Toscana Virus Encephalitis in a Traveler Returning to the United States

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In Italy, Toscana virus is the most common cause of meningitis from May to October. Though only a few cases have been reported in U.S. travelers returning from Europe, most cases are likely unrecognized due to lack of familiarity with the disease. Here, we describe the case of an 82-year-old man presenting with fever, profound weakness, and hearing loss after returning to the United States following a 2-week summertime vacation in southern Italy who was ultimately diagnosed with Toscana virus encephalitis. This case should alert clinicians to the possibility of Toscana virus infection in returning travelers and provides information on how to obtain testing if Toscana virus is suspected.

CASE REPORT

An 82-year-old man with a history of metastatic melanoma treated with local lymph node dissection presented to our hospital with complaints of fevers, anorexia, and profound fatigue. His symptoms began 2 days after returning from a 2-week mid-July sojourn on the Amalfi Coast of southern Italy and prompted a visit to a local emergency room. There, he was found to have a low-grade fever (100.1°F), and a chest X-ray demonstrated an opacity in the right middle lobe of the lung. He was prescribed a course of oral doxycycline for the treatment of community-acquired bacterial pneumonia but did not improve. Six days after illness onset, he received a dose of intravenous ceftriaxone and a prescription for a 7-day course of oral levofloxacin. Because of a persistent fever, he was admitted to the ward the next day for further evaluation. On admission, a contrast computed-tomography (CT) scan of the chest demonstrated nonspecific ground-glass bibasilar opacities, stable compared to a previous CT scan, and did not show evidence of consolidation. At this point, the Infectious Disease service was consulted. Further inquiry into his history revealed new onset bilateral hearing loss and increased apathy according to the patient’s wife. There was no history of headache, photophobia, neck pain or stiffness, cough, shortness of breath, motor weakness, paresthesias, arthralgias, or myalgias. A review of systems was otherwise negative. He was a retired office manager who lived with his wife in southern Connecticut. While in Italy, the patient recalled noticing two small raised lesions on his skin, one on his left arm and one on his abdomen, which he described as “bug bites.” He did not remember being bitten or seeing an insect on his body, and the lesions resolved spontaneously. He denied any recent insect bites while in Connecticut. His medical history was notable for a deep vein thrombosis and pulmonary embolism, melanoma resection, hypertension, hyperlipidemia. Medications included amlodipine, levothyroxine, and warfarin.

On physical examination, temperature was 39.4°C, blood pressure was 101/53 mm Hg, pulse was 66 beats per minute, respiratory rate was 17 breaths per minutes, and oxygen saturation was 94% while breathing room air. Examination revealed an ill-appearing, elderly man who was alert and oriented but extremely lethargic. No nuchal rigidity was appreciated. Soft crackles could be heard on auscultation of both lung bases. Skin exam was notable for a nonblanching petechial rash over his lower trunk and lower extremities that did not involve his soles. Neurological exam was notable for decreased auditory acuity and a resting tremor of both hands and lower lip as well as bilateral upper extremity dysmetria. Laboratory testing revealed a mild thrombocytopenia (109,000/µl) but was otherwise normal. PCR of the nasopharynx for respiratory syncytial virus (RSV), influenza viruses A and B, parainfluenza viruses types 1 to 3, rhinovirus, and adenovirus and bacterial cultures of blood, urine and, sputum were negative. A lumbar puncture was performed and revealed a protein level of 169 mg/dl, glucose of 59 mg/dl, and 86 nucleated cells/µl, of which 75% were lymphocytes. There was no growth on cerebrospinal fluid (CSF) culture. PCR tests for herpes simplex virus (HSV), varicella-zoster virus, cytomegalovirus, and West Nile virus (WNV) on CSF were negative, as were serum immunoglobulin assays for WNV, for California encephalitis, eastern equine encephalitis, Saint Louis encephalitis, and western equine encephalitis viruses, and for _Ehrlichia chaffeensis_ and _Rickettsia rickettsii_. Testing for Lyme disease was not performed. Formal auditory testing was not pursued, and magnetic resonance imaging (MRI) of the brain revealed no radiologic evidence of encephalitis.

Given the patient’s presentation, recent travel, and history of insect bites and the time of year, consideration was given to other arboviruses endemic to Italy. Searches of the Internet and the Manual of Clinical Microbiology (1) both yielded Toscana virus as a likely etiological agent.
an important pathogen. The inclusion of Toscana virus in the differential was also corroborated by a search for endemic infectious diseases using the commercially available, internet-based infectious disease database GIDEON (Global Infectious Diseases and Epidemiology Network). After the patient’s destination of travel, presumed incubation time, insect exposure, and clinical syndrome had been entered, GIDEON offered infection with Old World phleboviruses, which include Toscana virus, as the most likely diagnosis.

A day 9 CSF sample was sent to the Centers for Disease Control and Prevention (CDC) Arbovirus Diagnostic Laboratory in Ft. Collins, CO, to test for Toscana virus and tick-borne encephalitis virus. A plaque-reduction neutralization test (PRNT) on CSF demonstrated a Toscana virus-specific neutralizing antibody titer of 1:32, a highly specific and strongly positive result (1). IgM capture enzyme-linked immunosorbent assay (ELISA) on CSF for tick-borne encephalitis was negative. Our patient’s clinical status gradually improved with supportive care, and he was discharged to a rehabilitation center. At a follow-up outpatient visit 7 weeks after illness onset, his symptoms had all but resolved. He noted improvement in his bilateral hearing acuity, though it had not returned to baseline. A convalescent-phase serum sample collected at that time yielded a very high positive Toscana PRNT titer of 1:2,560. An acute-phase serum sample was not available for testing.

There are three recognized arboviruses transmitted by Phlebotomus species, otherwise known as sand flies, endemic to Italy. The sand fly fever Sicilian virus (SFSV) was first isolated in 1943 by Albert Sabin during an epidemic among American soldiers in Italy during World War II. This was followed by identification of the sand fly fever Naples virus (SFNV) in 1944 (2) and finally the sand fly fever Sicilian virus (SFSV) in 1943 by botomus species, otherwise known as sand flies, endemic to Italy.

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Toscana virus remains a rare diagnosis in the United States. There are only three reported cases of Toscana virus infection in travelers returning to the United States, the first described in 1987 (Table 1) (7–9). It is likely, however, that the true prevalence is much higher, since the months of highest incidence (May to October) coincide with the high season for tourism to areas where the disease is endemic. Most cases are likely unrecognized by U.S.-trained physicians due to a lack of familiarity with the diagnosis and the self-limited nature of the disease. Patients with a clinical syndrome consistent with meningoencephalitis are likely to undergo extensive testing and receive broad-spectrum antibacterial and/or antiviral agents if HSV encephalitis is suspected. The longer the diagnosis remains unclear, the more testing, procedures, and antimicrobials the patient is likely to unnecessarily receive (7). CDC’s Arbovirus Diagnostic Laboratory offers testing for common arboviral disease etiologies based on location of travel or residence. For Europe, this commonly includes serology for tick-borne encephalitis and WNV. Testing for Toscana virus infection is not routinely done. However, if TOSV testing is requested and a detailed travel and clinical history is provided, the CDC can provide testing. Consultation with the CDC and notification of the local state department of public health are essential. Then, a specimen submission form (Form 50.34) should be completed, and the specimens and form should be sent to the state public health laboratory, who will forward the sample to the CDC Arbovirus Diagnostic Laboratory.

Toscana virus should be on the differential for any patient returning from the Mediterranean, especially during the summer months of peak incidence, with signs or symptoms of meningitis or encephalitis. Because there are no vaccines or specific antiviral agents to prevent or treat TOSV, appropriate steps to prevent sand fly bites, such as the use of insect repellent, protective clothing, and nets, should be recommended.

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REFERENCES