Pathol. Oncol. Res. (2012) 18:383–389
DOI 10.1007/s12253-011-9456-x

RESEARCH

Wilms Tumor-1, Claudin-1 and Ezrin Are Useful Immunohistochemical Markers That Help to Distinguish Schwannoma from Fibroblastic Meningioma

Avninder Singh · Ashwani Kumar Mishra · Kris Ylaya · Stephen M. Hewitt · Karam Chand Sharma · Sunita Saxena

Received: 24 January 2011 / Accepted: 31 August 2011 / Published online: 10 September 2011

Abstract The aim of this study is to identify immunohistochemical (IHC) markers that can reliably separate schwannoma (SCHW) and fibroblastic meningioma (FM). We selected 106 cases of intracranial SCHW (n=56) and FM (n=50) and constructed a tissue microarray (TMA) of core diameter of 1.0 mm from archival formalin-fixed paraffin-embedded tissue. A TMA-IHC was performed using 14 antibodies. After IHC staining, 98 cores were found suitable for evaluation. The IHC staining was scored as 0–2+ (0, negative; 1+, weak and/or focal 2+ strong and/or diffuse positive). A discriminant analysis (DA) (Wilks'Lambda test) was performed to assess the relative importance of these biomarkers in classifying the two groups FM and SCHW. It showed that WT-1 (Wilks'λ 0.085, p<0.001), EMA (Wilks'λ 0.253, p<0.001), S100 (Wilks'λ 0.487, p<0.001), Claudin-1 (Wilks' λ 0.57, p< 0.001) and Ezrin (Wilks'λ 0.656, p<0.001), SPARC (Wilks'λ 0.751, p<0.01), NP-Y (Wilks'λ, 0.819, p<0.001) and EGFR (Wilks'λ 0.845, p=0.026) were some of the statistically significant markers that discriminated SCHW and FM. For sensitivity and specificity for SCHW the significant markers [Area under the curve (95% CI), p-value] by ROC analysis were WT-1 [0.990(0.000, 1.000), <0.001], S100 [0.880(0.808, 0.951), <0.001] while for diagnosing FM the most sensitive and specific markers were EMA [0.957(0.914, 1.000), <. 001], Claudin-1 [0.857(0.782, 0.932), <0.001] and ezrin [0.792(0.700,0.884),<0.001]. WT-1, Claudin-1 and Ezrin may be potentially useful immunohistochemical adjuncts to EMA and S100 that differentiate SCHW from FM

Keywords Biomarkers · Fibroblastic meningioma · Immunohistochemistry · Schwannoma · Tissue microarray

A. Singh (✉) · A. K. Mishra · S. Saxena
Safdarjung Hospital Campus,
National Institute of Pathology (ICMR),
Room 602, 6th floor,
New Delhi 110029, India
e-mail: dravninder@yahoo.co.in

K. Ylaya · S. M. Hewitt
TARP Lab, National Cancer Institute,
National Institutes of Health,
Bethesda, MD, USA

K. C. Sharma
Department of Neurosurgery, Safdarjung Hospital,
New Delhi, India

Introduction

SCHW and FM are usually distinguishable by their radiological and classic histomorphologic pattern on hematoxylin-eosin (HE) staining. However, in a small number of cases they might closely mimic one another especially when they are exclusively constituted by Antoni A areas or when nuclear palisading is not conspicuous. IHC markers routinely used to support the diagnosis of meningioma (MEN) and SCHW have been epithelial membrane antigen (EMA) and S100, respectively but these markers can be positive in both these tumors. In our experience we have felt that although EMA and S100 are essential in distinguishing these two entities, but these two alone may not be enough when tissue available for diagnosis is scant. With smaller size of the biopsies being now made available to the pathologist, there is a need to identify new IHC markers that would be beneficial in distinguishing SCHW from FM

Materials and Methods

Study Material

This is a retrospective study in which the records of neurosurgical specimens received at Institute of Pathology-ICMR were searched for reported intracranial SCHW from 2005 to 2008 and FM from 1994 to 2008. The institutional ethical committee of Safdarjung Hospital, New Delhi, approved this study. As the study was retrospective, the informed patient consent was waived. However, any form of patient identification was avoided. The case files of 106 patients (SCHW, n=56 and FM, grade 1, n=50) were selected as study material and their HE stained slides and paraffin blocks retrieved for further study.

Tissue Microarray (TMA) Construction

TMA construction was conducted at the 'Tissue Microarray Research Program' laboratory at National Cancer Institute, National Institutes of Health, MD, USA. HE stained slides for all these cases were studied and a consensus in diagnosis was reached. The cellular (Antoni A) areas of SCHW and FM were selected and marked on the H&E slide and subsequently on the paraffin blocks. Tissue cylinders of diameter 1.0 mm were punched from selected areas of the donor blocks and mounted into a recipient paraffin block with 0.8 mm intervals between the cores using a manual precision microarray instrument (Beecher Instruments, Silver Springs, MD, USA). The recipient block had a total of 106 tumor tissue samples. These samples were arranged in four sub arrays, two each for FM and SCHW and a separate row of 5 control tissues. To minimize the loss of tissue cores during cutting, a paraffin tape-transfer system (Instrumedics, St Louis. MO, USA) was used. The TMA block was tempered overnight at 37°C and 4-μm sections were cut for IHC staining.

Immunohistochemistry

A literature search was done in pubmed for antibodies done in the past for MEN and neural tumors and 14 antibodies were selected for immunohistochemical staining. For IHC staining all TMA sections were deparaffinized through xylene and rehydrated. Slides were then incubated in 0.3% H_2O_2 in methanol for 30 min to block endogenous peroxidase. Antigen retrieval using optimized protocols was performed before incubation with each of the primary antibodies. Detection system was LSAB and the details of primary antibodies included in this study are shown in Table 1. The sections were then incubated in 3.3' diaminobenzidine to develop the chromogenic substrate, washed and counterstained with hematoxylin. CD34(Dako) was also done on the TMA section to rule out another mimic, solitary fibrous tumor of meninges and none were found to be strongly CD34 positive. Positive controls used were as shown in Table 1. Negative controls included omission of primary antibodies.

Evaluation of Immunoreactivity

For each core on TMA, staining was recorded as 0–2+ (0, negative; 1+, weak and/or focal 2+ strong and/or diffuse positive). The cores were labeled as non-informative if the tissue was lost during processing, there was no recognizable tumor or the immunostaining was inappropriate. A TMA core was considered adequate representation of the tumor if each core had at least 75% of representive tumor tissue. The TMA-IHC evaluation was independently done by two of the authors (AS, SMH) using a double-headed

Table 1 Details of primary antibodies and staining conditions

S.No	Antibody	Clone	Dilution	Company	Positive control
1	EMA	E29	1:40	Dako	IDC
2	S100	Polyclonal	1:40	Dako	Melanoma
3	EGFR	H11	1:50	Dako	IDC
4	Merlin/NF2	Polyclonal	1:125	Ab Frontier	Cranial nerve
5	Nestin	Poyclonal	1:200	Millipore	Glioblastoma
6	Ezrin	18	1:1000	BD Biosciences.	Kidney
7	WT-1	6FH2	1:400	Dako	Wilms tumor
8	SPARC	15G12	1:40	Novocastra	OS
9	NP-Y	CPON	1:1000	Abcam	Brain
10	Claudin-1	polyclonal	1:50	Zymed	IDC
11	PR	SP2	1:200	Thermo Scientif.	IDC
12	E-cadherin	NCH38	1:50	Dako	IDC
13	Calretinin	Calret1	1:100	Dako	Mesothelioma
14	c-kit/CD117	polyclonal	1:200	Neomarkers	GIST

IDC infiltrating duct carcinoma, breast, *PR* progesterone receptor, *NP-Y* neuropeptide Y, *SPARC* serine protease acid rich in cysteine, *PLA* placenta, *OS* osteogenic sarcoma, *GIST* gastrointestinal stromal tumor

microscope and any discrepant cores were reassessed to arrive at a consensus score for each core. 98/106 (92%) cores were found suitable for IHC evaluation and their detailed IHC scoring pattern is shown in Table 2.

Statistical Analysis

Discriminant analysis was performed to assess the relative importance of these biomarkers in classifying SCHW and FM. For testing the significance of discriminant model as a whole, F test (Wilks' lambda) was estimated. The DA revealed many significant biomarkers, therefore to have a better idea for their discriminatory abilities Receiver Operating Characteristic (ROC) curve was drawn. The two sided $p<0.05$ was considered statistically significant. The data for the present study was analyzed by using SPSS software package, version 17, (SPSS Inc., Chicago, IL, USA).

Results

The TMA-IHC was evaluated in 50 SCHW (31 females, 19 males with age range 24–52, mean 38.5) and 48 FM (37 females and 11 males with age range 16–66 years, mean 42.5) each for IHC expression of the 14 markers. The IHC staining pattern of these proteins is shown in Fig. 1. EMA was expressed in 46/48 (95.8%) of FM but only 12% (6/50) of SCHW expressed this antigen. S100 was positively labeled in 41/50(82%) of SCHW and 19/48 (39.5%) of FM. WT-1 protein was strongly expressed in the cytoplasm and occasionally in the nuclei of SCHW (Fig. 2a) However, it was localized only in the endothelial cells of FM and was not expressed at all in the tumor cells(Fig. 2d).Claudin-1 did not show any positive labeling in any of the SCHW (Fig. 2b) but was expressed in the cytoplasm of 43/48 FM (Fig. 2e). Ezrin was expressed in cytoplasm of 38% of SCHW (Fig. 2c) but in contrast it was strongly and diffusely expressed in 95.8% of FM and was localized in both cytoplasm and membrane (Fig. 2f).

Discriminant analysis (Wilks' lambda test) was performed to assess the relative importance of these 14 biomarkers in distinguishing SCHW from FM the results are shown in Table 3. It showed that WT-1 (Wilks'λ 0.085, $p<0.001$), EMA (Wilks'λ 0.253, $p<0.001$), S100 (Wilks'λ 0.487, $p<0.001$), Claudin-1 (Wilks' λ 0.57, $p<0.001$), Ezrin (Wilks'λ 0.656, $p<0.001$), SPARC (Wilks'λ 0.751, $p<0.01$), NP-Y (Wilks'λ, 0.819, $p<0.001$) and EGFR (Wilks'λ 0.845, $p=0.026$) were some of the statistically significant markers that discriminated SCHW and FM. However, for analyzing the sensitivity and specificity of the two tumors it was noticed that for SCHW the significant markers [Area under the curve (95% CI), p] by ROC analysis were WT-1 [0.990(0.000, 1.000), <0.001], S100 [0.880(0.808, 0.951), <0.001] while for FM the most significant markers were EMA [0.957 (0.914, 1.000), <0.001], ezrin [0.792(0.700,0.884),<0.001], and Claudin-1 [0.857(0.782, 0.932), <0.001]. The ROC curve for SCHW and FM are shown in Fig. 3.

Discussion

Meningiomas comprise about 13–26% of all primary intracranial tumors with FM constituting approximately 10% of all intracranial MEN [1]. Intracranial SCHW on other hand comprise 8% of all primary intracranial tumors and approximately 80% of them are seen in the cerebellopontine

Table 2 Immunohistochemical scoring pattern in two tumor groups

Biomarker	Schwannoma ($n=50$)			Fibroblastic meningioma ($n=48$)		
	0	1	2	0	1	2
EMA	44 (88.0)	5 (10.0)	1 (2.0)	2 (4.1)	8 (16.6.0)	38 (79.1)
S100	2 (4.0)	7 (14.0)	41 (82.0)	29(60.4)	11(23.0)	8 (16.6)
EGFR	20 (40.0)	15 (30.0)	19 (38.0)	8 (16.6)	18 (37.5)	22 (45.8)
Merlin/NF2	4 (8.0)	19 (38.0)	27 (54.0)	1 (2.0)	14 (29.1)	33 (68.7)
Ezrin	5 (10.0)	26 (52.0)	19 (38.0)	0 (0)	2 (4.0)	46 (95.8)
WT-1	0 (0)	6 (12.0)	44 (88.0)	48 (100)	0 (0)	0(0)
SPARC	3 (6.0)	12 (24.0)	35 (70.0)	19 (39.5)	18 (37.5)	11 (23.0)
E-cadherin	37 (74.0)	12 (24.0)	1 (2.0)	39 (81.2)	7 (14.5)	2 (4.1)
Claudin 1	35 (70.0)	13 (26.0)	2 (4.0)	5 (10.5)	24 (50.0)	19(39.5)
PR	42 (84.0)	8 (16.0)	0 (0)	35 (73.0)	10 (20.8)	3 (6.2)
NP-Y	5 (10.0)	38 (76.0)	7 (14.0)	2 (4.1)	18 (37.5)	28 (58.3)
Nestin	9 (18.0)	26 (52.0)	15 (30.0)	13 (27.0)	25 (52.0)	10 (20.8)
Calretinin	43 (86.0)	5 (10.0)	2 (4.0)	44 (91.6)	4 (8.4)	0 (0)
c-KIT	12 (24.0)	25 (50.0)	13 (26.0)	1 (2.0)	32 (66.7)	15 (31.3)

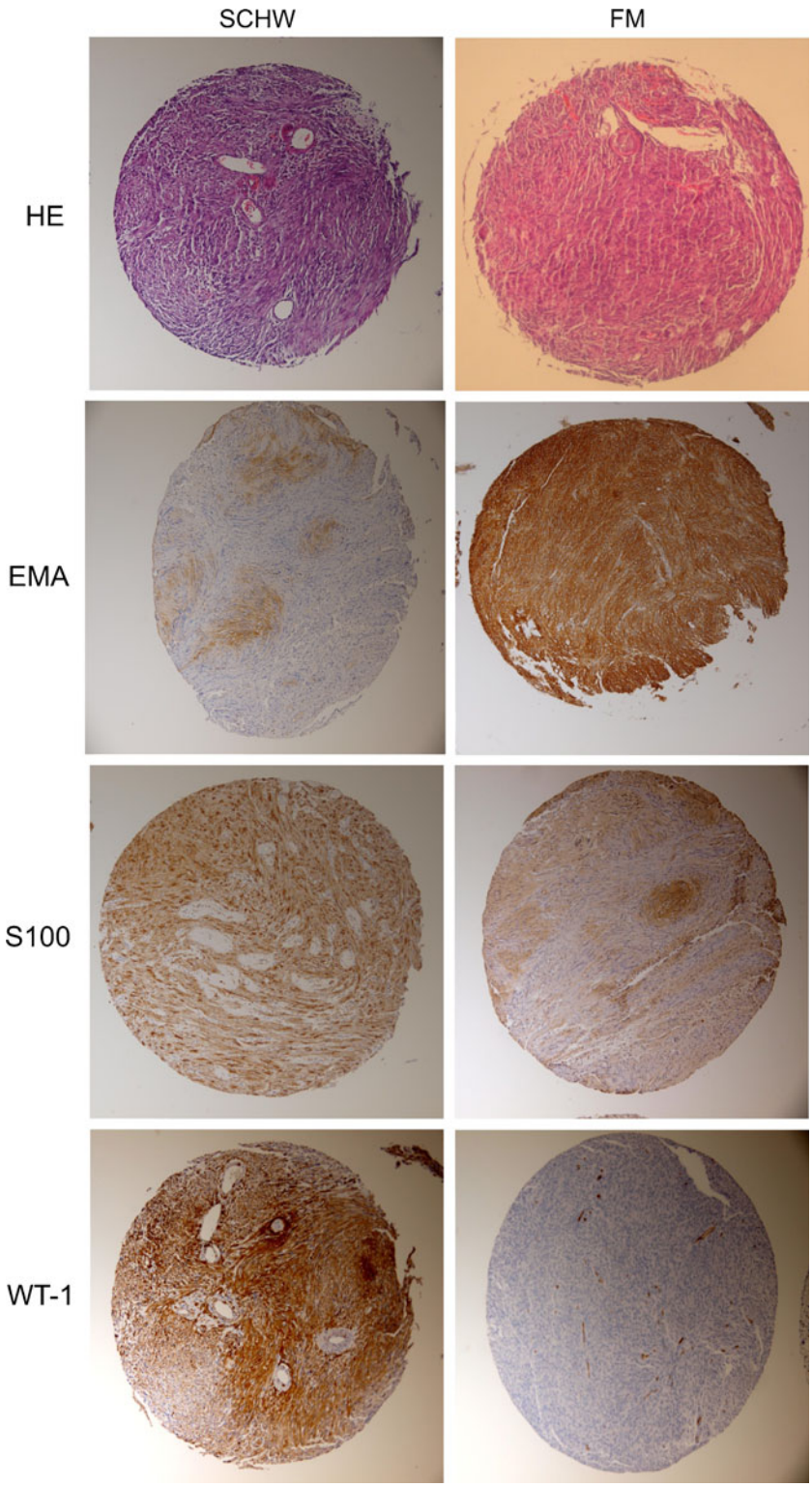

Fig. 1 Comparative immunohistochemical staining in TMA cores of FM and SCHW (×100)

angle in relation to the vestibular nerve [2]. Although SCHW and FM are usually a straightforward diagnosis based on their histological pattern and cellular composition, occasionally it may be difficult to diagnose them purely on morphology, particularly in cases where the biopsy is of small size and does not adequately represent the whole lesion. The present study aims to compare the IHC profiles of FM and SCHW in an effort to identify potentially useful diagnostic IHC markers that can reliably distinguish these two entities in challenging situations.

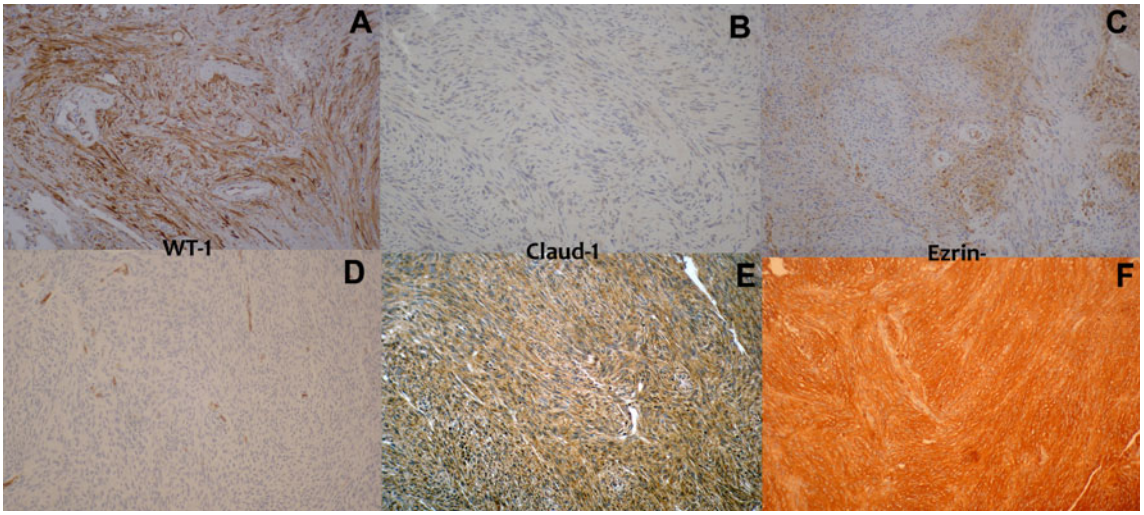

Fig. 2 Immunohistochemical localization of WT-1 in SCHW(**a**), FM(**d**), claudin-1 in SCHW(**b**), FM (**e**), and ezrin in SCHW(**c**), FM (**f**)

IHC expression of epithelial membrane antigen (EMA) and S100 are routinely used to support the diagnosis of MEN and SCHW, respectively. However, EMA and S100 can be expressed by both these tumors. In MEN the expression of EMA is diffuse and predominantly membranous while it is focal and usually cytoplasmic in SCHW. S100 expression is focal in MEN while it is more widespread in SCHW [3]. Theaker et al. [4] reported in their study on 13 MEN that all MEN were positive for EMA and S100 while Meis et al. [5] demonstrated that 25/50(50%) MEN were EMA positive but only 4/50(8%) were labeled by S100. Schnitt and Vogel [6] in their study on 22 MEN (including 3 FM) and 8 SCHW reported that majority of MEN expressed strong EMA while all SCHW were negative for EMA. S100 was diffusely positive in all SCHW but only in 9/22 of MEN stained with S100. Studies of EMA expression in SCHW [7, 8] have yielded conflicting results with no staining in SCHW while Winek et al. [9] studied 7 SCHW and 40 MEN (including 11 FM) and reported that all FM were EMA positive but 15% were S100 positive. SCHW on other hand were all labeled for S100 but 6/7(86%) were also focally positive for EMA. Artlich and Schmidt [10] in their series on MEN and SCHW reported that EMA and S100 were both positively labeled in 6/9(66.6%) of FM whereas EMA was negative and S100 positive in all 9/9 (100%) of SCHW. Both Perry et al. [11] and Carneiro et al. [12] in their studies on 20 cases each of FM demonstrated that both EMA and S100 were positive in 80% of the cases. More recently, Hahn et al. [13] have reported that 20/20 and 18/20(90%) FM showed strong EMA and S100 positivity respectively. Sometimes EMA and S100 alone are not sufficient to distinguish these histological mimics especially on small biopsies. Thus, additional IHC markers would be beneficial in distinguishing these two tumors.

Table 3 Result of discriminant analysis

Biomarkers	Wilks' lambda	F	df1	df2	Sig.
WT-1	0.085	1056.86	1	98	<0.001
EMA	0.253	289.834	1	98	<0.001
S100	0.487	103.173	1	98	<0.001
Claudin-1	0.57	73.961	1	98	<0.001
Ezrin	0.656	51.495	1	98	<0.001
SPARC	0.751	32.504	1	98	<0.001
NP-Y	0.819	21.613	1	98	<0.001
EGFR	0.845	18.01	1	98	<0.026
c-KIT	0.95	5.125	1	98	0.057
Merlin	0.971	2.913	1	98	0.091
PR	0.974	2.658	1	98	0.106
Nestin	0.987	1.329	1	98	0.252
Calretinin	0.99	0.987	1	98	0.323
E-cadh	1.0	0.035	1	98	0.851

Studying immunohistochemical markers on whole tissue sections is a valuable but laborious task especially when screening large number of samples and markers. TMA is a useful research tool for the pathologist where one can comparatively analyze large number of tissue samples in a single slide under uniform staining conditions with high speed and cost effectiveness [14, 15]. In the present study, using TMA-IHC approach we found that WT-1, the Wilms tumor- 1 protein, was the most useful marker to differentiate FM from SCHW as it was expressed by the endothelial cells but did not label the tumor cells in FM while it was strongly expressed by tumor cells (cytoplasm more than nuclei) in SCHW (Wilks lambda 0.085, $p<0.001$). There is only one report in published literature about IHC expres-

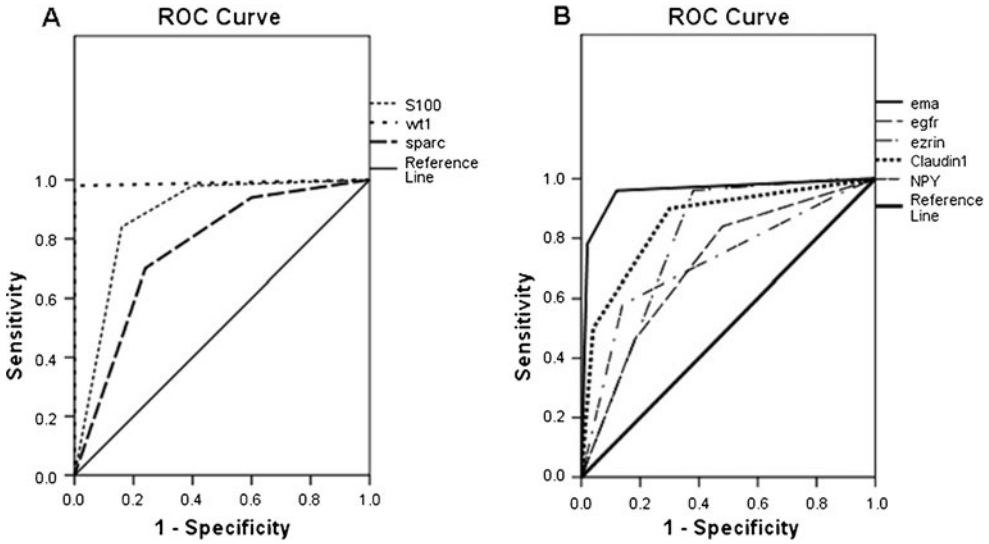

Fig. 3 **a** ROC for schwannoma, **b** ROC for fibroblastic meningioma

sion of WT-1 in SCHW [16]. WT-1 is a well-characterized tumor suppressor gene that is a transcriptional regulator with putative target genes including those for growth factors. The WT-1 protein overexpression in SCHW tumor cells suggests transcriptional activation of the WT-1 gene and its possible role in development of SCHW [17]. We had to change the diagnoses in four cases after using this combination of differentiating antibodies; 2 FM had been misdiagnosed as SCHW and 2 SCHW were wrongly diagnosed as FM. Since this study was performed on archival paraffin blocks of previously diagnosed cases and none of these four patients were under follow up they could not be informed about change in their diagnosis. It is important to differentiate FM from SCHW because FM if not resected completely, unlike SCHW they may have a propensity for aggressive clinical behavior like recurrence, hyperostosis and bone erosion.

Claudin-1 is a useful tight junction-associated protein that has been studied in MEN and SCHW and reported to be expressed in 17/20(85%) of MEN but not expressed at all in SCHW [13]. Bhattacharya et al. [18] have shown claudin-1 expression in 8/20(40%) of FM in comparison to no expression in SCHW. In our study we found that claudin-1 was expressed in 45/50(90%) of FM but in none of the SCHW. It has been previously documented that expression of ezrin-radixin-moesin (ERM) family of proteins is retained in SCHW despite loss of merlin [19]. However the only published study of immunohistochemical expression of ezrin in both FM and SCHW did not detect any ezrin expression [20]. More recently, reports about high-throughput microarray gene expression profiling studies in these tumors have shown that in SCHW, SPARC gene is upregulated while ezrin and merlin genes are downregulated [21, 22]. This finding was validated in our immunohistochemical observations where 46/48(95.8%) FM strongly expressed ezrin protein and in contrast there was under expression of ezrin protein in SCHW. More recently, Fine et al. [23] have reported calretinin immunoreactivity in 25 cases of extracranial SCHW and showed the usefulness of calretinin indistinguishing SCHW and neurofibroma. However in our study calretinin was not expressed in either FM or SCHW and were not useful in discriminating these two entities.

Relationship of PR with MEN and SCHW has been a subject of numerous studies in the past, both in terms of its diagnostic and prognostic utility. The higher incidence of MEN and SCHW in women, their increased growth rate during pregnancy, and their association with breast cancer has suggested their possible role in the development of these tumors. PR expression is reported to be higher in WHO grade 1 MEN as compared to the grade 2 and 3 MEN. However PR immunoreactivty alone cannot predict the prognosis in MEN. PR status in combination with MIB1 proliferation index and pathological evaluation can give useful insights in predicting the biological behavior of MEN [24, 25]. Omulecka et al. [26] studied 68 MEN for immunoexpression of PR and found that its positivity was 100% in meningothelial MEN but only 42% in fibrous MEN suggesting that PR is expressed in lower frequency in FM. PR status in SCHW is reported to be highly variable with staining pattern ranging from 0 to 100% [27, 28] and is unreliable as a diagnostic marker. Other antibodies like EGFR, Merlin, E-cadherin, nestin, NP-Y, and c-KIT were variably expressed in these two entities and were not very useful in differentiating FM from SCHW.

To conclude, our study suggests that WT-1, Claudin-1 and ezrin might be potential immunohistochemical markers in addition to traditionally available EMA and S100 to be used to distinguish SCHW and FM. For the purpose of practical utility and cost effectiveness, out of all these

markers we have been using a panel of 4 antibodies; EMA, S100, WT-1 and Claudin-1 in our laboratory whenever we face a diagnostic dilemma between these two entities and have been satisfied with the results. However, further validation is warranted before these markers are routinely used and recommended as a diagnostic panel

Acknowledgement The authors wish to thank the Indo-US Science and Technology forum, Department of Science and Technology, Government of India for the IUSSTF Research fellowship to Dr Avninder Singh to visit the TARP Lab, NCI, NIH, USA for construction of TMA. The authors also wish to thank Ms Preet Sayal for typing the manuscript and Mr JS Sayal for the adobe photoshop work

Conflict of interest None.

References

1. Louis DN, Scheithauer BW, Budka H, von Deimling A et al (2000) Meningiomas. In: Kleihues P, Cavenee WK (eds) Tumours of the nervous system. IARC, Lyon, pp 176–184
2. Sloof JL (1984) Pathological anatomical findings in the cerebellopontine angle. Adv Otorhinolaryngol 34:89–953
3. Weiss SW, Langloss JM, Enzinger FM (1983) Value of S-100 protein in the diagnosis of soft tissue tumors with particular reference to benign and malignant Schwann cell tumors. Lab Investig 49:299–308
4. Theaker JM, Gatter KC, Esiri MM, Fleming KA (1986) Epithelial membrane antigen and cytokeratin expression by meningiomas: an immunohistological study. J Clin Pathol 39:435–439
5. Meis JM, Ordonez NG, Bruner JM (1986) Meningiomas. An immunohistochemical study of 50 cases. Arch Pathol Lab Med 110:934–937
6. Schnitt SJ, Vogel H (1986) Meningiomas. Diagnostic value of immunoperoxidase staining for epithelial membrane antigen. Am J Surg Pathol 9:640–649
7. Sloan JP, Ormerod MG (1981) Distribution of epithelial membrane antigen in normal and neoplastic tissues and its value on diagnosis on diagnostic tumor pathology. Cancer 47:1786–1795
8. Perentes E, Nakagawa Y, Ross GW et al (1987) Expression of epithelial membrane antigen in perineurial cells and their derivatives. An immunohistochemical study with multiple markers. Acta Neuropathol 75:160–165
9. Winek RR, Scheithauer BW, Wick MR (1989) Meningioma, meningeal hemangiopericytoma (angioblastic meningioma), peripheral hemangiopericytoma, and acoustic schwannoma (1989) a comparative immunohistochemical study. Am J Surg Pathol 13:251–261
10. Artlich A, Schmidt D (1990) Immunohistochemical profile of meningiomas and their histological subtypes. Hum Pathol 21:843–849
11. Perry A, Scheithauer BW, Nascimento AG (1997) The immunophenotypic spectrum of meningeal hemangiopericytoma: a comparison with fibrous meningioma and solitary fibrous tumor of meninges. Am J Surg Pathol 21:1354–1360
12. Carneiro SS, Scheithauer BW, Nascimento AG, Hirose T, Davis DH (1996) Solitary fibrous tumor of the meninges: a lesion distinct from fibrous meningioma. Am J Clin Pathol 106:217–2242
13. Hahn HP, Bundock EA, Hornick JL (2006) Immunohistochemical staining for claudin-1 can help distinguish menigiomas from histologic mimics. Am J Clin Pathol 125:203–208
14. Avninder S, Ylaya K, Hewitt SM (2008) Tissue microarray: a simple technology that has revolutionized research in pathology. J Postgrad Med 54:158–162
15. Lusis EA, Chicoine MR, Perry A (2005) High throughput screening of meningioma biomarkers using a tissue microarray. J Neuro Oncol 73:219–223
16. Sarwat AM, Al-Salam S (2009) Expression of HIF-1, galectin, cox-2 and Wilms tumor-1 protein in multiple schwannomas of the conus medullaris. J Neuro Oncol 92:111–115
17. Lee SB, Huang K, Palmer R, Truong VB, Herzlinger D, Kolquist KA et al (1999) Wilms' tumor suppressor WT1 encodes a transcriptional activator of amphiregulin. Cell 98:663–673
18. Bhattacharjee M, Adesina AM, Goodman C, Powell S (2003) Claudin-1 expression in meningiomas and schwannomas: possible role in differential diagnosis [abstract]. J Neuropathol Exp Neurol 62:581
19. Stemmer-Rachamimov AO, Xu L, Gonzalez-Augusti C et al (1997) Universal absence of merlin, but not other ERM family members in schwannomas. Am J Pathol 151:1649–1654
20. Böhling T, Turunen O, Jääskeläinen J et al (1996) Ezrin expression in stromal cells of capillary hemangioblastoma. An immunohistochemical survey of brain tumors. Am J Pathol 148:367–373
21. Martinez-Glez V, Hernandez-Franco C, Rey JA (2008) Microarray gene expression profiling in meningiomas and schwannnomas. Curr Med Chem 15:826–833
22. Welling DB, Lasak JM, Akhmametyeva A, Ghaheri B, Chang LS (2002) A cDNA microarray analysis of vestibular schwannomas. Otol Neurotol 23:736–748
23. Fine SW, McClain SA, Maomi L (2004) Immunohistochemical staining for calretinin is useful for differentiating schwannomas from neurofibromas. Am J Clin Pathol 122:552–559
24. Perry A, Cai DX, Scheithauer BW, Swanson PE, Lohse CM, Newsham IF et al (2000) Merlin, DAL-1, and progesterone receptor expression in clinicopathologic subsets of meningioma: a correlative immunohistochemical study of 175 cases. J Neuropathol Exp Neurol 59:872–879
25. Roser F, Nakamuara M, Bellinzona M, Rosahl SK, Ostertag H, Samii M (2004) The prognostic value of progesterone receptor status in meningiomas. J Clin Pathol 57:1033–1037
26. Omulecka A, Papierz W, Nawrocka-Kunecka A, Lewy-Trenda I (2006) Immunohistochemical expression of progesterone and estrogen receptors in meningiomas. Folia Neuropathol 44:111–115
27. Jaiswal S, Agrawal V, Jaiswal AK, Pandey R, Mahapatra AK (2009) Expression of estrogen and progesterone receptors in vestibular schwannomas and their clinical significance. J Negat Results Biomed 8:9
28. Dalgorf DM, Roswell C, Bilbao JM, Chen JM (2008) Immunohistochemical investigation of hormone receptors and vascular growth factor concentration in vestibular schwannomas. Skull Base 18:377–384