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EXPRESSION OF ESTROGEN AND PROGESTERONE RECEPTORS IN MENINGIOMAS

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ABSTRACT

Background/objective: Meningiomas are the second most common primary tumors of the central nervous system. The aim of this study was to observe the expression of Estrogen and Progesterone receptors in meningiomas. Anti-progesterone therapy may be given to the patient to avoid recurrence.
Methods: This observational study was conducted at the Pathology Department of the Postgraduate Medical Institute, Lahore, Pakistan, from January 2013 to December 2013. The cases were collected from the Pathology Laboratory of the Lahore General Hospital, Lahore. This study was conducted on 50 cases of histologically diagnosed meningiomas. Data was entered and analyzed using SPSS version 17.
Results: Out of fifty cases of meningiomas, thirty cases were PR positive and 16 were ER positive. There was no statistical difference of ER score in males and females, p-value = 0.433. Also there was no statistical difference of PR score in males and females, p-value = 0.595.
Conclusion: It was concluded that meningiomas express progesterone receptors more than estrogen receptors and. Anti-progesterone therapy may be given to avoid recurrence of meningiomas.

Keywords: Meningioma; Estrogen Receptors; Progesterone Receptors.

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INTRODUCTION

The arachnoid cells in the brain give rise meningioma that is the most common brain tumour. They are subdivided into benign (90%), atypical and anaplastic (0.9%–10.6%)[1]. Intracranial meningiomas comprised of 75% and spinal 25% of total meningiomas[2]. WHO classification system 2016, distinguishes 3 grades of malignancy depending on microscopic morphological characteristics, which fail to predict clinical behavior because these tumors have a variable potential for growth[3]. It has been reported that PR expression had an inverse relationship with proliferation rate when compared to tumors with increased Ki67 and decreased PR expression. This indicates that PR expression is better prognostic marker for these tumors[4].

WHO grade I meningiomas have been reported to have significantly higher incidences of estrogen, progesterone, and androgen receptors than higher-grade meningiomas. However, differences in sex hormone receptor expression alone may not explain the observed increase in incidence in women[5]. It is suggested that meningiomas are hormone sensitive tumors because of its increased incidence in females as compared to males[6], increased growth during pregnancy and menses[7], increased incidence in patients having breast cancer and increased incidence in patients having lymphangio-leiomyomatosis[8].
Estrogen is produced by ovaries and placenta. Progesterone is a hormone produced mainly by the ovaries and placenta and to some extent by the adrenal glands. The main function of estrogen and

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progesterone is in the regulation of menstrual cycle and conception[9].
There are studies in which the expression of estrogen and progesterone receptors in meningiomas has been observed. In 2010, a case has been reported in which a patient was on progesterone agonist therapy and also having meningiomas. Withdrawal of therapy led to regression of many meningiomas and complete resolution of one[10]. Recently it has been shown that anti-progesterone drug (MIFEPRISTONE RU-486) inhibits the progression of meningiomas[11].
The purpose of this study is to observe the expression of estrogen and progesterone receptors in meningiomas in our population. Anti-estrogen and anti-progesterone therapy may be helpful in reducing the recurrence of ER and PR positive meningiomas.

MATERIAL AND METHODS

This study was an observational study, conducted at the Pathology Department of the Postgraduate Medical Institute Lahore, Pakistan. The cases were received at and collected from the Pathology Laboratory of the Lahore General Hospital, Lahore. This study was conducted on 50 cases of histologically diagnosed meningiomas. Written informed consent was taken on a consent proforma.

Inclusion Criteria:

Patients having meningiomas were selected according to the following inclusion criteria,
1. Patients of all ages and both sexes
2. Diagnosed histologically as meningiomas.

Exclusion criteria:

Patients with recurrent meningiomas
Patients who were already receiving chemo-radiotherapy for meningiomas
Patients with immunological disorders and patients on hormone replacement therapy

Tissue fixation and processing:-

Each biopsy was placed in a plastic jar and immersed in tenfold volume of 10% buffered formol saline. The jar was labeled with the patient's name, age, sex, registration number. A proforma was attached to each case. All relevant clinical information like presenting complaints, duration, reports of investigations etc. were recorded. Detailed gross examination of the specimens was carried out and findings like weight, colour, size and appearance was recorded in the proforma. All the specimens were fixed in 10% formalin solution. After 24 hours of fixation, sections were processed in an automated processor in ascending alcohol concentrations and several changes of xylene. After processing, paraffin blocks were prepared in L-shaped metallic molds. A rotary microtome was used to obtain 4 microns thick sections for staining and histopathological study. Sections were taken on the albuminized slides. These sections were processed for the staining[12].

H & E Staining (fig'4)

Hematoxylin and Eosin staining of the sections was done as per standard protocol. Histopathological evaluation was performed by 2 pathologists, using hematoxylin & eosin–stained sections. Microscopy was performed by using Binocular microscope (Olympus) for histological diagnosis and categorization of meningiomas according to WHO classification.

Estrogen Receptor and Progesterone Receptor immunostaining

This staining was performed by using commercially available antibodies (Dako, USA) and reagents according to manufacturer's instructions.

Selection of controls:

A system dependent on the detection of antigen by specific antibody is only as good as the antibody or antibodies employed in the methodology when performed along with controls[13]. Positive and negative controls were used along with each batch of ER and PR immunostaining in this study. A known case of meningiomas grade 1 was used as positive control while normal brain tissue was used as negative control.

Statistical analysis

The data was entered and analysed using SPSS 20.0. Mean ± S.D was given for quantitative variables like age, size of tumour reported by surgeon on biopsy form, histological grade and ER and PR immuno-histochemical score etc. Frequencies, percentages and graphs were given for qualitative variables like gender, distribution etc. Comparisons between clinical and microscopic parameters were performed with the sample t-test. A difference of $P<0.05$ was considered to be significant.

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RESULTS

Results are shown in tables and figures. In addition to routine hematoxylin and eosin staining, ER and PR immunostaining was carried out on all cases and its score was studied. In this study the mean age of patients was 47.28 ± 14.71 years. The minimum and maximum ages were 18 and 75 years and age range was 57 years. There were 22 (44%) male and 28 (56%) female patients in this study.

Histological grades of tumors were also assessed and Grade – I was seen in 40 (80%), grade II was present in 8(16%) and grade III was seen in 2 (4%) as shown in figure 1.

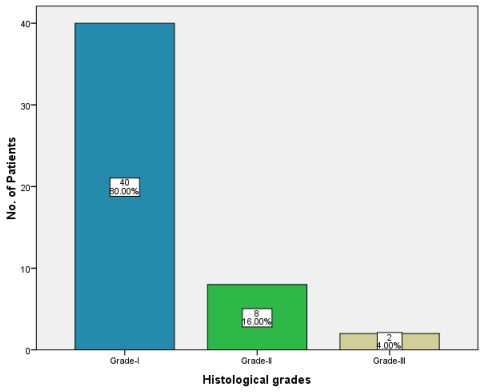

Fig 1: Histological grades of meningiomas in current study

Tables I,II show the frequency of ER score in different grades and histological types of meningiomas. Table 4 shows the frequency of PR score in different histological grades of meningiomas. Table 3 shows the frequency of PR in different types of meningiomas. There were 22 (44%) patients who were diagnosed meningiothelal meningiomas, out of which 12 were PR positive. Psammomatous meningiomas were seen in 21 (42%) patients out of whom 16 were PR positive. 5 (10%) patients had Clear cell meningiomas, 3 were PR positive. Rhabdoid Meningioma was seen in 2 (4%) patients, both were PR and ER positive. Tables V shows the comparison of ER and PR scores in males and females study subjects respectively.

Figure 2 shows the ER score in patients. Fig. 3 shows the PR score of the patients. PR score 0 was present in 20 (40%), score 2, 3 and 4 were seen in 15 (30%), 8(16%) and 7(14%) of the patients respectively. Table 6 shows the comparison of PR score in males and females. Score 0 was seen in 9 males (40.9%) and 11 females (39.3%). Score 1 was not seen in any patient. Score 2 was seen in 6 males (27.3%) and 9 females (32.1%). Score 3 was seen in 5 males (22.7%) and 3 females (10.7%) (Fig 4). Score 4 was seen in 2 males (9.1%) and 5 females (17.9%) (Fig 5a, Fig 5b). There was no statistical difference of PR score in both males and females, p-value = 0.595.

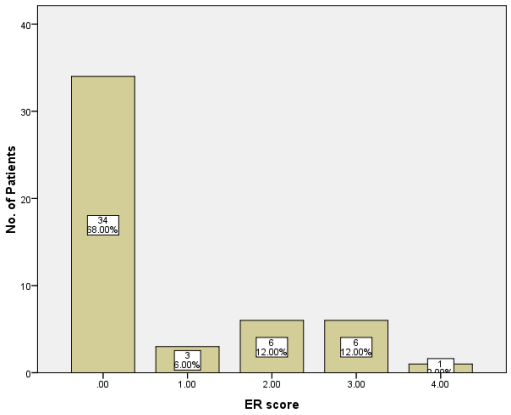

Fig 2: ER score of the patients

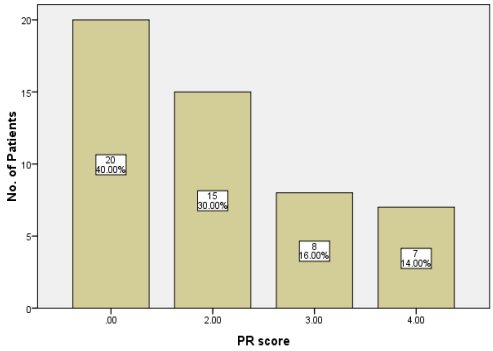

Fig 3: PR score of the patients

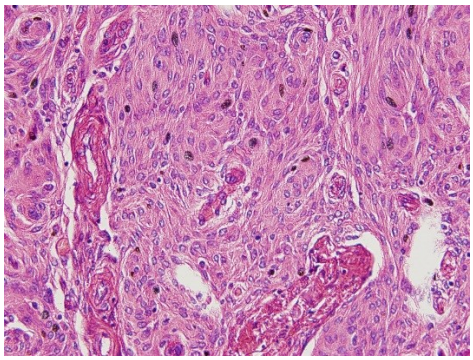

Figure 4: H&E Stain of Meningioma Grade II

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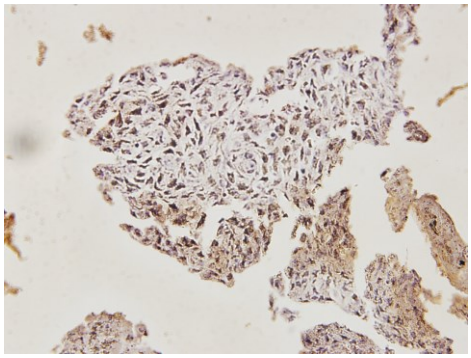
Figure 5a: ER Score 4 of Meningioma Grade I

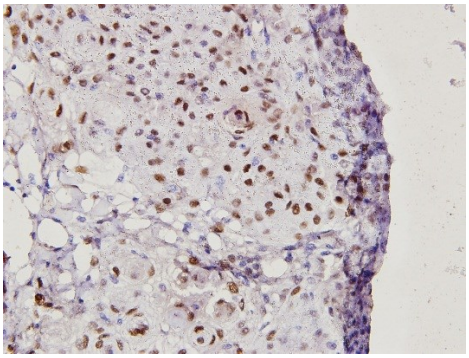
Figure 5b: PR Score4 of Meningioma Grade I

Table I: Frequency of ER in different grades of meningiomas

		ER score					Total
		0	1	2	3	4	
Histological grades	Grade-I	31	2	3	3	1	40
	Grade-II	3	1	2	2	0	8
	Grade-III	0	0	1	1	0	2
Total		34	3	6	6	1	50

p-value = 0.134

Table II: Frequency of PR in different grades of meningiomas

		PR score				Total
		0	2	3	4	
Histological grades	Grade-I	15	13	6	6	40
	Grade-II	5	1	1	1	8
	Grade-III	0	1	1	0	2
Total		20	15	8	7	50

p-value = 0.557

Table III: Frequency of ER in different types of meningiomas

		ER score					Total
		0	1	2	3	4	
Diagnosis	Meningiothelial meningioma	19	1	1	1	0	22
	Clear cell Meningioma	2	0	2	1	0	5
	Psammomatous meningioma	12	1	2	2	1	18
	Psammomatous meningioma invading the underlying glial tissue	1	1	0	1	0	3
	Rhabdoid Meningioma	0	0	1	1	0	2
Total		34	3	6	6	1	50

p-value = 0.161

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Table IV: Frequency of PR in different types of Meningiomas

		PR score				
		0	2	3	4	Total
Diagnosis	Meningiothelial meningioma	10	6	3	3	22
	Clear cell Meningioma	5	0	0	0	5
	Psammomatous Meningioma	5	7	3	3	18
	Psammomatous meningioma invading the glial tissue	0	1	1	1	3
	Rhabdoid Meningioma	0	1	1	0	2
Total		20	15	8	7	50

p-value = 0.257

Table V: comparison of ER Score in male and females

		Gender		Total
		Male	Female	
ER score	0	15	19	34
		68.2%	67.9%	68.0%
	1	2	1	3
		9.1%	3.6%	6.0%
	2	3	3	6
		13.6%	10.7%	12.0%
	3	1	5	6
		4.5%	17.9%	12.0%
	4	1	0	1
		4.5%	.0%	2.0%
Total		22	28	50

p-value = 0.433

Table VI: comparison of pr score in male and females

		Gender		Total
		Male	Female	
PR score	0	9	11	20
		40.9%	39.3%	40.0%
	2	6	9	15
		27.3%	32.1%	30.0%
	3	5	3	8
		22.7%	10.7%	16.0%
	4	2	5	7
		9.1%	17.9%	14.0%
Total		22	28	50
		100.0%	100.0%	100.0%

p-value = 0.595

DISCUSSION

This study shares several features common with other published studies. There was seen no marked differences in the expression pattern of the receptors between different histological subtypes of meningiomas which correlates with other studies[14,15]. Out of 50 cases of meningiomas, 40 were of grade 1, 8 cases were of grade II whereas 2 cases were of grade III. So we came to know that Grade I meningiomas are

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most common, then grade two, and lastly grade three as evidenced by Metellus et al. in 2008 and Omuleckaet al. in 2006[16,17].

The goal of this study was to observe the expression of estrogen and progesterone receptors in meningiomas in our population. As we have seen that these tumors may recur and they are hormone responsive, anti-progesterone therapy may be helpful to avoid the recurrence of meningiomas. In the current study, among 50 cases of meningiomas, ER was positive in 16 cases while PR positivity was observed in 30 cases, but there was seen no statistical correlation ER, PR scores and histological grades of meningiomas. Considering the importance of antiprogesteron therapy in meningiomas, Touat et al. (2014) treated three consecutive women with multiple meningiomas with mifepristone (RU 486). It is a synthetic steroid with high affinity for both progesterone and glucocorticoid receptors. They reported that treatment was well tolerated, and they observed an important and long-lasting clinical (3/3) and radiological response (2/3) or stabilisation[18].

In 2000, a study was conducted by Assimakopoulou[19], in which 64 human meningiomas of various histologic types were immunostained for estrogen and progesterone receptors. Strong PR nuclear immunoreactivity was observed in 51 of 64 meningiomas (80%). All neoplasms were negative for ER. Normal arachnoid tissue was positive for PR and negative for ER.

In 2006, a study was conducted by Omulecka et al.[17] in which 64 meningioma were examined. 100% meningothelial, 95% transitional, 46% fibrous and 78% atypical variants of meningiomas showed positivity for progesterone receptors. Grade I tumors were more strongly stained than grade II tumors. 48% of the meningiomas were positive for estrogen receptors.

Custer et al. in 2006 conducted a study on 142 patients having meningiomas, and it was seen that 130 expressed progesterone receptors and 2 expressed estrogen receptors[19]. Taghipour et al. in 2007 conducted a study in which 51 patients with histological diagnosis of meningiomas were observed for expression of estrogen and progesterone receptors, 35 (68.6%) cases were positive for progesterone receptors and 16 (31.37%) were negative. No case was positive for estrogen receptor expression[20].

In 2008, a study was conducted by Claus et al. on surgical specimens from 31 meningioma patients. Progesterone and estrogen hormone receptors were measured via immunohistochemistry. The sample was 77% females with a mean age of 55.7 years. Eighty percent were grade 1 meningiomas, whereas 33% and 84% were ER+ and PR+, respectively.

Saaverda et al. in 2009, conducted a study on 42 patients and concluded that 11 patients were ER positive and 27 were PR positive[21].

Korhonen et al. in 2010 conducted a study in which 264 cases and 505 controls were studied. 50% of the tumors were positive for estrogen receptor and 86.3% for progesterone receptors[5]. Guevara et al. in 2010 conducted a study which included 42 cases of meningiomas and observed that 26% were ER positive and 62% were PR positive[22].

Saitoh et al. in 1989 described a woman who had a meningioma which rapidly grew during two pregnancies. CT scan confirmed the rapid growth of tumor. Tumor was positive for ER and PR[7].

In current study, out of 50 cases of meningiomas, 28 were females and 22 were males. Female patients had more PRs ($p < \text{or} = 0.05$). In 2010, a study was conducted by Leaes et al. on 126 patients (29 men and 97 women). PR was positive in 60.3% of the tumors and 47.4% of the controls whereas ER was positive in 24.6% of the tumors and none of the controls. Women showed significantly higher expression of PR as compared to men[14].

Taghipour et al. in 2007 conducted a study in which 51 patients with histological diagnosis of meningiomas were observed for expression of estrogen and progesterone receptors. 35 (68.6%) cases were positive for progesterone receptors and 16 ones (31.37%) were negative. No case was positive for estrogen receptor expression[1].

In all the above mentioned studies, we have seen that expression of progestserone in meningiomas is higher than estrogen which matches with our study.

CONCLUSION

It was concluded that meningiomas express progesterone receptors more than estrogen receptors and. Anti-progesterone therapy may be given to avoid recurrence of meningiomas.

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