Idiopathic CD4 lymphopenia associated with neuroinvasive West Nile disease: Case report and review of the literature

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**KEYWORDS**

CD4 lymphopenia; West Nile virus

**Abstract**

Idiopathic CD4 lymphopenia is a very rare condition resulting in an immunodeficiency disorder that may or may not result in opportunistic infections. Since its description in the early 1990s, the reason for this immune deficiency has remained unclear. Its association with viral illnesses, such as West Nile virus infection, has yet to be described. We report a 26-year-old patient who presented with fever, ascending paralysis, and progressive weakness of the upper extremities. To our knowledge, this is the first case of neuroinvasive West Nile virus occurring in the context of a diagnosis of idiopathic CD4 lymphocytopenia.

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**Introduction**

Idiopathic CD4 lymphocytopenia (ICL) may be asymptomatic and diagnosed incidentally or may present with a variety of opportunistic infections, including some neurologic and autoimmune disorders [1–3]. Likewise, West Nile virus (WNV) may be asymptomatic, present with a mild febrile illness, or present in a neuroinvasive form with encephalitis, meningitis, and/or paralysis [4].

We report an unusual case in which a patient had both of these conditions concurrently. She presented with a high fever, lower extremity paralysis, and ascending progressive weakness of the upper extremities following a period of generalized weakness and malaise.

**Case report**

This patient was a 26-year-old Hispanic female who presented with a history of low-grade fever and mild back pain associated with progressive weakness of her lower extremities and mild urinary
incontinence. The patient stated that her symp-
toms began in March. She lived in the desert cli-
mate of southwest New Mexico, and there were sev-
ceral cases of WNV infection reported in that time
period and location. She did not recall receiv-
ing a mosquito bite but frequently spent time in
the yard. Her medical history included generalized
malaise, gastroenteritis-type symptoms, and inter-
mittent frontal headache with a vesicular rash over
her lower back that was treated with valacyclovir.

On admission, her temperature was 103 °F, her
blood pressure (BP) was 110/78 mmHg, and her
pulse was 102 beats/min.

A physical examination was unremarkable
except for grade 2/5 strength in the lower extrem-
ities, which progressed to 0/5 strength over the
first 48 h of her admission; deep tendon reflexes
were absent. Sensation was mildly impaired. Her
upper extremity strength was 4/5 bilaterally with
normal sensation.

On admission, labs showed the following: white
blood cell count, 5700 cells/mm³; hemoglobin,
11 g/dL; hematocrit, 34%; and platelet count,
212,000 cells/mm³. Serology for WNV IgG was pos-
itive using an enzyme-linked immunosorbent assay
(EIA) (LabCorp, Dallas, Texas). The patient’s per-
ipheral antineutrophil cytoplasmic antibody (pANCA)
titer was >1:640, and her antinuclear antibody
(ANA) titer was 1:320 with a homogeneous pattern.
An HIV test was negative. Serum IgG, IgA, and IgM
were normal.

Cerebrospinal fluid analysis revealed the follow-
ing: glucose at 25 mg/dL; protein at 140 mg/dL; red
blood cells (RBCs) at 30 cells/mm³; and white blood
cells (WBCs) at 1066 cells/mm³ with 69% polymor-
phonuclear and 31% mononuclear leukocytes.
The absolute CD4+ lymphocyte count was 73 cells/mm³.
Cerebrospinal fluid (CSF) culture was negative. A
CSF cryptococcal antigen test was negative. CSF
herpes simplex virus (HSV) 1 and 2 PCR results
were negative. CSF cytomegalovirus (CMV) PCR was
negative. CSF WNV IgM and IgG were positive by EIA
(LabCorp, Dallas, TX).

Brain magnetic resonance imaging (MRI) re-
vealed demyelination and an expansile appear-
ance of the spinal cord. MRI of the spinal cord
revealed marked cord expansion with hyperintense
signals from approximately C2 through
L1, suggesting diffuse myelitis. Abdominal
ultrasound and computed tomography (CT)
revealed splenomegaly and bilateral external
iliac chain lymphadenopathy, which was clinically
unremarkable.

She was started empirically on plasmaphere-
sis and high-dose intravenous steroid therapy
with a presumptive diagnosis of a Guillain–Barre
syndrome-like presentation versus transverse
myelitis. She was also started on IV valacyclovir
until the CSF HSV PCR results were available.
When the results were reported as negative, the
valacyclovir was discontinued. The rash resolved
on its own.

Despite the plasmapheresis, steroids, and intra-
venous valacyclovir; she made very little progress
in terms of improvement in strength. The use of
IV immunoglobulin was not deemed useful in this
situation and was therefore not used. The repeat
CD4 count performed 7 weeks after admission was
98 cells/mm³. Serum WNV IgG remained elevated
by EIA (LabCorp, Dallas, TX).

Based on these findings, a presumptive diagnosis
was made of ICL complicated by neuroinvasive WNV
disease.

Discussion

ICL was first described in 1992 by the Centers for
Disease Control and Prevention (CDC) as a deple-
tion of CD4+ lymphocytes (absolute count <300/µL
or <20% of total lymphocytes) at a minimum of two
separate time points at least 6 weeks apart, with
no evidence of HIV infection and an absence of
any defined immunodeficiency or therapy associ-
ated with reduced levels of CD4+ cells [1,7]. ICL
is very rare; several studies have been performed
to identify patients with ICL. One study screened
2028 blood donors and did not identify a single case;
another study of 275 blood donors, 970 transfusion
recipients, and 947 household contacts of trans-
fusion recipients identified 12 cases (0.5%). The
prevalence of ICL is generally accepted to be <1%,
although the true prevalence may be slightly higher
than the reported number, as the condition can be
asymptomatic [1].

The depletion of CD4+ T-lymphocytes in ICL may
go unnoticed, but ICL patients are predisposed to
a variety of diseases due to their immunodeficiency.
The clinical picture of ICL regarding opportunistic
infections closely parallels HIV due to the simi-
lar nature of the diseases. Common infections
associated with ICL include cryptococcosis, toxo-
plasmosis, histoplasmosis, and non-tuberculosis
mycobacterial infections [6,8]. Other associated
infections include herpes zoster (as observed in our
patient), Kaposi’s sarcoma, human papillomavirus,
Epstein–Barr virus, cytomegalovirus, and candidi-
asis [1,3,7]. Many cases of progressive multifocal
leukoencephalopathy have also been reported in
association with ICL [2,9,10] in addition to an
increased incidence of autoimmune diseases [3,6]
(Table 1).
Treatment for ICL varies depending on the presentation. Patients presenting with opportunistic infections should undergo therapy for the specific condition with which they present. Asymptomatic cases that are discovered incidentally should be monitored regularly to evaluate CD4 lymphocyte counts and to watch for the development of opportunistic infections, which are most likely to develop in the first few months after the initial presentation. Experimental cytokine therapy, such as synthetic IL-2 and IL-7 treatments, has had a varying degree of success in increasing CD4 lymphocyte counts, although specific therapy is difficult due to the unclear mechanism of ICL [3]. A handful of cases have reportedly been treated with allograft bone marrow transplantation, also with varying success [13]. Several studies have reported the recovery of CD4 lymphocyte counts to normal limits, whereas other studies have not shown significant effects. There are a very small number of reported attempts to treat ICL with bone marrow transplantation, which is generally used as a last resort for extreme cases; its clinical utility is not yet established [13]. We were unable to confirm whether ICL preceded WNV infection in our patient or began afterward.

WNV was first reported in New York in 1999. More recently, Texas was the primary site of an outbreak of the disease in 2012 [11]. According to data gathered by the CDC in 2011, the median age of WNV patients was 57 years (range 7–96 years), and 60% of patients were male. Moreover, 93% of the cases in that year occurred between July and September, with a peak onset in late August.

In our patient’s hometown in the southwestern USA, we have observed several cases of documented WNV disease with a variety of presentations ranging from asymptomatic to simple headaches to flaccid paralysis. The method used here to make the diagnosis included the clinical presentation, the current epidemiology, and EIA for serological and CSF analyses.

According to the reference laboratory (LabCorp, Dallas), the EIA test is 95% accurate when one considers the clinical presentation and the concurrent epidemiology and season in which the case presented. The case would have been more convincing if we had been able to obtain WNV CSF PCR results, but this information was not available to us.

The CDC reported 712 cases of WNV in 2011. Of those 712 cases, 486 (68%) were neuroinvasive; of those 486 cases, 30 (6%) had acute flaccid paralysis. Some cases of paralysis did not develop until 3–7 months after WNV infection [5], which is consistent with the presentation of our patient, although the onset of paralysis can also occur within hours of presentation in some cases [12]. WNV infection may present with concurrent autoimmune disorders, and the possible delayed onset of paralysis following initial infection may be due to an immune-mediated neuropathic process [4]. Our patient appears to follow the pattern described in the literature with delayed paralysis and with ICL being the predisposing cause for the infection (Table 2).

Neuroinvasive WNV with a background of immunodeficiency is very uncommon. According to a report from April 2013, there have been five reported cases of neuroinvasive WNV disease in HIV-infected patients in the USA. Of these five patients, two recovered with complete resolution of their symptoms, and one patient’s disease was complicated by pneumonia that progressed to respiratory failure and subsequent death; the outcomes of the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Opportunistic infections associated with idiopathic CD4 lymphocytopenia [7, CDC].</th>
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<tbody>
<tr>
<td>Class</td>
<td>Infectious agent</td>
</tr>
</tbody>
</table>
| Bacteria | *Fusobacterium nucleatum*  
*Mycobacterium avium intracellulare*  
*Mycobacterium mucogenicum*  
*Mycobacterium tuberculosis*  
*Nocardia spp*  
*Salmonella typhimurium* |
| Viruses | *Cytomegalovirus*  
*Herpes simplex virus*  
*Human herpes virus-8*  
*Human papillomavirus*  
*JC virus*  
*Varicella zoster virus* |
| Fungi | *Aspergillus spp*  
*Candida albicans*  
*Cryptococcus neoformans*  
*Histoplasma capsulatum*  
*Pneumocystis jirovecii* |
| Protozoa | *Leishmania spp*  
*Toxoplasma gondii* |

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<th>Table 2</th>
<th>Clinical syndromes associated with WNV infection, CDC 2011.</th>
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<tbody>
<tr>
<td>Presentation</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Non-neuroinvasive</td>
<td>226</td>
</tr>
<tr>
<td>Neuroinvasive</td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>183</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>273</td>
</tr>
<tr>
<td>Acute flaccid paralysis</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>712</td>
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</table>
final two patients were unknown [11]. No record of neuroinvasive WNV with a background of ICL was identified. Our patient’s neuroinvasive WNV disease appears to have been precipitated by the immunodeficiency (although we cannot be absolutely sure of this possibility) or might have been an unusual presentation of both diseases occurring simultaneously [5,6].

In summary, our case demonstrates a possible presentation of ICL concurrent with neuroinvasive WNV infection when considering the clinical presentation, the season in which it occurred, and serological findings. This case demonstrates several interesting points. (1) Clinical transverse myelitis may be a presenting feature of neuroinvasive WNV infection. (2) This case suggests the importance of an underlying immune deficiency syndrome in patients presenting with atypical neurological infections that are severe and progressive. (3) Although not therapeutically useful at this time, early diagnosis is beneficial in predicting prognosis and long-term morbidity. (4) If patients present with neurological syndromes associated with serology that may be positive for other autoimmune disorders, physicians should consider ICL with or without WNV disease. (5) The use of WNV PCR on serum and CSF samples would also help to confirm these cases. Further studies are warranted to clarify the etiology of ICL and the clinical syndrome associated with WNV infection.

Conflict of interest

There were no conflicts of interest during the writing of this paper.

References