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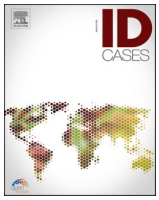

Case report

Probable West Nile Virus hepatitis: Case report

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ABSTRACT

West Nile Virus infections has become endemic in various locations around the world. Symptomatic cases manifest as an acute febrile illness and in less than 1% with neuroinvasive manifestations. We report one of the very few cases of probable WNV-mediated isolated hepatitis to shed light on a possibly underestimated clinical picture.

Introduction

West Nile virus (WNV) is a mosquito-borne *flavivirus* within the family *Flaviviridae* and is part of the Japanese encephalitis serocomplex [1,2]. Birds are the natural reservoir (amplifying hosts), and WNV is maintained in nature in a mosquito-bird-mosquito transmission cycle, primarily involving *Culex spp.* mosquitoes, while humans and other mammals are dead-end hosts [3]. In Italy, WNV appeared for the first time in Tuscany in 1998. After 10 years of absence, it reappeared in the areas surrounding the Po River delta. Thereafter, WNV epidemics caused by genetically divergent isolates have been documented every year in the country, affecting mainly northern Italy and peaking between August and September. 1145 WNV infections were notified in Italy between 2012 and 2020, including 487 WNNDs (West Nile Neuroinvasive Diseases) and 60 related deaths [4].

It is generally estimated that about 80% of persons infected with WNV remain asymptomatic and approximately 20% develop an acute, systemic febrile illness ("West Nile fever", WNF). Following an incubation period of approximately 2–14 days, infected persons typically experience the abrupt onset of fever, headache, fatigue, and myalgias. Gastrointestinal complaints, including nausea and vomiting, have been frequently described. Generalized lymphadenopathy has also been reported. WNF may sometimes be associated with a rash, which tends to be morbilliform, maculopapular, non-pruritic and predominates over the torso and extremities, sparing the palms and soles. In fewer than 1% of symptomatic individuals, virus entry into the central nervous system results in neuroinvasive manifestations (WNND). A plethora of risk factors have been associated with the development of severe neurological disease, the most recognized being older age and immunodeficiency. WNND includes encephalitis (50–71% of neuroinvasive cases), with fatality rates of 10–30%, aseptic meningitis (15–35%), or an acute poliomyelitis-like syndrome (3–19%). Some rarer neurological manifestations have also been outlined. Ocular manifestations (mainly chorioretinitis and vitritis) are the most reported clinical manifestation of WNV infection after fever and neuroinvasive disease. Several other clinical presentations have been described; generally, these manifestations have been described in case reports or small case series, and a definitive causal association with WNV infection is difficult to substantiate [5,6]. Rhabdomyolysis, myocarditis, and acute pancreatitis have been observed [7]. A single report of hepatitis has been described in 2004 in a child [8] and four adult cases of hepatitis have been described in 1983 in the Central African Republic (CAR) [9]. Serology constitutes the mainstay of laboratory diagnosis, although it suffers from broad cross-reactivity between various flaviviruses and the persistence of serum IgM for extended periods. Detection of the virus by molecular techniques can be useful in the first few days after symptoms's presentation, considering the low titer and short duration of viremia [10]. No antiviral drugs nor vaccines are available for WNV infection in humans, hence treatment of WNND is primarily supportive. Drug discovery studies have identified several candidate compounds, targeting either viral structural and non-structural proteins or host proteins that are required for viral infection or replication. However, all these candidates

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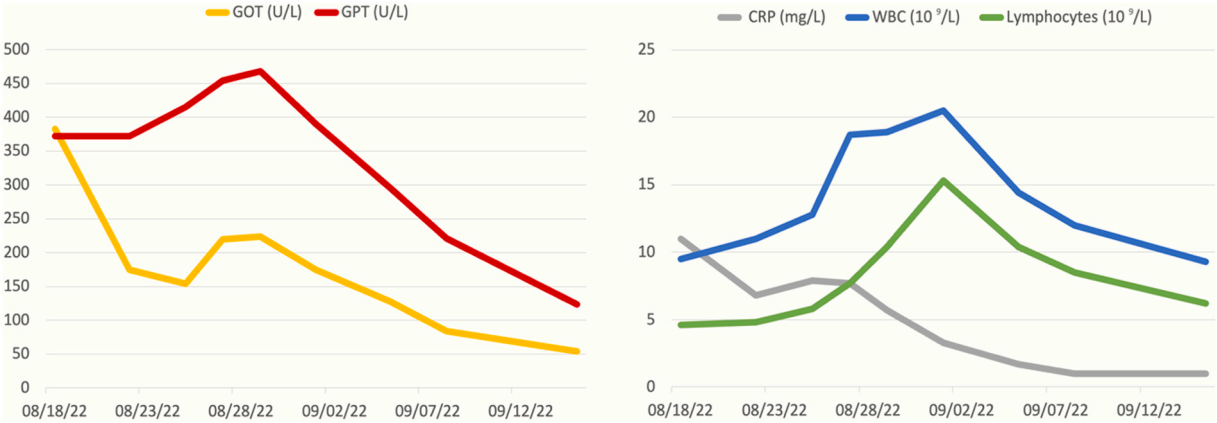

Fig. 1. Hepatic cytolysis markers, leukocyte formula and inflammatory marker. Abbreviations: CRP, C-reactive protein; GOT, aspartate transaminase; GPT, alanine transaminase; WBC, white blood cells.

are still in the preclinical stage [11].

We present a case of probable WNV-isolated non-fulminant hepatitis, to shed light on a possibly underestimated clinical picture.

Case description

A 39-year-old man presented on August 18, 2022 to the emergency room (ER) of a small town in Umbria, Italy, complaining of a 6-day course of fever, asthenia, headache and arthromyalgia. The physical examination was normal, chest radiography and SARS-CoV2 antigenic swab were negative, while blood examination revealed slightly elevated inflammatory indexes, leukocytosis with reversal of neutrophil-to-lymphocyte count ratio and a significant rise in transaminases (Fig. 1). The patient was discharged and serologies were performed, excluding HAV, HCV, HBV, CMV and EBV acute infections. Abdomen ultrasonography showed normal size and ecostructure of the liver, without focal lesion and with a normal biliary system. He subsequently came to the ER of IRCCS San Raffaele, Milan, for persisting fever without any other more specific symptom/sign. Blood cultures on pyrexia were negative and the patient was referred to our Infectious Diseases Day Hospital service, where we collected a more comprehensive medical history.

Remote medical history included only splenectomy following splenic rupture due to a car accident in 2001. He performed serologies for syphilis, HIV, HCV and HBV 2 years earlier, during a screening for sexually transmitted infections, resulting negative. He described no familiarity for autoimmune diseases and risk factors for STIs. He reported raw meat and fish consumption. Drug history was mute, apart from NSAID (ibuprofen) recently used as an antipyretic. Allergies comprised paracetamol. On August 9 he returned by car from Vipiteno, South Tyrol, to Turin crossing by Verona for two hours only, reporting no mosquito bites in that time frame. He then started to feel sick on August 12.

We started daily administration of 5% glucose solution. Blood exams confirmed lymphocytosis and elevated transaminases (Fig. 1), with slightly elevated C-reactive protein, normal cholestasis indices, albuminemia, and international normalized ratio (INR). Protein electrophoresis and immunofixation showed a monoclonal component in the gamma globulin area. We re-collected blood culture on pyrexia and performed a plasma dosage of copper, anti-LKM Ab, ANA, SMA, anti-SLA/LP, anti-Leptospira Ab, and polymerase chain reaction (PCR) for HEV, all resulting negative. We executed serology (CLIA alifax) and PCR for WNV, the latter being negative while the first demonstrated positive IgM and negative IgG. This result was confirmed in the convalescent plasma two weeks later, with index reduction, but without IgG seroconversion.

A complete resolution of symptoms was obtained in 15 days. We discharged the patient on August 8 and scheduled blood tests for the following week, showing almost complete normalization of blood counts and liver indices (Fig. 1).

Discussion

The reported case represents one of the few demonstrations of the viscerotropic manifestation of WNV. A Medline search on PubMed using the words “West Nile virus,” “hepatitis,” and “liver failure” yielded only 5 total descriptions of WNV-induced hepatic injury.

One pediatric case of fulminant non-fatal hepatitis in an 11-year-old white girl was reported in 2004 [8]. Four adult cases of hepatitis were recorded in 1983 in CAR, all but one were documented to be severe and progressed to hepatic coma. Two patients died, while 2 others recovered. In all cases, WNV was isolated from blood and liver biopsies. The virus strains were identified by plaque reduction neutralization test (PRNT), complement fixation, and mouse neutralization tests [9].

One limitation of our report is that we were not able to isolate the virus through PCR. However the patient presented to our department after a 17-days course of symptoms, and it is well known that WNV’s viremia is of short duration [3]. Additionally, we were unable to see an increase in IgM titer, nor were we able to prove seroconversion of IgG or confirm IgM positivity with a PRNT. Moreover cross-reactivity with Usutu virus (USUV) cannot be ruled out, even if symptomatic USUV infections are uncommon in humans and in 2022 only 6 cases of infection were reported in Italy [12,13]. Therefore, WNV infection should only be considered probable [10]. However, considering that the patient did not report either vaccination for tick-born encephalitis virus or tick bite, vaccination for Japanese encephalitis virus and yellow fever virus (YFV) or travel to endemic areas for Dengue virus (DENV), Zika virus, Spondwenii virus, Murray Valley encephalitis virus or St. Louis encephalitis virus, the likelihood of possible serological cross-reactivity is low, excluding USUV.

Conclusion

The occurrence of visceral disease and hepatitis in flaviviruses infection is well known (eg. Hepatic failure as an aspect of the viral hemorrhagic fever syndrome caused by both YFV and DENV) [14]. However, WNV’s liver tropism has probably been underestimated to date and all acute hepatitis occurring during periods of high WNV activity and with compatible epidemiology should be screened for this virus.

Ethical approval

This work does not require ethical approval.

Consent

The patient signed informed consent.

Funding

None.

CRediT authorship contribution statement

All authors take public responsibility for the content of the work. Giovanni Mori and Martina Strano drafted the original draft; Giovanni Mori edited the article; all co-authors were responsible for review. All authors read and approved the final manuscript. Giovanni Mori is the guarantor of the paper.

Declaration of Competing Interest

None.

Data Availability

All data needed to evaluate the conclusions in this article are included in the paper. Additional data related to this paper may be requested from the authors.

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