Case Report

Seoul Virus Infection in a Wisconsin Patient with Recent Travel to China, March 2009: First Documented Case in the Midwestern United States

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Abstract. Diagnosis of Seoul virus-associated hemorrhagic fever with renal syndrome (HFRS) cases among United States residents is rare. We describe confirmation of a Seoul virus infection in a 36-year-old scientist who worked with laboratory rats in Milwaukee, Wisconsin, but most likely acquired the infection during a trip to Shenyang, China.

Seoul virus, first identified in Korea in 1982,¹ is one of multiple hantaviruses (family Bunyaviridae, genus *Hantavirus*) that cause hemorrhagic fever with renal syndrome (HFRS), mainly in Europe and Asia. Common clinical features include fever, myalgias, thrombocytopenia, leukocytosis, renal failure, and shock in the most severe cases.² Elevation of liver enzymes is characteristic of HFRS caused by Seoul virus infection.³ Seoul virus is found worldwide and is transmitted by the brown Norway rat (*Rattus norvegicus*)¹; humans can become infected and experience HFRS after exposure to aerosolized urine, droppings, or saliva from infected rodents. Only one confirmed case has been reported in the United States.^{4,5}

CASE REPORT

On March 20, 2009, a Chinese-born male resident of Milwaukee, Wisconsin, 36 years of age, sought medical attention with a 3-day history of headache, fever, chills, fatigue, myalgias, and a nonproductive cough. The patient had returned from a month-long trip to Shenyang, in northeastern China, 1 month before illness onset. In Shenyang, where he felt well, he spent time only in urban areas, he denied rodent contact during his visit, and had no reported contact with ill persons. At the time of illness onset, he had resided in the United States for 18 months. He is a research scientist who works with laboratory rats; although he was not involved in animal care, he was exposed to rat excreta. His work entails implanting transducers in rat colons and then conducting necropsies of rat organs. His most recent rat contact was 3 days before illness onset.

On examination, the patient was drowsy; his temperature was 38.9°C; pulse 62 bpm; blood pressure 123/86; and pulse oximetry was 93% (room air). He had conjunctival suffusion but no other focal findings. Initial abnormal laboratory test results (Table 1) included white blood cell count 8,600/mm³ (normal 3,800–11,000/mm³) with 32% bands, decreased platelet count, and elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST); total bilirubin 1.7 mg/dL (normal, 0.1–1.3 mg/dL), ferritin 38,394 ng/mL, lactate dehydrogenase > 2,400/μL, and partial thromboplastin time elevated to 54 seconds. Serum creatinine was normal, but urinalysis showed 2+ proteinuria. Serologic tests for hepatitis A, B, and

C viruses, Epstein-Barr virus, human immunodeficiency virus, and leptospira; polymerase chain reaction (PCR) for cytomegalovirus; *Rickettsia* antibody panel; blood cultures and peripheral smears for malarial parasites were all negative.

The patient was febrile during hospital Days 1 and 2, and his ALT and AST peaked on hospital Day 3 when his hypoxia worsened to 90% saturation on room air. A chest computerized tomography examination showed bilateral moderate-sized pleural effusions but no consolidation. His serum creatinine increased to 1.53 mg/dL, but urine output remained normal. Liver tissue obtained by transvenous liver biopsy showed acute hepatitis with lobular necrosis without viral inclusions, atypical cells, vasculitis, or fibrosis (Figure 1).

His hypoxia and fever subsided on Day 5 and his liver enzymes and platelet count normalized. He was discharged from the hospital on Day 9. One week later, he reported only mild fatigue, and laboratory tests showed near-normal liver transaminases and serum creatinine of 1.15 mg/dL. His chest x-ray on that day showed resolution of the pleural effusions.

DIAGNOSIS

Acute- (sample 1, obtained Day 6 after illness onset) and convalescent-phase (sample 2, obtained Day 12 after onset) serum and whole blood specimens were sent to the Special Pathogens Branch, Centers for Disease Control and Prevention (CDC), Atlanta, GA, for hantavirus (Seoul and North American Sin Nombre viruses) serologic testing (Table 2). A Seoul virus infection was diagnosed on the basis of elevated immunoglobulin M (IgM) titers and a rise in IgG titer by using Seoul virus antigen. Acute- and convalescent-phase samples were negative for reactivity with Sin Nombre virus antigen. The identification of Seoul virus infection was confirmed by using a nested reverse transcriptase-PCR (RT-PCR) assay targeting the hantavirus polymerase gene (L segment).⁵ Only the acute-phase blood sample was RT-PCR positive, consistent with the findings of a rising Seoul virus-specific IgG titer and the expected corresponding rapid viral clearance.

EPIDEMIOLOGIC INVESTIGATION

Epidemiologic investigation was conducted by the Wisconsin Division of Public Health to assess whether the patient acquired a Seoul virus infection from the laboratory rats at his workplace. Analysis of the laboratory records and

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TABLE 1

Liver function (AST and ALT) test results and platelet count from a Seoul virus-infected patient during his hospitalization in a Milwaukee, WI hospital, by hospital day, March 2009

Day	AST μL^*	ALT $\mu\text{L}^\dagger$	Platelets $10^3/\text{mL}^\ddagger$
1	369	576	26
3	1,003	2,427	37
5	970	2,096	86
7	459	515	119
9	344	224	125
11	178	88	144
17	69	39	223

*AST = aspartate aminotransferase (normal range, 0–37 μL).

† ALT = alanine aminotransferase (normal range, 0–35 μL).

‡ Platelet count (normal range: $150\text{--}450 \times 10^3/\text{mL}$).

interview of personnel showed that the laboratory management follows correct biosecurity practices. All laboratory rats and mice housed in the animal facility in the building are obtained in weekly deliveries from a commercial supplier. The rats are 2 weeks old when they are delivered. A subset of these animals is screened for a panel of infectious agents, including Hantaan virus, a virus serologically related to Seoul virus, before each delivery. Approximately 116 research rats are kept in one room, separated among four racks of cages, with one sentinel rat cage assigned to each rack. The sentinel rats are monitored daily for any evidence of diseases and are euthanized, tested, and replaced every 3 months.

During the investigation, one research rat from each of the three age groups with which the patient had contact during the month before his illness onset was euthanized and tested, as were the four sentinel rats from each cage rack. The three research rats tested were aged 11, 12, and 13 weeks, respectively, and the sentinel rats were aged 16 weeks. Sera from these animals were submitted to CDC's Special Pathogens Branch and to a commercial veterinary diagnostic laboratory to test for IgG antibodies against Seoul virus. All specimens were seronegative. Six other researchers (age range 25–58 years) worked in the laboratory and had contact with the same research rats as the patient; serum specimens obtained

FIGURE 1. Transvenous liver biopsy, obtained on Day 6 of the patient's hospital stay, showed acute hepatitis with focal necrosis without viral inclusions, atypical cells, or vasculitis or fibrosis.

TABLE 2

Results of serologic tests for antibodies to Seoul and Sin Nombre viruses by day after illness onset on March 17, 2009*

Test name	IgM optical density †	IgM titer ‡	IgG optical density §	IgG titer ‡
Seoul antibody	6.86	$\geq 1:6,400$	1.36	1:400
Sample 1: acute phase (Day 6 postonset)	6.79	$\geq 1:6,400$	4.41	$\geq 1:6,400$
Sample 2: convalescent phase (Day 12 postonset)	0.32	$< 1:100$	0.15	$< 1:100$
Sin Nombre antibody	0.32	$< 1:100$	0.15	$< 1:100$
Sample 1: acute phase (Day 6 postonset)	0.14	$< 1:100$	0.36	1:100
Sample 2: convalescent phase (Day 12 postonset)				

* Sample 1 (acute phase) was obtained March 23, 2009, on Day 3 of hospitalization, and sample 2 (convalescent phase) was obtained March 29, 2009, on Day 9 of hospitalization.

† Cutoff value < 0.45 .

‡ Cutoff value $< 1:400$.

§ Cutoff value < 0.91 .

from all six researchers were tested at CDC and were negative for antibodies to Seoul virus.

DISCUSSION

The seronegative specimens from the laboratory rodents and the adherence to recommended animal room practices to minimize disease transmission to humans and to other animals, suggest that the patient was most likely infected with Seoul virus while visiting Shenyang, China, where Seoul virus is endemic.⁶ The HFRS has been recognized as a serious problem in Shenyang since the first outbreak was identified in 1958.⁶ Living in a rural environment is associated with higher risk of HFRS; however, cases among urban residents with no rural travel have been identified throughout Asia and depending on the virus and host, transmission may occur in rural, urban, or occupational settings.⁷ Symptoms of HFRS usually occur 2–3 weeks after exposure to infectious material; however, the maximum incubation period can be ≤ 8 weeks.⁸ The patient's suspected incubation period ranges from 4 weeks to 8 weeks (his first to last day in China) and, although long, the period is within the maximum incubation interval of 8 weeks. His recovery was complete, as is typical with the majority of Seoul virus infections.^{2,9}

No Seoul virus-associated HFRS cases have been documented previously in the Midwestern United States. However, Seoul virus has been detected among rat populations in port cities worldwide, including cities in the United States.^{4,10–12} In 2009, the first case of a domestically acquired Seoul virus infection was reported in Maryland in a patient who worked in an underground service tunnel where he might have had rodent contact.⁵ In one study of wild rats trapped in Baltimore, nearly half the rats had detectable antibody against Seoul virus.¹³

Hantavirus infections can cause substantial morbidity and mortality and are important public health concerns, especially in China. Within an epidemic area, individual risk is typically correlated with exposure to infected rodents,⁸ although other presumed sources of infection for humans exist and include other wild and domestic animal species.¹⁴ The risk for acquiring HFRS is low for international travelers; however, HFRS cases are increasingly being recognized in non-endemic areas because of increases in international travel to endemic areas,¹⁵ reduction of human-rodent contact is the key to prevention.¹⁶

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Disclaimer: The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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