RESEARCH ARTICLE

Meningeal Hemangiopericytomas and Meningomas: a Comparative Immunohistochemical and Genetic Study

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Abstract

Background: The meningeal hemangiopericytoma (MHPC) is a vascular tumor arising from pericytes. Most intracranial MHPCs resemble meningiomas (MNGs) in their clinical presentation and histological features and may therefore be misdiagnosed, despite important differences in prognosis. Materials and Methods: We report 8 cases of MHPC and 5 cases of MNG collected from 2007 to 2011 from the Neuro-Surgery and Histopathology departments. All 13 samples were re reviewed by two independent pathologists and investigated by immunohistochemistry (IHC) using mesenchymal, epithelial and neuro-glial markers. Additionally, we screened all tumors for a large panel of chromosomal alterations using multiplex ligation probe amplification (MLPA). Presence of the NAB2-STAT6 fusion gene was inferred by immunohistochemical staining for STAT6. Results: Compared with MNG, MHPCs showed strong VIM (100% of cases), CD99 (62%), bcl-2 (87%), and p16 (75%) staining but only focal positivity with EMA (33%) and NSE (37%). The p21 antibody was positive in 62% of MHPC and less than 1% in all MNGs. MLPA data did not distinguish HPC from MNG, with PTEN loss and ERBB2 gain found in both. By contrast, STAT6 nuclear staining was observed in 3 MHPC cases and was absent from MNG. Conclusions: MNG and MHPC comprise a spectrum of tumors that cannot be easily differentiated based on histopathology. The presence of STAT6 nuclear positivity may however be a useful diagnostic marker.

Keywords: Meningeal hemangiopericytoma - immunohistochemistry - NAB2-STAT6 fusion - molecular analysis

Asian Pac J Cancer Prev, **16 (16)**, 6871-6876

Introduction

Meningeal hemangiopericytoma (MHPC) is a malignant neoplasm which originates from meningeal capillary pericytes (Stout and Murray, 1942). It has been reported to represent 2 to 4% of meningeal tumors, comprising less than 1% of all intracranial tumors(Guthrie et al., 1989). Epidemiological studies reports that MHPC are rare tumors with lower average than meningiomas (MNGs) (Jazayeri et al., 2013) . Most intracranial MHPCs mimic MNGs in their clinical and histopathological presentation, as well as their immunohistochemical profile (Rajaram et al., 2004), and are hence often misdiagnosed.

Meningiomas are neoplasms arising from meningothelial cells of the meninges (Larijani et al., 2014). They constitute approximatively 13-26% of all intracranial tumours (Ozbayir et al., 2011). They are most often slow-growing benign tumors, however atypical or anaplastic tumors can be found (Ozbayir et al., 2011). Moreover, atypical anaplastic meningioma has diverse radiological manifestations and MRI technology has a certain diagnosis limitations (Wu et al., 2013).

However, MHPC metastasize outside the CNS in 25%-60% of cases, whereas meningiomas metastasize only occasionally (Rajaram et al., 2004). Given this important prognostic difference, the correct diagnosis and thus the appropriate treatment strategy should be adopted.

The recent WHO classification describes HPC, solitary fibrous tumours (SFT) and MNG as a new biomarkers has prompted us to look for potential differences in IHC. According to S.Barthelme et al. (2014) presence of the NAB2-STAT6 fusion gene distinguishes SFT from MHPC (Barthelmess et al., 2014). This fusion is not well described in MHPCs and has not been reported in the specific comparison between MNG and MHPC. Investigation of additional molecular markers in this differential diagnosis has also been lacking.

Materials and Methods

We investigated a cohort of 8 MHPCs and 5 MNGs from adults. MHPC were provided from 3 women and

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5 men; MNG patients were from 3 women and 2 men. Patients' ages ranged from 25 to 81 years. 7 of the 8 MHPC locations were supratentorial: 4 occipital, 2 frontal and 1 temporo-occipital. Only 1 MHPC was located in the cerebellum. MNG tumor location was supra-tentorial in 4 cases and infra-tentorial in 1 case. Clinical symptoms at diagnosis were variable: hemiparesis, disorientation, decreased visual acuity, and headache (Table 1).

Standard histology

Formalin-fixed paraffin-embedded tissue was sectioned at 4 μm and stained with haematoxylin and eosin and reviewed by two pathologists.

Immunohistochemistry

An immunohistochemical study was performed on formalin-fixed, paraffin-embedded tissue cut at 4μm using polyclonal antibodies (Table 2).

Immunohistochemistry for STAT6 was carried out as a surrogate for the NAB2-STAT6 fusion. Antigen retrieval was performed at 98°C with DAKO antigen retrival solution pH 6 for 20 min. Endogenous peroxidase activity

Table 1. Clinical and histopathological data of patients and their developping tumors

Patients #	Age at diagnosis (year)	Sexe	Tumor		
			location	subtype	grade
1	70	M	TP	MHPC	II
2	17	F	F	MHPC	II
3	61	M	O	MHPC	II
4	34	F	O	MHPC	III
5	46	M	F	MHPC	I
6	34	F	O	MHPC	III
7	52	M	C	MHPC	I
8	46	F	T	MNG/HPC	III
9	50	M	TO	MNG	III
10	81	M	NA	MNG	II
11	25	F	IE	MNG	II
12	65	F	P	MNG	II
13	45	M	F	MNG	II

*Footnotes: F: female, M: male, C: cerebellum, P: parietal, T: temporal, TP : temporo–parietal, F: frontal; O :Occipital , TO: temporo-occipital, NA: not available, IE: intradural extramedullar, MHPC: meningial hemangiopericytoma, MNG :meningioma

Table 2. Antibodies Results list and Methods in Immunohistochemical Analysis

Antigen	Antibody and manufacturers	Dilution	Antigen retrieval	Staining (%)	
				MHPC	MNG
EMA	Dako Clone E29	1:100	EDTA PH6	60%	37%
VIM	Dako Clone Vim 3B4	1:100	EDTA PH6	100%	50%
Bcl2	Dako Clone 124	1:50	EDTA PH6	87%	50%
CD56	Neomarker Clone 123C3D5	1:50	EDTA PH6	25%	40%
S100	Dako Clone	1:300	/	12%	40%
Synaptophysine	Neomarker Clone Rb-SP111-RM	1:200	EDTA PH6	0%	0%
P21	Novocastra Clone 4D10	1:40	EDTA PH6	62%	20%
P16	Dako Clone K334	1:50	EDTA PH6	75%	40%
CD34	Dako Clone Qbend 10	1:50	EDTA PH6	37%	40%
NSE	Dako Clone BBS/NC/V1H14	1:50	EDTA PH6	37%	80%
CD99	Novocastra clone HO36-1-1	1:20	EDTA PH9	62%	40%
ACE	Dako Clone 11-7	1:50	EDTA PH6	0%	0%
F8	Dako Clone F8/86	1:50	EDTA PH6	0%	0%
Des	Dako clone D33	1:50	EDTA PH9	0%	0%
GFAP	Dako Clone Poly ZCG23	1:300	EDTA PH6	0%	0%
KI67	Dako Clone MIB1	1: 300	EDTA PH6	27%	14%
STAT6	Santa Cruz (S-20; sc-621)	1: 300	EDTA PH6	37%	0%

Footnotes: (/) without antigen retrival

was blocked with 3% hydrogen peroxide in methanol. The detection system used was Novolink Polymer (Leica Microsystems, Newcastle Ltd) with diaminobenzidine as a chromogen. The slides were counterstained with hematoxylin.

DNA extraction

Tumor genomic DNA was extracted from either fresh tissue using a standard phenol:chloroform protocol, or FFPE tissues according to The QIAamp DNA FFPE Tissue kit according to the manufacturers protocol (QIAGEN).

Multiplex ligation probe amplification (MLPA)

MLPA is a multiplex PCR technique in which up to 45 specific sequences are simultaneously quantified in a single reaction. For this multigenic technique, a specifically designed set of probes was used to test for chromosomal abnormalities - SALSA MLPA Kits P105, P370 and P088 (MRC Holland, Amsterdam, The Netherlands).

Fragments were separated by electrophoresis on the ABI Prism 310 capillary genetic analyser. Data analysis was performed with "*GeneMarker®*" software (SoftGenetics). Thresholds to detect losses and gains of genetic material were set respectively at 0.75 and 1.25.

Results

Histology

Microscopically, MHPCs showed a variable cell proliferation rate and focal necrosis. All studied MNG showed a high cellular proliferation rate and are thus classified as a high grade MNG. The MHPC group showed oval and atypical cells with high vascularity. Areas presenting surrounding branched vessels exhibiting a staghorn pattern were specifically seen in MHPCs.

Table 3. Genetic and immunohistochemistry results

Tumor #		MLPA							
					CDKN2A	PTEN	EGFR	TP53	ERBB2
		1p36	19q13	7q36	9p21	10q26	11p11	17q	
MHPC	#1	NS	gain	NS	NS	Loss	NS	NS	NS
	#2	gain	NS	NS	NS	gain	gain	NS	NS
	#3	gain	gain	Loss	NS	NS	NS	NS	NS
	#4*	gain	gain	Loss	NS	Loss	NS	NS	NS
	#5	gain	gain	gain	NS	Loss	NS	NS	NS
	#6	gain	NS	Loss	NS	NS	NS	NS	NS
	#7	gain	NS	NS	NS	NS	NS	Loss	NS
	#8*	gain	gain	NS	NS	Loss	gain	NS	gain
MNG	#9	NS	NS	NS	NS	Loss	NS	NS	NS
	#10	gain	gain	NS	gain	Loss	gain	gain	gain
	#11*	NS	NS	NS	NS	Loss	NS	NS	gain
	#12	NS	gain	NS	loss	Loss	NS	NS	NS
	#13	gain	NS	NS	loss	Loss	gain	NS	NS
Tumor #		IHC							
		Antigen							
		VIM	Syn	ACE	F8	Des	GFAP	EMA	CD34
MHPC	#1	+++	-	-	-	-	-	-	+
	#2	+	-	-	-	-	-	-	-
	#3	+	-	-	-	-	-	+	+
	#4*	+	-	-	-	-	-	+f	-
	#5	+	-	-	-	-	-	-	-
	#6	++	-	-	-	-	-	+f	++
	#7	+++	-	-	-	-	-	+++	-
	#8*	+++	-	-	-	-	-	ND	++
MNG	#9	+	-	-	-	-	ND	+	++
	#10	+f	-	-	-	-	-	-	-
	#11*	+	-	-	-	-	-	++	-
	#12	ND	-	-	-	-	-	+	-
	#13	+	-	-	-	-	-	+f	+f

Tumor #		IHC							
		Antigen							
		CD99	Bcl2	P21	P16	CD56	S100	stat6	
MHPC	#1	-	+	-	+	-	-	-	
	#2	+	+	40%	+	+	-	-	
	#3	+	+	50%		ND	-	-	
	#4*	-	+	90%	+	-	-	n	
	#5	+	+	+	+	-	-	-	
	#6	+++	+	-	+f	-	-	n	
	#7	+	-	-	-	-	-	-	
	#8*	-	+	1%	-	-	ND	n/c	
MNG	#9	+	+	3%	++	+	-	-	
	#10	+	+	-	+	ND	+	-	
	#11*	-	-	1%	+f	+	+	-	
	#12	+	+f	++	-	-	-	-	
	#13	-	+	+	+	+	+	-	

Footnotes: MHPC: Meningial Hemaniopericytoma, MNG: meningioma, (NS): normal status, (-) : negative staining ,(+): weak positive staining, (++): moderate positive staining, (+++) : high positive staining, (+f) : focal staining, (n) : nuclear staining, (c) : cytoplasmic staining, (n/c): nuclear and cytoplasmic staining, ND : not determined. (*) : Tumor section with STAT6 staining presented in figure 1

Table 4. Hemangiopericytomas and Meningiomas histological description

Tumor #	Proliferation	Cell shape	Vascularity	Collagen	Mitosis	Necrosis	Tumor	
							Subtype	Grade
1	H	O,Fu	H	+	Rare	-	MHPC	II
2	Var	O,R	H	-	Frq	-	MHPC	II
3	H	O,Fu	H	-	Rare	+	MHPC	III
4	H	O	M	+	Rare	+	MHPC	III
5	H	O,Fu	H	+	Rare	+	MHPC	II
6	H	O	H	+	Rare	-	MHPC	III
7	H	O,R	/	-	Frq	-	MHPC	II
8	M	Fu	H	-	-	+	HPC,MNG	III
9	H	O	/	-	Frq	+	MNG	III
11	M	O	M	-	Rare	-	MNG	II
10	H	Fu,R	/	-	Frq	-	MNG	II
12	H	R	/	-	-	-	MNG	II
13	H	Fu	H	-	Frq	-	MNG	II

Footnotes: (H):high, (M): moderate, (/) : nothing to note, (Var): variable, (O): oval, (Fu) : fusiform, (R) : rounded, (-) : absent, (+): present, (frq) : frequent , (MHPC): meningial hemaniopericytoma, (MNG): meningioma

Mitoses were frequently observed in MNG but were rare in MHPC (Figure 1, suplementary Table).

Immunohistochemistry

No immunoreactivity was seen for ACE, F-VIII, Desmin, Synaptophysin and GFAP in any analysed samples. MHPCs express the VIM, CD34, CD99 and Bcl2 (#8,4,5,7 cases) in the neoplastic cells more than MNGs (#2,1,3,2). EMA expressing rates were higher in MNGs (#3) than MHPCs (#2) (Figure 1). p21 was positive in 62% of MHPCs and less than 1% in all MNGs.

Based on morphological and immunohistochemical staining features, a final diagnosis of anaplasic meningeal hemangiopericytoma was made in all 8 studied tumors.

STAT6 expression

As expected, the 5 MNGs were negative for STAT6 expression, used a surrogate for the NBA2-STAT6 fusion gene. Nuclear staining was exclusively present on 3 out of 8 MHPC specimens. 2 positive MHPCs specimens represent a first tumor and its relapse (tumor #4 and #6). The third positive MHPC for STAT6 was according to histology and IHC investigations set as an uncertain diagnosis case. The STAT6 labelling showed a focal area of nuclear positivity in addition to abundant cytoplasmic staining in the same tumor section (tumor # 8) (Figure 1).

Molecular analysis

We used a molecular approach based on copy

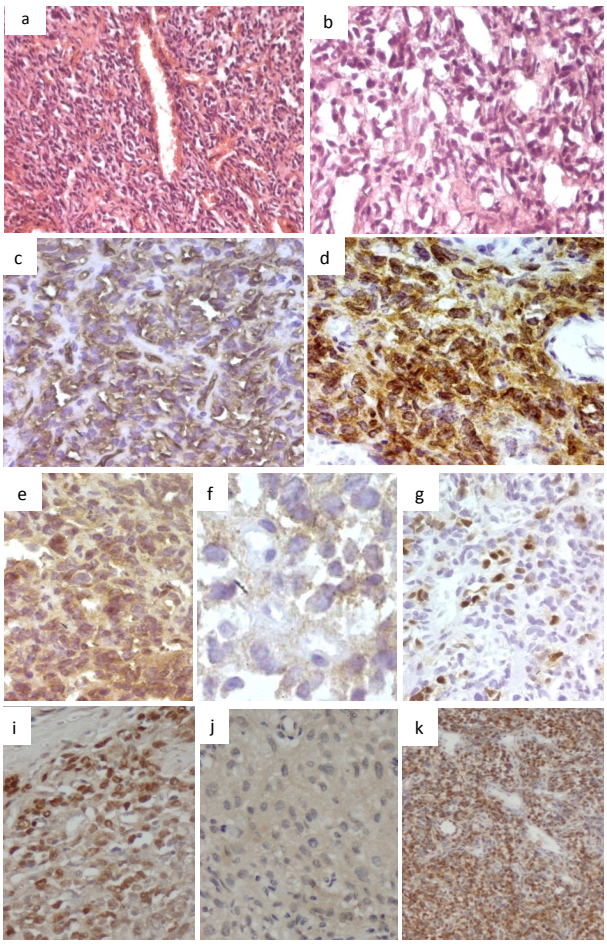

Figure 1. Histopathology of MHPC. a) HE staining x 200: proliferation of globular cells surrounding branched vessels exhibiting straghorn pattern; **b)** HE staining x 400: the tumoral cells show atypia and nuclear hyperchromasia; **c)** Anti-CD34 intense positivity of the tumor cells; **d)** Anti-bcl2 intense positivity of the tumor cells; **e)** Anti-CD99 mild positivity of the tumor cells; **f)** Anti-EMA weak positivity of the tumor cells; **g)** Anti-P16 nuclear positivity of the tumor cells; **i)** Anti STAT6 nuclear positivity of the HPC tumor cells (tumor # 4); **j)** Anti STAT6 negative stainig of the MNG tumor cells (tumor # 11); **k)** Anti STAT6 nuclear and cytoplasmic staining of the tumor cells (tumor # 8)

number analysis to investigate both MHPC and MNG. An overview of molecular results is included in Table 3.

Both MHPC and MNG presented alterations of 1p36 and ERBB2 regions, and had normal statuses of 3p, 7q3, 19q13. CDKN2A loss was exclusively detected on MNG samples. Of note, PTEN loss was present in both MHPCs (4 MHPC out of 8) and MNGs (3 MNG out of 5).

Discussion

Intracranial MHPC is a dural-based neoplasm that highly mimics MNGs. The World Health Organization has separated MHPCs from MNGs since 1993, and individualized MHPCs as a "*mesenchymal, non-meningothelial*" tumor (Chan et al., 2012). With the exception of MHPC clinical outcome, there are few distinguishing features between MHPC and MNG.

Chiechi et al reported that MHPC occurs in locations similar to MNG (Chiechi et al., 1996; Akiyama et al., 2004). They are found mostly at supratentorial, less frequently at infratentorial, very rarely intraventricular and even intraparenchymal locations have been reported (Muttaqin et al., 1991; Abrahams et al., 1999; Alen et al., 2001; Kuzeyli et al., 2003). Similarly, most of MHPC as well as MNG in our cases are in a supratentorial location.

The pathological features crucial for the diagnosis also remain the most controversial. Further, the immunoprofiles of MHPC and MNG were reported as slightly different (Shoji et al., 2002). The most important IHC markers thought to be diagnostically useful are EMA and CD34. The EMA is an epithelial marker reported positive in MNG but focal staining occurring in some MHPCs led to diagnostic uncertainty (Rajaram et al., 2004). CD34 is thought to be specific for MHPCs but was also reported to be controversial with a positive staining noted in MNG (Rajaram et al., 2004). However, Bcl-2 has been reported as very sensitive marker to MHPCs (Rajaram et al., 2004).

In our study, EMA as a highly sensitive meningothelial marker was found to be positive in 60% of our MNGs. Nonetheless, an EMA focal staining was observed in 33% of MHPCs. Thus EMA expression cannot exclude the diagnosis of MHPC. Bcl-2 was positive in 62% of MHPCs, however a focal weak signal was also observed in 40% of MNG. As reported by other studies CD99 proves to be another marker that MHPC strongly express (Rajaram et al., 2004). In our series it proved to be a sensitive marker with MHPC (62%) but still remains positive in MNG (40%). In fact, both CD99 and Bcl-2 highlight the extensive overlap between the two tumor groups.

In accordance with Shoji et al, the majority of MHPCs strongly express p21, whilst it is almost entirely absent from MNGs p21, is the product of the WAF1/CIP1/SDI1 gene and an inhibitor of cyclin-dependent kinases. It has been clearly demonstrated that prognostic significance of p21 is enhanced in combination with other apoptotic factors (i.e. p53) and associated with a better outcome (Shoji et al., 2002). The absence of p21 expression in MNG may be associated with their high grade.

We noted that the genetic profiles of MHPC and MNG were very similar except for CDKN2A loss predominantly present in MNGs. CDKN2A loss was previously described in anaplasic tumors and it matched with the high-grade histological description in our MNG samples (Bostrom et al., 2001).

ERBB2 belongs to the receptor tyrosine kinase family I. It has an important role in regulating the anti-apoptotic phosphatidyl inositol 3-kinase (PI3K)/protein kinase B (PKB)/AKT signalling pathway (Gilbertson et al., 1998; Elenius et al., 1999). ERBB2 is located on chromosome 17q11.2–q12, a region frequently gained in several tumors as found in our MNGs (de Bont et al., 2008).

PTEN is located at 10q23.3, a chromosomal region frequently implicated in tumor malignancy. In contrast to a previous report (Peters et al., 1998), we found PTEN loss in 3 MNG. This gene loss was also detected in 4 MHPCs and is therefore not specific to either entity.

In our study, both IHC markers and genetic profiles did not discriminate MNG from MHPC. A fusion gene between NAB2 and STAT6 has been recently identified as potential marker specific for SFT (Barthelmess et al.,

2014).

Based on Schweizer et al study, we use IHC staining with the STAT6 antibody that recognizes C-terminal portion of STAT6. STAT6 protein mainly localizes to in the cytoplasm whereas the NAB2 protein localizes to in the nucleus. In case of fusion between NAB2 and STAT6, the fusion protein preserves the C-terminal portion of STAT6 connected with the 3' portions of the NAB2 (UniProtKB Q15742). For this reason, if the fusion occurs we expect to find the STAT6 staining in the nucleus(Schweizer et al., 2013).

MHPC sections presented STAT6 nuclear staining in 3 samples, whereas MNG were all negative, adding more support to previous studies (Iwaki et al., 1988) that reported the presence of NAB2-STAT6 fusion gene more frequently in MHPCs then MNGs. This molecular difference could be attributed to distinctive tumor steam cell origin and/or tumorogenesis pathways. Our conclusions need to be followed up by an enlargement of our sample cohort.

Interestingly, a case with highly uncertain diagnosis presented high cell proliferation. According to the immunoprofile with CD34 and Bcl2 positivity, it is more likely consistent with MHPC but still uncertain. The STAT6 IHC results showed a focal area of nuclear staining in addition to abundant cytoplasmic staining in the same tumor section. This could provide a furthermore argument to propose the MHPC as a final diagnosis and show the utility of STAT6 in the differential diagnoses of such lesions.

Acknowledgements

We are grateful to all patients for their contribution. We also extend special thanks to all members of GETUC ''*Groupe d'Etude des Tumeurs Cerebrales*" and Glioma team at the Divisions of Molecular Pathology and Cancer Therapeutics at the Institute of Cancer Research in Sutton. UK.

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