation test: $P<0.001$).

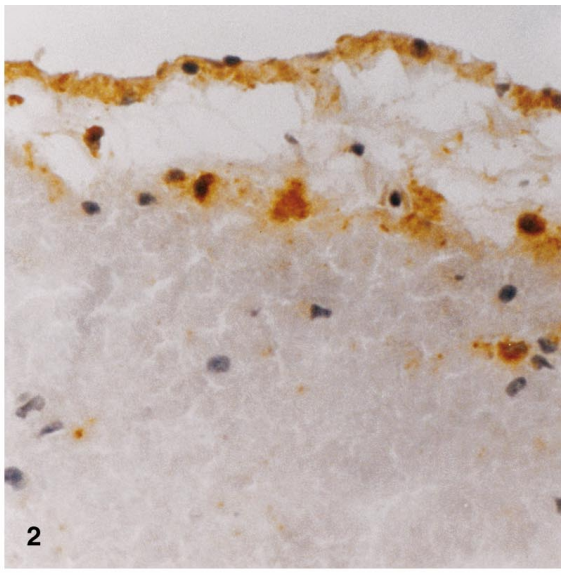
Stroma

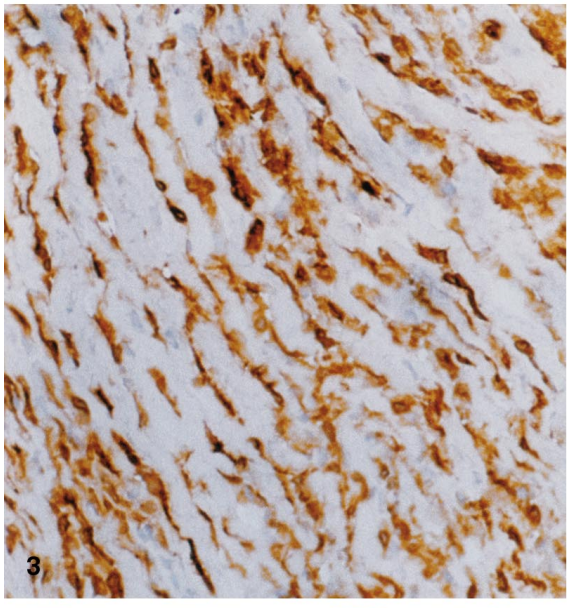
Macrophages were present in all the meningiomas, located between the tumour cells. They were immunostained for EBM11, HAM 56, CD14 and β2-integrin subunit. Given the strong immunoreactivity of meningiomas to KP1, macrophages lying between the tumour cells cannot be reliably detected using this antibody. The macrophages located between tumour cells displayed the morphological features of stellate cells (Fig. 5). The number of macrophages that immunolabelled for EBM11, HAM56, CD14 and β2-integrin subunit was similar in any given meningioma. Numerous macrophages filled tumorous necrotic areas of atypical and anaplastic meningiomas.

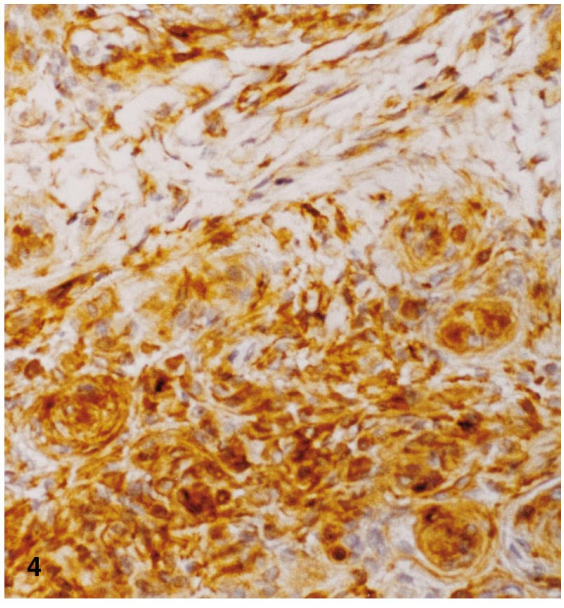
The macrophage densities were different in the meningiomas studied. The densities of the CD14-positive monocytes and macrophages were significantly lower in meningothelial meningiomas than in meningiomas with spindle tumour cells, i.e. transitional and fibrous meningiomas (Student's *t*-test: $P=0.03$). There were numerous macrophages between the tumour cells of hemangiopericytomas. They were less numerous in the solitary fibrous tumour. Monocytes and macrophages were more numerous than CD2-positive T cells in all meningiomas. CD2-positive T cells were detected between the tumour cells or around the vessels in all the meningiomas studied. Their density varied. Immune cells in the same tumour that immunolabelled for the αL-integrin subunit (LFA-1) were less numerous than those that immunolabelled for the β2-integrin subunit. These cells essentially had the morphology of lymphocytes. A few macrophages with the morphology of stellate cells, located between the tumour cells, were immunostained for αL-integrin subunit in some meningiomas. Most of the stellate cells located between the tumour cells were immunostained for αM-integrin subunit (Mac-1). Monocytes and polymorphonuclear leukocytes around the vessels and within their lumen were immunostained for αM (Mac-1) and αX (pg 150, 95), whereas the lymphocytes were immunostained for the αL-integrin subunit (LFA-1).

There was no statistical difference in the densities of CD2-positive T cells in either benign meningiomas or atypical and anaplastic meningiomas. Neither was there any statistical difference in the density of macrophages detected in atypical and anaplastic meningiomas or benign meningiomas. The histological findings of tumourous necrosis and the infiltration of adjacent tissue, i.e. bone, muscle and brain, were not associated with a statistical increase in the densities of β2, EBM11 and CD14-positive immunocompetent cells infiltrating the tumours. Although there was a strong correlation between the histological grade of the meningiomas and the Ki-67 proliferation index, there was no correlation between this index and macrophage infiltration.









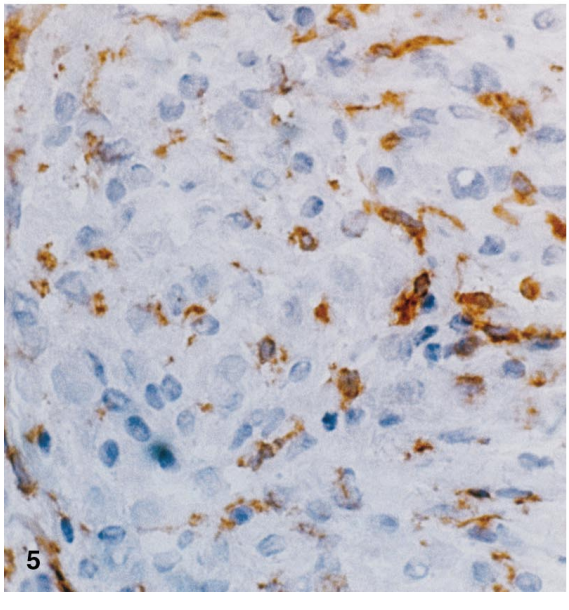


Fig. 1 Expression of β2-integrin subunit by arachnoid membrane (frozen section, β2-integrin subunit antibody, original magnification ×40)

Fig. 2 Expression of KP1 by arachnoid membrane (frozen section, KP1 antibody, original magnification ×40)

Fig. 3 Expression of β2-integrin subunit by most of tumour cells of a fibrous meningioma (frozen section, β2-integrin subunit antibody, original magnification ×20)

Fig. 4 Expression of KP1 by all the tumoral cells of a meningothelial meningioma (frozen section, KP1 antibody, original magnification ×40)

Fig. 5 Presence of some macrophages expressing EBM11 between tumoral cells of a meningothelial meningioma (frozen section, EBM11 antibody, original magnification ×40)

Discussion

It is difficult to explain why β2-integrin subunits and KP1 are expressed on leptomeningeal cells and their counterpart tumours, since the expression of these molecules is considered to be limited to white blood cells. This expression could be associated with some properties of meningeal cells, such as pinocytosis and phagocytosis [11]. KP1 is a glycoprotein expressed by granulocytes, monocytes and macrophages [26]. This antigen is clustered together with EBM11, HAM56, KiM6 as CD68. It recognises a 110-kDa glycoprotein, although the predicted mass of its polypeptide backbone is only 35 kDa. Most of the molecular mass of this glycoprotein is therefore thought to consist of carbohydrate [26]. The exact function of CD68 remains undefined; however, based on the structural homology between the predicted CD68 protein sequence and human lamp-1, a role in lysosomal function has been proposed [12].

The capacity of meningioma cells for phagocytosis has been demonstrated in culture, and meningioma cells have the capacity to endocytose particles of polyvinylpyrrolidone [6, 11]. Particles have been seen to be taken into lysosomal cavities in the perinuclear regions of tumour cells [6]. However, there is a striking discrepancy between the high level of KP1 expression and the inconstant ultrastructural detection of lysosomal granules in the tumour cells of meningiomas [17]. Moreover, although KP1 is known to recognise a formalin-resistant epitope [26], it is not always expressed by formalin-fixed paraffin-embedded meningiomas or arachnoid membranes. It has recently been suggested that KP1 could be present not only in the microsomal, subcellular fraction but also at the surface membrane of macrophages [12]. Epitopes recognised by KP1 might therefore be present principally at the surface of normal leptomeningeal cells and the tumour cells of meningiomas, since it is well known that these epitopes are destroyed by the paraffin-wax embedding process. Meningeal cells appear different to follicular dendritic cells and interdigitating reticular cells because they do not express their specific antigens DRC-1 and CD1a. It must finally be emphasised that the myelomonocytic antigen KP1 has recently been demonstrated to be present in other neurally derived tumours, such as granular cell tumours, schwannomas, melanomas and neurothekeomas [10, 20, 24]. It has also been suggested that schwann cells might acquire immunoreactivity for CD68 in parallel with their acquisition of lysosomes during phagocytosis of myelin.

We included in this study two recurrent meningeal tumours with histological findings of hemangiopericytomas – one expressed CD34 but not KP1, whereas the other was CD34 negative and KP1 positive. This raises the question of whether all meningeal tumours with histological findings of hemangiopericytomas are genuine hemangiopericytomas. Meningeal and peripheral hemangiopericytomas are currently considered as constantly immunoreactive for CD34 [4, 32]. Some fibrous meningiomas also show CD34 immunoreactivity. Our study shows that KP1 is expressed by all types of meningiomas except meningeal hemangiopericytomas. A variant of recurrent anaplastic meningiomas is constituted of small tumour cells growing in solid sheets associated with a focal hemangiopericytoma-like pattern of growth [8]. The presence of such hemangiopericytoma-like areas in occasional aggressive meningiomas is not surprising, as this growth pattern is non-specific and notoriously present in a number of soft-tissue sarcomas. We concluded that the meningeal tumour that is KP1-positive and CD34-negative, included in this study as a hemangiopericytoma, is probably an anaplastic meningioma with a hemangiopericytoma-like pattern.

This study shows that the stroma of meningiomas is essentially composed of CD34-positive vessels and immunocompetent cells intermingled with tumour cells, i.e. lymphocytes and macrophages/monocytes. The expression of β2-integrin subunits by tumour cells could explain, at least in part, the attraction of macrophages/monocytes and lymphocytes in the stroma of meningiomas, since these integrins play a major role in leukocyte localisation in vivo. The observation that the density of macrophage/monocytes is higher in those fibrous meningiomas that more strongly express β2-integrin subunits than in other meningiomas is an argument for this hypothesis. In contrast to Bo et al. [2] and Rossi et al. [28], we did not observe any correlation between macrophage density and histological signs of aggressiveness. It would be interesting to study such a correlation because the stroma is currently thought to play an important role in several steps of tumour behaviour through the development of their vascularisation [31]. Macrophage involvement in tumour vascularisation could occur through their release of angiogenic factors [31].

To summarise, this immunohistochemical study shows that normal leptomeningeal cells and meningiomas express leukocyte-associated antigens such as β2-integrin subunits and CD68. Although their precise role at the surface of leptomeningeal cells still needs to be determined, it could be suggested that β2 integrins play a role in the attraction of immunocompetent cells in the stroma of meningiomas. Their expression does not appear to be correlated with the behaviour of these tumours.

References

1. Artlich A, Schmidt D (1990) Immunohistochemical profile of meningiomas and their histological subtypes. Hum Pathol 21:843–849
2. Bo L, Mork SJ, Nyland H (1992) An immunohistochemical study of mononuclear cells in meningiomas. Neuropathol Appl Neurobiol 18:548–558
3. Burger PC, Scheithauer BW (1994) Tumours of the central nervous system. Armed Force Institute of Pathology, Washington DC
4. Chaubal A, Paetau A, Zoltick P, Miettinen M (1994) CD34 immunoreactivity in nervous system tumours. Acta Neuropathol 88:454–458
5. Chen WYK, Liu HC (1990) Atypical (anaplastic) meningioma: relationship between histological features and recurrence. A clinicopathological study. Clin Neuropathol 9:74–81

6. Chen WYK, Kepes JJ, Teglbjaerg PS (1985) Intracellular mucoid changes in tumour cells of meningiomas: a manifestation of polyvinylpyrrolidone (PVP) effect on tissues with mesenchymmal characteristics. J Neuropathol Exp Neurol 44: 606–616
7. Christensen D, Larsen H, Klinken L (1983) Prediction of recurrence in meningiomas after surgical treatment. Acta Neuropathol 63:130–134
8. d'Amore ESG, Manivel JC, Sung JH (1990) Soft-tissue and meningeal hemangiopericytomas: an immunohistochemical and ultrastructural study. Hum Pathol 21:414–423
9. De la Monte SM, Flickinger J, Linggood RM (1986) Histopathological features predicting recurrence of meningiomas following (sub)total resection. Am J Surg Pathol 10:836–843
10. Facchetti F, Bertalot G, Grigolato PG (1991) KP1 (CD68) staining of malignant melanomas. Histopathology 19:141–145
11. Feurer DJ, Weller RO (1991) Barrier functions of the leptomeninges: a study of normal meninges and meningiomas in tissue culture. Neuropathol Appl Neurobiol 17:391–405
12. Fukuda M (1991) Lysosomal membrane glycoproteins. Structure, biosynthesis, and intracellular trafficking. J Biol Chem 266:21327–21330
13. Graham RC, Karnovsky MJ (1966) The early stages of absorption of horseradish peroxidase in the proximal tubules of mouse kidney: ultrastructural cytochemistry by a new technique. J Histochem Cytochem 14:291–302
14. Hynes RO (1992) Integrins: versatility, modulation, and signaling in cell adhesion. Cell 69:11–25
15. Jääskeläinen J, Haltia H, Laasonen E, Wahlström T, Valtonen S (1985) The growth rate of intracranial meningiomas and its relation to histology: an analysis of 43 patients. Surg Neurol 24:165–172
16. Jääskeläinen J, Servo A, Haltia H, Wahlström T, Valtonen S (1985) Intracranial hemangiopericytoma: radiology, surgery, radiotherapy, and outcome in 21 patients. Surg Neurol 23: 227–236
17. Kepes JJ (1961) Electron microscopic studies of meningiomas. Am J Pathol 39:499–510
18. Kepes JJ (1986) Presidential address: the histopathology of meningiomas. A reflection of origins and expected behaviour? J Neuropathol Exp Neurol 45:95–107
19. Kleihues P, Burger PC, Scheithauer BW (1993) Histological typing of tumours of the central nervous system. In: WHO, International histological classification of tumours. Springer, Berlin Heidelberg New York, pp 33–37
20. Kurtin PJ, Bonin DM (1994) Immunohistochemical demonstration of the lysosome-associated glycoprotein CD68 (KP-1) in granular cell tumors and schwannomas. Hum Pathol 255:1172–1178
21. Ludwin SK, Rubinstein LJ, Russel DS (1975) Papillary meningioma: a malignant variant of meningioma. Cancer 36: 1363–1373
22. MacLean CA, Jolley D, Cukier E, Giles G, Gonzales MF (1993) Atypical and malignant meningiomas: importance of micronecrosis as a prognostic indicator. Histopathology 23: 349–353
23. Mason DY, Sammons RE (1979) The labeled antigen method of immunoenzymatic staining. J Histochem Cytochem 27: 832–840
24. Pasquier B, Barroud R, Peoc'h M, Pinel N, Bost F, Le Marc'Hadour D, Pasquier D (1994) Le neurothécome: revue générale à propos d'une observation anatomoclinique avec étude immunohistochimique et ultrastructurale. Arch Anat Cytol Pathol 42:133–140
25. Paulus W, Baur I, Schuppan D, Roggendorf W (1993) Characterization of integrin receptors in normal and neoplastic human brain. Am J Pathol 143:154–163
26. Pulford KAF, Rigney EM, Micklem KJ, Jones M, Stross WP, Gatter KC, Mason DY (1989) KP1: a new monoclonal antibody that detects a monocyte/macrophage associated antigen in routinely processed tissue sections. J Clin Pathol 42: 414–421
27. Roncaroli F, Riccioni L, Cerati M, Capella C, Calbucci F, Trevisan C, Eusebi V (1997) Oncocytic meningioma. Am J Surg Pathol 21:375–382
28. Rossi ML, Cruz-Sanchez F, Hughes JT, Esiri MM, Coakham HB (1988) Immunohistological study of the cellular response in meningiomas. J Clin Pathol 41:314–319
29. Springer TA (1990) Adhesion receptors of the immune system. Nature 346:425–434
30. Theaker M, Gatter KC, Esiri MM, Fleming KA (1986) Epithelial membrane antigen and cytokeratin expression by meningiomas: an immunohistological study. J Clin Pathol 39:435–439
31. Wernert N (1997) The multiple roles of tumour stroma. Virchows Arch 430:433–443
32. Winek RR, Scheithauer BW, Wick MR (1989) Meningioma, meningeal hemangiopericytoma (angioblastic meningioma, peripheral hemangiopericytoma, and acoustic schwannoma). A comparative immunohistochemical study. Am J Surg Pathol 13:251–261