Original Research Article

The role of vascular endothelial growth factor in predicting the tumor dynamics of meningiomas

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ABSTRACT

Background: Meningiomas are the most common tumors of the central nervous system with variable tumor dynamics. Histopathology is the gold standard but has its own constraints in predicting the tumor behavior. As intra-tumoral hypoxia leads to neo angio angiogenesis and subsequent tumor growth we envisage to establish the role of vascular endothelial growth factor (VEGF) in predicting the tumor dynamics of meningiomas.
Methods: This observational, descriptive, longitudinal follow up study included 38 patients and spanned over a period of 2 years. Surgical samples were grossed and histo-pathologically analyzed and subsequently immune-histochemically categorized. Cases showing VEGF positivity were subjected to yearly follow up to ascertain the number of recurrent cases.
Results: Majority of our cases belonged to WHO grade I (84.21%). The 73.68% were females. The 63.16% were aged >50 years. The 42.1 % of the total cases revealed moderate to strong VEGF expression. Majority of grade II and grade III meningiomas showed moderate to strong VEGF expression. However, a subgroup of grade I meningiomas also revealed a high immune-expression of VEGF (31.25%). Statistically significant association was found between VEGF expression and WHO grade (p=0.0001). On follow up 34.21% of the cases showed recurrence. Significant association was found between VEGF expression and recurrence of the tumor s (p=0.0005).
Conclusions: VEGF has a role in ascertaining the high-risk grade I meningiomas that have a potential to recur as well as grade II and grade III meningiomas that show adverse patient prognosis.

Keywords: VEGF, High risk, Meningiomas

INTRODUCTION

Meningiomas are tumors derived from arachnoid cap cells lining the meningeal covering of the brain and spinal cord. These are the most common primary brain tumors and also the most common intradural spinal tumors.[1] Meningiomas are classically graded by WHO (World health organization) into three basic grades.[2,3] Histopathology, though considered as gold standard, has constraints in ascertaining the exact fate of the tumor,

hence the need for immunohistochemical markers. As intra-tumoral hypoxia leads to increased HIF-1A and subsequent neo angio genesis, markers like VEGF might thus aid in determining the aggressive tumor potential.[4]

METHODS

This observational, descriptive, longitudinal follow up study included 38 patients who underwent neurosurgical interventions in the department of neurosurgery at NRS

medical college and hospital, Kolkata. The study spanned over a period of 15 months (March 2016 to May 2017). Ethical Approval and proper patient consent were taken prior to the study. Surgical samples were grossed and histo-pathologically analysed and graded according to the WHO classification. Subsequently immune-histochemistry was performed using VEGF as a marker to ascertain the tumor dynamics. VEGF expression was assessed by using a scoring system proposed by Raica et al.[5]

Score 0 (-): Reaction seen in <1% tumor cells; Score 1 (+): Weak reaction in 1-25% of tumor cells; Score 2 (++): Moderate reaction in 26-50% of tumor cells; Score 3 (+++): Strong intensity in >50% of tumor cells. Cases showing VEGF positivity were subjected to yearly follow up and subsequently recurrent cases were ascertained.

Inclusion criteria

All patients diagnosed as meningiomas both primary and recurrent cases were included in the study.

Exclusion criteria

Patients with CNS (central nervous system) tumors other than meningiomas and inadequate samples were excluded from the study.

Statistical analysis was done using Epi info TM 7.2.4.0. Epi info is statistical software of CDC (center for disease control and prevention). A probability value (p value) of <0.05 was taken to be statistically significant to establish the association between two variables. Ethical Approval was taken from institutional ethics committee

RESULTS

Total of 38 patients were studied including 2 cases having a previous history of meningioma. The 63.16% of the cases were aged >50 years whereas 36.84% were <50 years old. There was a gender bias with 73.68% of the cases showing female preponderance whereas 26.32% of the cases were seen in males. Majority (84.21%) of the cases belonged to WHO grade I whereas 5.26% and 10.53% belonged to WHO grade II and grade III, respectively (Table 1). 42.1% of the cases showed moderate to strong expression for VEGF (Figure 1). Statistically significant association was found between VEGF expression and WHO grade (p=0.0001) (Table 2). Considering the histopathological subtypes (Figures 2-5) moderate to strong expression for VEGF was noted in atypical (WHO grade II) and anaplastic and papillary (WHO grade III) meningiomas. However, 31.25% of the WHO grade I meningiomas also showed a moderate to strong VEGF expression. This presumably represents the high-risk category of grade I meningiomas. Statistically significant association was found between histopathological subtype and VEGF expression (p=0.0041).

On follow up recurrence was noted in 34.21% of the cases. 63.64% of the cases with VEGF score of 2 and 80% of the cases with VEGF score of 3 showed recurrence. In addition, 9.09% of the cases with VEGF score of 1 also recurred. Statistically significant association was found between VEGF score and recurrence of the tumor (p=0.0005) (Table 3). Besides high grade meningiomas 28.13% of grade I meningiomas also showed recurrence.
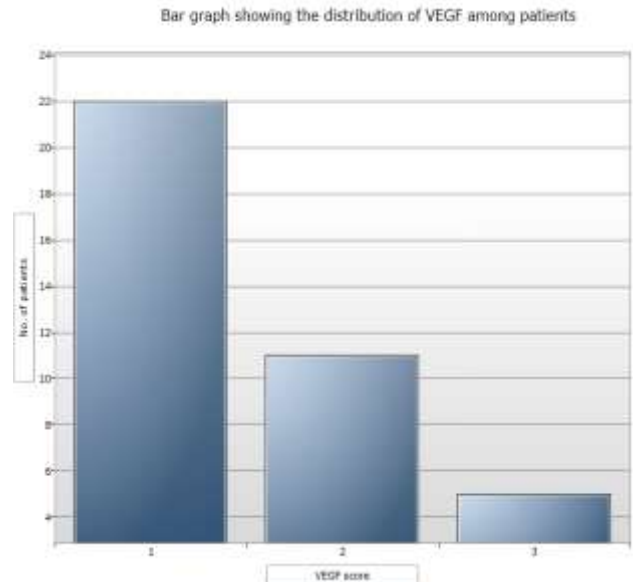
VEGF score 1: 22 patients (57.89%), VEGF score 2: 11 patients (28.95%) and VEGF score 3: 5 patients (13.16%)

Figure 1: The VEGF score distribution among patients.

Figure 2: CT scan of an intra-diploic mass later diagnosed as meningothelial meningioma (WHO grade I).
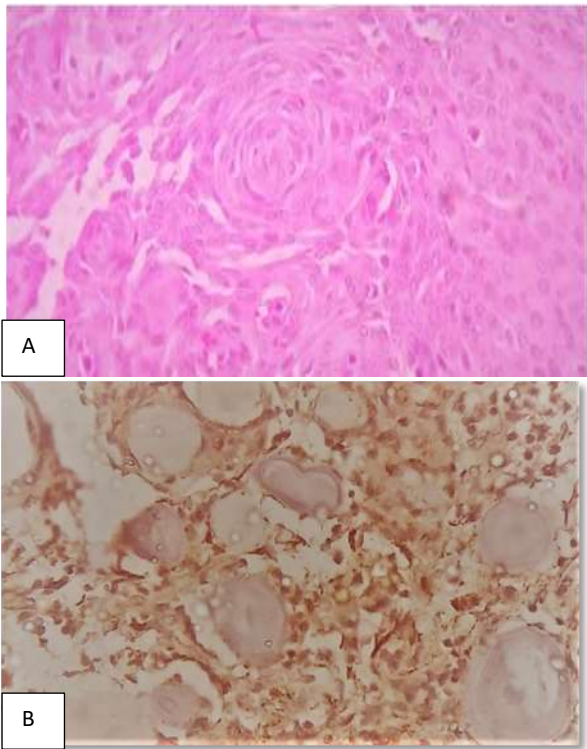
Figure 3 (A and B): Meningothelial meningioma with characteristic whorled pattern (WHO grade I, H and E, 100X). Meningothelial meningioma with psammoma bodies (VEGF score 2, 100X).

Figure 4 (A and B): Atypical meningioma, WHO grade II (H and E, 400X) and atypical meningioma (VEGF score 3, 400X).
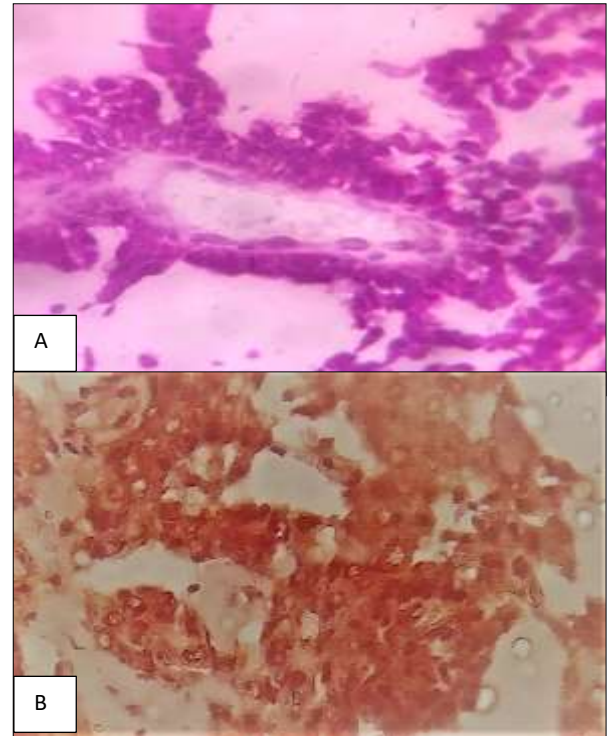

Figure 5 (A and B): Papillary meningioma with characteristic perivascular pseudopapillary pattern (WHO grade III, H and E, 400X) and papillary meningioma (VEGF score 2, 400X).
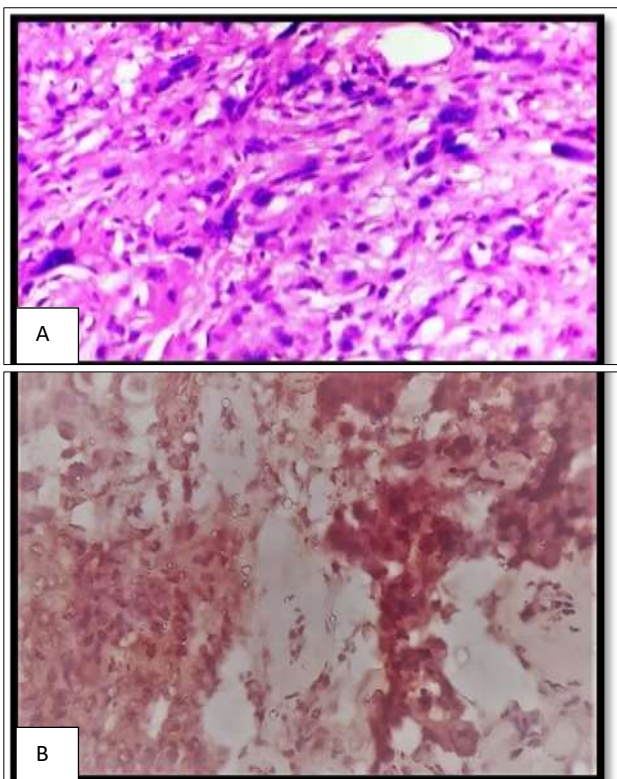
Table 1: Frequency distribution of WHO grade among patients of meningioma.

WHO grade	Frequency	Percentage (%)	Cum, percentage (%)
I	32	84.21	84.21
II	2	5.26	89.47
III	4	10.53	100
Total	38	100	100

Table 2: The relation between WHO grade of meningioma and VEGF score.

WHO grade	VEGF score			Total
	1	2	3	
I	22	9	1	32
Row%	68.75	28.13	3.13	100
Col%	100	81.82	20	84.21
II	0	0	2	2
Row%	0	0	100	100
Col%	0	0	40	5.26
III	0	2	2	4
Row%	0	50	50	100
Col%	0	18.18	40	10.53
Total	22	11	5	38
Row%	57.89	28.95	13.16	100
Col%	100	100	100	100

$P=0.0001.$

Table 3: The relation between VEGF score and recurrence of meningioma.

VEGF score	Recurrence		Total
	No	Yes	
1	20	2	22
Row%	90.91	9.09	100
Col%	80	15.38	57.89
2	4	7	11
Row%	36.36	63.64	100
Col%	16	53.85	28.95
3	1	4	5
Row%	20	80	100
Col%	4	30.77	13.16
Total	25	13	38
Row%	65.79	34.21	100
Col%	100	100	100

P=0.0005.

DISCUSSION

Meningiomas are a set of tumors showing a wide range of tumor dynamics. Histopathology alone cannot ascertain the tumor prognosis thus posing a need for immunohistochemical markers. Of the several markers we used the hypoxia induced angiogenic marker, VEGF in predicting the tumor outcome and risk potential.

Total of 38 patients were studied. 63.16% were aged >50 years. The ratio of male and female (Male:Female) was 1:2.7. Proportion of females was significantly higher (73.68%) than that of males (26.32%). Similar observations were advocated by Nuamy et al and Mukherjee et al.[6,7] The reason could be attributed to the possible hormonal influence on meningioma pathogenesis.[8,9] Two cases had a previous history of meningioma whereas out of 68 cases studied by Rao et al 6 cases were recurrent.[10] WHO grade-I meningiomas accounted for 84.21% of the cases whereas 5.26% belonged to WHO grade II and 10.53% belonged to WHO grade III. Perry et al also reported similar findings.[11] The 42.1% of the cases showed moderate to strong expression (score 2 and 3) for VEGF whereas 57.89% revealed a weak staining (score 1) for VEGF. Statistically significant association was found between VEGF expression and WHO grade (p=0.0001). Significant corroboration was found with Dharmalingam et al who revealed that 34.78% cases had a VEGF score of 1 whereas only 28.3% cases had a score of 2.[12] In addition, Dharmalingam et al who also showed that all the cases of grade II and grade III meningiomas were positive for VEGF whereas 65% of grade I meningiomas also showed VEGF positivity, representing the high risk category.[12] Considering the histopathological subtypes moderate to strong expression for VEGF was noted in atypical (WHO grade II) and anaplastic and papillary (WHO grade III) meningiomas. However, 31.25% of the WHO grade I meningiomas also showed a moderate to strong VEGF expression. This presumably represents the high-risk category of grade I meningiomas. Statistically

significant association was found between histopathological subtype and VEGF expression (p=0.0041). These findings were also consistent with Dharmalingam et al.[12]

On subsequent follow up after neurosurgical excision recurrence was noted 34.21% of the cases. 63.64% of the cases with VEGF score of 2 and 80% of the cases with VEGF score of 3 showed recurrence. In addition, 9.09% of the cases with VEGF score of 1 recurred. Statistically significant association was found between VEGF score and recurrence of the tumor (p=0.0005). Hence, revealing that the intensity of VEGF expression was a significant marker for tumor recurrence. Besides high grade meningiomas, 28.13% of grade I meningiomas also recurred. This accounted for the high-risk category of histo-morphologically benign meningiomas. Therefore. VEGF not only ascertains tumor recurrence but also helps in ascertaining the high risk benign meningiomas.

Similar findings were also observed by Yamasaki et al who studied 54 patients of meningioma and observed that 11.1% of the cases recurred on follow up.[13] These cases showed a moderate to strong immune-expression for VEGF. Yamasaki et al thus concluded that high expression for VEGF was associated with increased tumor recurrence.[13] In addition we found that amongst the WHO grade I category besides 1case each of meningothelial, microcystic, psammomata's and 2 cases of transitional meningiomas, 80% of angiomatous subtype (4 cases) recurred, whereas papillary and anaplastic meningiomas (WHO grade III) also showed recurrence.[13] Our findings corroborated with Budohoski et al and Lee et al who found that high grade meningiomas (WHO grade II and grade III) had a higher propensity to recur within 24 months of surgery.[14,15] In addition, Liu et al also found a 5 year recurrence rate for angiomatous meningiomas to be 5.3% while meningiomas in general to be about 7%.[16] The reason for recurrence can be attributed to the intra-tumoral hypoxia which leads to stabilization of HIF-1A and that in turn activates VEGF resulting in tumor neo-angiogenesis and subsequent tumor proliferation and recurrence. Hence, anti-VEGF agents like bevacizumab and hypoxia-activated pro-drug like tirapazamine are opening newer avenues to better patient management.[17,18]

However, the above study had certain limitations, one of which was a comparatively small sample size (n=38) and the other was a short duration spanning just 15 months. Therefore, several studies are required to establish VEGF as a potent marker for ascertaining the dynamics of meningiomas.

CONCLUSION

VEGF is thus can be a potential marker of high significance in ascertaining the dynamics of meningiomas. VEGF immuno-expression is high in WHO grade II and grade III meningiomas as well as a

subset of grade I high risk meningiomas depicting aggressive prognosis. VEGF not only ascertains tumor prognosis but also opens newer avenues of targeted therapy for improved patient outcome.

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