

성상세포종양에서 혈관내피증식인자의 발현

- 종양주변부 부종 및 미세혈관과의 상관관계 -

김태영 · 박종태 · 문성근 · 한원철*

= Abstract =

Expression of Vascular Endothelial Growth Factor in Astrocytic Tumors

- Correlation to Peritumoral Brain Edema and Microvasculature -

Tae Young Kim, M.D., Jong Tae Park, M.D.,
Seong Keun Moon, M.D., Weon Cheol Han, M.D.*

Department of Neurosurgery and Anatomical Pathology,* School of Medicine, Wonkwang University,
Iksan, Korea

Objectives : It has been known that vascular endothelial growth factor(VEGF), as an endothelial cell - specific mitogen, induces angiogenesis, and possesses vascular permeability and procoagulant properties. Peritumoral brain edema(PTBE) is a common accompaniment of malignant gliomas. It results from microvascular extravasation of plasma and proteins through the interendothelial spaces. The correlation between pathological grading, PTBE, neovascularization, and the expression of VEGF were analyzed in 31 patients with astrocytic tumors.

Methods : Astrocytic tumor samples(8 astrocytomas, 14 anaplastic astrocytomas, and 9 glioblastomas) from 31 patients(21 males and 10 females : average age 37 ± 24 years) who underwent surgery were examined retrospectively for the expression of VEGF and CD31(microvasculature) immunohistochemically. The extent of PTBE was examined by using preoperative CT or MRI as an edema index(EI). In addition to VEGF and CD31, several causative factors including tumor size, histologic type were compared with EI.

Results : Only one of 8 astrocytomas, and majority of high grade(21 of 23 anaplastic astrocytomas and glioblastomas) tumors demonstrated PTBE($p < 0.05$). The majority of high grade tumors showed higher expression of VEGF ($p < 0.01$). High grade tumors showed even higher CD31 expression($p < 0.05$), however, there was no close correlation between expression of VEGF and CD31. The EI was increased significantly, just as VEGF($p < 0.01$), but CD31 expression was not correlated with high EI.

Conclusion : These data suggest that VEGF expression is closely correlated with PTBE and histological grading in astrocytic tumors. Microvasculature(CD31) in tumors is highly correlated with histological grading, however, shows no correlation with the expression of VEGF and PTBE.

KEY WORDS : Astrocytic tumors · Vascular endothelial growth factor · Brain edema · Microvasculature · Edema Index.

서 론

2)3)7)14 - 16)21)

(vascular

endothelial growth factor : VEGF)가

Guinea pig
 (vascular permeability factor : VPF)

CT MRI
 (edema index)

folliculostriate cell
 가
 45 - kDa heparin - binding glycoprotein , platelet - derived growth factor placental growth factor

1. 혈관내피성장인자 및 미세혈관의 면역화학조직염색

VEGF - 121, VEGF - 165, VEGF - 189, VEGF - 206 가 가 , VEGF - 165가₂₎₄₎₁₁₎₂₁₎

4um , 3% 5
 endogenous peroxidase
 CD31 Pepsin
 Immuno/DNA 4
 protein blocker 10
 CD31(Dako Patts,Glostrup, Denmark)), VEGF(Calbiochem, La Jolla, CA) 2
 10 AEC Mayer's hema-toxylin
 universal mount
 CD31

(chemotactic factor)
 (mitogen)

가 가
 1000
 6)
 가
 5)6)8)14)16)22)23)

200 4
 (0 : , +1 : , +2 : , +3 :)
 CD31
 100
 가 7

2. 종양 및 종양 주변부 부종 용적의 측정

CT MRI
 (a and b)
 (c)
 4/3 x abc₂₀₎₂₂₎

(edema index) 1

대상 및 방법

3. 통계적 분석

가 31
 21 , 10 37 ± 24

Pearson correlation

, p - value가 0.05

결 과

($p=0.001$), 가 가 ($p=0.022$), 가 가 ($p=0.003$) (Table 1).

1. 조직학적 등급과 혈관내피성장인자 표현의 상관관계

0.38 ± 0.18 , 1.78 ± 0.22 , 14 ± 0.18 , 가 가 가 ($p=0.022$) (Fig. 1).

2. 조직학적 등급과 미세혈관과의 상관관계

17.25 ± 2.24 , 59.67 ± 22.04 , 45.14 ± 7.35 , 가 가

Table 1. Variables for edema index

Variables	p values
Age	0.001**
Sex	0.310
Tumor volume	0.097
Pathological subtype(grade)	0.022*
Microvessels(CD31)	0.069
VEGF	0.003**

Correlation is significant at the 0.05(*) and 0.01 level(**) with 2-tailed Pearson correlation

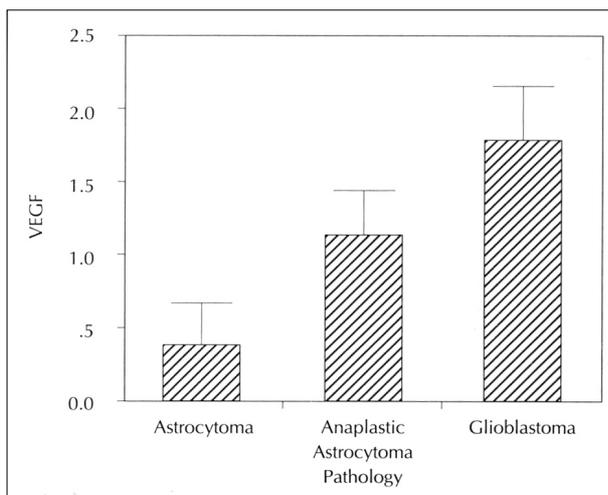


Fig. 1. Relationship between VEGF expression and pathological type. There was a significant difference ($p < 0.05$). The VEGF expression was related to the histological grade of astrocytoma.

($p=0.037$) (Fig. 2).

3. 부종 지수와 혈관내피성장인자 표현의 상관관계

(0) 7, +1 2, +2 7, +3 7, 가 가 ($p=0.003$)

(Fig. 3).

4. 조직학적 등급과 부종지수와와의 상관관계

1.18 ± 0.18 , 3.26 ± 0.69 , 3.84 ± 0.87 , 가 가

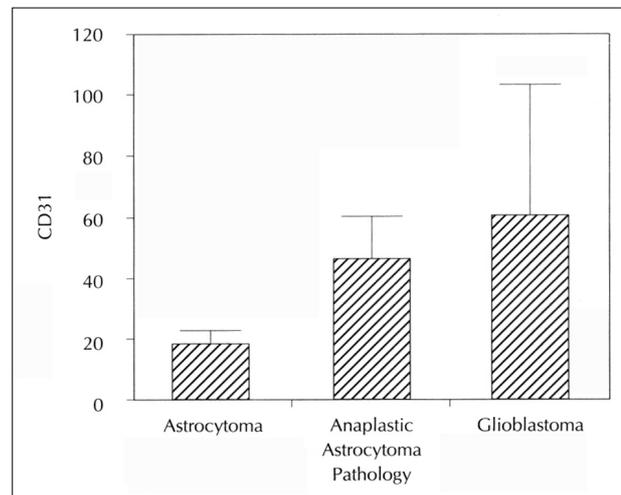


Fig. 2. Relationship between microvessels(CD31) and pathological type. A positive relationship between microvessel counting and tumor grade was observed ($p < 0.05$).

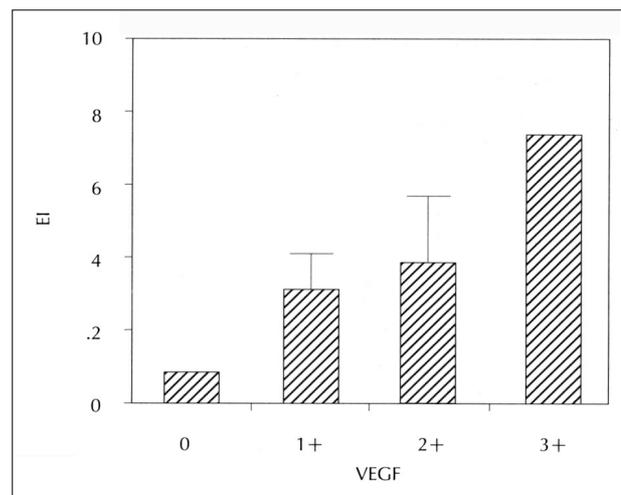


Fig. 3. Correlation between edema index(EI) and the expression of vascular endothelial growth factor(VEGF). EI is significantly increased in proportion to VEGF expression levels ($p = 0.006$).

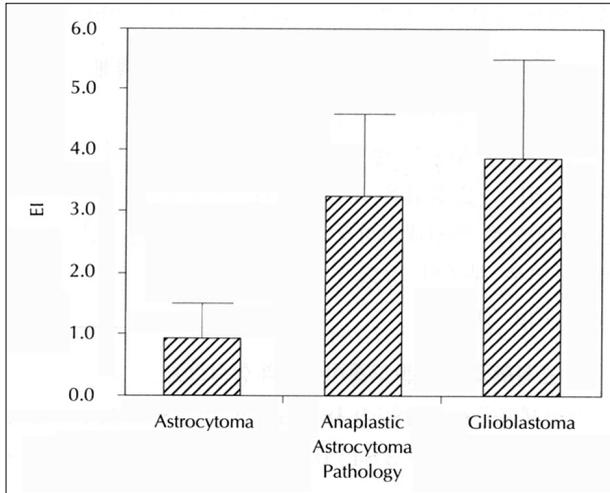


Fig. 4. Relationship between edema index(EI) and pathological type. There was a significant difference ($p < 0.05$).

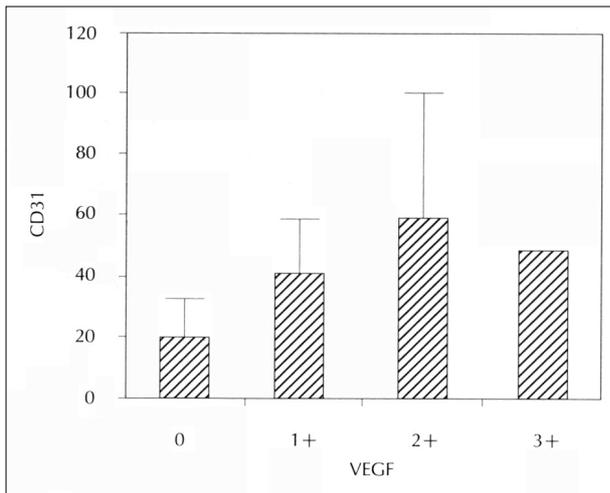


Fig. 5. Group showing the average level of CD31 for each VEGF expression. There was no significant correlation ($p = 0.3379$).

가
($p = 0.022$) (Fig. 4).

5. 미세혈관과 혈관내피성장인자의 표현도 및 부종지수와
의 상관관계

($p = 0.112$),
($p = 0.369$).

고 찰

anaplasia),
가
3)6)8)11)13)14)22)
up - regulation
가
가
8)11)13)23)
가
가
8 5
가
(1+) 3 2 1
2.4
가
가
(basic and acidic fibroblast growth factors, epid-
ermal growth factor, platelet - derived growth factor,
transforming growth factor alpha)
(thrombospondin - 1)
가 1)5)11)13)
3)5)6)9)14)17)
가

- 12) Kohn S, Nagy JA, Dvorak HF, Dvorak AM : *Pathways of macromolecular tracer transport across venules and small veins. Structural basis for the hyperpermeability of tumor blood vessels. Lab Invest* 67 : 596-607, 1992
- 13) Leon SP, Folkerth RD, Black PMcL : *Microvessel density is a prognostic indicator for patients with astroglial brain tumors. Cancer* 77 : 362-372, 1996
- 14) Machein MR, Kullmer J, Fiebich BL, Plate KH, Warnke PC : *Vascular endothelial growth factor expression, vascular volume, and, capillary permeability in human brain tumors. Neurosurgery* 44 : 732-740, 1999
- 15) Plate KH, Breier G, Weich HA, Mennel HD, Risau W : *Vascular endothelial growth factor and glioma angiogenesis : coordinate induction of VEGF receptors, distribution of VEGF protein and possible in vivo regulatory mechanisms. Int J Cancer* 59 : 520-529, 1994
- 16) Plate KH, Breier G, Weich HA, Risau W : *Vascular endothelial growth factor is a potent angiogenesis factor in human gliomas in vivo. Nature* 359 : 845-848, 1992
- 17) Pietsch T, Valter MM, Wolf HK, von Deimling A, Huang HJ, Cavenee WK, et al : *Expression and distribution of vascular endothelial growth factor protein in human brain tumors. Acta Neuropathol (Berl)* 93 : 109-117, 1997
- 18) Roberts WG, Palade GE : *Increased microvascular permeability and endothelial fenestration induced by vascular endothelial growth factor. J Cell Sci* 108 : 2369-2379, 1995
- 19) Roberts WG, Palade GE : *Neovasculature induced by vascular endothelial growth factor is fenestrated. Cancer Res* 57 : 765-772, 1997
- 20) Strugar JG, Criscuolo GR, Rothbart D, Harrington WN : *Vascular endothelial growth/permeability factor expression in human glioma specimens : correlation with vasogenic brain edema and tumor-associated cysts. J Neurosurg* 83 : 682-899, 1995
- 21) Tsai JC, Goldman CK, Gillespie GY : *Vascular endothelial growth factor in human glioma cell lines : induced secretion by EGF, PDGF-BB, and bFGF. J Neurosurg* 82 : 864-873, 1995
- 22) Weindel K, Moringale J, Marme D, Weich HA : *Detection and quantification of vascular endothelial growth factor/vascular permeability factor in brain tumor tissue and cyst fluid : The key to angiogenesis? Neurosurgery* 35 : 439-449, 1994
- 23) Wesseling P, van der Laak J, de Leeuw H, Ruiter DJ, Burger PC : *Quantitative immunohistochemical analysis of the microvasculature in untreated human glioblastoma multiforme. J Neurosurg* 81 : 902-909, 1994