von Willebrand Factor in glioma

Glioblastoma (GBM) is highly vascularized and von Willebrand Factor (VWF) plays a potent pro-angiogenic role. Dynamic contrast enhanced (DCE-) and dynamic susceptibility contrast (DSC-) MRI represent a widely accepted method to assess GBM microvasculature.

The aim of Navone et al. from the Laboratory of Experimental Neurosurgery and Cell Therapy, Neurosurgery Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Postgraduate School in Radiodiagnostics Department of Neuroradiology, Milan, was to investigate the correlation between plasma von Willebrand Factor (VWF):Ag, permeability and perfusion MRI parameters, and examine their potential in predicting GBM patient prognosis.

They retrospectively analysed pre-operative DCE-, DSC-MRI, and VWF:Ag level of 26 GBM patients. They assessed the maximum values of relative cerebral blood flow (rCBF) and volume (rCBV), volume transfer constant Ktrans, plasma volume (Vp) and reflux rate constant between fractional volume of the extravascular space and blood plasma (Kep). Non-parametric Mann-Withney test and Kaplan-Meier survival analyses were conducted and a p-value<0.05 was considered statistically significant.

The median VWF:Ag value was 248 IU/dL and the median follow-up duration was about 13 months. They divided patients according to low- and high-VWF:Ag and found significant differences in the median follow-up duration (19 months vs 10 months, p=0.04) and in Ktrans (0.31 min-1 vs 0.53 min-1, p=0.02), and Kep (1.79 min-1 vs 3.89 min-1, p=0.005) values. The cumulative 1-year survival was significantly shorter in patients with high-VWF:Ag and high-Kep compared to patients with low-VWF:Ag and low-Kep (37.5% vs. 68%, p = 0.05).

These findings, in a small group of patients, suggest a role for VWF:Ag, similar to Ktrans, and Kep as a prognostic indicator of postoperative GBM patient survival [1)].

Lehrer et al. examined The Cancer Genome Atlas (TCGA) data to assess the effect of VWF gene expression on prognosis in patients with lower grade gliomas (LGGs).

For newly diagnosed gliomas, they evaluated the association between and overall survival in the genomic data commons TCGA LGG dataset in TCGA. Survival data of the glioma subgroup were extracted for analysis and generation of Kaplan-Meier curves for overall survival.

Lower grade gliomas with less VWF gene expression had significantly better survival than those with more VWF gene expression (hazard ratio 0.64, 95% confidence interval 0.44-0.92, P 0.015 log rank test). The effect of VWF gene expression on survival was even more evident when the sample was analyzed as three groups (P = 0.00019). IDH1, TP53, and ATRX mutations are present in 40% or more adult LGGs.

The deleterious prognostic effect of VWF expression in LGGs is not surprising, given its role in other cancers. Therefore, VWF gene expression may be a clinically important risk marker in LGG [2)].

To investigate whether preoperative antigen plasma level of von Willebrand Factor (VWF:Ag) might be possible marker for GBM onset, progression, and prognosis, Marfia et al retrospectively examined 57

patients with histological diagnosis for GBM and 23 meningiomas (MNGs), benign intracranial expansive lesions, enrolled as controls. Blood samples were collected from all the patients before tumor resection. Plasma von Willebrand Factor (VWF):Ag levels were determined by using a latex particle-enhanced immunoturbidimetric assay. The median levels of vWF:Ag were significantly higher in GBMs than in meningiomas (MNGs) (183 vs. 133 IU/dL, P = 0.01). The cumulative 1-year survival was significantly shorter in patients with VWF:Ag levels >200 IU/dL than in those with levels <200 IU/dL and increased VWF levels were associated with a threefold higher risk of death in GBM patients. The data suggest that VWF:Ag could be a circulating biomarker of disease malignancy, that could be considered, in association with other genetic and epigenetic factors, currently available in the GBM management. Future studies should investigate whether plasma VWF:Ag levels could also be used to monitor therapeutic effects and whether it may have a prognostic value [3)].

Angiopoietin-2 mRNA expression in cultured human malignant glioma cells (U105, U251, and U373 MG) by reverse transcriptase-PCR. Western blot analysis and immunocytochemical analysis with antihuman Ang2 antibody revealed that Ang2 protein was expressed and secreted by these cells. Furthermore, hypoxia increased the Ang2 protein level in cultured glioma cells. Serial sections of 32 human glioma tissues (14 glioblastomas, eight anaplastic astrocytomas, seven astrocytomas, and three pilocytic astrocytomas) were immunostained against Ang2, vascular endothelial growth factor, Tie2, von Willebrand factor, and alpha smooth muscle actin. The immunoreactivity of each angiogenic factor was higher in malignant gliomas than in low-grade gliomas.

Angiopoietin 2 protein was detected not only in endothelial cells but also in glioma cells, and its expression was prominent in both the area surrounding the necrosis and the periphery of glioblastomas.

In the area surrounding necrosis, Ang2 was highly expressed and tumor vessels showed regression. In the tumor periphery, Ang2 was highly expressed and many small vessels stained positively for von Willebrand factor but not for alpha smooth muscle actin, suggesting angiogenesis. Statistical analysis revealed that the Ang2 expression was negatively correlated with vessel maturation in malignant gliomas and that vascular endothelial growth factor expression was positively correlated with vessel maturation in low-grade gliomas ($P < 0.05$). These results suggest that glioma cells themselves express Angiopoietin 2 and that expression may be induced by hypoxic stimulation and may play a crucial role in the vessel maturation, angiogenesis, and vessel regression in malignant glioma [4)].

The expression of factor VIII/von Willebrand factor (FVIII/vWF), a marker for endothelial cells, and of glial fibrillary acidic protein (GFAP), a marker for glial cells, was examined in 10 glioblastomas and seven mixed glioma-sarcomas using the peroxidase-antiperoxidase immunohistochemical technique. Hyperplasia of small blood vessels was observed in all 10 glioblastomas; in five, the vascular proliferation had resulted in the formation of prominent glomeruloid structures. FVIII/vWF was detected in the endothelial cells in these vascular structures, but not in the adventitial cells. In the mixed glioma-sarcomas. FVIII/vWF was detected only in endothelial cells; there was no staining for FVIII/vWF in the neoplastic mesenchymal cells. The gliomatous components of the mixed tumors stained intensely for GFAP. These observations indicate that both endothelial and nonendothelial cell types contribute to the small vessel hyperplasia in glioblastomas, and that the sarcomatous components of mixed glioma-sarcomas are derived from either non-endothelial cells or endothelial cells that have undergone antigenic loss following transformation [5)].

[1)]

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