Malignant Glial Neuronal Tumors After West Nile Virus Neuroinvasive Disease: A Coincidence or a Clue?

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Abstract

Following acute West Nile virus (WNV) infection in humans, there is upregulation of pro-inflammatory molecules that promote neuroinflammation, including S100 calcium binding protein B (S100B), high-mobility group box-1 (HMGB1), and osteopontin (OPN). The effects of S100B and HMGB1 are transduced by the receptor for advanced glycation end products (RAGE). Interestingly, the same immunoregulatory proteins that fuel neuroinflammation can also promote tumorigenesis. We present 2 cases of glial neuronal tumors, a glioblastoma multiforme and dysembryoplastic neuroepithelial tumor, in patients with severe West Nile neuroinvasive disease (WNND). In these cases, the viral infection was a precursor to the development of the aggressive brain tumors. We describe a potential mechanism where the presence of tumorigenic proteins in the micro-environment induced by WNV, and subsequent RAGE and OPN signaling, may contribute to development or aggressive growth of these tumors. Although it is certainly possible that the occurrence of primary brain tumors following WNND is coincidental, the ability of WNV to alter cellular signaling and increase expression of pro-inflammatory and tumorigenic molecules merits further investigations to determine whether there is an association between these disease processes or implications for brain tumor patients who develop WNV infection.

Keywords

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

Introduction

West Nile virus (WNV) is a single-stranded RNA flavivirus with well-described tropism for the central nervous system (CNS). It commonly causes a febrile illness (WNV fever) or West Nile neuroinvasive disease (WNND), classified as meningitis, encephalitis, or acute flaccid paralysis. West Nile neuroinvasive disease occurs in as few as 1 in 150 infected persons¹ and is considered a rare disease by the National Organization for Rare Disorders (NORD).

On a molecular level, WNV infection results in a significant upregulation of glial signaling protein S100B and intracellular protein high-mobility group box-1 (HMGB1), 2 important pro-inflammatory molecules that are increased in human serum and cerebrospinal fluid (CSF) postinfection.^{2,3} The effects of S100B and HMGB1 on neurons are transduced by the receptor for advanced glycation end products (RAGE). Receptor for advanced glycation end products and its ligands have been reported to induce a postinfectious

pro-inflammatory state in humans that promotes chronic inflammation and various diseases that have a presumed autoimmune pathogenesis.⁴ West Nile virus infection also increases expression of osteopontin (OPN), a multifunctional cytokine that also plays a role in promoting autoimmune diseases.⁵ Interestingly, many lines of evidence have shown that

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Figure 1. Images in panel A are FLAIR and T1-weighted postgadolinium images of the patient obtained 2.5 years prior to presentation with tumor. Images in panel B were obtained when the patient presented with a left temporal lobe lesion. Panel C demonstrates tumor progression toward the end of patient's life. FLAIR indicates fluid attenuation inversion recovery.

the same immunoregulatory proteins that can fuel chronic inflammation in the WNV postinfectious state can also promote tumorigenesis. For example, RAGE signaling regulates cellular interactions during neoplastic transformation and malignant progression, including cell differentiation, proliferation, invasion and motility, resulting in increased tumor aggressiveness and a poorer prognosis.⁶ Osteopontin impacts cell proliferation, survival, invasion, and stemlike behavior and serves as a cancer biomarker.⁷ These findings suggest interplay between the neurotropic WNV and resulting pro-inflammatory and tumorigenic alteration of cellular signaling pathways.

We report 2 novel cases of pathology-proven malignant glial neoplasms that presented within a span of 8 months to 2.5 years after initial diagnosis of WNND. In both cases, the neoplasms resulted in death in less than 3 years following WNND. We hypothesize that the effect of complex pro-inflammatory and tumorigenic molecular interactions following WNND may, in some cases, contribute to development or aggressive growth of primary brain tumors.

Case 1

An 81-year-old right-handed male presented with 1 week of frontal headache, neck stiffness, fever, and emesis. His exam was

remarkable for severe encephalopathy and diffuse maculopapular rash. Contrast-enhanced magnetic resonance imaging (MRI) showed generalized atrophy without evidence of an active intracranial process. Cerebrospinal fluid analysis revealed 490 white cells with 94% polymorphonuclear leukocytes and elevated protein of 113 mg/dL. He was empirically treated for bacterial meningitis until excluded, and workup revealed serum WNV immunoglobulin G (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. At this time, brain MRI demonstrated a large heterogeneously enhancing left temporal mass (Figure 1). Biopsy of the lesion revealed pathology consistent with glioblastoma multiforme (GBM). He underwent chemoradiation, but no immunotherapy or surgery, and died 4 months after the diagnosis.

Case 2

A 35-year-old 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. Cerebrospinal fluid analysis was significant for 317 white blood cells with 53% monocytes and an elevated protein of 62 mg/dL. Cerebrospinal fluid WNV-specific IgM antibody and polymerase chain reaction 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. 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 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 died 2 years after initial presentation. Autopsy confirmed disseminated dysembryoplastic neuroepithelial tumor (DNET).

Discussion

Following human WNV infection, serum and CSF levels of RAGE ligands S100B and HMGB1 are increased and correlate with severity of the WNV infection, being higher in neuroinvasive disease than fever cases, with both case groups significantly higher than controls.^{2,3} Irrespective of the source of these ligands, the interaction of S100B and HMGB1 with RAGE triggers a pro-inflammatory cascade that bridges chronic inflammation and cancer.^{6,8} Receptor for advanced glycation end products signaling also contributes to the development and accumulation of myeloid-derived suppressor cells (MDSC), which result in T-cell tolerance and suppression of the antitumor immune response, thereby facilitating tumor growth.⁸ Data with mouse *de novo* gliomas indicate critical roles of MDSC in glioma development, and blockade of the ligand-RAGE axis suppresses tumor growth in mouse models, providing evidence for an *in vivo* tumorigenic function of RAGE.⁹ West Nile virus infection in humans also induces OPN, a chemokine-like protein that is secreted by several tissues in the human body and by tumor cells. There is compelling evidence that increased levels of circulating OPN, whether derived from tumor cells or nontumor sources (eg, infection, autoimmune disease, tissue injury), can lead to

Figure 2. Panels A and B present T1-weighted postgadolinium images of the brain and spine of the patient. The images in panel A were obtained when patient first presented with the tumor, and those in panel B were obtained 2 years after, toward the end of patient's life.

enhanced tumor growth, metastasis, and poor prognosis.^{7,10} This is consistent with reports from many cancer studies, which have implied that the presence of tumorigenic proteins in the microenvironment, regardless of the source, can influence multiple steps in tumor development. Accordingly, given the evidence that WNV infection can induce RAGE and OPN signaling to initiate chronic inflammation,^{2,3} and the even larger body of evidence that these same immunoregulatory cascade can promote tumorigenesis,^{6-8,10} it seems reasonable to speculate on the potential for WNV to create a microenvironment that is ideal for neoplastic transformation and malignant conversion.

Glioblastoma multiforme is the most common malignant primary CNS neoplasm in adults but remains a rare disease listed in the NORD, with an incidence estimated to be 2 to 3 people per every 100 000 in the United States. Glioblastoma multiforme is not curable, and treatment involves various therapies, including immunotherapy, chemotherapy, radiation therapy, and surgery. The median survival period after receiving treatment is 15 months, although age also plays a key role in outcome with older adults having a poorer prognosis.¹¹ Without treatment, survival is only 4 to 5 months. 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, tumor cells express RAGE and its ligands (S100 proteins, HMGB1). Many lines of evidence suggest that RAGE signaling results in increased tumor aggressiveness and a poorer prognosis^{6,12} and may also contribute to the resistance of cancer to treatment.^{8,9} Interestingly, S100 proteins also induce expression and secretion of OPN in gliomas.^{5,7} The tumor-promoting effect of OPN may provide a survival advantage, including increased GBM cell resistance to apoptosis, increased radiation resistance in adjacent tumor cells, and increased angiogenesis.^{7,10}

Pertinent to this case, the neuro-oncologists speculated that the GBM may have started within the first year following WNN, given that the tumor was relatively advanced at the time of diagnosis and associated with increasing neurological deficits. Despite chemoradiation, the patient died within 4 months of diagnosis.

Dysembryoplastic neuroepithelial tumors are rare, generally benign, supratentorial tumors, usually occurring in children and younger adults. They are slow growing, centered in the cortical gray matter with a predilection for the temporal lobe, and are associated with intractable partial epilepsy but may be curable with surgery alone.¹³ 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. Although the DNET was not seen on the imaging from the time of the WNV infection, these are generally very slow growing tumors that likely would have been present at that time and then undergone malignant transformation. 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.¹³

Conclusion

We presented 2 intriguing cases following WNN that prompted us to hypothesize that the effect of complex pro-inflammatory and tumorigenic molecular interactions may contribute to development or aggressive growth of primary brain tumors. Although there is no *direct* evidence that a WNV post-infectious microenvironment influenced development of the

GBM (case 1) or the unusually aggressive behavior in what is typically a benign neuroepithelial tumor (case 2), the same immunoregulatory molecules (S100B, HMGB1, and OPN) that are upregulated following WNV infection to promote neuroinflammation also promote tumorigenesis. Although it is certainly plausible that the occurrence of 2 rare primary brain tumors following a rare viral encephalitis is merely a coincidence, there is sound data and compelling evidence that the presence of tumorigenic proteins in the microenvironment, whether derived from tumor or nontumor sources, can enhance tumor development and progression. Accordingly, we believe that our hypothesis merits additional testing, perhaps using a longitudinal cohort design or a case-control design. It may also be interesting to explore the prevalence of primary brain tumors following neuroinvasive disease with other flaviviruses (dengue, yellow fever, and Zika) or other viral meningoencephalitides and to look for secondary GBM or other changes in tumor behavior in patients with brain tumors who develop WNV infection.

Authors' Note

This study was approved by the Mayo Clinic institutional review board and informed consent was obtained. Akanksha Sharma, Marie F. Grill, Scott Spritzer, A. Arturo Leis, and Alyx B. Porter contributed equally to the manuscript. Akanksha Sharma and Scott Spritzer contributed to the literature review and manuscript writing; Arturo Leis, Marie Grill, and Alyx Porter contributed to concept and design, case analysis, supervision, and manuscript revision; Mark Anderson contributed to concept and design and case analysis; and Parminder Vig contributed to concept and design.

Declaration of Conflicting Interests

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