Title

Somatostatin receptor 2a is a more sensitive diagnostic marker of meningioma than epithelial membrane antigen

Journal

Acta Neuropathologica, 130(3)

ISSN

0001-6322

Authors

Menke, JR
Raleigh, DR
Gown, AM
et al.

Publication Date

2015-09-21

DOI

10.1007/s00401-015-1459-3

Peer reviewed

Acta Neuropathol (2015) 130:441–443
DOI 10.1007/s00401-015-1459-3

CORRESPONDENCE

Somatostatin receptor 2a is a more sensitive diagnostic marker of meningioma than epithelial membrane antigen

Joshua R. Menke[1] · David R. Raleigh[2] · Allen M. Gown[4] · Sean Thomas[3] · Arie Perry[1] · Tarik Tihan[1]

Received: 1 June 2015 / Revised: 8 July 2015 / Accepted: 10 July 2015 / Published online: 21 July 2015

Meningioma is the most common extraaxial primary central nervous system tumor. While most are diagnosed on routine hematoxylin- and eosin-stained sections, the morphologic spectrum is wide and immunohistochemistry (IHC) is occasionally necessary for diagnosis. Currently, the most reliable IHC markers for meningioma are epithelial membrane antigen (EMA) and progesterone receptor (PR), though both have suboptimal sensitivities and specificities [4, 7]. Previous studies suggest that meningiomas express somatostatin receptors, especially somatostatin receptor 2a (SSTR2a) [1, 5, 6, 8], and one prior study found that a polyclonal SSTR2a antibody stained 87 % of WHO grade I and grade II meningiomas, although EMA stained 97 % of the same cohort [2]. A commercially available monoclonal SSTR2a antibody was recently developed [3]. STAT3 is a potential downstream target of SSTR2a in mouse embryonic stem cells [9]. Therefore, we studied a large meningioma tissue microarray (TMA) with SSTR2a, EMA, PR and phosphorylated STAT3 (pSTAT3) immunohistochemistry.

Representative blocks from 176 meningiomas resected between 2002 and 2012 at UCSF were retrieved. Small biopsy material and decalcified or frozen tissues were excluded, yielding a study cohort of 128 WHO grade I, 36 WHO grade II, and 12 WHO grade III meningiomas. The following rare histologic variants of meningioma were included: 7 angiomatous, 3 secretory, 2 osseous metaplasia, 4 psammomatous, 2 microcystic, 2 chordoid, 1 lymphoplasmacyte rich, and 1 rhabdoid meningioma. The remaining 147 meningiomas represented more common subtypes, such as meningothelial, fibrous, and transitional forms. Two 2 mm cores were taken from each block to generate the TMA, along with control tissue from normal adult brain, normal adult meninges, 2 lung adenocarcinomas, and placenta. TMAs containing 13 cellular schwannomas, 23 schwannomas, and 33 malignant peripheral nerve sheath tumors, 38 metastatic carcinomas, 48 metastatic melanomas were also studied, along with 13 whole section meningeal hemangiopericytomas/solitary fibrous tumors.

The following antibodies were used for IHC after optimization of pretreatment and primary antibody dilutions: EMA (DAKO, E29, 1:200); SSTR2a (Epitomics, UMB1, monoclonal, 1:2000); PR (DAKO, PgR 636, 1:500); and pSTAT3 (Cell Signaling, D3A7, 1:100). Each tissue core was scored based on percentage of tumor cells staining (0, 1+ for <25 % staining, 2+ for 26–75 % staining, or 3+ for more than 75 % staining) by two independent observers. All meningiomas stained strongly with SSTR2a; therefore, intensity was not scored.

Somatostatin receptor 2a stained both duplicate cores from all 176 meningiomas (100 %). EMA stained both duplicate cores in 168 cases (95 %), one duplicate core in 4 cases (2 %), and did not stain 4 cases (2 %). PR stained both duplicate cores in 136 (77 %) cases, one duplicate core in 14 cases (8 %), and did not stain 26 cases (15 %). For the meningiomas with discrepant SSTR2a and EMA staining on small TMA cores ($n = 8$), whole tissue sections were stained with both SSTR2a and EMA and confirmed the above findings. When immunostaining scores were analyzed based on differences among normal meninges,

✉ Joshua R. Menke
joshua.menke@ucsf.edu; jrmenk@email.wm.edu

1 Department of Pathology, University of California San Francisco, San Francisco, CA, USA

2 Department of Radiation Oncology, University of California San Francisco, San Francisco, CA, USA

3 Department of Bioinformatics, University of California San Francisco, San Francisco, CA, USA

4 PhenoPath Laboratories, Seattle, WA, USA

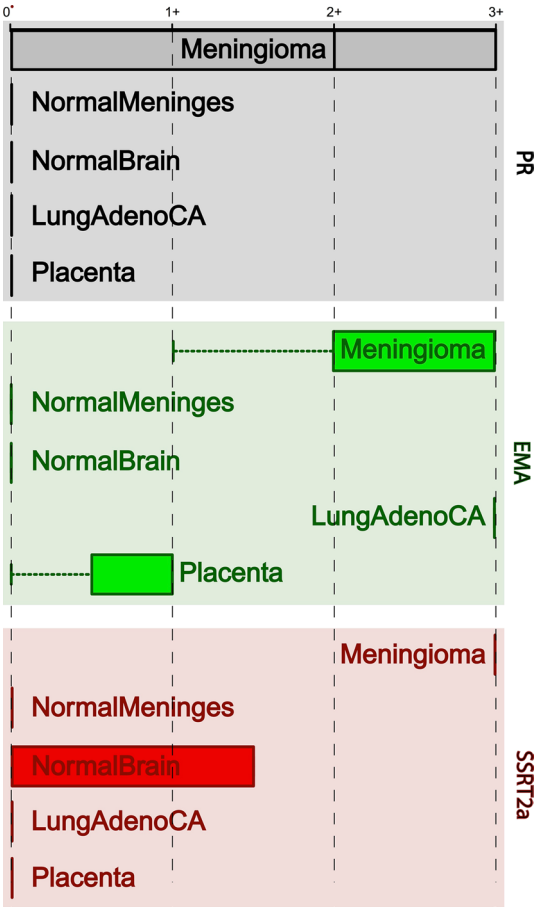

Fig. 1 Interquartile ranges of IHC scores demonstrate that SSTR2a is the most reliable marker for distinguishing meningioma from normal meninges. SSTR2a showed at least 1+ staining in every core and over 75 % of cores showed 3+ staining. In contrast, EMA stained meningioma less reliably and also stained lung adenocarcinoma and placenta. PR was inconsistent in its staining of meningioma

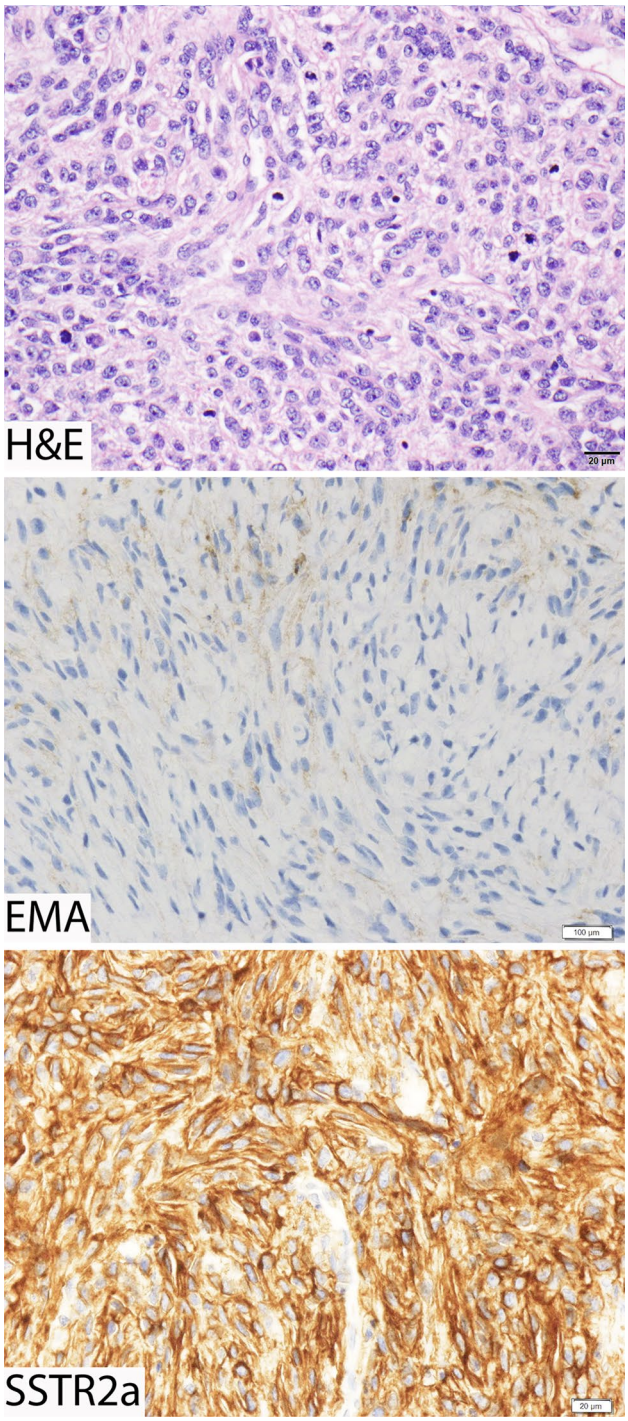

Fig. 2 Hematoxylin- and eosin-stained sections of this WHO grade III meningioma show a proliferation of atypical ovoid to spindle cells with enlarged, irregular nuclei, open chromatin, indistinct nucleoli, and multiple mitotic figures. An EMA immunohistochemical stain is negative in tumor cells. SSTR2a immunohistochemical stain shows strong, diffuse membranous and cytoplasmic positivity in tumor cells

meningioma, and lung adenocarcinoma by the Mann–Whitney Wilcoxon test, SSTR2a ($p < 6.3$ e-7) was again superior to EMA ($p < 4.8$ e-6) and PR ($p < 0.01$). Interquartile ranges of the different immunostain scores (Fig. 1) confirm that SSTR2a was the most reliable marker for the identification of meningioma. In particular, SSTR2a was positive in all cases for which EMA ($n = 8$) and PR ($n = 40$) failed to stain the tumor, including one WHO grade III meningioma (Fig. 2).

Somatostatin receptor 2a was also able to distinguish meningioma from other mesenchymal neoplasms in a manner comparable to EMA. Of 36 traditional and cellular schwannomas, only 1 case (3 %) stained with SSTR2a in both cores, 6 cases (17 %) stained discrepantly between cores and the remaining 29 cases (80 %) were negative for SSTR2a. Of 33 MPNST cases, 5 cases (15 %) stained with SSTR2a in both cores, 9 cases (27 %) stained discrepantly between cores, and 19 cases (58 %) were negative for SSTR2a. Importantly, none of the mesenchymal tumors tested showed 3+ SSTR2a staining. The entire data set was analyzed defining 1+ or greater staining in both tissue

cores as SSTR2a positive and all other staining patterns as negative and showed a 100 % sensitivity, 88 % specificity, 94 % positive predictive value, and 100 % negative predictive value for meningioma. Thirteen hemangiopericytomas/solitary fibrous tumors were evaluated for SSTR2a staining and while two tumors showed faint patchy SSTR2a staining by IHC, none showed strong, diffuse staining. None of the metastatic carcinomas (0/38) or metastatic melanomas (0/48) showed staining for SSTR2a. No correlation between pSTAT3 and SSTR2a immunoscoring was found using ordinal regression analysis ($p = 0.963$).

In summary, the monoclonal antibody for SSTR2a is a highly sensitive and specific marker for meningioma. SSTR2a is expressed in cases that do not express EMA or PR and does not frequently stain metastatic melanomas, metastatic carcinomas, or mesenchymal neoplasms that are often considered in the differential diagnosis of meningioma, including schwannomas, cellular schwannomas, malignant peripheral nerve sheath tumors, and hemangiopericytomas/solitary fibrous tumors. Thus, SSTR2a immunohistochemistry can be useful in establishing the diagnosis of meningioma, including high-grade meningiomas with poor differentiation.

Acknowledgments The authors would like to thank Ms. Kim Thompson, who performed the immunohistochemistry studies at PhenoPath, and Dr. Abul Abbas, Chair of the Department of Pathology at University of California San Francisco, who funded this work.

References

1. Arena S, Barbieri F, Thellung S, Pirani P, Corsaro A, Villa V, Dadati P, Dorcaratto A, Lapertosa G, Ravetti JL, Spaziante R, Schettini G, Florio T (2004) Expression of somatostatin receptor mRNA in human meningiomas and their implication in vitro antiproliferative activity. J Neurooncol 66:155–166
2. Agaimy A, Buslei R, Coras R, Rubin BP, Mentzel T (2014) Comparative study of soft tissue perineurioma and meningioma using a five-marker immunohistochemical panel. Histopathology 65:60–70
3. Körner M, Waser B, Schonbrunn A, Perren A, Reubi JC (2012) Somatostatin receptor subtype 2A immunohistochemistry using a new monoclonal antibody selects tumors suitable for in vivo somatostatin receptor targeting. Am J Surg Pathol 36:242–252
4. Lusis EA, Chicoine MR, Perry A (2005) High throughput screening of meningioma biomarkers using a tissue microarray. J Neurooncol 73:219–223
5. Reubi JC, Maurer R, Klijn JG, Stefanko SZ, Foekens JA, Blaauw G, Blankenstein MA, Lamberts SW (1986) High incidence of somatostatin receptors in human meningiomas: biochemical characterization. J Clin Endocrinol Metab 63:433–438
6. Reubi JC, Schaer JC, Waser B, Mengod G (1994) Expression and localization of somatostatin receptor SSTR1, SSTR2, and SSTR3 messenger RNAs in primary human tumors using in situ hybridization. Cancer Res 54:3455–3459
7. Schnitt SJ, Vogel H (1986) Meningiomas. Diagnostic value of immunoperoxidase staining for epithelial membrane antigen. Am J Surg Pathol 10:640–649
8. Schulz S, Pauli SU, Schulz S, Händel M, Dietzmann K, Firsching R, Höllt V (2000) Immunohistochemical determination of five somatostatin receptors in meningioma reveals frequent overexpression of somatostatin receptor subtype sst2A. Clin Cancer Res 6:1865–1874
9. Xu XX, Zhang LH, Xie X (2014) Somatostatin receptor type 2 contributes to the self-renewal of murine embryonic stem cells. Acta Pharmacol Sin 35:1023–1030