RESEARCH ARTICLE

Fatal Fulminant Pan-Meningo-Polioencephalitis Due to West Nile Virus

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We report a case of fatal fulminant West Nile virus (WNV) meningoencephalitis in an 87-year-old white male gardener. The Pennsylvania patient presented with a 3-day history of flu-like symptoms. His hospital course was gravely precipitous with onset of coma, ventilator dependence, loss of cortical and brainstem functions within ten days of admission. Acute serum and cerebrospinal fluid samples revealed elevated levels of WNV IgM antibodies by ELISA as well as elevated CSF white blood cells, protein and glucose. A complete autopsy revealed a multifocal lymphocytic myocarditis and severe chronic tubulointerstitial nephritis. Viral culture and PCR analysis of post-mortem samples of the spleen, kidney and brain were positive for WNV. Histological sections from all regions of the brain and spinal cord demonstrated a severe, non-necrotizing, subacute, polio-meningoencephalitis. While both gray and white matter were inflamed, gray matter was much more severely involved. Many gray matter nuclei showed severe neuronal loss with residual dying neurons surrounded by activated microglia. Immunohistochemical stains revealed profuse infiltration of the meninges and cerebral parenchyma by CD8 T-lymphocytes and perivascular B-lymphocytes. Electron micrographs revealed diffuse intracellular and extracellular edema but no viral particles were identified. Immunohistochemical and immunofluorescent staining for WNV filled the cytoplasm of residual neurons. West Nile virus mediates a predominantly polioencephalitis secondary to direct infection of neurons.

Introduction

West Nile virus infection has been identified by the Centers for Disease Control as an emerging infectious disease in the United States following documentation of 62 human cases in 1999 in New York City and the northeastern United States. Since 1937, when the first human case was isolated and identified in the West Nile district of Uganda, in Africa, infrequent human outbreaks of this virus with increasing virulence and case fatality generated by international travel and commerce (6, 12) has spread to Asia, the Middle East, Europe and North America

West Nile virus is an enveloped single-stranded sense, non-segmented RNA virus that belongs to the *Flaviviridae* family of viruses, which contains several medically important viruses associated with human encephalitis including Japanese encephalitis, St. Louis encephalitis, and Murray Valley encephalitis viruses (5, 13). WNV primarily maintains an enzootic transmission cycle involving culicine mosquitoes and birds with episodic epizootic phenomenon infecting humans through the bites of infected female *Culex pipiens*, *Culex restuans* and *Culex quinquefasciatus* mosquitoes (5, 13).

Despite the expansion of annual epidemics of the WNV in the United States and an accompanying abundance of epidemiologic and clinical reports, there are few published reports on the neuropathology of the fatal cases of human WNV infection (12, 15, 16). We report a case of fatal fulminant WNV pan-meningo-polioencephalitis in an 87-year-old white male gardener with detailed and comprehensive neuropathology comprising histomorphology, electron microscopy, immunohistochemistry and confocal florescent laser-scanning microscopy. WNV predominantly mediates a polioencephalitis secondary to direct infection of neurons.

Case Report

Clinical history. An 87-year-old Italian-American male gardener with no recent travel presented to the emergency room of a local Pittsburgh hospital in late August, with a 3-day history of persistent fever, chills, lethargy and anorexia without cough, sore-throat, dyspnea or abdominal pain and with a history of recent mosquito bites on his forearm. The review of systems and clinical examination revealed a well nourished man who was well oriented in time, place and person and in no obvious respiratory distress with mild dehydration, oral thrush, basal rales and decreased breath sounds in the right lower lobe. Rectal temperature was 101.9°F, pulse: 102 per minute, blood pressure: 89/39 mmHg. Neurological examination was unremarkable with no focal lateralizing signs. A chest x-ray revealed a possible

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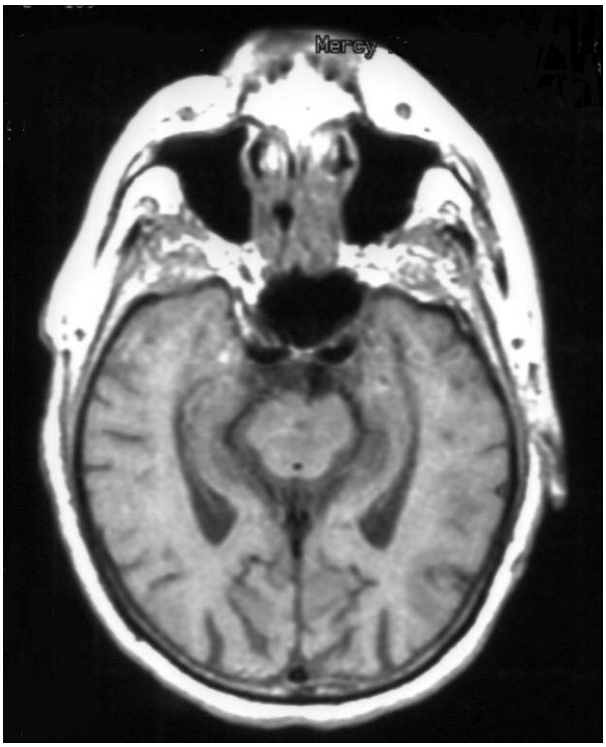

Figure 1. Magnetic resonance image of the head with contrast showed no contrast enhancing lesions within the meninges or brain parenchyma. (TR:683, TE:16)

right lower lobe infiltrate with atelectasis. Complete blood count showed a leukocytosis of 14 200/μL with a differential count of 88.4% neutrophils, 7.7% lymphocytes, 3.4% monocytes, 0.3% eosinophils and 0.2% basophils. Further laboratory workup was unremarkable except for mild hyponatremia and mildly elevated BUN and creatinine. Electrocardiographic studies revealed a sinus rhythm with supraventricular extrasystoles, left axis deviation and a right bundle branch block with an old inferior infarct. Urinalysis, bacterial blood and urine cultures were all negative.

The patient was initially admitted for rehydration and intravenous/oral antibiotics for possible community acquired lobar pneumonia, oro-pharangeal candidiasis and pre-renal azotemia. The antibiotic regimen was later changed to a broad-spectrum bacterial meningitic regimen. His past medical history was significant for coronary arteriosclerotic disease with stable angina and a remote inferior wall myocardial infarct, status post intraluminal stenting of the right coronary artery. There was also a past medical history of benign rectal polyps, colonic diverticulosis, cystic disease of the kidney, osteoarthritis and hematuria.

During his hospital stay, the fever persisted despite intravenous antibiotics. CT-scans of the head, chest, abdomen and pelvis performed as part of an infectious disease evaluation were negative except for mild leukoariaosis. On the third day of admission his mental status deteriorated accompanied by hypoxia and dyspnea. He was transferred to the intensive care unit where he was intubated and placed on full ventilator support. A lumbar puncture was performed on the fourth day of hospital admission and revealed colorless, clear cerebrospinal fluid with elevated red and white blood cell counts of 37/mm^3 and 240/mm^3 respectively with a predominance of polymorphonuclear leukocytes (neutrophils: 68%, mononuclear leukocytes: 32%) as well as elevated protein (187 mg/dl) and glucose (87 mg/dl). Bacterial antigen panel and cultures were negative. Magnetic resonance imaging on the fifth day of hospital admission revealed minimal periventricular leukoariaosis and mild age-related neuronal loss without any evidence of a meningeal inflammation, mass effect, midline shift or hydrocephalus (Figure 1). No contrast enhancing abnormalities were noted in the meninges or brain parenchyma. Tremulous movements of the right arm and right side of face were observed on the fifth day of admission and an electroencephalogram revealed Grade II generalized dysrhythmia without electrographic discharges or epileptiform abnormalities.

On days 7 and 8 of hospital admission, he became comatose and manifested no cortical activity with progressive loss of brain stem functions which culminated in complete loss of brain stem functions 2 days later when he met clinical criteria for brain death. On the ninth day of admission, Enzyme Linked Immunosorbent Assay (ELISA) revealed elevated and diagnostic serum levels of WNV-IgM.

On the 11th day of admission, he was pronounced dead while still on ventilator support, which was later withdrawn the same day.

Post-mortem examination. A complete autopsy was performed at the Allegheny County Coroner's office, following a post-mortem interval of approximately 22 hours, and revealed a well developed and well nourished 87-year-old white male with edematous palpebral conjunctivae and unremarkable head, face, trunk and extremities. There was cardiomegaly (560 g) with patchy biventricular myofibrillary hypertrophy accompanied by moderate triple vessel coronary atherosclerosis. The lungs revealed moderate acute pulmonary congestion and edema without acute intra-alveolar

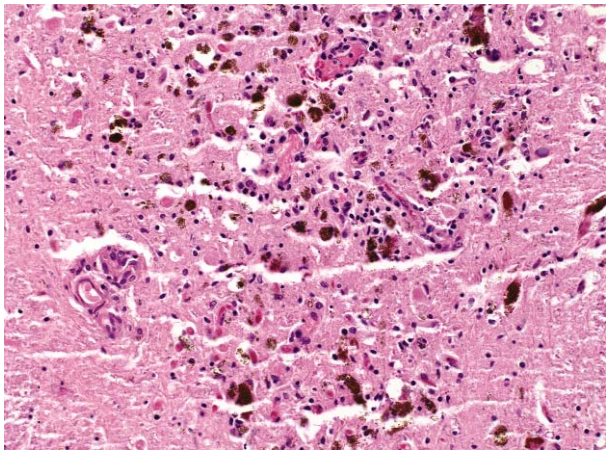

Figure 2. Paraffin section of the substantia nigra showing severe polymorphous inflammatory infiltrates, with severe neuronal loss and abundant extra-neuronal neuromelanin (H&E, ×200).

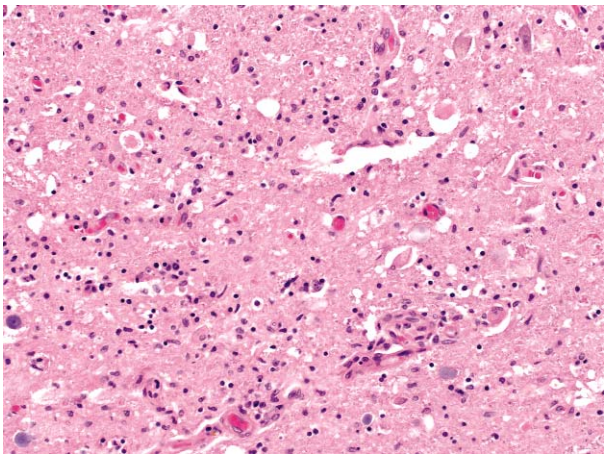

Figure 3. Paraffin section of the anterior horn of the spinal cord showing severe polymorphous inflammatory cellular infiltrate and loss of anterior horn neurons. (H&E, ×200).

neutrophilic infiltrates. The kidneys revealed multiple bilateral simple cortical cysts.

Microscopic examination of histological sections from the heart and kidney revealed multifocal lymphoplasmacytic infiltration of the myocardium with focal myocyte necrosis. The kidneys revealed severe multifocal chronic tubulointerstitial nephritis.

The dura mater and dural venous sinuses were unremarkable without intraluminal thrombi. The leptomeninges were smooth, thin and glistening except for focal dorsal hemispheric fibrosis, without extravasates or abnormal fluid collections in the subarachnoidal cisterns. The cerebrospinal fluid was clear and colorless. The brain was fixed in 10% buffered formaldehyde for approximately 24 days and weighed 1230 g. It showed a normal development with mild frontal lobar atrophy. The basilar and middle cerebral arteries revealed marked dolichoectasia with mild eccentric atherosclerosis. The cerebral and cerebellar hemispheres appeared symmetrical without significant gyral expansion or flattening. Coronal sections of the cerebral hemispheres and horizontal sections of the brainstem and cerebellum revealed normal gross morphology without any significant gross pathologic changes except for acute parenchymal congestion of the centrum semiovale and the left red nucleus. The pituitary gland and spinal cord appeared unremarkable without any significant gross pathological changes.

Post-mortem polymerase chain reaction (PCR) analysis for WNV was performed on autopsy samples of the CSF, brain, kidney and spleen and all samples contained viral RNA. The virus was isolated from viral cell cultures of post-mortem samples of the CSF, brain, kidney and spleen. Both the PCR and viral cell culture analyses were performed at the Pennsylvania state public health laboratory and confirmed by the Centers for Disease Control according to previously published protocols (7). Viral quantitation analyses were not performed on any of the samples.

Histological examination of the central nervous system. Examination of hematoxylin and eosin stained sections revealed sparse perivascular lymphoplasmacytic infiltration of the dura mater and leptomeninges with diffuse vacuolation and spongiosis of the centrum semiovale. There was hypercellularity of the cortical gray and white matter comprising activated astrocytes, hyperplastic microglia and lymphocytes. Scattered microglial nodules were identified in the corpus callosum and cortical white matter. The caudate nucleus, putamen, globus pallidus and thalamus exhibited similar histomorphological changes with scattered eosinophilic neurons in the putamen. Neuronophagia was evident as typified by degenerating neurons surrounded by macrophages with cytoplasmic extensions engulfing these neurons (Figure 4). The Sommer's sector exhibited many eosinophilic neurons. The degree of diffuse inflammation in the thalamus, caudate nucleus, lentiform nucleus and hippocampus appeared slightly more severe than that in the neocortex.

The most severe inflammation was observed in the midbrain, pons, medulla oblongata and spinal medulla, which revealed a profuse neuropil infiltration by lymphocytes with marked perivascular and intramural lymphoplasmacytic infiltration of deep penetrating

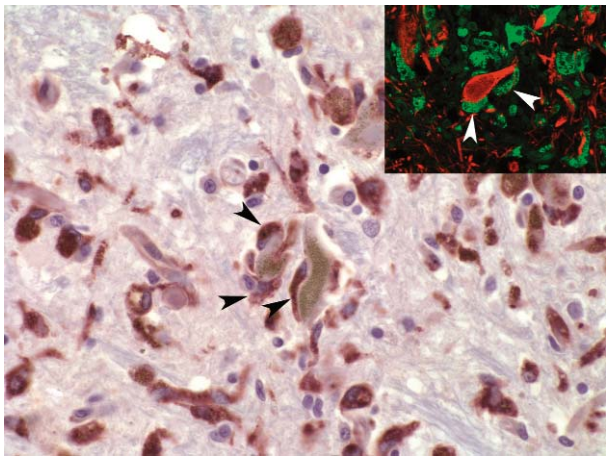

Figure 4. Paraffin section of the substantia nigra immunostained for CD-68 showing neuronophagia with CD-68 positive macrophages (arrow head) surrounding and engulfing a degenerating nigral neuron (×400). Insert: laser confocal microscopy image of the substantia nigra showing CD-68 positive (green) macrophages (arrow head) surrounding a WNV infected neuron (red).

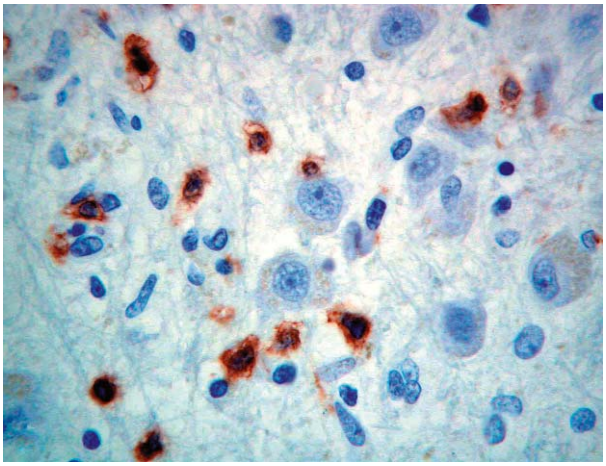

Figure 5. Paraffin section of lateral geniculate nucleus immunostained for CD-8 showing profuse parenchymal infiltration by CD-8 positive cytotoxic T-lymphocytes. (×200).

parenchymal blood vessels. The white matter appeared hypercellular showing activated astroglia and microglia. Although cranial nerve nuclei were difficult to discern, the Hypoglossal nucleus and the dorsal efferent nucleus of the Vagus nerve showed severe neuronal loss and neuronophagia as well as the substantia nigra and the inferior olivary nucleus. The substantia nigra exhibited the most severe degree of inflammation in the brain stem (Figure 2). The inflammation in the brain stem appeared neuronocentric as demonstrated by an accentuation of inflammation around clusters of neurons and nuclei.

The cerebellum demonstrated severe Purkinje cell loss and Bergmann gliosis with degenerating Purkinje cells accompanied by rare torpedoes. The cerebellar cortex and white matter revealed a similar histomorphology to that in the thalamus with a higher degree of inflammation involving the Purkinje cell layer.

Sections of the cervical, thoracic and lumbar spinal cord showed sparse perivascular infiltration of the leptomeninges by lymphocytes and plasma cells accompanied by diffuse spongiosis of the white matter funiculi. The degree of inflammation in all segments of the spinal cord was similar to that of the brain stem with neuronocentricity and severe drop out of anterior horn cells (Figure 3). Neuronophagia was evident as well as astroglial and microglial proliferation.

Table 1 depicts the severity of inflammation and frequency of infected cells through out the brain and spinal cord. Inflammation and infection was most severe in the spinal medulla and brain stem followed by the thalamus, subcortical ganglia, cerebellum and mesial temporal lobe with the least inflammation found in the neocortical gray and white matter. The adenohypophysis revealed reactive adrenocorticotroph hyperplasia and the neurohypophysis appeared unremarkable.

A panel of immunohistochemical stains was performed using antibodies to CD3, CD20, CD4, CD8, CD68, GFAP and the envelope and NS1 proteins of WNV. Polyclonal antisera to WNV E and NS1 proteins were produced commercially (Lampire Biological Laboratories, Pipersville, Pa), by immunizing rabbits with recombinant protein expressed in E. coli using the vector pDes17 (Invitrogen, Carlsbad, Calif). Specificity was confirmed in immunofluorescence and western blot assays of Vero, BHK, and OL cells. CD68 revealed profuse and global microglial proliferation in the gray and white matter accentuated in regions delineated above (Figure 4). GFAP immunostains highlighted moderate global astrocytosis. CD20 and CD3 immunostains revealed sparse perivascular B-lymphocytes and profuse, global parenchymal infiltration by T-lymphocytes. CD4 and CD8 immunophenotypic characterization of the T-lymphocytes revealed few CD4 positive T-helper cells with a marked predominance of infiltrating CD8 positive T-suppressor/cytotoxic cells (Figure 5). The few remaining neurons in the substantia nigra and tegmentum of the midbrain showed focal cytoplasmic immunopositivity for WNV.

Confocal florescent laser scanning microscopy using antibodies for CD3, CD68 and WNV revealed diffuse positive cytoplasmic viral immunoflorescence of many neurons in the substantia nigra, spinal anterior horn cells, pontine neurons, neurons of the CA2 and 3 of the hippocampus, the entorhinal cortex and neurons of the thalamus with rare neurons in the caudate nucleus and arcuate nucleus (Figure 6). Double label staining for WNV and leukocyte markers CD68 and CD3 confirmed H&E impression of T-lymphocyte infiltration and macrophage engulfment of infected neurons (Figure 6E, F). Screening sections from the lungs, heart, liver, spleen, kidneys and pancreas did not identify any infected systemic cells.

Electron microscopy of the substantia nigra using formalin fixed tissue post-fixed in glutaraldehyde and osmium tetroxide revealed diffuse extracellular and intracellular edema and neuromelanin. No neuronal cytoplasmic viral particles were identified.

Brain Region	Degree of Inflammation	Viral infected neurons detected by ICC
Cerebral hemispheres:		
Gray matter	+/-	-
White matter	++	-
Cingulate cortex	+/-	-
Insula cortex	+	-
Entorhinal cortex	++	++
Hippocampus	++	++
Dentate gyrus	-	-
Ventricle/ choroid plexus	-	-
Lateral geniculate nucleus	+++	+
Caudate, Putamen and Globus Pallidus	++	+
Thalamus	++	++
Brainstem:		
Substantia nigra	+++	++
Central midbrain	+++	++
Cruz cerebri	+	-
Pons	++	++
Medulla	++	++
Cerebellum:		
Purkinje cell layer	+++	++
Molecular layer	++	-
Dentate nucleus	++	-
Granule cell layer	-	-
Deep white matter	+/-	-
Spinal cord:		
Gray matter	+++	++
White matter	+/-	-
Pituitary gland	-	-

Table 1. Differential topographic severity of inflammation and infection in various brain regions based upon degree of cellular infiltrates and abundance of infected neurons.
(ICC: immunocytochemistry)
Degree of inflammation rating: (-: minimal or no inflammation;+/-: very mild; +: mild; ++: moderate; +++: severe)
Frequency of viral infected cells: (-: no infected neurons; +: 1-3 infected neurons per 20 power field; ++: > 3 infected neurons per 20 power field)

Discussion

The flaviviruses include such clinically important arboviruses as Japanese encephalitis virus, Saint Louis encephalitis virus, Murray Valley encephalitis virus, Rocio virus, Central European encephalitis virus, Russian spring-summer encephalitis virus, Dengue fever virus, yellow fever virus, Louping virus, Omsk hemorrhagic fever virus, Kayasnur forest disease virus, Wesselbron virus, Ilheus virus, Rio Bravo hemorrhagic fever virus and WNV. These viruses are transmitted by a variety of insect vectors, which vary in different parts of the world. Following human infection, enveloped RNA virus particles probably enter targeted cells of the body by receptor-mediated endocytosis followed by fusion with cellular lysosomes and release of viral genome (10).

Despite the emergence of annual epidemics of WNV in the United States since 1999, the histomorphologic features of the neuropathology of WNV infection have not been clearly elucidated. This may be explained by the rarity of the fatal encephalitic complication of WNV infection in humans since approximately 0.67% of individuals who are infected by the virus suffer encephalitis, meningitis or meningoencephalitis (12, 13). It has been suggested that patients developing neurological symptoms have a less robust IgM response to primary WNV infection (1). The majority of individuals who are infected with WNV do not manifest any symptoms. Approximately 20% of infected individuals suffer from a 3 to 14 day incubation period followed by a 3 to 6 day illness of flu-like symptoms, which may consist of a febrile illness (West Nile fever), erythematous macular, papular, or morbilliform rash involving the neck, trunk, arms or legs, lymphadenopathy, pharyngitis, malaise, anorexia, myalgia, headache, fatigue, nausea and/ or vomiting. However, recovery is commonly rapid and complete (5, 13, 10).

In 1979, Gadoth et al (3) reported the first case of WNV infection in the literature that presented with a self-

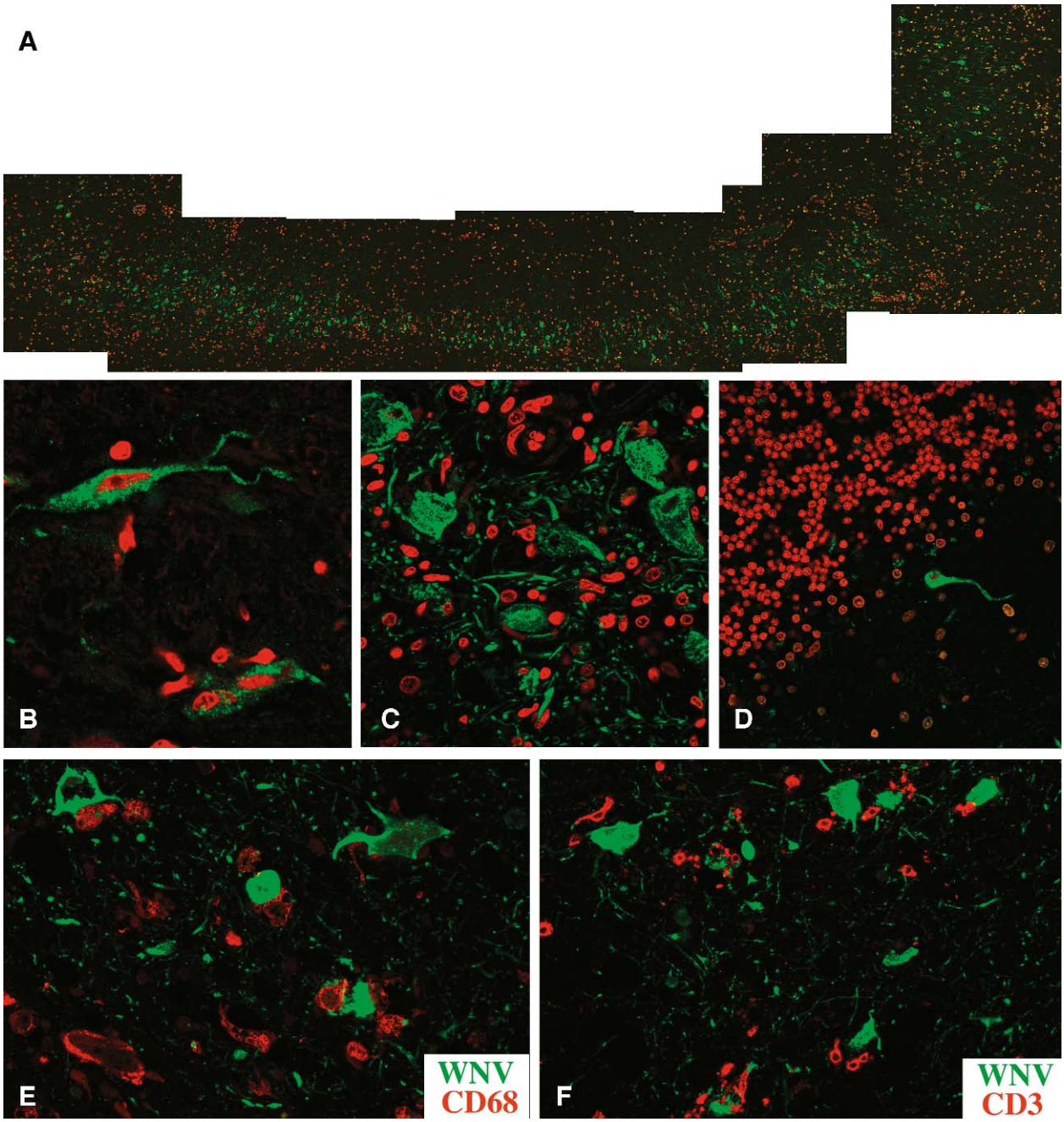

Figure 6. Laser confocal microscopy of paraffin sections of hippocampus (**A**), thalamus (**B**, **E**, **F**), substantia nigra (**C**) and cerebellum (**D**). A: Low power montage of CA2/3 region of hippocampus showing layer of pyramidal neurons immunostained for WNV (green) and counterstained with propidium iodide (red). **B, C**: Cytoplasm of individual thalamic (**B**) and substantia nigra (**C**) neurons are immunostained for WNV (green) and surrounded by nuclei of inflammatory cells counterstained with propidium iodide (red). **D.** Remaining residual cerebellar Purkinje cells immunostain intensely for WNV (green). Propidium iodide counterstain highlights uninfected cerebellar granule cells and Bergmann glia (red). **E.** Remaining thalamic neurons stain intensely for WNV antigens (green) and are surrounded by activated macrophages immunostained for CD68 (**E** red) and T-lymphocytes immunostained for CD3 (**F** red).

limiting acute anterior myelitis in a 22-year-old man who presented with the so-called polio syndrome characterized by asymmetrical, flaccid, areflexic monoparesis, muscle wasting, lack of sensory impairment and without mental changes. Since then there have been several published reports that confirm the existence of a clinical poliomyelitis-like syndrome and histopathologic poliomyelitis, which may accompany meningoencephalitis due to West Nile virus infection (4, 8, 9, 11, 12).

We report a typical case of fatal fulminant WNV infection of the central nervous system showing composite neuropathology of pan-meningoencephalitis and poliomyelitis. The presenting clinical history was typical of the established epidemiology of the virus with a history of recent environmental exposure and mosquito bites in a summer month (6, 13). However, the clinical course was fulminant, culminating in clinical brain death in less than 2 weeks. Neuropathological examination revealed a global non-necrotizing inflammation of the dura mater, leptomeninges, gray and white matter of the cerebral hemispheres, brain stem, cerebellum and spinal medulla. The severity of infection and inflammation exhibited an increasing gradient from the cerebral hemispheres, which showed the least severe inflammation, to the basal ganglia and cerebellum and to the brainstem and spinal cord, which showed the greatest involvement. Immunocytochemistry for viral antigens demonstrated a prominent neurotropism. Whether other cells were infected earlier can not be excluded on the basis of this single case analysis and require animal model studies with timed sacrifices to further elucidate (14). It would be intriguing to know the extent of infection early and types of cells infected. How the virus trafficked into the CNS remains a mystery. Other systemic tissues showed no evidence of infection; however, this may be secondary to viral clearance that might be more efficient in the periphery than in the CNS. The precipitous clinical course with onset of coma, loss of brain stem functions and clinical brain death is commensurate with the extensive infection of brainstem nuclei and secondary inflammation consistent with published reports of CNS infection by members of the flaviviridae family of viruses which have shown selective involvement of the brainstem and basal ganglia (10). The distinct distribution of viral infected cells might be explained by a similar distribution of cells with surface viral receptors (currently unknown) or perhaps cells with transcriptional complexes capable of replicating WNV proteins. The predominance of infiltrating parenchymal T-suppressor/cytotoxic cells admixed with a paucity of T-helper cells is consistent with the sub-acute phase of a viral induced immune response. The wave of T-cytotoxic cell infiltration and lysis of infected cells coincides with the most severe acute pathological damage (2).

The insensitivity of CT and MRI with and without contrast is puzzling given the severity of neurological damage. Perhaps the imaging studies were done too early in the course of the disease to identify involved regions. But if that is the case then how and when the virus traffics into the CNS are even more enigmatic. Some of the insensitivity may be explained by the diffuse non-necrotizing nature of the inflammation (5, 6, 13).

The failure to identify cytoplasmic viral particles by electron microscopy (EM) in this case reflects published reports regarding the remarkably compromised sensitivity of electron microscopy in detecting viral particles in formalin fixed brain tissue post-fixed in glutaraldehyde and osmium tetroxide .

In summary we present a fatal case of WNV meningo-polioencephalitis, with primarily neuronal infection and a non-necrotizing cytotoxic T-cell immune response. The histomorphology/ histotopography of this case somewhat resembles those described by Armbrustmacher et al (15, 16) in their 4 fatal cases from New York City in 1999. However, while they described a focal and slight inflammatory encephalitis without vasculitis, our case depicts a global/ diffuse pan-meningo-polioencephalitis with focal vasculitis, which was typically accentuated in the brain stem and spinal medulla.

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