Immunohistochemical Assessment of Progesterone Receptor in Meningioma

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ABSTRACT:

BACKGROUND:

Meningiomas are the most common tumor of central nervous system with a higher prevalence in women. Clinical and epidemiological data reveal that meningiomas are hormone sensitive tumors and they have been found to express hormone receptors.

Meningiomas are common slow growing primary intracranial neoplasms attached to the dura matter and are composed of neoplastic meningiothelial cells and these tumors fall in to WHO grades I, II and III.

AIM OF STUDY:

The aim of this study is to determine the progesterone receptor status in meningiomas by using specific monoclonal antibody and to evaluate the effect of age, gender, tumor grade, location and histological types on hormone receptor status.

MATERIALS AND METHODS:

This is a retrospective study of fourty patients who were diagnosed histopathologically as meningioma. Formalin fixed, paraffin embedded tissue blocks were collected from pathology departments of Ghazi AL Hariri teaching hospital, for the period from May 2015 to June 2020 and from neurosurgery hospital, for the period from January 2018 to December 2019.

All the clinical details including age, gender, location, histological type and pathological grade have been taken from the patients archive files.

Two sections of 5 µm were taken from each block, the first was stained with hematoxylin and eosin stain (H&E) for histological revision, the other section was stained immunohistochemically for progesterone receptor (PR).

RESULTS:

Fourty patients were studied 27(67. 5%) female and 13(32.5 %) male, age was ranging from 12-70 years with a mean of 49.47 years. Female to male ratio of 2.07:1.Cerebral site was the dominant site of lesion (60%), followed by olfactory groove, parasagittal site (10% for both of them), orbital, sphenoid site (7.5% for both of them) and spinal site (5%).

Regarding histopathological types of meningioma, meningiothelial type was the most common (32.3%), followed by Atypical (20%), Angiomatous (15%), Anaplastic, fibroblastic, psammomatous and transitional (7.5 for each of them), then Anaplastic papillary (2.5%).

In all stained slides of meningiomas, there were positivity for PR (62.5%) with different scores from +1(20%), +2(17. 5%) and +3(25%).

There is a significant statistical correlation between the grade of meningioma **(p=0.003)**, histological types **(p=0.014)** and PR expression.

There is no significant statistical correlation between age, sex, location and PR expression.

CONCLUSION:

There is a significant correlation between tumor grade, histological types and PR expression and PR immunohistochemical staining is a reliable test when used to predict a low-grade meningioma.

KEYWORDS: PR expression, histopathological types of meningiomas.

INTRODUCTION:

Meningioma is a common tumor of the central nervous system (CNS) that originates from meningeal covering of the brain and spinal cord, they are probably derived from arachnoid cap cells and it accounts for about 30% of primary intracranial and intraspinal tumors [(1)].

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Despite the fact that meningioma has a benign pathophysiology in 95% of cases, but like carcinoma it always results from a clonal outgrowth derived from a single cell as exemplified by cytogenetic and array comparative genomic hybridization (CGH) studies[2]. Meningioma as defined by world health organization (WHO) are meningothelial (arachnoid cell) neoplasms typically attached to inner surface of the dura mater and these tumors fall in to WHO grades I, II and III [3].

Most meninigiomas are slow growing and histologically benign [4]. Certain histological subtypes are associated with less favorable clinical outcomes are correspond to WHO Grade II (atypical) and III (anaplastic or malignant)[4][5]. Atypical meningioma have been reported up to 20%; anaplastic (malignant) meningiomas account for between 1.0% and 3% [5]. The major prognostic factor in meningiomas is the prediction of recurrence. This depends on the extent of resection, its histological type, grading and proliferation indices [6]

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Expected results & scoring:

A Positive stain is indicated by a golden brown colored at site of specific cellular antigen localization **(nucleus).**

The quantitative evaluation of PR was expressed as the percentage of positive nuclei among 100 cells and classified the results as the following scoring system [7].

0 = zero
1= 1-10% of cells
2= 11-50 % of cells
3= >50 % of cells.

Statistical analysis

The data analyzed using Statistical Package for Social Science (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categories data were presented by frequencies and percentages. Chi square test was used to assess the association between PR status and certain information, while fisher exact test was used instead when the expected frequency was less than 5.A level of P-value less than **0. 05** was considered significant.

RESULTS:

The total number of study patients was 40. All of them were diagnosed with meningioma. In all stained slides of meningiomas, there were positivity for PR (62.5%) with different scores from +1(20%), +2(17. 5%) and +3(25%).

There is a significant statistical correlation between the grade of meningioma **(p=0.003)**, histological types **(p=0.014)** and PR expression.

There is no significant statistical correlation between age, sex, location and PR expression.

Grade of meningiomas

As shown in table (1), patients with grade I were 28 (70 %), patients with grade II were 8 (20%) and 4 (10%) patients with grade III.

Table 1: Distribution of study patients by grade of meningioma.

Grade of meningioma	No. (n= 40)	Percentage (%)
I	28	70. 0
II	8	20. 0
III	4	10. 0

Location distribution of meningioma

As shown in table (2), cerebral site was the dominant, cerebral location was the site of lesion in 24 patients (60%), olfactory groove site in 4 patients (10%), parasagittal site in 4(10%), orbital site in 3(7. 5%), sphenoid site in 3(7.5%) and spinal site in only 2 patients(5%).

Table 2: Distribution of study cases by location

Variable	No. (n= 40)	Percentage (%)
Location of meningioma		
Cerebral	24	60. 0
Olfactory Groove	4	10. 0
Parasagittal	4	10. 0
Orbital	3	7. 5
Sphenoid	3	7. 5
Spinal	2	5.0

Histopathological types of meningiomas

As shown in table (3), the most common histopathological type was Meningiothelial in 13 patients (32.3%), Atypical in 8 (20%), Angiomatous in 6 (15%), Anaplastic in 3 (7. 5%), Fibroblastic in 3 (7. 5%), Psammomatous in 3 (7.5%), Transitional in 3 (7.5%) and Anaplastic papillary in only one patient (2.5%).

Table 3: Distribution of histopathological types of meningioma

Variable	No. (n= 40)	Percentage (%)
Histopathological type of meningioma		
Meningothelial	13	32.5
Atypical	8	20. 0
Angiomatous	6	15.0
Anaplastic	3	7. 5
Fibroblastic	3	7.5
psammomatous	3	7.5
Transitional	3	7.5
Anaplastic papillary	1	2.5

Progesterone receptor status

Progesterone receptors were positive in 25 patients (62.5%), furthermore, it had been found that the positivity was +1 in 8 patients (20%), +2 in 7 patients (17. 5%) and +3 in 10 (25%) (all scores were considered as positive). Progesterone receptor negative patients were 15(37. 5%).

Association between PR status and both age and gender

The association between PR status and both of age and gender revealed no significant associations **($P \geq 0.05$)** between PR status and both of age and gender.

Table 4: Association between PR status and both of age and gender.

Variable	PR Status		Total (%) n= 40	P – Value
	Positive (%) n= 25	Negative (%) n= 15		
Age (Year)				
< 40	4 (57. 1)	3 (42.9)	7 (17. 5)	0. 927
40 – 59	15 (62.5)	9 (37. 5)	24 (60. 0)	
≥ 60	6 (66. 7)	3 (33.3)	9 (22.5)	
Gender				
Male	8 (61. 5)	5 (38. 5)	13 (32.5)	0. 931
Female	17 (63.0)	10 (37. 0)	27 (67. 5)	

Association between PR status and grade of meningiomas

As shown in table (5), positive progesterone receptors were significantly more frequent in patients with grade I meningiomas (78.6%) compared to grade II (37. 5) and III (0%), when compared total positive versus negative progesterone receptor status (p=0. 003)

Table 5: Association between PR status and grade of meningiomas.

Grade of meningioma	PR Status		Total (%) n= 40	P – Value
	Positive (%) n= 25	Negative (%) n= 15		
I	22 (78. 6)	6 (21. 4)	28 (70. 0)	0. 003
II	3 (37. 5)	5 (62.5)	8 (20. 0)	
III	0 (0)	4 (100. 0)	4 (10. 0)	

Association between PR status and histopatological types of meningiomas

As it shown in table (6), the positive progesterone receptors were significantly more frequent in patients with meningiothelial type of meningioma (92.3%) with a significant association **(P= 0. 014)** between PR status and histopathological types of meningioma.

Table 6: Association between PR status and histopathological type of meningiomas.

Histopathological type	PR Status		Total (%) n= 40	P – Value
	Positive (%) n= 25	Negative (%) n= 15		
Meningothelial	12 (92.3)	1 (7. 7)	13 (32.5)	0. 014
Atypical	3 (37. 5)	5 (62.5)	8 (20. 0)	
Angiomatous	5 (83.3)	1 (16. 7)	6 (15.0)	
Anaplastic	0 (0)	3 (100. 0)	3 (7. 5)	
Papillary	0 (0)	1 (100. 0)	1 (2.5)	
Fibroblastic	1 (33.3)	2 (66. 7)	3 (7. 5)	
Psammomatous	2 (66. 7)	1 (33.3)	3 (7. 5)	
Transitional	2 (66. 7)	1 (33.3)	3 (7. 5)	

Association between PR status and location of meningiomas

No statistically significant differences had been found in progesterone receptor status in between the different locations of meningiomas **(P = 0. 982)** (table 7).

Table 7: Association between PR status and location of meningiomas.

Location	PR Status		Total (%) n= 40	P – Value
	Positive (%) n= 25	Negative (%) n= 15		
Cerebral	15 (62.5)	9 (37. 5)	24 (60. 0)	0. 982
Olfactory Groove	2 (50. 0)	2 (50. 0)	4 (10. 0)	
Parasagittal	3 (75.0)	1 (25.0)	4 (10. 0)	
Orbital	2 (66. 7)	1 (33.3)	3 (7. 5)	
Sphenoid	2 (66. 7)	1 (33.3)	3 (7. 5)	
Spinal	1 (50. 0)	1 (50. 0)	2 (5.0)	

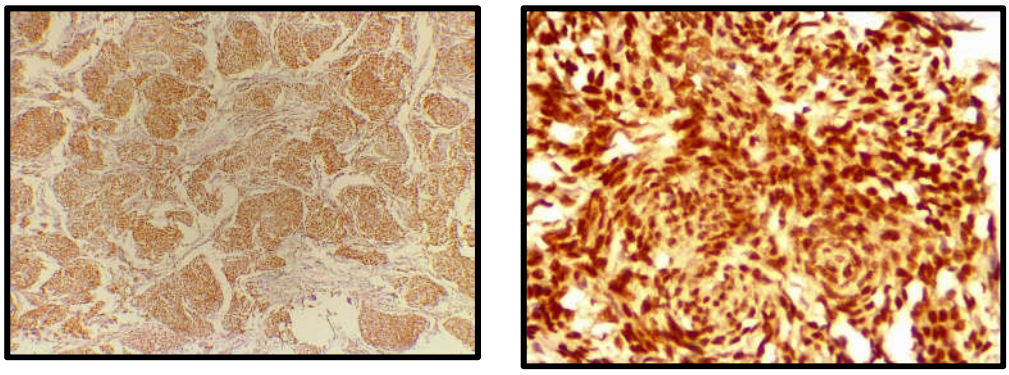

Figure 1: A(X4),B(X40)
Figure 1 (A&B): Sections of meningiothelial meningioma stained IHC by PR showing strong nuclear positivity (+++)

DISCUSSION:

Progesterone receptor (PR) expression:
Progesterone receptors were **positive in (62.5%)**, this finding is correlated well with other studies done by **Shenbagam et al** [8] showed that the PR expression was 66. 7% and **Taghipour M et al** [9] showed that the PR expression was 68. 6% while lower than that reported by another studies done by **Hsu DW et al** [10] showed that the PR expression was 83% and **pertuiset et al** [11] showed that the expression of PR was 88%.

Clinicopathological parameters:

- **Pathological grade:**

This study showed positive progesterone receptors were **significantly** more frequent in patient with grade I meningiomas and PR expression in grade II and III meningiomas were weak to absent. This finding of the current study is correlated well with studies done by **Kandemir NO et al** [12], **Shayanfar N et al** [13], **Taghipour, et al** [9], **and Hibig A et al** [14] they found that the immunohistochemical expression of PR in grade II and III meningiomas were weak to absent. Although the reason for this relationship is not clearly known yet, it could be probably due to the higher incidence of mitosis in tumor cells in presence of low number of progesterone receptors and cellular turn-over or it could be that the different cells in grade I are more differentiated than cells in grade II and III, hence it expresses the PR more than that of grade II and III [15].
Other studies done by **Blaauw G et al** [16], **Carrol RS et al** [17] **and Schwartz MR et al** [18], showed no relationship between the tumor grade and the presence of PR.

- **Age**:

The distribution of progesterone receptor status by age group revealed **no significant** differences in between different age groups in progesterone positivity of meningiomas patients, which agreed with other studies done by **Hayward E et al** [19]

- **Gender:**

There is a **no significant** relationship between PR and gender in this study, the finding which is similar to other studies done by **Whittle et al** [20] **and Ironside et al** [21] differs from other studies done by, **perrot et al** [22] showed that the presence PR immunostaining in 79% of women (versus 58% in male) and **Brandis et al** [23] noted that 60% of the female and 62% of the male patients had the PR expression.

- **Location**:

In regard to location, no statistically differences had been found in progesterone receptor status in between the different locations of meningiomas, this finding is in agreement with other studies done by **Valeria et al** [24].

- **Histological types of tumor**:

In this study, there is a significant relationship between PR expression and histologic subtypes; the study showed that among all types of grade I meningioma, meningiothelial meningioma had increased expression and fibrous type of meningioma had the weakest expression of PR, this agrees with another study done by, **Omulecka A et al** [25], found that among all types of grade I meningiomas, meningiothelial meningiomas had increased expression and fibrous type of

meningiomas had the weakest expression of PR. This might be because the line of differentiation of cells in fibrous meningiomas are more towards a mesenchyme rather than epithelial like cells.

In regarding to the histologic types of grade II and III, most of the grade II histologic types were negative and all grade III histologic types were negative. The cause of that is most probably the same of that mentioned above in pathological grades, were this might be due to differentiation of cells is more in well differentiated cells (grade I) rather than that of moderately (grade II) and poorly differentiated cells (grade III). Studies done by, **Carrol RS et al** [17], **Halper J et al** [26], **Schrell et al** [27], **Blaauw G et al** [16], found that the histological subtypes was unrelated to the PR status.

CONCLUSION:

1. There is a significant relationship between PR and grades and histological subtypes of meningiomas.
2. PR immunohistochemical staining is a reliable test when used to predict a low grade meningioma.
3. No significant relationship exists between PR and age, gender of patient and location of meningioma.
4. PR present in large numbers of meningiomas and its presence may have a useful value in choosing the modalities of treatment.

REFERENCES:

1. Markus J, ArieP , Guido R etal: Histopathological classification and molecular genetics of meningioma .Lancet neural 2016;5:1045 -54.
2. Hansson CM , Buckley PG , Jarbo C etal: Comprehensive genetic analysis of sporadic meningioma for macromutation on 22q and micromutation within the NF2 locus . BMC genomic 2007;8:16.
3. Perry A, Stafford SL, Scheithauer BW , Suman VJ, lohse CM Meningioma grading: an analysis of histologic parameters .Am J Surg Pathol 2017; 21:1455-65.
4. Black PM . Meningiomas . Neurosurgery. 2014;32:643-57
5. Willim J , Smith C , Ironside JW , Erridge S , Whittle IR , Everington D . The accuracy of meningiomas grading : A 10-year retrospective audit. Neuropathol Appl Neurobiol.2013;31:141-49.
6. LouisDN , Budka , Von Deimlingb A. Meningiomas . In : Kleihuse p . Cavenee WK editor .pathology and genetics of tumors of the Nervous System . Loyon : IARC; 2014: 134-41.
7. Tamoxifen for early breast cancer : an overview of the randomized trials .Lancet 2015;351:1451-67.
8. Shenbagam Jeevakarunyam Muthukanagarajan: progesterone receptor Expression in meningiomas, Journal of Clinical and Diagnostic Research. 2018;12: EC01-ECO5.
9. Taghipour M, Rakei SM, Monabati A, Nahavandi-Nejad M. The role of ostrogen and progesterone receptors in grading of the malignancy of meningioma. Iranian Red Cescent Medical Journal. 2015 ; 9: 17-21.
10. Hsu DW, Efird JT, Tessa Hedley-Whyte E Progesterone and estrogen in meningiomas prognostic considerations. JnEUROSURG 2014;86: 113-20.
11. Pertuiset BF, Moguilewsky M, Magdalenat H, et al Sex steroid receptors in human meningioma and glioma. in BrescianiF(ed) prog. in Cancer Research and Therapy,. Raven press, New York, 2016; 31:561-68.
12. Kandemir NO, Gul AE, Gun BD, Karadayi N, Yurdakan G, Ozamar SO. Her-2/Neu, Estrogen and progesterone receptor expression in WHO Grade in meningiomas. Trakya Univ Tip Fak Derg. 2010;27:292-96.
13. Shayanfar N, Mashayekh M, Mohammadpour M. Expression of progesterone receptor and proliferative marker Ki-67 in various grades of meningioma. Acta Med iran. 2016;48:142-47.
14. Hibig A, BarboSA- Coutinho LM. Meningiomas and hormonal receptors immunohistochemical study in typical and non typical tumors. Arq Neuropsiquiatr. 2014;56:193-99.
15. Fewing PE, Battersby RD, Tempoerly WR .Long- term follow up of progesterone :A prognostic indicator of recurrence ? J Neurosurg. 2011;92:401-5.
16. Blaauw G, Blankenstein MA, Lamberts SWJ sex steroid receptors in human meningiomas. Acta Neurochir(wien) 2015;79: 42-47.
17. Carrol RS, Glowacka D, Dashner, et al progesterone receptor expression in meningiomas. Cancer Res 2013;53: 1312-16.
18. Schwartz MR, Randolph, Cech DA, et al Steroid hormone binding macromolecules in meningiomas. Cancer 2016;53: 9922-27.

19. Hayward E, Whitwell H, Paul KSS et al steroid receptor in human meningiomas. Clin Neuropharmacol 2015:7351-56,

20. Whitle IR, foo MS,BesserM, et al Preogesterone and esterogen receptor in meningioma Biological and clinicopathological consideration .Aust N Z Surg 54325-330,2011

21. Iron side JW,Battersby RDA,Dangerfield VJM, et al cryostate section assay of estrogen and progesterone receptors in memingiomas.A clinicopathological study . J Clin pathol 3944-50,2018

22. Perrot –Applant M, Broyer-picard MT, Kujas M immunohistchemical study of progesterone receptoe in human meningioma. Acta Neurochir 2014;115: 20-30.

23. Brandis A, Mirazai S, Tatagiba M, et al immunohistochemical detection of female sex hormone receptors in meningiomas correlation with clinical and histological features . Neurosurgery 2015;33: 212 -18.

24. Valeria Barresi, ConcettaAllafaci, Maria Caffoetal: Clinicopathological characteristic, hormone receptor status and matrix metallo-proteiase -9(MMP-9) immunohistochemical expression in spinal meningiomass pathology – Reserch and practice 2012;208:350 -55.

25. Omulecka A, Papierz W, Nawrocka –Kunecka A, Lewy-Trenda I. Immunohistochemical expression of progesterone and estrogen receptors in meningiomas. Folia Neiropathol. 2009;44:11-15.180F.

26. Halper J, Colvard DS, Scheithauer BW, et al Estrogen and progesterone receptors in meningiomas comparison of nuclear binding, dextran-coated charcoal, and immunoperoxi – dase staining assay. Neurosurgery 2014;25: 546-53.

27. Schrell JF, Gomerz F, LeMarchand- Beraud T, et al presence of sex steroid hormone receptors in meningiomas tissue . Neural Surg 2015;15 :415-18.