J Neuropathol Exp Neurol
Vol. 76, No. 4, April 2017, pp. 289–298
doi: 10.1093/jnen/nlx008

ORIGINAL ARTICLE

Immunohistochemical Approach to the Differential Diagnosis of Meningiomas and Their Mimics

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Abstract

The differential diagnosis between meningioma and others tumors can be challenging. This study aimed to evaluate different immunohistochemical markers for the differential diagnosis between meningioma and their morphological mimics. Immunohistochemistry was performed on tissue microarray with antiepithelial membrane antigen (EMA), progesterone receptor, somatostatin receptor 2A (SSTR2A), CD34, STAT6, S100, SOX10, HMB45, MelanA, GFAP, inhibin, and BCL2 antibodies. One hundred and twenty-seven meningiomas, 26 solitary fibrous tumor/hemangiopericytomas (SFT/HPC), 39 schwannomas, 17 hemangioblastomas, 21 melanomas, 9 gliosarcomas, 5 neurofibromas, 9 peripheral primitive neuroectodermal tumors, 7 synovial sarcomas, and 5 malignant peripheral nerve sheath tumors were included in the microarray. SSTR2A was the most sensitive (95.2%) and specific (92%) marker of meningiomas. In combination, SSTR2A and/or EMA positivity reached maximal sensitivity (100%). Coexpression of SSTR2A and EMA was the most specific (94.8%) for the diagnosis of meningioma, regardless of the grade or subtype, with the exception of the differential diagnosis with synovial sarcoma. All synovial sarcomas were EMA-positive and 6/7 SSTR2A-positive. STAT6 showed optimum sensitivity and specificity (100%) for SFT/HPC. SOX10 was the most sensitive (94.3%) and specific (100%) marker to discriminate meningiomas from schwannomas. In conclusion, SSTR2A, STAT6, and SOX10 were the most sensitive and specific markers to distinguish meningiomas from their morphological mimics.

Key Words: Epithelial membrane antigen, Immunohistochemistry, Meningioma, Schwannoma, Solitary fibrous tumor, SOX10, SSTR2A, STAT6.

INTRODUCTION

Meningiomas are common neoplasms that originate from archnoidal cells and most often attach to the inner surface of the dura mater. They account for 13%–30% of primary intracranial tumors and 25% of intraspinal tumors; they occur in adults with a median age of 65 years and are predominantly observed in females. The vast majority of meningiomas arise in intracranial, intraspinal, or orbital locations. Intraventricular and epidural meningiomas are uncommon (1, 2). Rare primary extradural meningiomas have been reported outside the neural axis (2, 3). According to the World Health Organization (WHO) criteria, meningiomas are classified into 3 grades (2). Grade I meningiomas are the most frequent and are considered as benign with a low risk of recurrence. Grade II meningiomas are less common and have a higher rate of recurrence, and grade III tumors are rare, and are associated with poor overall survival rates.

Meningiomas exhibit a wide range of histological appearances. Among the different WHO subtypes, the most commonly encountered are the meningothelial, fibrous, and transitional meningiomas (2). While the majority of cases are diagnosed on routine hematoxylin and eosin-stained sections, certain cases can show overlapping morphology with other less common intracranial, intraspinal, or orbital neoplasms that require different treatments. The most common differential diagnoses are schwannomas and other rare meningeal tumors, such as solitary fibrous tumor/hemangiopericytoma (SFT/HPC), predominantly with the fibrous variant of meningioma. Microcystic or clear cell variants of meningioma can overlap morphologically with hemangioblastomas. Anaplastic meningioma can be difficult to differentiate from sarcoma, melanoma, or carcinoma. The diagnosis of meningiomas can be also challenging when they arise in uncommon locations, such as with primary extradural meningioma or as metastases. In these contexts, differential diagnoses depend on the tumor location and morphology. In such challenging cases, immunohistochemistry (IHC) can help to establish a definitive diagnosis.

Currently, the most commonly used IHC markers for the diagnosis of meningiomas are epithelial membrane antigen (EMA) and progesterone receptor (PR), CD34 for the diagnosis of SFT/HPC, and S100 for the diagnosis of schwannoma. However, these markers have suboptimal sensitivities and specificities and vary with regard to the grades or subtype of

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The authors have no duality or conflicts of interest to declare.

Supplementary Data can be found at http://www.jnen.oxfordjournals.org.

meningioma (2, 4–6). Newer markers such as somatostatin receptor 2A (SSTR2A) for meningiomas, signal transducer and activator of transcription 6 (STAT6) for SFT/HPC, and SRY-box 10 (SOX10) for schwannomas, have recently been shown to have better diagnostic performances than classic IHC markers (5–10). These 3 new markers have only been tested separately on intracranial tumors in a few studies.

The aim of this study was to evaluate the sensitivities and specificities of several IHC markers used to differentiate meningioma and their morphological mimics in order to determine the best markers to use in daily practice.

MATERIALS AND METHODS

Cases

A retrospective computer-based search of the surgical pathology database of the University Hospitals of Reims and Nancy was conducted to select patients with intracranial or intraspinal meningiomas of various types and grades, SFT/HPC of various grades, schwannomas, hemangioblastomas, melanomas (primary or metastatic), gliosarcomas, neurofibromas, and peripheral primitive neuroectodermal tumors ([pPNET] or Ewing sarcoma). Cases of synovial sarcomas and malignant peripheral nerve sheath tumors (MPNST) with epidural or juxta-spinal localization were also included in the study.

Two pathologists who had experience with CNS tumors (C.B.-R., G.G.) reevaluated the diagnoses according to the 2016 CNS WHO criteria (2). The diagnosis of soft tissues tumors were based on 2013 WHO criteria and confirmed by expert consultation (11).

A total of 127 meningiomas of various grades (81 grade I, 38 grade II, 8 grade III) and subtypes (22 meningothelial, 19 transitional, 16 fibrous, 5 microcystic, 5 secretory, 10 psammomatous, 4 myxoid, 5 chordoid, and 3 clear cell meningiomas), 26 SFT/HPC of various grades (11 grade I, 6 grade II, 9 grade III), 39 schwannomas, 17 hemangioblastomas, 21 melanomas (3 primary, 18 metastatic), 9 gliosarcomas, 5 neurofibromas, 9 pPNET, 7 synovial sarcomas, and 5 MPNST, were included in the study.

Immunohistochemistry

All tissue samples were analyzed via tissue microarrays (TMAs). For each tumor, 2 cores each with a 2-mm diameter were obtained from the same original formalin-fixed paraffin-embedded tumor block. The cores were precisely arrayed into a recipient paraffin block using the MiniCore Tissue Arrayer (Excilone, Elancourt, France). Four micrometer thick sections were cut and mounted on SuperFrost Plus Gold adhesive slides (Thermofisher Scientific, Waltham, MA). Antibodies and dilutions are detailed in Table 1. One negative and 1 positive control were added onto each slide and for each immunostain. IHC was performed with the BenchMark XT automated slide stainer (Ventana Medical Systems, Tucson, AZ), at the University Hospital of Reims. After deparaffinization, the TMA section was incubated with the Cell Conditioner 1 (EDTA, pH 8.4) for 64 minutes, followed by preprimary peroxidase inhibition, and incubation with the corresponding antibody at 37 °C for 8 (PR, S100), 16 (AE1/AE3, CD34, MelanA), 24 (EMA), 32 (GFAP, SOX10, SSTR2A, STAT6), or 60 minutes (HMB45, α-Inhibin). The staining reaction was then performed using the ultraView Universal DAB v3 Kit (Ventana Medical Systems). The counterstain and postcounterstain were comprised of hematoxylin and bluing reagents.

Analysis

Two pathologists (C.B.-R. and C.F.) from the same laboratory reviewed the TMA IHC slides independently. In the event of a discrepancy, a consensus diagnosis was reached after collegial discussion. The 2 cores were scored independently before being paired. If scores for the 2 samples were discordant, the final score for the tumor was upgraded to the higher score. Staining was rated in a binary manner as either positive or negative. All tumors in which the tumor cells either completely lacked immunostaining or showed faint staining in a minority (<5%) of tumor cells were scored as negative. IHC findings were rated as positive when at least 5% of the tumor cells were unequivocally stained in the nucleus for PR, SOX10, and STAT6, in the cytoplasm for AE1/AE3, CD34, GFAP, HMB45, α-Inhibin, MelanA, and SSTR2A, and in the cytoplasm and/or nucleus for S100. Additionally, for PR and SSTR2A, staining was scored semiquantitatively, as previously described by combining intensity score (0, absent; 1, faint; 2, moderate, and 3, strong) and the percentage of positive nuclei for PR (12) or cytoplasm for SSTR2A (13).

The concordance between the scoring results obtained by the 2 independent investigators was evaluated with the use of contingency tables and by calculation of Cohen's kappa indexes. The sensitivity was considered true positive/(true positive + false negative) and the specificity as true negative/(true negative + false positive). Positive predictive values (PPV) were calculated as true positive/(true positive + false positive); negative predictive values (NPV) were calculated as true negative/(true negative + false negative). Categorical variables were compared using the Chi square test. p values less than 0.05 were considered significant. Statistical analyses were performed using Epi Info statistical software version 3.5.4 (Center for Disease Control and Prevention, Atlanta, GA).

RESULTS

A total of 13 markers were tested on 10 different tumor types. Eleven subtypes of meningiomas and the 3 WHO grades were tested. Results are summarized in Tables 2 (all types of tumor) and 3 (meningioma subtypes).

Interobserver Reproducibility

Interobserver agreement assessed by Cohen's Kappa was almost optimum for EMA (0.84), SSTR2A (0.91), SOX10 (0.87), HMB45 (0.91), and MelanA (0.91); substantial for S100 (0.79), CD34 (0.67), and inhibin (0.69); moderate for AE1/AE3 (0.59) and STAT6 (0.52); fair for BCL2 (0.37); and weak for GFAP (0.09).

TABLE 1. Antibodies Used for Immunohistochemistry

Antibody	Reference	Brand	Clone	Dilution
AE1/AE3	M3515	Dako, Carpinteria, CA	AE1/AE3	1:50
CD34	PA0212	Leica Biosystems, Wetzlar, Germany	QBEnd/10	RTU
EMA	M0613	Dako	E29	1:50
GFAP	M0761	Dako	6F2	1:400
HMB45	M0634	Dako	HMB45	1:50
α-Inhibin	IR058	Dako	R1	RTU
MelanA	M7196	Dako	A103	1:100
PR	790-2223	Ventana Medical System, Tucson, AZ	1E2	RTU
S100	IR504	Dako	Polyclonal	1:400
SOX10	RMPD 077	Diagnostic Biosystems, Pleasanton, CA	EP268	RTU
SSTR2A	ab134152	Abcam, Cambridge, MA	UMB1	1:100
STAT6	sc-621	Santa Cruz Biotechnology, Dallas, TX	S-20	1:250

RTU, ready to use.

Meningioma Markers

EMA was expressed by 90% (113/126) of all meningiomas; there was no statistical difference between grades and types ($p = 0.75$ and 0.23, respectively, χ^2 test). EMA was expressed by 24% (6/25) of SFT-HPC, 5% of schwannomas and melanomas (2/39 and 1/21, respectively), and 100% (7/7) of synovial sarcomas.

SSTR2A had a slightly better sensitivity than EMA, with 95% (120/126) positivity in meningiomas, irrespective of the grade ($p = 0.23$, χ^2 test). SSTR2A was diffusely and strongly expressed by almost all meningiomas. SSTR2A was significantly less frequently expressed in fibrous, and myxoid meningiomas compared with other meningioma subtypes ($p = 0.004$, χ^2 test). SSTR2A was expressed by 86% (6/7) of cases of synovial sarcomas, 8% (2/25) of SFT/HPC, 22% (2/9) of pPNET, and 11% (1/9) of gliosarcomas. SSTR2A immunolabeling was significantly more intense and diffuse in meningioma ($p < 0.001$, Mann–Whitney test) than in other diagnoses (Supplementary Data Tables S1 and S2).

PR had a lesser sensitivity than EMA and SSTR2A, with 75% (69/92) positivity in meningiomas. PR expression was grade dependent ($p = 0.001$, χ^2 test), with decreasing expression from grade 1 to grade 3 meningiomas. There was no difference in PR expression between subtypes ($p = 0.45$, χ^2 test). PR expression was also observed in proportions of SFT/HPC (19%), schwannomas (3%), MPNST (20%), melanomas (5%), synovial sarcomas (43%) and pPNET (22%).

Schwannoma Markers

All schwannomas with the exception of 1 expressed S100 protein (38/39, 97%). The other tumors also expressed S100 protein, although this was to a lesser extent and intensity. In particular, 34% (43/126) of all meningiomas expressed S100. S100 was significantly more expressed in fibrous and psammomatous meningiomas compared with the other subtypes ($p = 0.001$, χ^2 test).

SOX10 was only expressed by tumors of schwannian and melanocytic origin: schwannomas (94%, 33/35), melanomas (85%, 17/20), neurofibromas (80%, 4/5), and MPNST (20%, 1/5). The sensitivity of SOX10 for the diagnosis of schwannoma was slightly less than that of S100, with 94% (33/35) positivity. None of the meningiomas expressed SOX10.

SFT/HPC Markers

CD34 was expressed by 73% (16/26) of SFT/HPC cases and there was no significant difference between grades. CD34 was also expressed in 8% (10/126) of meningiomas, 13% (5/40) of schwannomas, and 40% (2/5) of neurofibromas. STAT6 was expressed by all SFT/HPC. No other tumor showed STAT6 positivity.

Other Markers

AE1/AE3 was expressed in 6% (7/116) of meningiomas, and involved predominantly secretory meningiomas (80%, 4/5). Weak and focal positivity was observed in 5% of meningothelial and transitional meningiomas (both 1/19) and in 4% of atypical meningiomas (1/26). This type of positivity was also observed in 15% (3/20) of melanomas, 11% (1/9) of pPNET, and in 1 grade 3 SFT/HPC. AE1/AE3 was strongly but heterogeneously expressed in 50% (3/6) of synovial sarcomas.

Melanoma markers (HBM45 and MelanA) were expressed only in melanomas, with 71% sensitivity for MelanA and 85% for HMB45. Inhibin was expressed only in hemangioblastomas, with a sensitivity of 56%. GFAP was expressed only in hemangioblastomas and gliosarcomas, with a sensitivity of 44% in both cases.

BCL2 was expressed by all tumor types selected for this study, with 40% (2/5) positivity in neurofibromas and 100% positivity in hemangioblastomas (17/17), synovial sarcoma (7/7), and PNET (9/9). BLC2 expression was slightly more intense and diffuse in SFT/HPC than in meningiomas or schwannomas.

Diagnostic Performance of Markers and Panels

The diagnostic performance was estimated for single markers and a panel of markers for the diagnosis of meningioma

TABLE 2. Sensitivity of the Different Antibodies Among the Diagnoses

Diagnosis	*N*	EMA *n* (%)	SSTR2A	PR	S10	SOX10	CD34	STAT6	AE1/AE3	MelanA	HMB45	Inhibin	GFAP	BCL2
Meningioma	127	113/126 (90)	120/126 (95)	69/92 (75)	43/126 (34)	0/123 (0)	10/126 (8)	0/123 (0)	7/116 (6)	0/123 (0)	0/123 (0)	0/123 (0)	0/123 (0)	96/120 (80)
Grade 1	81	72/81(89)	76/81 (94)	52/61 (85)	34/80 (43)	0/80 (0)	5/80 (6)	0/80 (0)	6/78 (8)	0/80 (0)	0/80 (0)	0/80 (0)	0/80 (0)	61/78 (78)
Grade 2	38	35/37 (95)	36/37 (97)	17/26 (65)	7/38 (18)	0/37 (0)	4/38 (11)	0/37 (0)	1/33 (3)	0/37 (0)	0/37 (0)	0/37 (0)	0/37 (0)	32/37 (86)
Grade 3	8	6/8 (75)	8/8 (100)	1/5 (20)	2/8 (25)	0/6 (0)	1/8 (13)	0/6 (0)	0/5 (0)	0/6 (0)	0/6 (0)	0/6 (0)	0/6 (0)	3/5 (60)
SFT/HPC	26	6/25 (24)	2/25 (8)	3/16 (19)	2/24 (8)	0/24 (0)	16/26 (73)	26/26 (100)	1/19 (5)	0/24 (0)	0/24 (0)	0/19 (0)	0/24 (0)	19/23 (83)
Grade 1	11	2/10 (20)	1/10 (10)	2/5 (40)	0/10 (0)	0/9 (0)	9/11 (82)	11/11 (100)	0/7 (0)	0/9 (0)	0/9 (0)	0/7 (0)	0/9 (0)	6/9 (67)
Grade 2	6	1/6 (17)	1/6 (17)	0/5 (0)	1/5 (20)	0/6 (0)	3/6 (50)	6/6 (100)	0/6 (0)	0/6 (0)	0/6 (0)	0/6 (0)	0/6 (0)	6/6 (100)
Grade 3	9	3/9 (33)	0/9 (0)	1/6 (17)	1/9 (11)	0/9 (0)	7/9 (78)	9/9 (100)	1/6 (17)	0/9 (0)	0/9 (0)	0/6 (0)	0/9 (0)	7/8 (88)
Schwannoma	39	2/39 (5)	0/39 (0)	1/32 (3)	38/39 (97)	33/35 (94)	5/39 (13)	0/39 (0)	0/35 (0)	0/35 (0)	0/35 (0)	0/32 (0)	0/35 (0)	24/32 (75)
Neurofibroma	5	0/5 (0)	0/5 (0)	0/5 (0)	4/5 (80)	4/5 (80)	2/5 (40)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	2/5 (40)
MPNST	5	0/5 (0)	0/5 (0)	1/5 (20)	1/5 (20)	1/5 (20)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	3 (60)
Melanoma	21	1/21 (5)	0/21 (0)	1/21 (5)	14/20 (70)	17/20 (85)	0/20 (0)	0/21 (0)	3/20 (15)	15/21 (71)	17/20 (85)	0/21 (0)	0/21 (0)	20/21 (95)
Hemangioblastoma	17	0/16 (0)	0/17 (0)	0/15 (0)	6/16 (38)	0/17 (0)	0/16 (0)	0/17 (0)	1/16 (6)	0/16 (0)	0/16 (0)	9/16 (56)	7/16 (44)	17/17 (100)
Gliosarcoma	9	0/9 (0)	1/9 (11)	0/9 (0)	6/9 (67)	0/9 (0)	0/9 (0)	0/9 (0)	0/9 (0)	0/9 (0)	0/9 (0)	0/9 (0)	4/9 (44)	8/9 (89)
Synovial sarcoma	7	7/7 (100)	6/7 (86)	3/7 (43)	3/7 (43)	0/7 (0)	0/7 (0)	0/7 (0)	3/6 (50)	0/7 (0)	0/7 (0)	0/7 (0)	0/7 (0)	7/7 (100)
pPNET	9	1/9 (11)	2/9 (22)	2/9 (22)	5/9 (56)	0/9 (0)	0/9 (0)	0/9 (0)	1/9 (11)	0/9 (0)	0/9 (0)	0/9 (0)	0/9 (0)	9/9 (100)

TABLE 3. Sensitivity of the Different Antibodies Among the Meningioma Subtypes

Meningioma Subtype	*n*	EMA *n* (%)	SSTR2A	PR	S100	SOX10	CD34	STAT6	AE1/AE3	MelanA	HMB45	Inhibin	GFAP	BCL2
Meningothelial	22	20/22 (91)	22/22 (100)	11/12 (92)	6/21 (29)	0/21 (0)	2/21 (10)	0/21 (0)	1/19 (5)	0/21 (0)	0/21 (0)	0/19 (0)	0/21 (0)	14/20 (70)
Transitional	19	18/19 (95)	19/19 (100)	11/15 (73)	6/19 (32)	0/19 (0)	1/19 (5)	0/19 (0)	1/19 (5)	0/19 (0)	0/19 (0)	0/19 (0)	0/19 (0)	17/19 (89)
Fibrous	16	14/16 (88)	12/16 (75)	9/12 (75)	13/16 (81)	0/16 (0)	2/16 (13)	0/16 (0)	0/16 (0)	0/16 (0)	0/16 (0)	0/16 (0)	0/16 (0)	12/15 (80)
Microcystic	5	3/5 (60)	5/5 (100)	3/4 (75)	2/5 (40)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	4/5 (80)
Secretory	5	3/5 (60)	5/5 (100)	4/4 (100)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	4/5 (80)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	3/5 (60)
Psammomatous	10	10/10 (100)	10/10 (100)	9/10 (90)	8/10 (80)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	0/10 (0)	8/10 (80)
Myxoid	4	4/4 (100)	3/4 (75)	4/4 (100)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	3/4 (75)
Chordoid	5	4/4 (100)	4/4 (100)	2/2 (100)	0/5 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	0/4 (0)	3/4 (75)
Clear cell	3	3/3 (100)	3/3 (100)	2/3 (67)	0/3 (0)	0/3 (0)	0/3 (0)	0/3 (0)	0/3 (0)	0/3 (0)	0/3 (0)	0/3 (0)	0/3 (0)	3/3 (100)
Atypical	30	28/30 (93)	29/30 (97)	13/21 (62)	7/30 (23)	0/30 (0)	4/30 (13)	0/30 (0)	1/26 (4)	0/30 (0)	0/30 (0)	0/26 (0)	0/30 (0)	26/30 (87)
Anaplastic	8	6/8 (75)	8/8 (100)	1/5 (20)	2/8 (25)	0/6 (0)	1/8 (13)	0/6 (0)	0/5 (0)	0/6 (0)	0/6 (0)	0/6 (0)	0/6 (0)	3/5 (60)

TABLE 4. Diagnostic Performance of Selected Single Antibodies or Panels to Distinguish Meningioma From Other Tumors

Meningioma	Markers (panel)	vs all tumors							
		Sensitivity	95% CI	Specificity	95% CI	Positive predictive value	95% CI	Negative predictive value	95% CI
All type/grade	EMA+	89.6	82.6–94	87.5	80.5–92.3	86.9	79.6–91.9	89.9	83–94.3
	PR +	75	64.6–83.2	90.7	83.7–95	86.3	76.3–92.6	82.4	74.6–88.3
	SSTR2A+	95.2	89.5–98	92	85.7–95.7	91.6	85.1–95.5	95.4	89.9– 98.1
	EMA+ and PR +	71.7	61.2–80.4	97.5	92.3–99.3	95.6	87–98.9	81.7	74.1–87.5
	EMA+ and SSTR2A+	84.9	77.2–90.4	94.8	89.4–97.7	93.8	87.3–97.3	87.2	80.6–91.9
	EMA+ and/or SSTR2A+	100	96.3–100	83.8	76.3–89.4	85.1	78.1–90.2	100	95.9–100
Grade I	EMA+	88.9	79.5–94.5	87.5	80.5–92.3	80.9	70.9–88.2	92.9	86.7–96.5
	PR +	85.2	73.3–92.6	90.7	83.7–95	82.5	70.5–90.5	92.3	85.5–96.2
	SSTR2A+	93.8	85.5–97.7	91.9	85.7–95.7	87.3	78–93.2	96.2	90.8–98.5
	EMA+ and PR +	73.8	60.7–83.8	97.5	92.3–99.3	93.7	81.8–98.4	88.9	80.8–92.7
	EMA+ and SSTR2A+	82.7	72.3–89.9	94.8	89.4–97.7	90.5	80.9–95.8	90.2	83.8–94.3
	EMA+ and/or SSTR2A+	100	94.3–100	83.8	76.3–89.4	78.6	69.2–85.8	100	95.9–100
Grade II	EMA+	94.6	80.4–99	87.5	80.5–92.3	67.3	52.8–79.3	98.3	93.6–99.7
	PR +	65.4	44.4–82	90.7	83.7–95	60.7	40.7–77.9	92.3	85.5–96.2
	SSTR2A+	97.3	84.2–99.8	91.2	84.8–95.2	75	60.1–85.9	99.2	95–100
	EMA+ and PR +	65.4	44.4–82	97.5	92.3–99.3	85	61.1–96	92.8	86.4–96.4
	EMA+ and SSTR2A+	91.9	77–97.9	94.8	89.4–97.7	82.9	67.3–92.3	97.3	91.6–99.3
	EMA+ and/or SSTR2A+	100	88.3–100	83.8	76.3–89.4	62.7	49.1–74.6	100	95.9–100
Grade III	EMA+	75	35.6–95.5	87.5	80.5–92.3	26.1	11–48.7	98.3	93.6–97.7
	PR +	20	1–70.1	90.7	83.7–95	8.3	0.4–40.2	96.7	90.6–98.6
	SSTR2A+	100	59.7–100	91.2	84.8–95.2	40	20–63.6	100	96.3–100
	EMA+ and PR +	20	1–70.1	97.5	92.3–99.3	25	1.3–78	96.7	91.2–98.9
	EMA+ and SSTR2A+	75	35.6–95.5	94.8	89.4–97.7	46.2	20.4–73.9	98.5	94.1–99.7
	EMA+ and/or SSTR2A+	100	59.7–100	83.8	76.3–89.4	26.7	13–46.2	100	95.9–100
Fibrous	EMA+	87.5	60.4–97.8	87.5	80.5–92.3	45.2	27.8–63.7	98.3	93.6–99.7
	PR +	75	42.8–93.3	90.7	83.7–95	42.1	21.1–66	97.3	91.7–99.3
	SSTR2A+	75	47.4–91.7	91.2	84.8–95.2	50	29.6–70.4	96.9	91.8–99
	EMA+ and PR +	66.7	35.4–88.7	97.5	92.3–99.3	70	37.4–91.9	96.7	91.2–98.9
	EMA+ and SSTR2A+	62.5	35.9–83.7	94.8	89.4–97.7	58.8	33.5–80.6	95.6	90.2–98.2
	EMA+ and/or SSTR2A+	100	75.9–100	83.8	76.3–89.4	42.1	26.7–59	100	95.9–100

CI, confidence interval.

and the differential diagnosis with other tumors. The results are summarized in Tables 4–6. Expression patterns of selected IHC markers are represented in Figure 1.

For the diagnosis of meningioma, the single marker SSTR2A showed the best sensitivity (95.2%), specificity (92%), PPV (91.6%) and NPV (95.4%). All meningiomas expressed at least one of the 2 markers EMA or SSTR2A. Thus, the panel "EMA-positive and/or SSTR2A-positive" showed optimal sensitivity and NPV (both 100%) regardless of the grade, with a specificity of 83.8%. In addition, 107/126 (84.9%) meningiomas expressed both markers concomitantly. The sensitivity of the panel "EMA-positive and SSTR2A-positive" was lower than the panel "EMA-positive and/or SSTR2A-positive" (84.9% vs 100%), but showed a higher specificity (94.8% vs 83.8%).

For the fibrous subtype of meningioma, the single marker EMA-positive had the best sensitivity and NPV (87.5% and 98.3%, respectively). The panel "EMA-positive and/or SSTR2A-positive" showed the best sensitivity and NPV, (both 100%), and the panel "EMA-positive and PR-positive" had the best specificity for fibrous meningioma.

The panels "EMA-positive and PR-positive", "EMA-positive and SSTR2A-positive" showed the best specificity, (97.5% and 94.8%, respectively) irrespective of the grade and type of meningioma. Among these 2 panels, the combination "EMA-positive and SSTR2A-positive" had the highest sensitivity. However, these 2 markers were not sufficient to differentiate meningioma from synovial sarcoma. In this situation, AE1/AE3 was able to assist. AE1/AE3 was expressed by half of the synovial sarcomas assessed, and was rarely expressed in meningiomas, except in the secretory subtype, which showed a characteristic morphology with pseudopsammoma bodies, and thus did not require IHC analysis.

For differential diagnosis with SFT/HPC (Table 5), STAT6 showed perfect (100%) sensitivity, specificity, PPV, and NPV, and thus was sufficient for use alone to confirm or exclude SFT/HPC. CD34 had good sensitivity (92%) although

TABLE 5. Diagnostic Performance of Selected Single Antibodies or Panels to Distinguish Meningiomas From Solitary Fibrous Tumor/Hemangiopericytomas

Meningioma	Markers (panel)	vs SFT/HPC							
		Sensitivity	95% CI	Specificity	95% CI	Positive PV	95% CI	Negative PV	95% CI
All type/grade	EMA+	89.7	82.7–94.2	76	54.5–89.8	95	88.9–97.9	59.4	40.8–75.8
	PR +	75	64.7–83.2	81.3	53.7–95	95.8	87.5–98.9	36.1	21.3–53.8
	SSTR2A+	95.2	89.5–98	92	72.5–98.6	98.3	93.6–99.7	79.3	59.7–91.3
	EMA+ and PR +	71.7	61.2–80.4	100	75.9–100	100	93.1–100	38.1	24–54.3
	EMA+ and SSTR2A+	84.9	77.2–90.4	96	77.7–99.8	99.1	94.2–100	55.8	40–70.6
	EMA+ and/or SSTR2A+	100	96.3–100	72	50.4–87.1	94.7	89–97.7	100	78.1–100
	CD34−	92.1	85.5–95.9	73.1	51.9–87.6	94.3	88.2–97.4	65.5	45.7–81.4
	STAT6−	100	96.2–100	100	84–100	100	96.2–100	100	84–100
Fibrous	EMA+	87.5	60.4–97.8	76	54.5–89.8	70	34.1–65.9	90.5	68.2–98.3
	PR +	75	42.8–93.3	81.3	53.7–95	75	42.8–93.3	81.3	53.7–95
	SSTR2A+	75	47.4–91.7	92	72.5–98.6	85.7	56.2–97.5	85.2	65.4–95.1
	EMA+ and PR +	66.7	35.4–88.7	100	75.9–100	100	59.8–100	80	55.7–93.4
	EMA+ and SSTR2A+	62.5	35.9–83.7	96	77.7–99.8	90.9	57.1–99.5	80	60.9–91.6
	EMA+ and/or SSTR2A+	100	75.9–100	72	50.4–87.1	69.6	47–85.9	100	78.1–100
	CD34−	87.5	60.4–97.8	73.1	51.9–87.6	66.7	43.1–84.5	90.5	68.2–98.3
	STAT6−	100	75.9–100	100	84–100	100	75.9–100	100	83.4–100

CI, confidence interval; PV, predictive value.

TABLE 6. Diagnostic Performance of Selected Single Antibodies or Panels to Distinguish Meningiomas From Schwannomas

Meningioma	Markers (panel)	vs Schwannoma							
		Sensitivity	95% CI	Specificity	95% CI	Positive PV	95% CI	Negative PV	95% CI
All type/grade	EMA+	89.7	82.7–94.2	94.9	81.4–99.1	98.3	93.2–99.7	74	59.4–84.9
	PR +	75	64.7–83.2	96.9	82–99.8	98.6	91.2–99.9	57.4	43.3–70.5
	SSTR2A+	95.2	89.5–98	100	88.8–100	100	96.1–100	86.7	72.5–94.5
	EMA+ and PR +	71.7	61.2–80.4	100	86.6–100	100	93.1–100	55.2	41.6–68
	EMA+ and SSTR2A+	84.9	77.2–90.4	100	88.8–100	100	95.7–100	67.2	53.5–78.6
	EMA+ and/or SSTR2A+	100	96.3–100	94.9	81.4–99.1	98.4	93.9–99.7	100	88.3–100
	S100−	65.8	56.8–73.9	97.4	84.9–99.9	98.8	92.6–99.9	46.9	35.8–53.3
	SOX10−	100	96.2–100	94.3	79.5–99	98.4	93.7–99.7	100	87–100
Fibrous	EMA+	87.5	60.4–97.8	94.9	81.4–99.1	87.5	60.4–97.8	94.9	81.4–99.1
	PR +	75	42.8–93.3	96.9	82–99.8	90	54.1–99.5	91.2	75.2–97.7
	SSTR2A+	75	47.4–91.7	100	88.8–100	100	69.9–100	90.7	76.9–97
	EMA+ and PR +	66.7	35.4–88.7	100	86.6–100	100	59.7–100	88.9	73–96.4
	EMA+ and SSTR2A+	62.5	35.9–83.7	100	88.8–100	100	65.5–100	86.7	72.5–94.4
	EMA+ and/or SSTR2A+	100	75.9–100	94.9	81.4–99.1	88.9	63.9–98	100	88.3–100
	S100−	18.7	5–46.3	97.4	84.9–99.9	75	81.9–99.9	74.5	60–85.2
	SOX10−	100	75.9–100	94.3	79.5–99	88.9	63.9–98	100	87–100

CI, confidence interval; PV, predictive value.

its specificity was insufficient (73%) to be used alone for the diagnosis of SFT/HPC.

For the differential diagnosis of schwannoma (Table 6), SSTR2A had perfect (100%) specificity and PPV, and good sensitivity (95.2%). SOX10 had perfect sensitivity and NPV, and good specificity (94.3%) and PPV (98.4%). However, SSTR2A was less sensitive (75%) than SOX10 for fibrous meningioma diagnosis, although it was still specific (100%). Thus, these 2 markers can be used alone or in combination, particularly for fibrous meningiomas, to differentiate schwannoma from meningioma.

According to all the IHC markers diagnostic performance results, we proposed a diagnosis algorithm to distinguish meningioma from their mimics (Fig. 2).

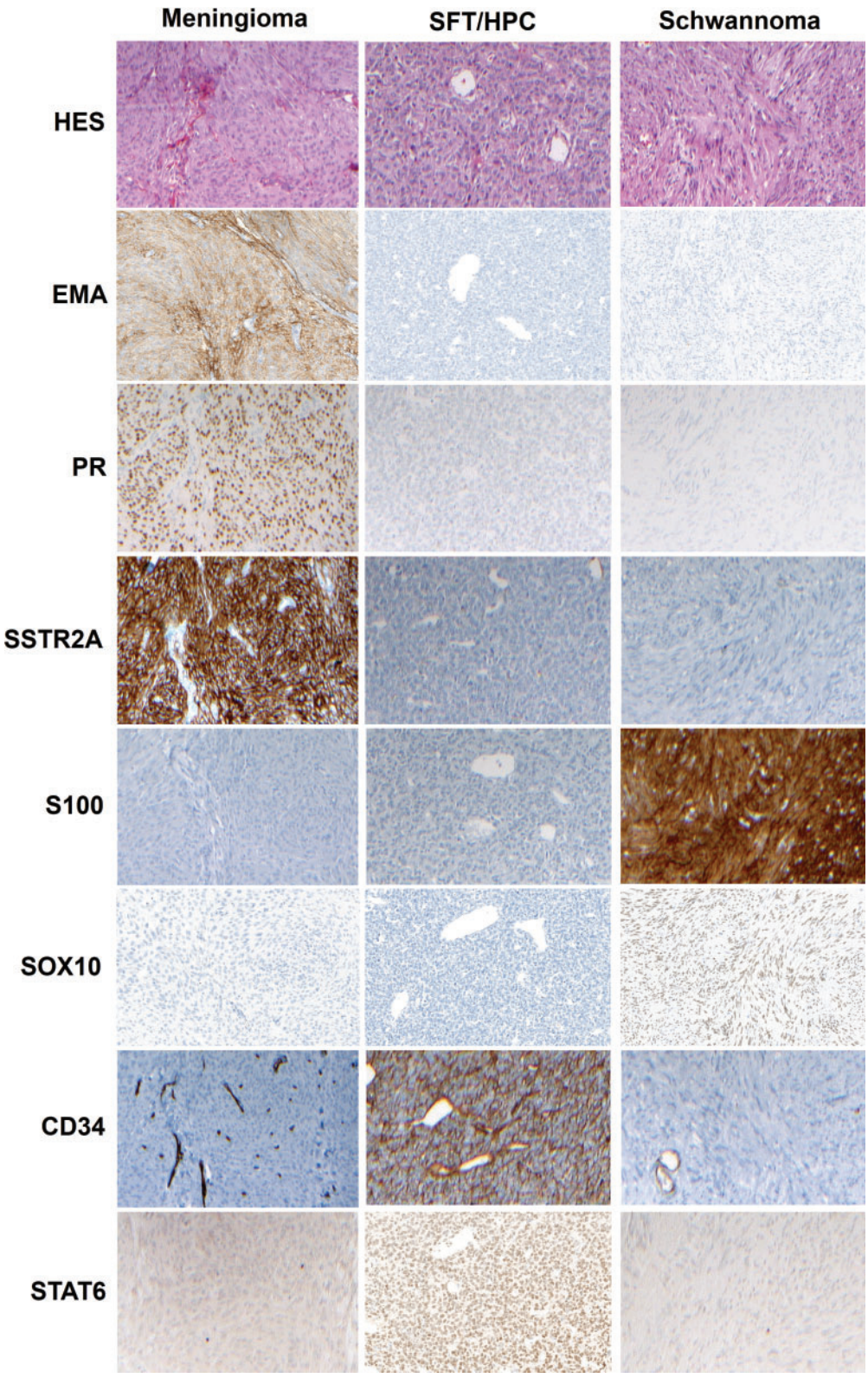

FIGURE 1. Expression patterns of selected antibodies in cases of meningothelial meningioma, SFT/HPC, and schwannoma. The vast majority (>90%) of meningothelial meningiomas show diffuse and strong staining for EMA, PR (progesterone receptor) and SSTR2A. Characteristic positivity for CD34 and STAT6 was observed in cases of SFT/HPC, and for S100 and SOX10 in cases of schwannoma. All photographs were taken at × 100 magnification. HES, hematoxylin and eosin.

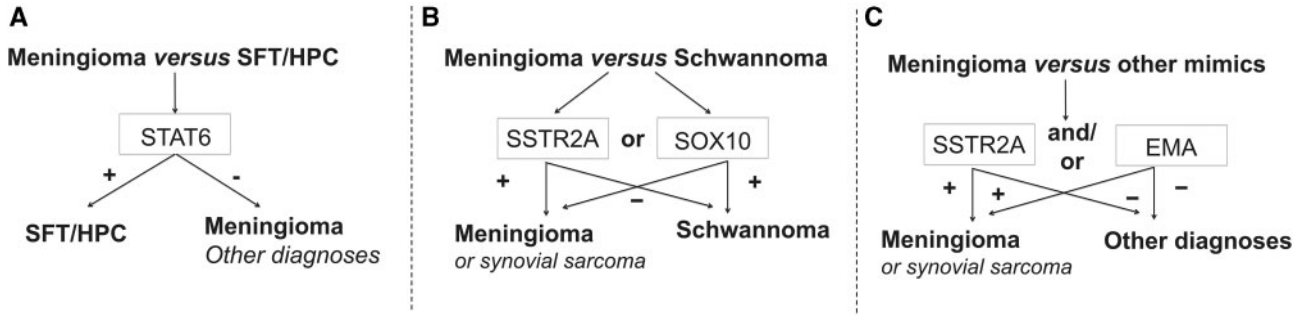

FIGURE 2. Immunohistochemical algorithm to differentiate meningioma and their mimics. **(A)** Algorithm to differentiate meningioma and solitary fibrous tumor/hemangiopericytoma (SFT/HPC). **(B)** Algorithm to differentiate meningioma and schwannoma. **(C)** Algorithm to differentiate meningioma and other meningeal tumors.

DISCUSSION

In this study, we analyzed a data set of 13 antibodies in 265 tumors of 10 different types that could be found in the CNS or in the adjacent soft tissue, and that could have overlapping morphologies. Specifically, we focused on IHC performance for the differential diagnosis of meningiomas from their mimics.

SSTR2A was the single most sensitive and specific marker for the diagnosis of meningioma, with good sensitivity (95.2%) and specificity (92%). SSTR2A is a member of the somatostatin receptor family. It was found to be highly expressed in meningioma, and thus its ligand can be used as a scintigraphy tracer. SSTR2A was also assessed as a potential therapeutic target for somatostatin analogue-based therapies in the treatment of meningioma (13, 14). In our study, SSTR2A IHC expression in meningioma was not grade dependent. However, SSTR2A was less sensitive than EMA for the diagnosis of fibrous meningioma (75% vs 87.5%). In previous studies, SSTR2A has been found to be expressed by 73%–100% of meningiomas (6, 9, 13, 15). Only 1 previous study has reported that SSTR2A expression was influenced by the grade of meningiomas, with the degree of expression increasing from grade I (54%) to grade III (100%) (13). In previous studies, IHC and mRNA expression of SSTR2A was also higher in meningothelial and transitional meningiomas than in fibrous meningiomas (6, 16). In our study, all SSTR2A negative meningiomas, especially those of the fibrous subtype, expressed EMA and inversely all EMA negative meningioma expressed SSTR2A. Thus, the combination of these 2 markers facilitates the detection of all meningiomas. The panel EMA-positive and PR-positive were the most specific for the diagnosis of meningioma, although it lacked sufficient sensitivity.

SSTR2A was also strongly expressed by almost all synovial sarcomas (6/7) and sporadically expressed by 8% (2/25) of SFT/HPC, 22% (2/9) of pPNET, and 11% (1/9) of gliosarcomas. Few studies have evaluated SSTR2A expression for the differential diagnosis of meningioma from other tumors with overlapping morphologies such as schwannoma, SFT/HPC, MPNST, melanoma, pPNET, and perineurioma (6, 9, 17). In these studies, SSTR2A was expressed by 33% of pPNET, 15% of MPNSTs, 15% of SFTs/HPCs, 5% of perineuriomas, and 3% of schwannomas. We are the first to assess SSTR2A expression in synovial sarcomas, gliosarcomas, and hemangioblastomas. SSTR2A was not expressed by glioblastomas and hemangioblastomas, and thus can be helpful to distinguish these tumors from meningiomas, especially in cases of anaplastic, clear cell, or microcystic subtypes. However, almost all synovial sarcomas expressed SSTR2A. Thus, SSTR2A, like EMA, is not a useful marker to distinguish meningioma from synovial sarcoma. In this infrequent differential diagnostic situation, AE1/AE3 IHC is useful. Indeed, in our study, AE1/AE3 was expressed by half of the synovial sarcomas and rarely expressed by meningiomas, except those of the secretory subtype. No fibrous meningioma expressed AE1/AE3. However, identification of the translocation t(X;18)(SS18-SS1/2) is the most specific test for the diagnosis of synovial sarcoma, and should be systematically performed when synovial sarcoma is suspected (18).

Recently, the *NAB2-STAT6* gene fusion has been identified as the molecular hallmark of SFT/HPC (19–21). The detection of nuclear relocation of STAT6 with IHC indicates the presence of the *NAB2-STAT6* fusion or other alterations involving STAT6, and can helps to discriminate SFTs from histological mimics (22). STAT6 IHC is a valuable and high-performing tool for the indirect detection of this gene fusion. STAT6 IHC was evaluated in meningeal SFT/HPC in 2 studies (7, 23) and in meningiomas in 1 (7). In our study, STAT6 showed perfect (100%) sensitivity, specificity, PPV, and NPV. Thus, this single assessment is sufficient for the diagnosis or exclusion of SFT/HPC. In previous studies concerning meningeal SFT/HPC, STAT6 IHC had good (94.6%) to perfect (100%) sensitivity and a perfect (100%) specificity (7, 10, 23). Among the different studies on meningeal SFT/HPC and meningiomas, *NAB2-STAT6* fusion has been found in only 1 case of meningioma. This case was a grade III meningioma with an unusual histological appearance and immunophenotype of both meningioma and SFT/HPC (24). STAT6 IHC was not performed for this case.

For the differential diagnosis between meningioma and SFT/HPC, CD34 had, in our study, good sensitivity (92%) but insufficient specificity (73%). As in previous studies, CD34 was more frequently expressed in grade I (SFT type) than in grade II (HPC type) SFT/HPC (23).

As in a previous study (25), BCL2 positivity was not specific of SFT/HPC, as expression was observed in all the tumors tested.

In our study, SOX10 was the single most sensitive and specific marker to differentiate schwannoma from meningioma, showing good sensitivity (94%) and perfect specificity and PPV (100%). S100 was very sensitive (97%) but lacked specificity, especially for the differentiation between fibrous meningioma and schwannoma (19%). SOX10 is a neural crest transcription factor crucial for the specification, maturation, and maintenance of Schwann cells and melanocytes. In our study, SOX10 was expressed by almost all schwannomas (33/35, 94%), neurofibromas (4/5, 80%) and melanomas (17/20, 85%). Only 1 of the 5 MPNSTs (20%) expressed SOX10. None of the meningiomas, SFT/HPC, gliosarcomas, or synovial sarcomas expressed SOX10. Thus, this marker had optimum specificity and PPV to differentiate schwannoma from these entities. In previous studies (5, 8, 26), SOX10 was expressed by 98.7%–100% of schwannomas, 100% of neurofibromas, 87%–97% of melanomas, and 20%–67% of MPNST. The highest percentage of positivity for MPNST was obtained in a study using whole slide sections for IHC (27). Other studies (8, 26) using TMA had 21%–30% SOX10 positivity, as in our study. Thus, TMA could underestimate SOX10 positivity. SOX10 expression had been assessed in meningiomas in 2 previous studies. In one of these studies, similar to the results of our study, none of the 219 meningiomas expressed SOX10 (8). In the remaining study, 4 (1 fibrous, 3 other subtypes) of the 166 meningiomas expressed SOX10. Thus, this marker appears to be highly specific for the distinction of schwannoma from its mimics, with the exception of melanomas.

We evaluated other markers that could be useful for the distinction of meningioma from other mimics, such as melanoma, hemangioblastoma, gliosarcoma, and pPNET. For melanoma, HMB45 and MelanA showed good sensitivity and perfect specificity, and thus can be used in combination with SSTR2A and/or EMA to distinguish melanoma from meningioma.

SSTR2A, EMA, and PR were rarely expressed by gliosarcomas, and pPNET. In 1 previous study regarding meningeal pPNET, none of the cases expressed EMA (28). SSTR2A and PR were not evaluated. In this study, all cases of pPNET expressed FLI1, which is a specific marker for PNET.

GFAP positivity can help to identify glioblastoma components in gliosarcomas. In the present study, only half of the cases showed GFAP positivity. This lack of GFAP expression may be due to the selection of the sarcomatous components for TMA construction.

None of the hemangioblastomas expressed EMA, SSTR2A, or PR. Moreover, in our study, inhibin was exclusively expressed by hemangioblastomas. However, slightly more than half (56%) of hemangioblastomas expressed this marker. In previous studies, inhibin was found to be expressed in 88%–100% of hemangioblastomas (29–33). This difference may be due to a patchy inhibin expression observed in some hemangioblastomas (33). Only 1 study assessed inhibin expression in meningiomas (29). In these studies 14 of 20 meningiomas expressed inhibin. This discrepant result regarding inhibin expression in meningiomas requires clarification in future studies.

In conclusion, when considering the diagnosis of meningeal SFT/HPC vs meningioma, we recommend determining the expression of STAT6 as the first step. When considering a diagnosis between schwannoma and meningioma, SSTR2A or SOX10 IHC can be used alone or in combination as the initial assessment. For other differential diagnoses, SSTR2A alone or in combination with EMA are the most specific markers for the diagnosis of meningioma, with the exception of meningioma vs synovial sarcoma. Other specific IHC markers such as SOX10, MelanA, or HMB45 for melanoma, and FLI1 for pPNET, could be combined with SSTR2A or EMA. In our study, inhibin had excellent specificity for the differential diagnosis of meningioma vs hemangioblastoma; however, another study found discrepant results. Thus, in this situation, we recommend the use of SSTR2A and/or EMA first.

ACKNOWLEDGMENT

The authors thank Nicole Bouland, Stephanie Vicente, and Marylene Couval for their excellent technical assistance.

REFERENCES

1. Ligon KL, Mokhtari K, Smith TW, Tumors of the central nervous system. In: Gray F, Duyckaerts C, De Girolami U, eds. Escourolle and Poirier's Manual of Basic Neuropathology, Fifth Edition. Oxford, UK: Oxford University Press 2013:20–58
2. Perry A, Louis DN, Budka H, et al. Meningioma. In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, eds. WHO classification of tumours of the central nervous system, Fourth Edition revised. Lyon, France: IARC press 2016:232–45
3. Liu Y, Wang H, Shao H, et al. Primary extradural meningiomas in head: A report of 19 cases and review of literature. Int J Clin Exp Pathol 2015; 8:5624–32
4. Mezmezian MB, Carassai MB, Dopazo V, et al. Immunohistochemical expression of progesterone receptors in nonmeningothelial central nervous system tumors. Appl Immunohistochem Mol Morphol 2016; doi: 10.1097/PAI.0000000000000318
5. Ng J, Celebre A, Munoz DG, et al. Sox10 is superior to S100 in the diagnosis of meningioma. Appl Immunohistochem Mol Morphol 2015;23: 215–9
6. Agaimy A, Buslei R, Coras R, et al. Comparative study of soft tissue perineurioma and meningioma using a five-marker immunohistochemical panel. Histopathology 2014;65:60–70
7. Macagno N, Figarella-Branger D, Mokthari K, et al. Differential diagnosis of meningeal SFT-HPC and meningioma: Which immunohistochemical markers should be used?. Am J Surg Pathol 2016;40:270–8
8. Miettinen M, McCue PA, Sarlomo-Rikala M, et al. Sox10: a marker for not only schwannian and melanocytic neoplasms but also myoepithelial cell tumors of soft tissue—a systematic analysis of 5134 tumors. Am J Surg Pathol 2015;39:826–35
9. Menke JR, Raleigh DR, Gown AM, et al. Somatostatin receptor 2a is a more sensitive diagnostic marker of meningioma than epithelial membrane antigen. Acta Neuropathol 2015;130:441–3
10. Schweizer L, Koelsche C, Sahm F, et al. Meningeal hemangiopericytoma and solitary fibrous tumors carry the NAB2-STAT6 fusion and can be diagnosed by nuclear expression of STAT6 protein. Acta Neuropathol 2013;125:651–8
11. Fletcher CDM, Bridge JA, Hogendoorn PCW, et al. Who Classification of Tumours of Soft Tissue and Bone, Fourth Edition. Lyon, France: IARC press, 2013
12. Roser F, Nakamura M, Bellinzona M, et al. The prognostic value of progesterone receptor status in meningiomas. J Clin Pathol 2004;57:1033–7
13. Barresi V, Alafaci C, Salpietro F, et al. Sstr2A immunohistochemical expression in human meningiomas: Is there a correlation with the histological grade, proliferation or microvessel density?. Oncol Rep 2008;20: 485–92
14. Collamati F, Pepe A, Bellini F, et al. Toward radioguided surgery with β-decays: Uptake of a somatostatin analogue, DOTATOC, in meningioma and high-grade glioma. J Nucl Med 2015;56:3–8

15. Silva CB, Ongaratti BR, Trott G, et al. Expression of somatostatin receptors (SSTR1-SSTR5) in meningiomas and its clinicopathological significance. Int J Clin Exp Pathol 2015;8:13185–92
16. Durand A, Champier J, Jouvet A, et al. Expression of c-Myc, neurofibromatosis Type 2, somatostatin receptor 2 and erb-B2 in human meningiomas: relation to grades or histotypes. Clin Neuropathol 2008;27:334–45
17. Johnson MD, O'Connell MJ, Silberstein, et al. Differential expression of somatostatin receptors, P44/42 MAPK, and mTOR activation in medulloblastomas and primitive neuroectodermal tumors. Appl Immunohistochem Mol Morphol 2013;21:532–8
18. Foo WC, Cruise MW, Wick MR, et al. Immunohistochemical staining for TLE1 distinguishes synovial sarcoma from histologic mimics. Am J Clin Pathol 2011;135:839–44
19. Robinson DR, Wu YM, Kalyana-Sundaram S, et al. Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. Nat Genet 2013;45:180–5
20. Chmielecki J, Crago AM, Rosenberg M, et al. Whole-exome sequencing identifies a recurrent NAB2-STAT6 fusion in solitary fibrous tumors. Nat Genet 2013;45:131–2
21. Mohajeri A, Tayebwa J, Collin A, et al. Comprehensive genetic analysis identifies a pathognomonic NAB2/STAT6 fusion gene, nonrandom secondary genomic imbalances, and a characteristic gene expression profile in solitary fibrous tumor. Genes Chrom Cancer 2013;52:873–86
22. Koelsche C, Schweizer L, Renner M, et al. Nuclear relocation of STAT6 reliably predicts NAB2-STAT6 fusion for the diagnosis of solitary fibrous tumour. Histopathology 2014;65:613–22
23. Fritchie KJ, Jin L, Rubin BP, et al. NAB2-STAT6 gene fusion in meningeal hemangiopericytoma and solitary fibrous tumor. J Neuropathol Exp Neurol 2016;75:263–71
24. Gao F, Ling C, Shi L, et al. Inversion-mediated gene fusions involving NAB2-STAT6 in an unusual malignant meningioma. Br J Cancer 2013;109:1051–5
25. Chilosi M, Facchetti F, Dei Tos AP, et al. Bcl-2 expression in pleural and extrapleural solitary fibrous tumours. J Pathol 1997;181:362–7
26. Nonaka D, Chiriboga L, Rubin BP. Sox10: A pan-schwannian and melanocytic marker. Am J Surg Pathol 2008;32:1291–8
27. Kang Y, Pekmezci M, Folpe AL, et al. Diagnostic utility of SOX10 to distinguish malignant peripheral nerve sheath tumor from synovial sarcoma, including intraneural synovial sarcoma. Mod Pathol 2014;27:55–61
28. Ke C, Duan Q, Yang H, et al. Immunohistochemical and FISH study of four cases. Neuropathology 2016;37(1):35–44
29. Gurses I, Scheithauer BW. Inhibin-A immunoreactivity in nervous system lesions. Appl Immunohistochem Mol Morphol 2012;20:277–84
30. Jung SM, Kuo TT. Immunoreactivity of CD10 and inhibin alpha in differentiating hemangioblastoma of central nervous system from metastatic clear cell renal cell carcinoma. Mod Pathol 2005;18:788–94
31. Hoang MP, Amirkhan RH. Inhibin alpha distinguishes hemangioblastoma from clear cell renal cell carcinoma. Am J Surg Pathol 2003;27:1152–6
32. Weinbreck N, Marie B, Bressenot A, et al. Immunohistochemical markers to distinguish between hemangioblastoma and metastatic clear-cell renal cell carcinoma in the brain: Utility of aquaporin1 combined with cytokeratin AE1/AE3 immunostaining. Am J Surg Pathol 2008;32:1051–9
33. Carney EM, Banerjee P, Ellis CL, et al. PAX2(−)/PAX8(−)/inhibin A(+) immunoprofile in hemangioblastoma: A helpful combination in the differential diagnosis with metastatic clear cell renal cell carcinoma to the central nervous system. Am J Surg Pathol 2011;35:262–7