Malignant glial neuronal tumors after west nile virus neuroinvasive disease

Abstract

Background: Acute West Nile Virus (WNV) infection can cause a spectrum of neurological disorders, including meningitis, encephalitis, and acute flaccid paralysis. Relatively little is described regarding the etiology of delayed neurological deficits or long-term sequelae in survivors of WNV neuroinvasive disease (WNND).

Results: We present two cases of glial neuronal tumors in patients with severe WNND in which viral infection appears to have been a precursor to the development of aggressive brain tumors. We describe a potential mechanism where changes on a molecular signaling level by the WNV infection may result in tumor promotion.

Conclusions: West Nile virus infection increases expression of pro-inflammatory and tumor-promoting proteins S100 calcium binding protein B (S100B), high-mobility group box-1 (HMGB1), and osteopontin (OPN). S100B and HMGB1 bind the receptor for advanced glycation end products (RAGE), a protein documented to be in overabundance in glial tumors. Activation of RAGE may contribute to proliferation and invasiveness of tumor cells. The presence of OPN in the tumor milieu, irrespective of its source, also leads to enhanced tumor growth and metastasis. To our knowledge, these are the first reported cases of their type. Given that WNV has the potential for altering cellular signaling at a molecular level and increasing expression of tumorigenic molecules known to be overexpressed in glial tumors, further investigations are warranted to clarify the relationship between these disease processes and potential risk for developing CNS neoplasm. In addition, there may be significant implications for brain tumor patients who develop WNV infection.

Keywords: glioblastoma multiforme, West Nile virus, West Nile neuroinvasive disease, dysembryoplastic neuroepithelial tumor, osteopontin

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; GBM, glioblastoma multiforme; RAGE, receptor for advanced glycosylation end-products; WNV, west nile virus; WNND, west nile neuroinvasive disease; OPN, osteopontin; HMGB1, high-mobility group box-1; S100B, S100 calcium binding protein B; DNET, dysembryoplastic neuroepithelial tumor

Introduction

West Nile virus (WNV) is a single-stranded RNA flavivirus with tropism for the central nervous system (CNS). On a molecular level, WNV infection results in elevations of pro-inflammatory and tumorigenic protein biomarkers, including S100 calcium binding protein B (S100B), an astrocytic signaling protein affecting intracellular and extracellular functions, and high-mobility group box-1 (HMGB1), a versatile protein with nuclear and extracellular functions. The effects of S100B and HMGB1 on neurons are transduced by the receptor for advanced glycation end products (RAGE). The pro-inflammatory and tumor-promoting effects of RAGE and its ligands have been reported in many cancers, and have been associated with poor prognosis and tumor aggressiveness. The phosphoglycoprotein osteopontin (OPN), a cancer biomarker, may also be elevated in patients with WNV infection. OPN has been highlighted in pathways that facilitate tumor cells in resisting apoptosis, evading growth suppressors, avoiding immune destruction, and increasing angiogenesis, resulting in increased tumor aggressiveness. These findings suggest interplay between the neurotropic WNV and resulting pro-inflammatory and tumorigenic alteration of cellular signaling pathways.

We report two novel cases of pathology-proven malignant glial neoplasm that presented within a span of 8 months to 2.5 years after initial diagnosis of WNND. We hypothesize that the effect of complex pro-inflammatory and tumorigenic molecular interactions following WNND contributes to development or aggressive growth of primary brain tumors.

Case 1

An 81-year-old right-handed male presented with one week of frontal headache, neck stiffness, fever and emesis. His exam was remarkable for a severe encephalopathy and diffuse maculopapular rash. Contrast-enhanced MRI showed generalized atrophy without evidence of an active intracranial process. Cerebrospinal fluid (CSF) analysis revealed 490 white cells with 94% polymorphonuclear leukocytes and elevated protein of 113mg/dL. He was empirically treated for bacterial meningitis until excluded, and workup revealed serum WNV IgG and IgM positivity confirming diagnosis of WNND. Ultimately the patient was discharged after receiving supportive care and rehabilitation.

Two and a half years after recovery from the WNND, the patient was brought to the emergency department due to increasing somnolence, language disturbance, and incoordination. Subsequent brain MRI demonstrated a heterogeneously enhancing left temporal...
mass (Figure 1). Biopsy of the lesion revealed pathology consistent with glioblastoma multiforme (GBM). He underwent abbreviated chemoradiation, and died four months after the diagnosis.

Case 2

A 35-year-old right-handed male was hospitalized with fever, altered mental status, arthralgias, ataxia, incontinence and a maculopapular rash involving the upper limbs and trunk. Notably, he had donated blood the prior week and was informed his serum was positive for WNV. Contrast-enhanced MRI showed findings consistent with meningoencephalitis, with bilateral leptomeningeal T2 prolongation in the posterior fossa and parasagittal anterior frontal regions without enhancement. Neurological examination revealed encephalopathy, pathologic hyperreflexia, left leg weakness, and gait ataxia. CSF analysis was significant for 317 white blood cells with 53% monocytes and an elevated protein of 62 mg/dl. CSF WNV-specific IgM antibody and PCR were positive. A diagnosis of WNV meningoencephalitis was made and he was discharged after 10 days of supportive care.

Eight months later, he presented with headaches and vomiting. Repeat MRI of the brain revealed hydrocephalus and a multifocal cystic lesion in the cerebellum, suggestive of a low-grade glioneuronal tumor. Spinal MRI revealed a thoracic and lumbar spine lesion with meningeal enhancement. Lumbar spine biopsy revealed chronic inflammation and myxoid-like foci in the tissue. No evidence of neoplasm was found, and the lesion was thought to be sequelae of WNV meningoencephalitis as he still had IgM antibodies present in his CSF. The patient was treated with chronic steroids with minor clinical improvement. Over the year, the patient developed progressive leptomeningeal enhancement encasing the entire brain and spinal cord, and eventually became quadriparetic (Figure 2). Biopsy of a cerebellar lesion and meninges demonstrated only thickened, inflamed dura.

Despite aggressive workup, the patient’s neurologic syndrome progressed and he ultimately elected hospice care, passing away approximately two years after initial presentation. On autopsy, he was found to have disseminated dysembryoplastic neuroepithelial tumor (DNET).

Discussion

GBM, the most common malignant primary CNS neoplasm in adults is treated with chemoradiation and typically causes death within two years of diagnosis. Due to the rapid growth of the tumor, vascular proliferation and cellular adaptation to hypoxic environments are crucial to the tumor’s ability to survive. In response to cellular stressors, signaling molecules trigger transcription of genes involved in angiogenesis, glucose transport, apoptosis resistance, metastasis, and inflammation. One major molecule expressed as a downstream effect of this pathway is RAGE, which has been found to be overexpressed in GBM. RAGE expression can also be induced by its ligands, including the family of S100 proteins and HMGB1. Directly pertinent to these cases, RAGE and its S100B and HMGB1 ligands have been reported to act as pro-inflammatory and tumor-promoting molecules. These ligands are secreted by a broad range of cancer cells and can stimulate cell growth, invasion, and angiogenesis, resulting in increased aggressiveness of the tumor and increased metastases. Activation of RAGE may also contribute to the resistance of cancer to treatment.

S100B has been found to be over-expressed on gliomas and plays a role in modulating cell differentiation and stimulating proliferation. Following WNV infection, S100B levels are increased in CSF and serum, and symptoms are greater in patients with pathologically elevated serum S100B. Many lines of evidence also suggest that altered expression of S100 proteins is associated with tumor progression, cell proliferation, invasion and motility, and prognosis. WNV infection induces OPN expression in humans. In glial tumors, OPN overexpression provides a survival advantage, including increased GBM cell resistance to apoptosis and increased angiogenesis. Interestingly, S100 proteins also induce expression and secretion of OPN in multiple cancer cell lines. Thus, OPN may mediate the pro-inflammatory and metastatic effects of S100 proteins.

DNETs are rare, generally benign, supratentorial tumors, usually occurring in children and younger adults. They are slow growing, centered in the cortical grey matter with a predilection for the temporal

lobe, and are associated with intractable partial epilepsy but may be curable with surgery alone. Malignant transformation of a DNET is extremely rare with only 10 such cases reported in a literature review; even rarer is the widespread leptomeningeal spread that we report here. Thus, information on malignant transformation of a DNET is still limited.

Immunohistochemical findings of DNETs reveal that the cells in these tumors are diffusely positive for S-100 proteins, making it likely that their tumor activation pathways are similar to those of other gliomas. The cases raises the possibility that the post-infectious tumorigenic microenvironment, marked by increased S100B, HMGB1, and OPN concentrations, may have influenced tumor development by promoting unusually aggressive behavior in what is typically a benign tumor. Upregulation of tumorigenic proteins may have played a role in both cases illustrated. This is consistent with reports from many cancer studies, which have implied that the presence of tumorigenic proteins in the tumor milieu can lead to enhanced tumor growth and metastasis and consequently poor prognosis.

**Conclusion**

These cases highlight not only the extent of neurological disease associated with WNND, but also a potential long-term sequela in patients who have recovered from the acute meningoencephalitis. The alteration at a molecular level of CNS protein signaling elicited by WNV infection may lead to long-term risk of other neurological disorders, such as glial neuronal tumors. The relationship between WNV infection and resulting overexpression of RAGE and other pro-inflammatory and tumorigenic molecules should be further explored to determine if WNND may contribute to future risk of developing CNS neoplasms and other cancers.

**Author contributions**

Akanksha Sharma: Literature review and manuscript writing
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Marie Grill: Concept and design, case analysis, supervision, manuscript revision
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**Conflict of interest**

The authors declare no conflict of interest.

**References**