Rapidly progressive neurologic decline and morbilliform rash presenting in a patient with lymphoma

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Abstract

A 67-year-old male with past medical history of mantle cell lymphoma and atrial fibrillation presented with a truncal rash, bilateral lower extremity weakness, and confusion. Within three days of presentation, his condition rapidly deteriorated with the onset of diffuse flaccid paralysis, aphasia, and severe alteration in mental status. Initial results from serum studies, lumbar puncture, magnetic resonance imaging, and electroencephalogram were not diagnostic. However, on the ninth day after initial presentation, the West Nile Virus (WNV) immunoglobulin M antibody returned positive from the cerebrospinal fluid. West Nile Virus encephalitis is endemic worldwide, and is the most common viral encephalitis in the United States. WNV presents in a variety of ways, and the recognition by physicians is crucial due to the estimated 2-12% mortality rate and significant long-term morbidity of neuroinvasive disease. The initial management and long term prognosis are points of ongoing research. This case represents a particularly profound example of neuroinvasive WNV. Our patient made a significant recovery after his initial presentation with aggressive supportive care, however still suffers from bilateral lower extremity weakness more than a year later.

Introduction

West Nile Virus (WNV) is endemic worldwide and was first recognized in the United States in 1999. Since then, WNV encephalitis has become the most common viral encephalitis in the United States. The recognition of neuroinvasive WNV by physicians is crucial due to the estimated 2-12% mortality rate and significant long-term morbidity. We present a case of severe neuroinvasive WNV in a 67-year-old male with lymphoma who presented with ascending paralysis and morbilliform rash.

Case Report

A 67-year-old Caucasian male with past medical history of mantle cell lymphoma and atrial fibrillation presented to a tertiary hospital with acute altered mental status. Two weeks prior to this presentation, the patient developed a truncal rash. This was thought to be a drug reaction to Ibrutinib, a small molecule drug that binds permanently to Bruton's tyrosine kinase, that he was receiving as therapy for his underlying lymphoma. The medication was discontinued despite excellent disease response over the past two years. On the day of presentation to an outside hospital (three days prior to presentation at our tertiary hospital), the patient was found mildly confused by his family members and unable to stand without assistance. In the emergency department he was tachycardic with high fever, but normotensive. Physical exam demonstrated altered sensorium with a Glascow Coma Score (GCS) of 14 and intact cranial nerves, however there were absent reflexes in bilateral upper and lower extremities and notable weakness in his legs, with equivocal plantar reflexes. Meningismal signs were absent. The patient had a morbiliform rash throughout his trunk without pruritus.

Laboratory values were significant for leukocytosis with neutrophilic predominance and acute kidney injury. The patient was initiated on broad spectrum antibiotics including vancomycin and piperacillin-tazobactam. Over the course of the next three days the patient became increasingly disoriented, and his aphasia progressively worsened. Antibiotics were broadened to include azithromycin and acyclovir. Lumbar puncture at that time was deferred due to recent use of an anticoagulant and high risk of bleeding. The patient was transferred to a tertiary hospital for further management.

Upon presentation to our institution, the patient was found to be altered and unable to follow commands. Per the patient's family, he had no recent travel, no bug bites, no new drug or herbal use. He had no seizure-like activity. On examination, the patient was afebrile, tachycardic, tachypneic and normotensive. He had a GCS of 6 that was a significant decline from his initial presentation, with weakness throughout all four extremities, absent reflexes, and aphasia. Punctate erythamatous papules were noted covering his back, with healed lesions on the lower extremities but sparing the soles. He was initiated on vancomycin, ceftriaxone, ampicillin, and acyclovir. Lumbar puncture demonstrated 126 white blood cells with neutrophilic predominance, protein of 0.69 gm/L, glucose of 6.88 mmol/L, and negative gram stain. Brain magnetic resonance imaging showed non-specific changes and lack of intra-cerebral lymphoma involvement, while an electroencephlogram showed diffuse background irregular delta and theta slowing (a non-specific finding). Serum thyroid hormone levels, HIV, anti-nuclear antibody, a paraneoplastic panel and blood cultures were negative. Cerebrospinal fluid (CSF) cytology, and fluid antibodies for herpes, zoster, cryptococcus, and coccidiodes were negative. On the ninth day after initial presentation, the CSF West Nile Virus IgM antibody returned positive. All antibiotics and antiviral medications were discontinued and the patient was managed conservatively with close monitoring. He made significant progress over the next few weeks with supportive care alone, regaining the ability to speak and follow complex commands. Motor strength in his lower extremities improved with physical therapy but he still required the use of a cane and displayed a persistent fine tremor at the time of discharge.

Over the following year, the patient has continued to make significant improvement

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Acknowledgements: appreciation and gratitude to the patient and UCLA Health.

Key words: Lymphoma; Neurologic decline; Morbilliform rash.

Contributions: the authors contributed equally.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Ethical statement: no patient specific details, images, or videos included in this report.

Received for publication: 27 July 2018.
Revision received: 19 November 2018.
Accepted for publication: 19 November 2018.

Clinics and Practice 2018; 8:1097
doi:10.4081/cp.2018.1097

with aggressive rehabilitation. He still requires the occasional use of a walker for intermittent dizziness but has returned to his baseline with complete recovery of his neurologic functions. He was restarted on ibrutinib and his mantle cell lymphoma remains in remision.

Discussion and Conclusions

This case demonstrates a particularly profound example of WNV. Infection with WNV causes a range of presentations, from a self-limited non-specific viral syndrome (termed West Nile Fever) to West Nile Neuroinvasive Disease (WNND), which includes syndromes of encephalitis and poliomyelitis-like flaccid paralysis that can overlap, like in our patient.[1] WNND typically presents in a similar manner to other viral and bacterial CNS infections, however clinical signs that may suggest a WNV central nervous system infection include neuromuscular findings like tremor, flaccid paralysis, and parkinsonism.[1]

Less than 1% infected with the WNV actually develop neuroinvasive disease,[2] but WNV encephalitis is actually the most common viral encephalitis in the United States. The best described risk factors for WNND include advanced age, malignancy, and organ transplantation, two of which our patient had.[3-5] Per Center of Disease Control guidelines, a *probable* diagnosis of WNND can be made with a positive CSF WNV IgM antibody, however a *confirmed* diagnosis requires more specific viral antibody testing or isolation of the virus because the WNV IgM can cross-react between flaviviruses.[6] In our case, WNND fit the clinical picture and is the only flavivirus endemic to the region, therefore more specific testing at a specialized laboratory was not required to make the diagnosis. Interestingly, the neutrophilic predominant (rather than lymphocytic predominant) CSF found in our patient is actually well described in WNND, despite its viral etiology.[7]

The primary treatment of WNND is supportive care. While data is limited on other treatment options, there is experience in the literature with using interferon, ribavirin, or intravenous immunoglobulin (IVIG). Interferon has in-vitro activity and some animal model data supporting its use, but has only been tried in two patients (with apparent benefit).[8-10] Ribavirin was tried during the WNV outbreak in Israel in 2000 and results suggested a possible detrimental rather than therapeutic effect.[11] As WNV has increased in prevelance, antibody titers amongst the general population have increased, thereby creating a theoretical benefit for IVIG use.[12] There is proof of concept in animal models,[12,13] but a single randomized controlled trial in humans did not show survival benefit.[14] Given the paucity of data guiding management, in consultation with our neurology team we opted for supportive care alone.

Once the diagnosis is made, discussions about prognosis become very challenging as data regarding morbidity and mortality rates vary.[4,14] Age (>50) is the most important risk factor for mortality and lasting complications.[4,15] In the Houston West Nile Cohort followed since 2002, 86% of patients and 43% of patients with WNV encephalitis had neurologic deficits 1-3 years and 8-11 years post-infection, respectively.[15] Wide variability in the literature between individual studies makes prognostication difficult, but based on a recent review of all known WNV studies, persistent long-term sequelae are likely.[16] The most common physical lasting sequelae are muscle weakness, fatigue, and myalgia, while mental sequalae include memory loss, depression and difficulty with concentration.[16] Patients and families must be counseled that recovery will be slow and may continue to progress over time. Therefore, setting the expectations upfront and providing physical and psychological support is critical in managing these patients.[15]

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