American Journal of Biomedical Science & Research

www.biomedgrid.com

ISSN: 2642-1747

Case Report

Copyright © *Daniele Mannina*

Early Infection by West-Nile Virus Causing Neuroinvasive Disease After Haploidentical Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia

Daniele Mannina[1]*, Ciro Maria Improta[1], Federico Arturo Villa[2], Chiara De Philippis[1], Jacopo Mariotti[1], Barbara Sarina[1], Daniela Taurino[1], Elena Costantini[2] and Stefania Bramanti[1]

[1]*Cancer Center, IRCCS Humanitas, Rozzano, Italy*

[2]*Anesthesiology Department, Humanitas, Rozzano, Italy*

***Corresponding author:** Daniele Mannina, Cancer Center, IRCCS Humanitas, Rozzano, Italy.

To Cite This Article: *Daniele Mannina*, Ciro Maria Improta, Federico Arturo Villa, Chiara De Philippis, Jacopo Mariotti, et al. Early Infection by West-Nile Virus Causing Neuroinvasive Disease After Haploidentical Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia. Am J Biomed Sci & Res. 2024 21(1) AJBSR.MS.ID.002799,* DOI: 10.34297/AJBSR.2024.21.002799

Received: December 20, 2023; **Published:** January 05, 2024

Introduction

West Nile Virus (WNV), one of the most widespread arboviruses in the world, causes seasonal epidemics in summer and autumn in many temperate countries. WNV circulates with an enzootic cycle between ornithophilic mosquitoes (vectors and reservoirs) and avian host species (amplification). Humans can be infected as accidental hosts [1-3]. The virus can also be transmitted through organ transplantation and blood transfusions [4-6]. In Italy, in accordance with the National Blood Center's WNV prevention measures against WNV, NAT testing is recommended for blood and hematopoietic stem cell donors, who have stayed at least one night in areas at high risk of WNV infection. Disease presentation ranges from mild, self-limiting flu-like syndrome to severe neurological illness [1,2]. Around 1% of infected patients develop neuroinvasive disease (WNND). WNND presents as meningitis, encephalitis, or myelitis and can lead to cognitive impairment, vigilance alteration, parkinsonian movement disorders, seizures, and/or flaccid paralysis [7]. WNND occurs more frequently in elderly or compromised patients. Blood transfusions, and organ or bone marrow transplant can increase the risk of WNND, probably due to lack or delayed formation of neutralizing antibodies in the immunodeficient host. The mechanism of Central Nervous System (CNS) invasion by WNV is still largely unknown [7]. Preclinical models show that high levels of circulating cytokines can increase the permeability of the blood-brain barrier, facilitating WNND [8]. WNV and other neurotropic flaviviruses may break blood brain barrier by endothelial permeability alteration regulated by Tumor Necrosis Factor-Alpha (TNF-a) signaling [7- 9]. Greater viral burden in serum is correlated with earlier viral CNS invasion, suggesting that WNV infects the CNS by hematogenous dissemination [9]. Infection of olfactory neurons and subsequent spread to the olfactory bulb through retrograde axonal transport is an additional "Trojan horse" mechanism that may contribute to WNND development [10]. WNV is cytolytic and triggers apoptosis in several cell types, including neurons [11,12]. The mechanism of WNV-induced cell death in vivo has not been thoroughly clarified, but it has demonstrated that expression of WNV specific proteins NS3 or capsid protein resulted in caspase-dependent cell death of in vitro and in vivo models [13,14].

Case Report

Here we describe the case of a female 43-year-old patient with Acute Myeloid Leukemia with unfavorable risk according to ELN-2017 classification (complex karyotype). After primary induction failure, complicated by probable pulmonary aspergillosis, she received salvage treatment with Decitabine + Venetoclax, obtaining complete morphological remission with cytogenetic persistence. She underwent T-cell replete haploidentical Hematopoietic Stem Cell Transplantation (HSCT) after myeloablative conditioning regimen with thiotepa, busulfan and fludarabine. GVHD prophylaxis consisted of post-transplant Cyclophosphamide on days +3 and +4, cyclosporine A, mycophenolate. After primary engraftment, at day +28 the patient was re-admitted to the hospital due to febrile neutropenia. Because of already known fecal colonization by Klebsiella pneumoniae ESBL, treatment with meropenem was started. Chest CT-scan, blood cultures, blood test for galactomannan, Beta-D-glucan, CMV, EBV, HHV6 viremia by PCR were negative. After two days of antibiotics, in consideration of persistent fever,

This work is licensed under Creative Commons Attribution 4.0 License

negative of blood cultures and known history of fungal infection, antimycotic treatment with amphotericin-B was added. In the subsequent days, the patient experienced subacute onset of cognitive impairment and upper limb tremors without focal neurological deficits. Magnetic Resonance Imaging (MRI) of brain showed abnormal bilateral pial enhancement of both occipital lobes. At the time of the onset of the neurological symptoms, blood count was notable for leukopenia with 1300 white blood cells/μL, with Absolute Neutrophil Count (ANC) of 900 cells/μL. On day 33 after HSCT diagnostic lumbar puncture was performed, in the suspicion of encephalitis or CNS leukemia involvement. Cerebrospinal Fluid (CSF) examination showed hypoglycorrhachia (45% of glycaemia), elevated protein level and abnormal cellularity (5 cells/μl). CSF cytofluorimetry showed the prevalence of NK lymphocytes (70% of white blood cells, WBC) and the absence of abnormal myeloid cells. On day 43 after HSCT, foscarnet was started as empirical treatment of meningoencephalitis. CSF examination was negative for CMV, HHV6, EBV, VZV, HSV1/2, Enterovirus, JCV and Mycobacteria. Because of clonic seizures, levetiracetam was started. Despite the treatment, rapidly progressive worsening of vigilance status was observed, up to impaired vegetative reflexes and desaturation. The Electroencephalogram (EEG) showed a moderate global slowing of the background rhythm without epileptic signs. Due to worsening hypoxia and inadequate protection of the airways, transfer to the intensive care unit, orotracheal intubation and mechanical ventilation were needed. Diagnostic lumbar puncture was repeated, in order to extend the microbiological investigation to WNV, BKV and adenovirus. CSF analysis confirmed hypoglycorrhachia (43% of glycemia) and hypercellularity (42 cells/μl) with prevalence of NK lymphocytes (78% of WBC). WNV PCR assay resulted negative on CSF but positive on urine sample. Brain MRI was repeated on day 42 from the admission, showing bilateral focal alterations of dentate nuclei, fourth ventricle floor, anterior mesencephalon and hypothalamus on both sides without gadolinium enhancement, and persistent pial enhancement of the superior cerebellar folia. Overall, the findings were consistent with WNDD. At the time of MRI reassessment and clinical deterioration, white blood cell count was significantly improved (WBC 5280/μL, ANC 4000/μL). After the diagnosis of WNDD, foscarnet and meropenem were suspended, and switched to usual antimicrobial prophylaxis. Due to the difficult weaning, we opted for tracheostomy placement. During the next days, we observed rapid worsening of vital signs, relapse of fever and onset of severe hypotension. On day 55 the patient died for multiorgan failure.

Discussion

The reported case of infection by WNV during the early immune recovery from HSCT represents a unique model of impaired host-virus interaction that facilitates the progression to WNND. We observed a rapid neurological deterioration beginning at a very early post-transplant time and worsening in conjunction with the hematopoietic reconstitution. Past evidence suggests that cell-mediated antiviral immune response within the CNS is needed for viral control, but it can also be involved in inflammatory injury of the CNS, and the pattern of cytokines and chemokines produced in response to WNV infection impacts on WNND progression [15]. These data are in line with the hypothesis that WNND depends on the synergy of viral cytotoxicity and neuroinflammation [7,8,15-17]. Among the immunocompromised patients, such as transplant recipients, HIV carriers, and patients receiving chemotherapy and transfusions, the risk of WNND is higher: 50-75% of patients with donor-derived WNV infection are at risk for WNND, compared to 40% of patients with mosquito-borne infections [18-20]. In the setting of HSCT, just a few cases of WNND have been reported, with occurrence up to 2 years after transplantation [21]. Furthermore, the time from transplantation to WNV infection is not significantly associated with the severity of WNND, whose outcome is generally poor [22]. WNND represents a diagnostic and therapeutic challenge. We reported a fatal conclusion, in absence of any specific treatment, at the end of a long and complex diagnostic process. In fact, despite the large number of reports exploring various therapeutic approaches for WNND, the treatment is still primarily palliative. Interferon and ribavirin have been used as anti-WNV agents, without any clear benefit [23]. In the setting of transplantation, administration of high-dose immunoglobulins has not been associated with a better outcome in comparison with supportive care only [24]. Due to the rarity of the condition, multicenter data collection is required to define risk factors, facilitate diagnosis and propose treatment strategies for WNND in the setting of HSCT.

Acknowledgements

None.

Conflict of Interests

None.

References

1. Campbell GL, Marfin AA, Lanciotti RS, Gubler DJ (2002) West Nile virus. Lancet Infect Dis 2(9): 519-529.
2. Rossi SL, Ross TM, Evans JD (2010) West Nile virus. Clin Lab Med 30(1): 47-65.
3. Gould EA, Solomon T (2008) Pathogenic flaviviruses. Lancet 371(9611): 500-509.
4. Mrzljak A, Dinjar Kujundzic P, Santini M, Barbic L, Kosuta I, et al. (2020) West Nile Virus: An Emerging Threat in Transplant Population. Vector Borne Zoonotic Dis 20(8): 613-618.
5. Kasule SN, Gupta S, Patron RL, Grill MF, Vikram HR (2023) Neuroinvasive West Nile virus infection in solid organ transplant recipients. Transpl Infect Dis 25(1): 14004.
6. Pealer LN, Marfin AA, Petersen LR, Lanciotti RS, Page PL, et al. (2003) West Nile Virus Transmission Investigation Team. Transmission of West Nile virus through blood transfusion in the United States in 2002. N Engl J Med 349(13): 1236-1245.
7. Shives KD, Tyler KL, Beckham JD (2017) Molecular mechanisms of neuroinflammation and injury during acute viral encephalitis. J Neuroimmunol 308: 102-111.
8. Zidovec Lepej S, Vilibic Cavlek T, Barbic L, Ilic M, Savic V (2021) Antiviral Cytokine Response in Neuroinvasive and Non-Neuroinvasive West Nile Virus Infection. Viruses 13(2): 342.

9. Samuel MA, Diamond MS (2006) Pathogenesis of West Nile Virus infection: a balance between virulence, innate and adaptive immunity, and viral evasion. J Virol 80(19): 9349-9360.

10. Suen WW, Prow NA, Hall RA, Bielefeldt Ohmann H (2014) Mechanism of West Nile virus neuroinvasion: a critical appraisal. Viruses 6(7): 2796-2825.

11. Peng BH, Wang T (2019) West Nile Virus Induced Cell Death in the Central Nervous System. Pathogens 8(4): 215.

12. Clarke P, Leser JS, Quick ED, Dionne KR, Beckham JD, et al. (2014) Death receptor-mediated apoptotic signaling is activated in the brain following infection with West Nile virus in the absence of a peripheral immune response. J Virol 88(2):1080-1089.

13. Samuel MA, Morrey JD, Diamond MS (2007) Caspase 3-dependent cell death of neurons contributes to the pathogenesis of West Nile virus encephalitis. J Virol 81(6): 2614-2623.

14. Yang JS, Ramanathan MP, Muthumani K, Choo AY, Jin SH, et al. (2002) Induction of inflammation by West Nile virus capsid through the caspase-9 apoptotic pathway. Emerg Infect Dis 8(12): 1379-84.

15. Suthar MS, Diamond MS, Gale M (2013) West Nile virus infection and immunity. Nat Rev Microbiol 11(2): 115-128.

16. Bigham AW, Buckingham KJ, Husain S, Emond MJ, Bofferding KM (2011) Host genetic risk factors for West Nile virus infection and disease progression. PLoS One 6(9): 24745.

17. King NJ, Getts DR, Getts MT, Rana S, Shrestha B, et al. (2007) Immunopathology of flavivirus infections. Immunol Cell Biol 85(1): 33-42.

18. Yango AF, Fischbach BV, Levy M, Chandrakantan A, Tan V, et al. (2014) West Nile virus infection in kidney and pancreas transplant recipients in the Dallas-Fort Worth Metroplex during the 2012 Texas epidemic. Transplantation 97(9): 953-957.

19. Abbas A, Qiu F, Sikyta A, Fey PD, Florescu DF (2022) Neuroinvasive West Nile virus infections after solid organ transplantation: Single center experience and systematic review. Transpl Infect Dis 24(6): 13929.

20. Winston DJ, Vikram HR, Rabe IB, Dhillon G, Mulligan D, et al. West Nile Virus Transplant-Associated Transmission Investigation Team. (2014) Donor-derived West Nile virus infection in solid organ transplant recipients: report of four additional cases and review of clinical, diagnostic, and therapeutic features. Transplantation 97(9): 881-889.

21. Kitagawa MG, Ettinger N, Breen D, Erklauer J, Chang E, et al. (2018) Transmission of West Nile Virus Through a Hematopoietic Stem Cell Transplant. J Pediatric Infect Dis Soc 7(2): 52-54.

22. Hong DS, Jacobson KL, Raad II, De Lima M, Anderlini P, et al. (2003) West Nile encephalitis in 2 hematopoietic stem cell transplant recipients: case series and literature review. Clin Infect Dis 37(8): 1044-1049.

23. Alli A, Ortiz JF, Atoot A, Atoot A, Millhouse PW (2021) Management of West Nile Encephalitis: An Uncommon Complication of West Nile Virus. Cureus 13(2): 13183.

24. Haley M, Retter AS, Fowler D, Gea Banacloche J, O Grady NP (2003) The role for intravenous immunoglobulin in the treatment of West Nile virus encephalitis. Clin Infect Dis 37(6): 88-90.