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RESEARCH STUDY

EKSPRESI STAT6 DAN SSTR2A YANG SIGNIFIKAN DALAM MEMBEDAKAN TUMOR FIBROUS SOLITER / HEMANGIOPERICYTOMA (SFT/HPC) DAN MENINGIOMA

Bela Bagus Setiawan[1], Vega karlowee[2], Awal prasetyo[2],
[1]Residen Departemen Patologi Anatomik, Fakultas Kedokteran Universitas Diponegoro, semarang, Indonesia.
[2]Staf Pengajar Departemen Patologi Anatomik, Fakultas Kedokteran Universitas Diponegoro, Semarang, Indonesia
Penulis korespondensi: Bela Bagus Setiawan. Email: belabagus08@gmail.com

ABSTRAK

Latar Belakang: *Solitary fibrous tumor* / *hemangiopericytoma* (SFT / HPC) dan meningioma tipe fibroblastic terdapat kemiripan sehingga sulit dibedakan berdasarkan histologi. Immunohistokimia STAT6 dan SSTR2A adalah biomarker yang handal pada kedua tumor. Fusi yang dimediasi inversi antara dua gen, NAB2 dan STAT6, terdeteksi di SFT / HPC yang menginduksi proliferasi dalam sel. Reseptor SSTR2 yang berlokasi di 17q25.1, terekspresi difus pada meningioma.
Tujuan: Penelitian ini bertujuan untuk mengetahui ekspresi STAT6 dan SSTR2A pada SFT/HPC dan meningioma.
Metode: Penelitian observasional analitik dengan *consecutive sampling* pada 64 sampel yang didiagnosis SFT/HPC dan meningioma. Kami membagi sampel menjadi 3 kelompok, kelompok 1 terdiri dari meningioma derajat I, kelompok 2 adalah meningioma derajat II dan III dan kelompok 3 adalah solitary fibrous tumor/Hemangiopericytoma (SFT/HPC).
Hasil : Berdasarkan uji beda *Mann Withney* ekspresi STAT6 terdapat perbedaan yang bermakna pada kelompok 1 dan 2, serta kelompok 2 dan 3 ($P < 0.05$). Ekspresi SSTR2A pada kelompok 1 dan 3, serta kelompok 2 dan 3 juga memiliki perbedaan yang bermakna ($P < 0.05$).
Kesimpulan: Immunohistokimia STAT6 dan SSTR2A terekpresi kuat pada SFT/HPC dan meningioma.
Kata Kunci: Meningeal solitary fibrous tumor (SFT)/hemangiopericytoma (HPC), Meningioma, STAT6, SSTR2A.

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SIGNIFICANTLY STRONG EXPRESSION OF STAT6 AND SSTR2A IN DISTINGUISHING SOLITARY FIBROUS TUMOR / HEMANGIOPERICYTOMA (SFT/HPC) AND MENINGIOMA

Bela Bagus Setiawan[1], Vega karlowee[2], Awal prasetyo[2],
[1]Resident of the Department of Anatomic Pathology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia.
[1]Lecturer of the Department of Anatomic Pathology, Faculty of Medicine, Diponegoro University, Semarang, Indonesia
Correspondence writer: Bela Bagus Setiawan. Email: belabagus08@gmail.com

Background: Solitary fibrous tumor / hemangiopericytoma (SFT / HPC) and fibroblastic types of meningioma have similarities that is difficult to distinguish based on histology. Immunohistochemistry of STAT6 and SSTR2A are definitive biomarkers in both tumors. Inversion-mediated fusions between two genes, *NAB2* and *STAT6*, were detected in SFT / HPC that inducES proliferation in cells. The somatostatin receptor (SSTR) 2 is located on chromosome 17q25.1 which is expressed diffusely in meningiomas.
Objective: This study aimed to determine the expression of STAT6 and SSTR2A in SFT/HPC and meningiomas.
Methods: An analytical observational study with consecutive sampling on 64 samples diagnosed with SFT/HPC and meningioma. Samples divided into 3 groups, group 1 consisted of grade I meningoma, group 2 consisted of grade II and III meningioma and group 3 consisted of solitary fibrous tumor/Hemangiopericytoma (SFT/HPC).
Results: Based on the Mann Withney comparative test, STAT6 expressions showed significant differences in group 1 and 3, as well as group 2 and 3 ($P < 0.05$). SSTR2A expressions in group 1 and 3, as well as group 2 and 3 also showed significant differences ($P < 0.05$).
Conclusion: Immunohistochemistry of STAT6 and SSTR2A is strongly expressed in SFT/HPC and meningioma.

Keywords: Meningeal solitary fibrous tumor (SFT)/hemangiopericytoma (HPC), Meningioma, STAT6, SSTR2A.

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INTRODUCTION

Solitary fibrous tumor/hemangiopericytoma (SFT/HPC) is one among thetypes of fibroblastic mesenchymal tumors which holds morphological properties similar to fibroblastic meningioma.[1] The incidence of SFT/HPC is still considered very low, in contrast to the incidence of meningiomas. According to WHO (World Health Organization), the prevalence of SFT/HPC is less than 1% compared to 36%of meningioma cases.[2,3]

Histopathological examination has been found to be challenging due to the morphologic similarities with that of meningiomas. Hence, further medical examinations may be required to differentiate SFT/HPC and meningioma since therapeutic management plans may differ between the two. SFT/HPC is classified into three grades histologically, whereby 1st grade SFT/HPC is considered benign andmay be treated by surgical resection, whilst 2nd and 3rd grade SFT/HPC is considered malignant and may require adjuvant radiotherapy. Meningiomas are histologically classified into three grades as well, whereby 1st grade meningioma is relativelybenign and is usually treated by subtotal resection, whereas 2nd (atypical) and 3rd (anaplastic) grade meningioma also requires subtotal resection, however in additionto the latter may also require radiotherapy such as radiosurgery and fractionated irradiation.[4,5]

In cases of meningeal tumors with suspects of SFT/HPC currently requires immunohistochemistry CD 34 examination which has a sensitivity and specificity 88%, whereas tumors with suspects of meningioma would require Epithelial Membrane Antigen (EMA) which has a sensitivity and specificity of 95%.[5] Updated studies reported better sensitivity and specificity in immunohistochemistry examinations compared to EMA and CD 34. Signal transducer and activator oftranscription (STAT6) was reported to have a sensitivity of 96% and specificity of 100% in SFT/HPC.[5] SFT/HPC is related to NAB2 – STAT6 gene fusions which was proven to be very specific and sensitive.[4] Somatostatin 2A Receptors (SSTR2A) havea sensitivity and specificity up to 100% in all grades of meningioma. Somatostatin or its analogue binds to SSTR2, leading to the activation of specific tyrosine phosphates (SHP1 and SHP2) and inhibition of PI3K/Akt pathways, which in turn mediates an anti-tumor effect through the induction of kinase inhibition that relies on cyclin and the inhibition of cell cycle.[6]

Both markers show highly promising results in assisting diagnostic workups for SFT/HPC and meningioma, therefore is highly expected to improve management approaches. Previous studies show sensitive and specific results of STAT6 markers in SFT/HPC as well as SSTR2A in meningioma, however there has not been a study that combines the two markers in differentiating SFT/HPC and meningioma in Indonesia.

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MATERIALS AND METHODS

This study was performed after obtaining ethical clearance from the Ethical Clearance Committee from the Health Research Ethics Commission (KEPK) RSUP Dr.Kariadi, with the reference number No.1062/EC/KEPK-RSDK/2022 and research permit with the reference number No.DP.02.01/I.II/2202/2022. The study applied a retrospective, descriptive analytic, cross-sectional design by performing immunohistochemistry examinations of paraffin blocks from SFT/HPC and meningioma tissue samples.

The study was performed in the Anatomical Pathology Laboratory, RSUP Dr.Kariadi, Semarang from January 2020 to December 2021. The study population consisted of HE (Hematoxylin and Eosin) slides and paraffin blocks diagnosed with SFT/HPC and meningiomas of all degrees from January 1st, 2017 to December 31st, 2020.

64 samples were obtained and divided into 3 groups based on WHO 2016, namely:

1. Group 1: Meningioma grade I (30 samples)
2. Group 2: Meningioma grade II and III (23 samples)
3. Group 3: Solitary fibrous tumor/Hemangiopericytoma (SFT/HPC) (11 samples).

Paraffin blocks were collected at the Anatomical Pathology Laboratory, RSUP Dr.Kariadi, Semarang as primary data, whereas patients' medical records were collected as secondary data. Sampling was done by consecutive sampling, where the researcher includes all samples that meet the inclusion criteria until the number of samples required was fulfilled.

In the paraffin block, immunohistochemical examination was performed to determine the expression of STAT6 and SSTR2A. Immunohistochemical examination is an examination of tissue that has been labeled with specific antibodiesto see the expression of specific antigen proteins under a microscope.

Interpretation of STAT6 and SSTR2A were collected as primary data whereas patient medical records (based on age, sex and location) for PA number, patient identity, clinical diagnosis and PA diagnosis were collected as secondary data. The tools needed for this research were: microtome water bath, hot plate, freezer, incubator, staining jar, object glass rack, micro pipette, filter paper, 15 ml centrifuge tube, entelan and light microscope. STAT6 and SSTR2A expression in cases of SFT/HPC and grade I, II and III meningiomas were assessed.

STAT6 and SSTR2A examinations were performed on all samples, with the positivity assessment being based on the distribution of brown staining on tumor cell nucleus for STAT6 and brown staining on the cytoplasm for SSTR2A, according to percentage (0 – 5) and intensity (0 – 3). The scoring is based on the percentage of positive tumor cells and the color intensity of the positive tumor cells. The distribution index score was assessed based on the percentage of tumor cells multiplied by the staining intensity. A score of less than 1 is considered negative, a score of 1 – 6 is considered a weak positive and 6 to 12 is considered a strong positive, by using allred modiffied.[6,7,8,9]

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Percentage of tumor cells that are immunopositive:
0 = Positive cell count: < 5%
1 = Positive cell count: 5% - 25%
2 = Positive cell count: 26% - 50%
3 = Positive cell count: 51% - 75%
4 = Positive cell count: 76 - 100%
Color intensity of positive tumor cells:
0 = Uncolored
1 = Weak intensity
2 = Moderate intensity
3 = Strong intensity

RESULT

80 samples of paraffin blocks were obtained at RSUP dr. Kariadi, Semarang. However, only 64 samples met the inclusion criteria. 16 samples were excluded due to several reasons, namely block damage, small sized samples and inability of immunohistochemical staining. Sixty-four of the samples that were used were divided into 3 groups, group 1 consisted of 30 cases of grade I meningioma, group 2 consisted of 23 cases of grade II and III meningioma and group 3 consisted of 11 cases with a diagnosis of solitary fibrous tumor/hemangiopericytoma (SFT/HPC). All samples were subjected to immunohistochemical examination of STAT6 and SSTR2A. This amount corresponds to the minimum number of samples based on the sample size formula.

Tabel 1. Data Characteristics

Variable	Diagnosis SFT/HPC		Meningioma		Total	
	N	%	N	%	N	%
Age						
< 30 years	1	20	4	80	5	100
30 - 60 years	9	15.8	48	84.2	57	100
> 60 years	1	50	1	50	2	100
Gender						
Male	6	46.2	7	53.8	13	100
Female	5	9.8	46	90.2	51	100
Location						
Parasagittal	6	23.1	20	76.9	26	100
Basal	3	11.5	23	88.5	26	100
Convex	2	16.7	10	83.3	12	100
Grade						

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I	0	0	24	100	24	100
II	1	4.2	23	95.8	24	100
III	10	62.5	6	37.5	16	100

STAT6 Expression

STAT6 expression was determined positive when tumor cell nucleus was stained brown. Semi-quantitative and semi-qualitative scores were summed to obtain a negative, weak or strong final score.

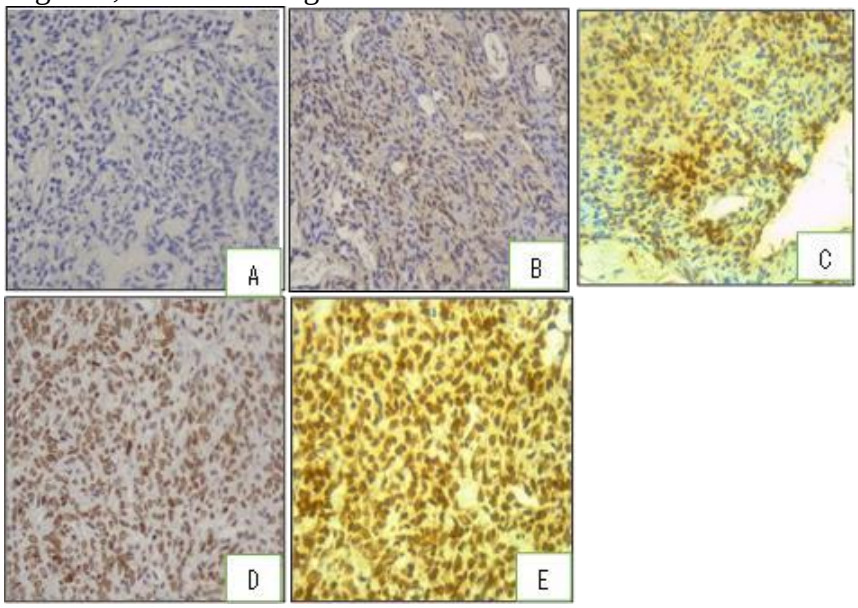

Figure 1. STAT6 expression in solitary fibrous tumor/hemangiopericytoma (SFT/HPC) tumor cells and meningiomas based on semi-quantitative scores (immunohistochemistry, 400x magnification). A. Zero score (< 5%). B. One score (5% - 25%). C. Two scores (26% - 50%). D. Three scores (51% 75%). E. Four scores (76% - 100%).

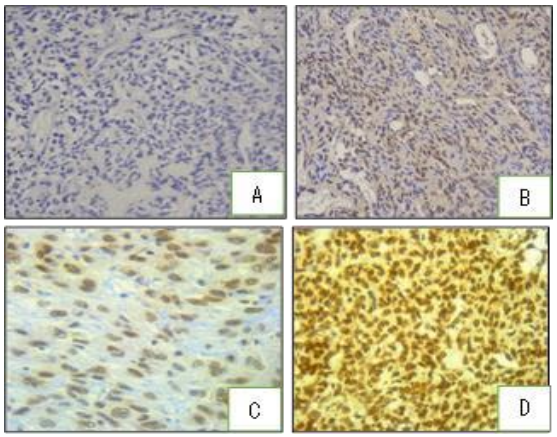

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Figure 2. Expression of STAT6 in solitary fibrous tumor/hemangiopericytoma (SFT/HPC) tumor cells and meningiomas based on semi-qualitative scores (immunohistochemistry, 400x magnification). A. Zero (negative) score. B. One score (weak). C. Two score (medium). D. Three score (strong).

SSTR2A expression

SSTR2A expression was determined positive cell membrane and/or cytoplasm was stained brown. Semi-quantitative and semi-qualitative scores were summed to obtain a negative, weak or strong final score.

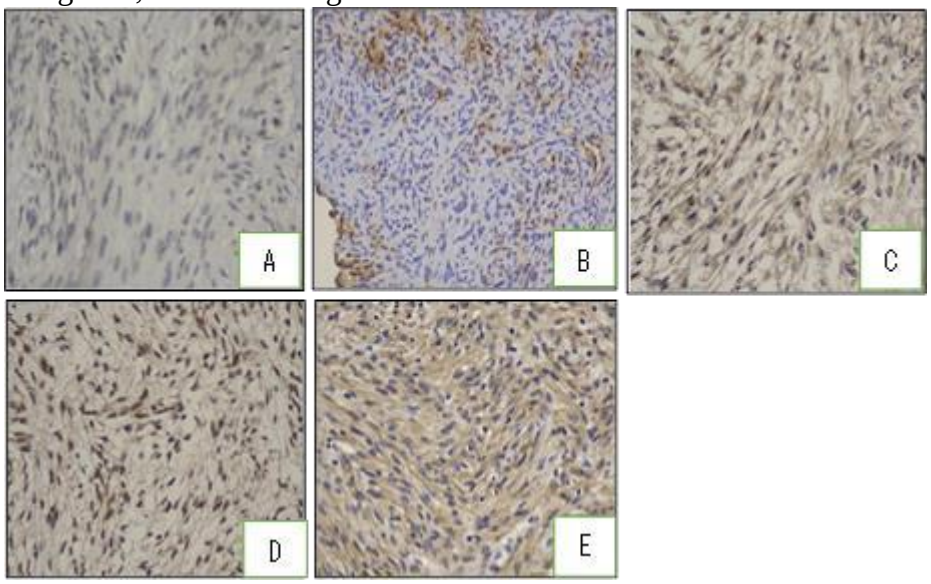

Figure 3. SSTR2A expression in solitary fibrous tumor/hemangiopericytoma (SFT/HPC) and meningioma tumor cells based on semi-quantitative scoring (imunohistochemistry, 400x magnification). A. Zero score (< 5 %). B. One score (5 % - 25%). C. Two scores (26 % - 50%). D. Three scores (51 % - 75%). E. Four scores (76 % - 100 %).

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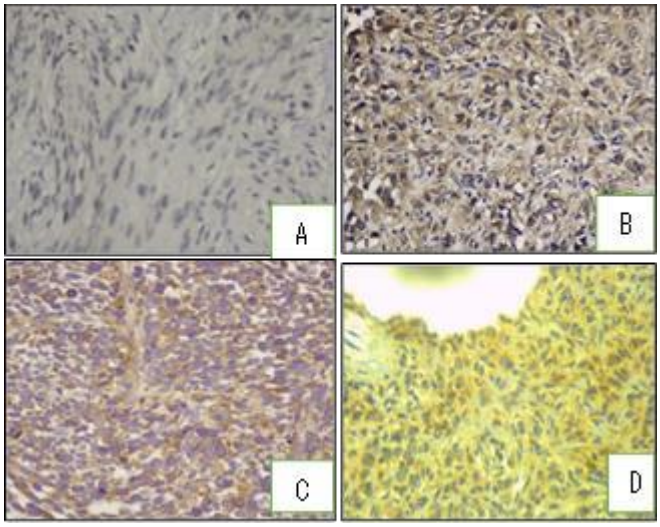

Figure 4. SSTR2A in solitary fibrous tumor/hemangiopericytoma (SFT/HPC) and meningioma tumor cells based on semi-qualitative scoring (imunohistochemistry, 400x magnification). A. Zero score (negative). B. One score (lemah). C. Two scores (moderate). D. Three scores (strong).

Kruskal Wallis results showed significant difference between the diagnoses of group 1, group 2 and group 3 with $p < 0.05$. Comparison of STAT6 expression in each diagnosis group was determined by Mann Whitney test as seen on table 3.

Table 3. **Comparative test (Kruskal Wallis) of STAT6 expression in group 1, 2 and 3**

Diagnosis	STAT 6			*p**
	Negative	Weak positive	Strong positive	
Group 1	18 (60%)	8 (26,7%)	4 (13,3%)	0,010
Group 2	9 (39,1%)	13 (56,5%)	1 (4,3%)	
Group 3	2 (18,2%)	3 (27,3%)	6 (54,5%)	

Mann Whitney test results showed insignificant difference in STAT6 expression between group 1 and group 2 ($P > 0.05$). Significant difference however was obtained between group 1 and group 3 ($P < 0.05$), as well as group 2 and group 3 ($P < 0.05$) as seen on table 4.

Table 4. Comparative test (*Mann Whitney*) of STAT6 expression in Group 1, 2 and 3

Diagnosis		*p**
Group 1	Group 2	0,317
	Group 3	0,006
Group 2	Group 3	0,011

Kruskal Wallis test for SSTR2A expression obtained $p < 0.05$, which concluded significant difference in SSTR2A based on the diagnosis of group 1, group 2 and group 3. Results are as seen on table 5.

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Table 5. **Comparative test (*Kruskal wallis*) SSTR2A Expression in group 1, 2 and 3**

Diagnosis	SSTR2A			p*
	Negative	Weak positive	Strong positive	
Group 1	0 (0%)	1 (3,3%)	29 (96,7%)	<0,001
Group 2	0 (0%)	0 (0%)	23 (100%)	
Group 3	0 (0%)	5 (45,5%)	6 (54,5%)	

Mann Whitney results showed that expression of SSTR2A between group 1 and group 2 obtained insignificant difference (P > 0.05). Significant differences however were observed between group 1 and group 3 (P < 0.05) as well as group 2 and group 3 (P < 0.05), as seen on table 6.

Table 6. **Comparative test (*Mann Whitney*) of SSTR2A expression in Group 1, 2 and 3**

Diagnosis		P
I	II	
Group 1	Group 2	0,381
	Group 3	0,001
Group 2	Group 3	0,001

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DISCUSSION

Based on the age variable, this study showed that the majority of SFT/HPC cases occurred between age 30 to 60 years. This is in accordance with previous studies that reported the prevalence of SFT/HPC often occurred during the 5thdecade and 6th decade, with the youngest age ranging up to 5 months and the oldest 88 years.[2,6,10]

This study showed that the majority of meningioma cases occurred between the age 30 to 60 years, which is in line with several previous studies that reported the incidence of meningioma cases increasing with age, and the average age reported for meningiomas occurred at 66 years.[1,11]

Based on the gender variable, this study showed insignificant difference in the incidence of SFT/HPC between men and women. This was in line with previous studies which reported that the incidence of cases by gender in SFT/HPC did not have a significant difference.[6]

Meningiomas, however, were significantly different based on the incidence ratio between men and women, whereby occurrence was highest among women. This finding was in accordance with several previous studies which stated that the ratio of women to men was 2.3:1, especially in African Americans with a ratio of 2.3:1 for women and 2.27:1 for men. Higher incidence in women is probably influenced by hormonal factors, which was reported that 72% of cases showedprogesterone receptors being present in tumors. In addition, tumors will experience changes in size during pregnancy and the luteal phase of the menstrual cycle.[1,11]

Based on the tumor location, most cases of SFT/HPC were found in parasagittal locations whereas meningiomas in basal and convex locations. This is different from previous studies which reported that SFT/HPCs were often found in the supratentorial area (lateral hemisphere/convex), whereas in our study only 16.7%were found in the convex location.[11]

In cases of meningiomas the most common sites reported in previous studies were the following areas: convex (lateral hemisphere) (20–37%); parasagittal (medial hemisphere area) (13–22%), and basal (frontobasal) (10–20%). These site-specific differences derived from the prognostic value of the Simpson classification which has been rarely investigated but may influence surgical strategy.[12]

Solitary fibrous tumor/hemangiopericytoma (SFT/HPC) in this study was dominated by grade III which is in line with previous studies whereby findings of SFT/HPC cases were based on the grade of the tumor from 133 cases, most of which were grade III (36.8%).[7]

In the case of meningioma, this study was dominated by grade I. This was similar in several previous studies which stated that most cases of meningioma tumors were classified as grade I (benign) and only 1% to 3% were categorized as grade II and III. This is in line with other studies that reported as many as 80% to 81% were grade I, 17% to 18% of them were atypical or grade II, and 1.7% were anaplastic or grade III meningiomas.[11,13]

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Differences of STAT6 and SSTR2A Expressions between Group 1, 2 and 3

In this study, the expression of STAT6 in group 1 compared to group 3 was significantly different, as well as between groups 2 and 3. This is in line with previous studies which stated that STAT6 expression in SFT/HPC showed a much higher expression (96%) compared to meningiomas (0%). The results of another study stated that the signal transducer and activator of transcription (STAT6) had sensitivity (96%) and specificity (100%) in the case of SFT/HPC, it was associated with the fusion of the NAB2 – STAT6 gene in SFT/HPC, where fusion products suchas exon 2, exon 4, exon 6, exon 16, and exon 17 predicted to contain the early growthresponse binding domain (EGR) of NAB2 fused with the STAT6 activation domain detecting protein levels, resulting in high STAT6 specificity and sensitivity in SFT/HPC.[4,14]

STAT6 expression at various grades of SFT/HPC cases in our study did not show significant differences, supported by the findings in this study that showed STAT6 expression by gene and molecular fusion, as well as tumorigenesis at various grades of SFT/HPC were the same. Therefore, STAT6 expression could not be used to determine the degree of SFT/HPC.[4,14]

The STAT6 biomarker may be recommended to improve the diagnosis of SFT/HPC compared to the previously frequently used CD 34 biomarker with a sensitivity and specificity of 88%.[15]

In this study, the results showed that the expression of SSTR2A in group 1 compared to group 3 was significantly different, as was the case between groups 2 and 3. This was in line with previous studies which stated that the expression of SSTR2A in meningiomas cases (95.2%) was greater than the expression in SFT/HPC(8.0%). Another study also stated that the somatostatin receptor 2A (SSTR2A) had sensitivity and specificity up to 100% in all grades of meningioma cases and 15% or 8% in SFT/HPC cases.[1,14]

In line with previous studies, the somatostatin receptor (SSTR) 2 gene is located on chromosome 17q25.1 which is known to be expressed diffusely in meningiomas. The major signalling cascade of SSTRs 1 to 5 inhibits adenylatecyclase activation and decreases cAMP. SSTR 1, 2, and 3 also have antiproliferative effects by inducing one or more PTPs (Protein tyrosine phosphatases), thus influencing the mitogenic MAP kinase proliferative pathway and the PI3K pathway for cell survival. The expression of SSTR2A at various grades of meningioma cases in our study did not show significant difference, whereby expressions of SSTR2A by gene and molecular fusion, tumorigenesis at various grades of meningioma was the same. Therefore, SSTR2A expression could not be used to determine the degree of meningioma.[7]

Based on the results obtained, the SSTR2A biomarker may be recommended to sharpen the diagnosis of meningioma, especially in types of meningioma that

holds fibroblastic morphology such as SFT/HPC, compared to the previously frequently used EMA biomarker with sensitivity and specificity (94.8%).[15]

The limitation of this study was the unbalanced proportion of samples in groups 1, 2 and 3 which may affect the results of the study. Further research is expected to heed more attention to the proportion of samples between groups.

CONCLUSION

The results of this study proved that the expression of STAT6 and SSTR2A in solitary fibrous tumor/hemangiopericytoma (SFT/HPC) compared with grade I, II and III meningiomas obtained significant results. Based on the results of the researchand discussion carried out, it can be concluded as of the following: STAT6 expression was strongly stained with SFT/HPC. There was a difference in the expression of STAT6 in grade I, II and III meningiomas. There was a difference in the expression of SSTR2A in SFT/HPC and grade I, II and III meningiomas. SSTR2A expression was strongly marked in grade I, II and III meningiomas. There was a difference in the expression of STAT6 in SFT/HPC compared to grade I, II and III meningiomas. There was a difference in the expression of SSTR2A in SFT/HPC and grade I, II and III meningiomas.

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