ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2018 Feb 15; 6(2):248-253.
https://doi.org/10.3889/oamjms.2018.062
eISSN: 1857-9655
Basic Science

Value of SSTR2A and Claudin - 1 in Differentiating Meningioma from Schwannoma and Hemangiopericytoma

Shady E. Anis[1*], Mira Lotfalla[1], Muhammad Zain[2], Nora N. Kamel[3], Ahmed A. Soliman[1]

[1]Cairo University School of Medicine - Pathology, Cairo, Egypt; [2]Al - Azhar University School of Medicine - Pathology, Cairo, Egypt; [3]National Research Center - Pathology, Giza, Egypt

Citation: Anis SE, Lotfalla M, Zain M, Kamel NN, Soliman AA. Value of SSTR2A and Claudin - 1 in Differentiating Meningioma from Schwannoma and Hemangiopericytoma. Open Access Maced J Med Sci. 2018 Feb 15; 6(2):248-253. https://doi.org/10.3889/oamjms.2018.062

Keywords: Meningioma; Hemangiopericytoma; Schwannoma; Claudin - 1; SSTR2A

***Correspondence:** Shady E. Anis. Cairo University School of medicine - Pathology, Cairo, Egypt. E-mail: shadyeliaanis76@yahoo.com

Received: 30-Sep-2017; **Revised:** 15-Oct-2017; **Accepted:** 20-Oct-2017; **Online first:** 29-Jan-2018

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: The distinction between meningioma, schwannoma and solitary fibrous tumour/ hemangiopericytoma can be challenging in some cases. This study evaluates the expression of Somatostatin receptor 2A (SSTR2A) and Claudin-1 in these different tumours.

MATERIAL AND METHODS: Thirty-five cases of meningioma, 10 cases of intracranial schwannoma and 10 cases of hemangiopericytoma were assessed. The immunohistochemical expression of SSTR2A and Claudin-1 was evaluated and scored according to the percentage of immunostained tumour cells (0: 1+, 2+ and 3). The intensity of staining was classified as weak, moderate and strong.

RESULTS: Positivity for SSTR2A and Claudin-1 was encountered in 89% and 49% of meningiomas respectively. None of the schwannomas or hemangiopericytomas was positive for any of both markers. All grade I and II meningiomas were positive for SSTR2A, and only 20% of grade III showed positive staining ($p < 0.05$). Claudin-1 positivity was detected in 50%, 43% and 60% of grade I, II and III meningioma respectively, with significantly higher intensity in grade III ($p < 0.05$).

CONCLUSION: SSTR2A is highly sensitive and specific for meningioma. Claudin-1 is highly specific for meningioma, with low sensitivity. The adjunctive use of both markers can be very helpful in the diagnosis of meningioma and its distinction from schwannoma and hemangiopericytoma.

Introduction

Meningiomas are the most common primary central nervous system (CNS) tumours accounting for 36% of all primary CNS tumours [1].

Since the first classification of meningioma introduced by Cushing in 1920 [2]; according to anatomical location; different classification schemes, adopted histology as the main factor in grading meningioma [3]. The recent WHO 2016 classification system, has grouped meningioma according to biological behavior into two groups, (1) Meningiomas with low risk of recurrence and aggressive behavior, including variants of WHO grade I meningiomas, and (2) Meningiomas with greater likelihood of recurrence and aggressive behavior, including variants of WHO grade II and grade III meningiomas and any subtype with high proliferation index, defined in one study as > 20 mitosis /10 HPF [4].

Both schwannomas of the cranio/spinal axis and meningeal Solitary fibrous tumour/ Hemangiopericytoma occur at a much lower frequency than meningioma. However, the distinction between these entities and meningioma can be challenging in some cases. Additional immunohistochemical studies are needed to resolve such cases [3]. The traditionally used immunohistochemical markers show some overlap in the expression between these entities [5][6][7].

Somatostatin receptors (SSTR) belong to a family of seven alpha-helical transmembrane spanning domains G protein-coupled receptors. They mediate the action of Somatostatin [8]. Somatostatin (SST) exerts inhibitory actions on some physiologic processes including pituitary and pancreatic hormone secretion, gastrointestinal peptide secretion and

motility. In the CNS, it plays a role as a neurotransmitter and neuromodulator affecting behaviour and cognition [9]. Finally, SST has a potent antiproliferative and antiangiogenic activity. Thus it can be used as an anti-neoplastic agent in tumours that express Somatostatin receptors [10][11].

The expression of somatostatin receptors is known to be frequent in meningioma [12]. There are five subtypes of somatostatin receptors (SSTR1-5). Among the five subtypes, SSTR2A was the most frequently detected in meningioma [8][13].

Claudin - 1 is one of the main components of tight junction, normally expressed in epithelial, endothelial and arachnoid cap cells, functioning as a regulator for paracellular space; controlling the barrier function of the cells and preserving cellular polarity and integrity [14].

Claudin - 1 has been recently identified as a tumor marker expressed in many tumors; e.g.: renal cell carcinoma, colonic adenocarcinoma and melanoma, where its increased expression and mislocalization were correlated with the bad behavior encountered in such tumors, e.g. metastatic potential [15]; through its inhibitory effect on E - cadherin and Beta-catenin inducing epithelial-mesenchymal transmission; a major step in metastatic process [16].

This study evaluates SSTR2A and Claudin-1 immunohistochemical staining in meningiomas versus cranio - spinal schwannomas and meningeal solitary fibrous tumours/hemangiopericytomas, to determine if these two markers can help in this differential diagnosis and to add specific markers for meningioma that can be targeted therapeutically.

Materials and Methods

A total of 55 cases of CNS tumours were retrieved from the neuropathology files at Cairo University Hospital between 2012 and 2015. The ethics committee of Cairo University Hospital approved the study. The cases include 35 meningiomas (22 females, 13 males), ten schwannomas (5 females, five males) and ten solitary fibrous tumours/hemangiopericytomas (6 females, four males). The mean age of patients was 42 years in cases of meningioma, 40 years in cases of schwannoma and 44 years in cases of solitary fibrous tumours/hemangiopericytoma. All cases were previously diagnosed by examination of Hematoxylin and Eosin stained sections and by routine immunohistochemical markers.

Histological review: Five microns - thick tissue sections were cut from the archived paraffin blocks and stained by Hematoxylin and Eosin for histological re-evaluation according to the WHO criteria [3], the cases of meningioma are classified as grade I (n = 16), grade II (n = 14) and grade III (n = 5). Among grade I meningiomas, five were transitional, four fibroblastic, three meningothelial, two psammomatous, one microcystic and one angiomatous. Grade II meningiomas included ten atypical and four chordoid and grade III meningiomas included three papillary and two rhabdoid variants.

Immunohistochemical staining and evaluation: Additional cuts were prepared from the paraffin blocks, heat mediated antigen retrieval was performed (with low pH for SSTR2A and high pH for Claudin - 1) in automated water bath (Dako PT Link), and sections were stained with antibodies for SSTR2A (Abcam, UMB1, rabbit monoclonal, 1:100) and Claudin - 1 (Cell Marque, rabbit polyclonal, ready to use). Staining was performed in an autostainer (Dako autostainer link 48) using a polymer-based detection system (Dako EnVision FLEX^{TM}K8000).

Immunohistochemical staining for SSTR2A and Claudin - 1 was scored according to the percentage of immunostained tumour cells (0: less than 5%, 1+: 5% to 25%, 2+: 26% to 50%, 3+: more than 50%). The intensity of staining was classified as weak, moderate and strong. In claudin - 1 evaluation, the perineurial cells in peripheral nerves are used as a control for moderate intensity [14].

Statistical methods: Comparison of numerical variables between the study groups was done using Mann Whitney *U* test for independent samples. For comparing categorical data, Chi-square (χ^2) test was performed. The exact test was used instead when the expected frequency is less than 5. *P* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

Results

Somatostatin receptor 2A

Positive immunohistochemical staining for SSTR2A was encountered in 31 of 35 (89%) cases of meningioma (Table 1). All positive cases showed cytoplasmic and/or membranous staining. Among the positive cases, 24 of 31 (77%) showed diffuse staining in more than 50% of tumour cells (scored as 3+). Among these 24 cases, 16 showed strong immunostaining intensity, 7 showed moderate intensity, and only 1 showed weak staining (Figure 1).

In contrast, none of the cases of

schwannoma and solitary fibrous tumour/ hemangiopericytoma showed any positive staining for SST2A (Table 1). Therefore, the expression of SSTR2A was statistically significant in meningioma versus schwannoma or solitary fibrous tumours/ hemangiopericytoma (P <0.05) (Figure 2).

Table 1: Summary of immunohistochemical staining results for meningioma, schwannoma and Solitary fibrous tumors/Hemangiopericytoma [number (percentage)]

	Meningioma (n=35)	Schwannoma (n = 10)	Hemangiopericytoma (n = 10)
SSTR2A positive	31 (89)	0 (0)	0 (0)
Claudin-1 positive	17 (49)	0 (0)	0 (0)
SSTR2A&/or Claudin - 1 positive	34 (97)	0 (0)	0 (0)

SSTR2A, somatostatin receptor 2A

Regarding the different grades of meningioma, a significant correlation was found between the positive expression of SSTR2A and the lower grades of meningioma (grades I and II) (P <0.05) (Table 2).

Table 2: Summary of immunohistochemical staining results for different grades of meningioma [number (percentage)]

	Grade I (n = 16)	Grade II (n = 14)	Grade III (n = 5)
SSTR2A positive	16 (100)	14 (100)	1 (20)
Claudin-1 positive	8 (50)	6 (43)	3 (60)

In grade I, all cases (16/16) showed positive SSTR2A expression. Among these cases, 13 showed diffuse staining in more than 50% of tumour cells (Score 3+). The majority of these cases displayed strong immunostaining intensity. In grade II, all cases (14/14) showed positive SSTR2A expression. 10 out of these 14 cases showed diffuse staining in more than 50 % of cells (Score 3+), but only 4 of them showed strong intensity. In grade III, only a single (1/5) case of papillary subtype showed positive SSTR2A expression. The staining, in this case, was diffuse in more than 50% of tumour cells (Score 3+); however, the intensity was weak.

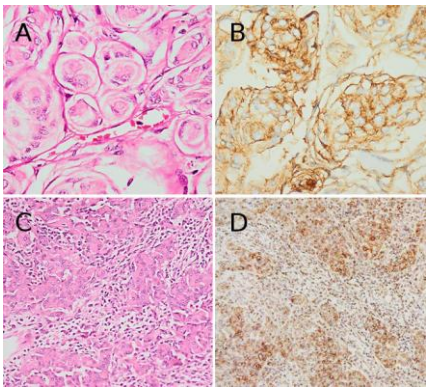

Figure 1: Transitional meningioma, WHO grade I (A: H&E, x400) showing strong diffuse SSTR2A immunostaining (B: SSTR2A, x400). Rhabdoid meningioma, WHO grade III (C: H&E, x200) showing strong diffuse Claudin - 1 immunostaining (D: Claudin-1, x200) immunostaining of claudin 1 (D: claudin 1x400)

Claudin-1

Positive immunohistochemical staining was encountered in 17 of 35 (49%) cases of meningioma. Tumor cells showed cytoplasmic and/or membranous staining. Unlike SSTR2A, Claudin - 1 showed only focal staining in less than 50% of tumour cells in all positive cases (Figure 1).

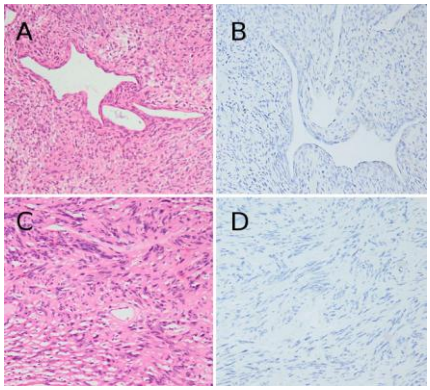

Figure 2: Hemangiopericytoma (A: H&E, x400) showing negative immunostaining for SSTR2A (B: SSTR2A, x400). Schwannoma (C: H&E, x400) showing negative

However, a significant expression of Claudin - 1 was still detected in meningioma in comparison to schwannoma and solitary fibrous tumour/ hemangiopericytoma (P< 0.05) since none of them showed any positive staining (Table 1) (Figure 2).

Table 3: Intensity of immunohistochemical staining of Claudin-1 in different grades of meningioma [number (percentage)]

	Grade I (n=16)	Grade II (n=14)	Grade III (n=5)
Negative	8 (50)	8 (57)	2 (40)
Weak	2 (13)	3 (21.5)	0 (0)
Moderate	5 (31)	3 (21.5)	0 (0)
Strong	1 (6)	0 (0)	3 (60)

As for the three grades of meningioma, positive Claudin - 1 expression was detected in 8 out of 16 grade I cases, 6 out of 14 grade II cases and 3 out of 5 grade III cases. The intensity of Claudin - 1 staining was significantly stronger in grade III than in grades I and II (P <0.05) (Table 3). Interestingly, the three positive cases of grade III were negative for SSTR2A. More details of SSTR2A and Claudin - 1 staining in different grades and subtypes of meningioma are shown in (Table 4).

Discussion

Although the diagnosis of most meningiomas can be based merely on routine examination of Hematoxylin and Eosin stained sections, the histologic mimicry between certain subtypes and other CNS tumours warrants the use

of immunohistochemical tests. A common example is a distinction between meningioma, particularly the fibroblastic subtypes, and schwannoma, especially if arising at the cerebello - pontine angle.

Table 4: Details of immunohistochemical staining of SSTR2A and Claudin - 1 in all cases of meningioma

Case	Grade	Subtype	SSTR2A		Claudin-1	
1	I	Transitional	3+	Strong	1+	Moderate
2	I	Transitional	3+	Strong	1+	Moderate
3	I	Transitional	3+	Strong	1+	Moderate
4	I	Transitional	3+	Moderate	0	0
5	I	Transitional	1+	Weak	0	0
6	I	Fibroblastic	3+	Strong	2+	Moderate
7	I	Fibroblastic	3+	Strong	0	0
8	I	Fibroblastic	3+	Strong	0	0
9	I	Fibroblastic	3+	Strong	0	0
10	I	Meningothelial	3+	Strong	1+	Weak
11	I	Meningothelial	2+	Moderate	2+	Moderate
12	I	Meningothelial	2+	Moderate	0	0
13	I	Psammomatous	3+	Strong	2+	Strong
14	I	Psammomatous	3+	Strong	0	0
15	I	Microscystic	3+	Strong	0	0
16	I	Angiomatous	3+	Strong	1+	Weak
17	II	Chordoid	3+	Moderate	1+	Weak
18	II	Chordoid	3+	Moderate	1+	Weak
19	II	Chordoid	3+	Moderate	0	0
20	II	Chordoid	2+	Moderate	0	0
21	II	Atypical	3+	Strong	1+	Moderate
22	II	Atypical	3+	Strong	1+	Weak
23	II	Atypical	3+	Strong	0	0
24	II	Atypical	3+	Strong	0	0
25	II	Atypical	3+	Moderate	1+	Moderate
26	II	Atypical	3+	Moderate	0	0
27	II	Atypical	3+	Moderate	0	0
28	II	Atypical	2+	Moderate	0	0
29	II	Atypical	2+	Weak	2+	Moderate
30	II	Atypical	1+	Weak	0	0
31	III	Papillary	3+	Weak	0	0
32	III	Papillary	0	0	1+	Strong
33	III	Papillary	0	0	0	0
34	III	Rhabdoid	0	0	2+	Strong
35	III	Rhabdoid	0	0	1+	Strong

This differential diagnosis should also be considered in patients diagnosed with Neurofibromatosis type 2 since these patients are prone to develop both tumours. Histologically, fibroblastic meningioma and schwannoma are formed of spindle cells with the variable collagenous background. Occasionally, well-formed whorls that are characteristic for meningioma are seen in schwannoma. On the other side, meningioma can show Verocay body - like structures similar to those seen in schwannoma. Although most meningiomas express epithelial membrane antigen (EMA), a small subset of cases does not. Also, S100 - which is routinely used for diagnosis of schwannoma- can stain up to 70% of fibroblastic meningiomas [5].

Another problematic case is the differential diagnosis of meningioma versus solitary fibrous tumour/hemangiopericytoma. Some meningiomas develop branching staghorn vessels like those encountered in solitary fibrous tumour/ hemangiopericytoma [5]. Previous studies had shown that occasional cases of solitary fibrous tumour/ hemangiopericytoma might focally express EMA [7]. Also, CD34, which is a marker of solitary fibrous tumour/hemangiopericytoma, can be expressed in up to 60% of fibroblastic meningiomas [6].

In the present study, we compared the immunohistochemical expression of SSTR2A and Claudin - 1 in meningioma versus their expression in schwannoma and solitary fibrous tumour/ hemangiopericytoma.

The expression of somatostatin receptors is known to be frequent in meningioma [12]. Among the five subtypes of somatostatin receptors, SSTR2A was the most frequently detected in meningioma [13]. This wide expression has made it a useful tool in tumour imaging by PET/CT using radiolabeled somatostatin analogues [17].

In our study, we detected the immunohistochemical expression of SSTR2A in meningiomas with a sensitivity of 89%. This is comparable with the findings detected by Bacchi et al. [18], Agaimy et al. [19] and Menke et al. [20] in their studies that showed sensitivities of 100%, 87% and 100 % respectively. Lower sensitivities of 74% and 63% were stated by Barresi et al. [21] and Durand et al. [22] respectively. This difference may be because they used polyclonal antibodies in their studies, in contrast to the monoclonal antibody used in the current study.

We further analysed the expression of SSTR2A in different grades and subtypes of meningioma. The highest expression was linked to lower grades of meningioma (grade I and II) ($p < 0.05$). It was also noted that despite the positive expression of SSTR2A in all cases of grade I and II, there was still a difference in the intensity of immunostaining among the grades. Most of the cases of grade I (75%) showed strong staining intensity while only 28% of grade II cases showed strong intensity and the rest showed moderate or weak intensity. As for grade III meningiomas, only one case was positive for SSTR2A, and the intensity of staining was weak.

Our findings are in concordance with those reported by Durand et al. [22] who analysed the expression of SSTR2A in meningiomas by both immunohistochemistry and RT - PCR. By immunohistochemistry, the expression of SSTR2A was negative in grade III meningiomas. By RT - PCR, the SSTR2A mRNA was detected in all grades of meningioma with higher levels expressed in grade I more than in grade II and III.

Since the expression of SSTR2A was more intense in grade I meningiomas and became lost in most of grade III cases, we suggest that detection of strong immunohistochemical staining of SSTR2A may predict a better outcome. Previous studies were done on other types of tumours also reached the same conclusion. For example, Sestini et al. [23] and Raggi et al. [24] studied SSTR2A expression in neuroblastoma and found out that it was inversely related to the tumour stage and was shown to be a good independent prognostic factor. Similarly, in colorectal carcinoma, SSTR2A expression was increased in well and moderately differentiated tumours and with lower proliferation indices [25].

In all cases of schwannoma and solitary

fibrous tumor/hemangiopericytoma selected for the present study, SSTR2A showed negative staining. Accordingly, the specificity of SSTR2A for meningioma is 100%. This was statistically highly significant. Bacchi et al. [18] and Menke et al. [20] reported slightly lower specificities of 90% and 88% respectively.

Regarding Claudin - 1, its sensitivity for meningioma was 49% in our study. The previous study done by Rajaram et al. [7] included anaplastic (grade III) meningiomas only and showed a sensitivity of 54%. Hahn et al. [14] included grade I and II meningiomas and showed a sensitivity of 53 %, which is relatively close to our results. Slightly lower sensitivity (22%) was reported by Soini et al. [26] who included all grades of meningioma. This difference may be because they used tissue micro-array blocks with a 2 mm diameter.

Despite its low sensitivity for meningiomas, Claudin - 1 did not stain any of the schwannomas or solitary fibrous tumours/ hemangiopericytomas included in our study, denoting a very high specificity (100%) for meningioma. Similar to our results, Singh et al. [27] reported negative Claudin-1 staining in the 50 cases of schwannoma included in their study. Hahn et al. [14] also reported negative Claudin - 1 staining in all the studied cases of meningeal solitary fibrous tumour/ hemangiopericytoma and schwannoma. Rajaram et al. [7] studied Claudin - 1 expression in 15 cases of meningeal solitary fibrous tumour/ hemangiopericytoma and found positive staining in 2 cases.

We detected positive expression of Claudin - 1 in the different grades of meningioma without a significant difference in positivity (50% of grade I, 43% of grade II and 60% of grade III). Soini et al. [26] also reported no difference in the Claudin - 1 expression among the three grades of meningioma. However, we detected that the intensity of staining was significantly higher in grade III than in grades I and II ($p > 0.05$).

In the current study, we found out that 34 of 35 meningiomas expressed either SSTR2A or Claudin - 1, or both of them, i.e. the sensitivity of both markers combined is 97%. Interestingly, the cases of grade III meningiomas that showed positive Claudin - 1 staining was negative for SSTR2A. On the other side, the single case of grade III meningioma (papillary subtype) that was positive for SSTR2A did not stain for Claudin - 1. Thus SSTR2A and Claudin - 1 can be used as complimentary markers with high sensitivity.

Therapeutic strategies in meningiomas include mainly surgery and radiotherapy, while chemotherapy has been used for a patient with the progressive disease, and patients with histologically malignant meningioma as an adjuvant for radiotherapy, however, the response to chemotherapy was disappointing; so the targeted therapy in such cases can be a new hope [28]. In vitro studies proved that somatostatin analogues have a cytostatic effect on tumor cells and inhibits the tumor growth [10][29]. However, the efficacy of the use of somatostatin analogues in a clinical setting is still debatable with some trials showing benefit for their use and others do not [30][31][32]. The loss of expression of SSTR2A in malignant meningioma, as shown in the present study, may explain the failure of some clinical trials to prove the efficacy of somatostatin analogues in treating recurrent high-grade meningioma [33].

Recently, Hashimoto and his colleagues generated mouse anti - Claudin-1 monoclonal antibodies and assessed their activity on mice bearing human Claudin - 1 expressing tumours. They concluded that one of these antibodies might be of benefit in cancer therapy [34]. So Claudin - 1 can be one of the targeted therapy lines in meningioma therapy.

In summary, our study demonstrates that SSTR2A is highly sensitive and specific for meningioma. Claudin - 1 is highly specific for meningioma; however its sensitivity is low. The adjunctive use of both markers can be very helpful in the diagnosis of meningioma and its distinction from schwannoma and solitary fibrous tumor/ hemangiopericytoma. Further clinicopathological studies are recommended to correlate the pattern of SSTR2A and Claudin - 1 expression in meningiomas with their potential prognostic and predictive roles in such tumors, specifically aggressive and recurring ones.

References

1. Ostrom QT, Gittleman H, Liao P, Rouse C, Chen Y et al. Statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007– 2011. Neuro-oncology. 2014; 16 (suppl-4):iv1-63. https://doi.org/10.1093/neuonc/nou223 PMid:25304271 PMCid:PMC4193675

2. Cushing H. The meningiomas (dural endotheliomas): their source and favored seats of origin (Cavendish Lecture). Brain. 1922; 45: 282-316. https://doi.org/10.1093/brain/45.2.282

3. Perry A, Louis DN, Scheithauer BW, Budka H and Von Deimling A. Meningioma. In Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds). WHO classification of tumors of the central nervous system; pp 164-172. Lyon: IARC, 2007.

4. Perry A, Louis DN, Scheithauer BW, Budka H and Von Deimling A. Meningioma. In Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (eds). WHO classification of tumors of the central nervous system; Lyon: IARC, 2016: 223-224. PMid:27512595 PMCid:PMC4967785

5. Perry A. Meningiomas. In Perry A and Brat DJ (eds). Practical surgical neuropathology; pp 185-217, Chruchill Livingstone, Philadelphia, 2010. https://doi.org/10.1016/B978-0-443-06982-6.00010-9

6. Perry A, Stafford SL, Scheithauer BW, Suman VJ, Lohse CM. Meningioma grading: an analysis of histologic parameters. The American journal of surgical pathology. 1997; 21(12):1455-65. https://doi.org/10.1097/00000478-199712000-00008

PMid:9414189

7. Rajaram V, Brat DJ, Perry A. Anaplastic meningioma versus meningeal hemangiopericytoma: immunohistochemical and genetic markers. Human pathology. 2004;35(11):1413-8. https://doi.org/10.1016/j.humpath.2004.07.017 PMid:15668900

8. Barnett P. Somatostatin and somatostatin receptor physiology. Endocrine. 2003; 20(3):255-64. https://doi.org/10.1385/ENDO:20:3:255

9. Cervia D, Bagnoli P. An update on somatostatin receptor signaling in native systems and new insights on their pathophysiology. Pharmacology & therapeutics. 2007; 116(2):322-41. https://doi.org/10.1016/j.pharmthera.2007.06.010 PMid:17719647

10. Arena S, Barbieri F, Thellung S, Pirani P, Corsaro A et al. Expression of somatostatin receptor mRNA in human meningiomas and their implication in in vitro antiproliferative activity. Journal of neuro-oncology. 2004; 66(1-2):155-66. https://doi.org/10.1023/B:NEON.0000013498.19981.55 PMid:15015781

11. Florio T. Molecular mechanisms of the antiproliferative activity of somatostatin receptors (SSTRs) in neuroendocrine tumors. Front Biosci. 2008; 13(1):822-40. https://doi.org/10.2741/2722

12. Dutour A, Kumar U, Panetta R, Ouafik L, Fina F et al.. Expression of somatostatin receptor subtypes in human brain tumors. International journal of cancer. 1998; 76(5):620-7. https://doi.org/10.1002/(SICI)1097-0215(19980529)76:5<620::AID-IJC2>3.0.CO;2-S

13. Schulz S, Pauli SU, Schulz S, Händel M, Dietzmann K et al. Immunohistochemical determination of five somatostatin receptors in meningioma reveals frequent overexpression of somatostatin receptor subtype sst2A. Clinical Cancer Research. 2000; 6(5):1865-74. PMid:10815909

14. Hahn HP, Bundock EA, Hornick JL. Immunohistochemical staining for claudin-1 can help distinguish meningiomas from histologic mimics. American journal of clinical pathology. 2006; 125(2):203-8. https://doi.org/10.1309/G659FVVBMG7U4RPQ PMid:16393681

15. Morin PJ. Claudin proteins in human cancer: promising new targets for diagnosis and therapy. Cancer research. 2005; 65(21):9603-6. https://doi.org/10.1158/0008-5472.CAN-05-2782 PMid:16266975

16. Stebbing J, Filipović A, Giamas G. Claudin-1 as a promoter of EMT in hepatocellular carcinoma. Oncogene. 2013; 32(41):4871-2. https://doi.org/10.1038/onc.2012.591 PMid:23318416

17. Rachinger W, Stoecklein VM, Terpolilli NA, Haug AR, Ertl L et al. Increased 68Ga- DOTATATE uptake in PET imaging discriminates meningioma and tumor-free tissue. Journal of Nuclear Medicine. 2015; 56(3):347-53. https://doi.org/10.2967/jnumed.114.149120 PMid:25635133

18. Bacchi CE, Kandalaft PL, Hwang HC, Goldstein LC, Lopes LL et al. Somatostatin Receptor 2A: A Novel Immunohistochemical Marker of Meningioma. In Laboratory Investigation. 2013 Feb 1; (Vol. 93, pp. 414A-414A). 75 Varick St, 9th Flr, New York, NY 10013-1917 USA: Nature Publishing Group.

19. Agaimy A, Buslei R, Coras R, Rubin BP, Mentzel T. Comparative study of soft tissue perineurioma and meningioma using a five-marker immunohistochemical panel. Histopathology. 2014; 65(1):60-70. https://doi.org/10.1111/his.12366 PMid:24393170

20. Menke JR, Gown AM, Thomas S, Perry A, Tihan T. Reliability of Somatostatin Receptor 2a as a Marker of Meningioma: An Immunohistochemical Study. Laboratory Investigation. 2014; 94:439a-439a).

21. Barresi V, Alafaci C, Salpietro F, Tuccari G. Sstr2A immunohistochemical expression in human meningiomas: is there a correlation with the histological grade, proliferation or microvessel density? Oncology reports. 2008; 20(3):485-92. PMid:18695896

22. Durand A, Champier J, Jouvet A, Labrousse F, Honnorat J et al. Expression of c- Myc, neurofibromatosis Type 2, somatostatin receptor 2 and erb-B2 in human meningiomas: relation to grades or histotypes. Clinical neuropathology. 2007; 27(5):334-45.

23. Sestini R, Orlando C, Peri A, Tricarico C, Pazzagli M et al. Quantitation of somatostatin receptor type 2 gene expression in neuroblastoma cell lines and primary tumors using competitive reverse transcription-polymerase chain reaction. Clinical cancer research. 1996; 2(10):1757-65. PMid:9816127

25. Qiu CZ, Wang C, Huang ZX, Zhu SZ, Wu YY et al. Relationship between somatostatin receptor subtype expression and clinicopathology, Ki-67, Bcl-2 and p53 in colorectal cancer. World Journal of Gastroenterology: WJG. 2006; 12(13):2011. https://doi.org/10.3748/wjg.v12.i13.2011 PMid:16610049 PMCid:PMC4087677

26. Soini Y, Rauramaa T, Alafuzoff I, Sandell PJ, Kärjä V. Claudins 1, 11 and twist in meningiomas. Histopathology. 2010; 56(6):821-4. https://doi.org/10.1111/j.1365-2559.2010.03538.x PMid:20546350

27. Singh AB, Sharma A, Dhawan P. Claudin family of proteins and cancer: an overview. Journal of oncology. 2010; 2010.

28. Kantarjian HM, Wolff RA. The MD Anderson manual of medical oncology. McGraw Hill Educational, 2016:848.

29. Graillon T, Defilles C, Mohamed A, Lisbonis C, Germanetti AL et al. Combined treatment by octreotide and everolimus: Octreotide enhances inhibitory effect of everolimus in aggressive meningiomas. Journal of neuro-oncology. 2015; 124(1):33-43. https://doi.org/10.1007/s11060-015-1812-3 PMid:26015296

30. Chamberlain MC, Glantz MJ, Fadul CE. Recurrent meningioma Salvage therapy with long-acting somatostatin analogue. Neurology. 2007; 69(10):969-73. https://doi.org/10.1212/01.wnl.0000271382.62776.b7 PMid:17785665

31. Bural GG, Lieberman F, Mountz JM. Use of 111In-pentetreotide scan in a subject with treatment refractory atypical meningioma. Clinical nuclear medicine. 2014; 39(4):342-5. https://doi.org/10.1097/RLU.0000000000000326 PMid:24445268

32. Norden AD, Ligon KL, Hammond SN, Muzikansky A, Reardon DA et al. Phase II study of monthly pasireotide LAR (SOM230C) for recurrent or progressive meningioma. Neurology. 2015; 84(3):280-6. https://doi.org/10.1212/WNL.0000000000001153 PMid:25527270 PMCid:PMC4335993

33. Simó M, Argyriou AA, Macià M, Plans G, Majós C et al. Recurrent high-grade meningioma: a phase II trial with somatostatin analogue therapy. Cancer chemotherapy and pharmacology. 2014; 73(5):919-23. https://doi.org/10.1007/s00280-014-2422-z PMid:24619496

34. Hashimoto Y, Tada M, Iida M, Nagase S, Hata T et al. Generation and characterization of a human–mouse chimeric antibody against the extracellular domain of claudin-1 for cancer therapy using a mouse model. Biochemical and biophysical research communications. 2016; 477(1):91-5. https://doi.org/10.1016/j.bbrc.2016.06.025 PMid:27286708