67-Year-Old Man With Fever, Back Pain, and Lower Extremity Weakness

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A 67-year-old man presented to his local clinic in September 2004 with a 2-week history of low back pain and generalized malaise. A viral syndrome was diagnosed, and he was treated conservatively with over-the-counter analgesics. During the next few days, his clinical condition deteriorated markedly, with development of fever, lumbar pain, lower extremity weakness, and urinary retention. The patient was admitted to his local hospital, where initial laboratory evaluation revealed moderate leukocytosis (white blood cell [WBC] count, 20 × 10^9/L) with a left shift. He was treated empirically with piperacillin-tazobactam for broad-spectrum antimicrobial coverage. Findings on noncontrast computed tomography (CT) of the head and abdomen were unremarkable. Blood and urine cultures yielded negative results.

The patient’s medical history was notable for diabetes mellitus, degenerative lumbar disk disease, benign prostatic hyperplasia, chronic renal insufficiency, and a remote history of poliomyelitis. His medications included insulin, lisinopril, aspirin, furosemide, doxazosin, and diclofenac.

During the next 48 hours, the patient developed lethargy and confusion. He was transferred to the intensive care unit and underwent intubation for airway protection. A Foley catheter was inserted in light of the urinary retention. He was treated conservatively with over-the-counter analgesics. During the next few days, his clinical condition deteriorated markedly, with development of fever, lumbar pain, lower extremity weakness, and urinary retention. The patient was admitted to his local hospital, where initial laboratory evaluation revealed moderate leukocytosis (white blood cell [WBC] count, 20 × 10^9/L) with a left shift. He was treated empirically with piperacillin-tazobactam for broad-spectrum antimicrobial coverage. Findings on noncontrast computed tomography (CT) of the head and abdomen were unremarkable. Blood and urine cultures yielded negative results.

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During the next 48 hours, the patient developed lethargy and confusion. He was transferred to the intensive care unit and underwent intubation for airway protection. A Foley catheter was inserted in light of the urinary retention. Magnetic resonance imaging (MRI) of the head and spine showed unremarkable findings. A lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis revealed the following: WBC count, 160 cells/mm^3 (55% lymphocytes, 32% monocytes, and 13% neutrophils); protein, 150 mg/dL; glucose, 26 mg/dL (serum glucose, 70 mg/dL); and Gram stain, no organisms detected.

1. On the basis of the available clinical information, which one of the following diagnoses can be excluded?
   a. Viral meningitis
   b. Tuberculous meningitis
   c. Bacterial meningitis
   d. Vertebral osteomyelitis
   e. Subdural abscess

   The patient’s clinical presentation and the presence of CSF lymphocytic pleocytosis are consistent with aseptic meningitis, which can be viral or mycobacterial. However, partially treated bacterial meningitis can sometimes yield similar results and therefore cannot be entirely excluded. The onset of lower extremity weakness and urinary retention in the context of back pain suggests a myelopathic process, and a structural spinal lesion must be considered. Inflammation from vertebral osteomyelitis can extend posteriorly into the meninges, producing lymphocytic pleocytosis in the CSF. A subdural abscess would be confined to the subdural space and would not affect the underlying arachnoid and subarachnoid space. It is usually visible on MRI, which was unremarkable in this patient.

   With a presumptive diagnosis of infectious meningitis, the patient’s antibiotic therapeutic regimen was adjusted.

2. At this time, which one of the following is the most appropriate antibiotic regimen for this patient?
   a. Vancomycin and ceftriaxone
   b. Ceftriaxone
   c. Amoxicillin, ceftriaxone, and vancomycin
   d. Amoxicillin, ceftriaxone, vancomycin, and acyclovir
   e. Piperacillin-tazobactam, ampicillin, vancomycin, and acyclovir

   The pathogens involved in infectious meningitis vary with the age of the patient. In adults younger than 60 years, Streptococcus pneumoniae, Neisseria meningitides, and Haemophilus influenzae are prevalent, whereas in adults older than 60 years, most cases are due to either S. pneumoniae or Listeria monocytogenes. A third-generation cephalosporin (eg, ceftriaxone) combined with vancomycin is appropriate empirical therapy for S. pneumoniae, N. meningitides, and H. influenzae but does not adequately cover L. monocytogenes. In light of increasing pneumococ-
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4. Which one of the following is the most likely diagnosis in this patient?
a. Herpes simplex encephalitis
b. Equine encephalitis
c. Guillain-Barré syndrome
d. Postpolio syndrome
e. West Nile encephalitis

The differential diagnosis of encephalitis with flaccid paralysis is fairly limited. Neither herpes simplex nor equine encephalitis presents with motor symptoms. Guillain-Barré syndrome does not manifest with encephalitis and is characterized by demyelination on electromyography and marked protein cell dissociation on CSF examination. Moreover, it is often symmetrical and generally involves sensory changes. Both poliomyelitis and West Nile virus (WNV) can attack the anterior horn of the spinal cord and produce motor polyradiculoneuropathy with CSF pleocytosis. However, postpolio syndrome manifests as progressive fatigue, myalgia, weakness, and muscle atrophy, not the acute flaccid paralysis seen in primary poliovirus infection. West Nile encephalitis is sometimes associated with acute flaccid paralysis similar to that noted in our patient and should be considered as a diagnostic possibility, especially in late summer or early autumn.

Our patient’s neurologic status improved minimally during the subsequent few days, and he remained intubated for airway protection. Serum serology for WNV was IgM positive, consistent with an acute infection. Polymerase chain reaction studies were not performed on a CSF specimen.
5. At this stage, which one of the following therapeutic options is most appropriate for this patient?

a. Supportive care
b. Oral corticosteroids
c. Interferon alfa
d. Ganciclovir
e. WNV intravenous immunoglobulin (IVIG)

Current treatment guidelines for West Nile encephalitis consist of supportive care. Experimental treatment trials with corticosteroids, interferon alfa, and several antiviral drugs including acyclovir and ganciclovir have not shown consistent clinical efficacy to support their use. A National Institutes of Health study investigating the efficacy of WNV IVIG is currently under way. The study is expected to be completed by December 2005.

Antibiotic treatment was discontinued. Over the next 10 days, the patient’s respiratory status improved, and he was successfully extubated. His lower extremities remained weak. He was transferred to a general medical ward for convalescence, then dismissed to a nursing home for continued rehabilitation. Limited ambulation was achieved with the assistance of a walker.

DISCUSSION

West Nile virus is a mosquito-borne flavivirus that is transmitted primarily among birds; humans serve as incidental hosts. Although endemic in the Middle East, Africa, and Asia, WNV was unknown in the United States until the 1999 outbreak in New York City. Most persons infected with WNV are asymptomatic. When symptoms occur, they usually involve fever, headache, malaise, back pain, myalgias, anorexia, and a maculopapular rash. The acute symptoms typically last from 3 to 10 days, followed by fatigue and sometimes by a several-week course of muscle weakness.

In the United States, WNV infection has primarily affected older adults, in whom neurologic manifestations have been prevalent. Nonetheless, meningoencephalitis, the most serious manifestation of WNV infection, remains relatively infrequent, affecting approximately 1 in 150 infected individuals. Signs of encephalitis associated with asymmetrical muscle weakness are particularly suggestive of WNV infection. Fever occurs in at least 90% of cases, with nausea, vomiting, and headache present in approximately one half. About 30% of patients with West Nile encephalitis develop frank paralysis, also called acute flaccid paralysis syndrome. Affected individuals exhibit lower motor neuron–pattern weakness with flaccid tone, areflexia, or hyporeflexia. Typically asymmetrical and rapidly progressive, the weakness reaches a nadir within 2 to 8 days of symptom onset. Sphincteric dysfunction may develop, and respiratory muscle weakness may necessitate prolonged mechanical ventilation. Although initially attributed to Guillain-Barré syndrome, recent evidence suggests that paralysis associated with WNV infection is the result of destruction of anterior horn cells and closely resembles a poliomyelitis-like syndrome. Acute flaccid paralysis can also occur in the absence of meningitis or encephalitis.

Other neurologic manifestations of WNV infection include tremor, myoclonus, and parkinsonian features such as rigidity, postural instability, and bradykinesia. Older age and decreased immunity are the most important predictors of neuroinvasive disease, and among such patients, outcomes include death.

The diagnosis of WNV infection relies on a high index of suspicion. The incidence of infection peaks in late summer or early autumn, and the disease has a predilection for elderly and immunocompromised persons. The most common vector of transmission is a culicine mosquito. Since 2002, other modes of transmission have been reported: blood transfusion, organ transplantation, breastfeeding, transplacental contamination, and laboratory acquisition. Direct human-to-human transmission has not been reported.

Typical laboratory features of WNV infection include hyponatremia and either leukocytosis or leukopenia. Recently, it was suggested that prolonged lymphopenia and an increased ferritin level (>500 µg/mL) may indicate early infection. In patients with WNV meningoencephalitis, CSF examination usually reveals a lymphocytic pleocytosis with elevated protein and normal glucose levels. Head CT is usually unremarkable, but MRI may show leptomeningeal or periventricular enhancement in approximately one third of individuals with WNV encephalitis.

The most efficient means of diagnosis is the detection of IgM antibody to WNV in the CSF or serum. IgM is produced shortly after symptoms occur, and both serum and CSF are positive in most WNV-infected patients within 8 days of onset of illness. Current enzyme-linked immunosorbent assays for WNV IgM have sensitivity rates approaching 100%. Demonstration of WNV IgM antibody in CSF is considered diagnostic and strongly suggests an acute central nervous system infection. Demonstration of WNV IgM in serum is also diagnostic; however, false-positive results and cross-reactivity can occur in patients recently vaccinated against or infected with related flaviviruses (eg, St Louis encephalitis, yellow fever, Japanese encephalitis, dengue). Moreover, because most WNV-infected persons are asymptomatic and because serum IgM antibody may persist for 6 months or longer, residents in endemic areas may have persistent IgM anti-
body from a previous infection that is unrelated to their current clinical illness.  

Although it is possible to directly isolate WNV or to detect its nucleic acid in blood, CSF, and tissue, the short viremic period in humans precludes the use of these methods as routine screening tests. However, testing for WNV nucleic acid in CSF may prove valuable in severely immunocompromised patients, who may have prolonged periods of viremia and delayed or absent IgM antibody development.

The treatment of WNV infection is supportive. In experimental treatment trials, corticosteroids, interferon alfa, and antiviral drugs have failed to show consistent clinical efficacy. A National Institutes of Health study investigating the efficacy of WNV IVIG is currently under way. The most important preventive strategies include the use of insect repellent and the implementation of mosquito control programs. An experimental inactivated vaccine against WNV is available for horses, but a human form is still under development.

REFERENCES


Correct answers: 1. e, 2. d, 3. c, 4. e, 5. a