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BRIEF REPORT

Domestically Acquired *Seoul* Virus Causing Hemophagocytic Lymphohistiocytosis—Washington, DC, 2018

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Seoul orthohantavirus (SEOV) infections, uncommonly reported in the United States, often result in mild illness. We report a case of hemophagocytic lymphohistiocytosis secondary to SEOV infection that was domestically acquired in Washington, DC.

Keywords hantavirus; hemophagocytic lymphohistiocytosis; hemorrhagic fever renal syndrome; seoul Virus.

Seoul orthohantavirus (SEOV) is an enveloped RNA virus in the genus *Orthohantavirus* of the family *Bunyavirales*. Although the virus and its natural host, the Norway rat (*Rattus norvegicus*), are globally distributed, the majority of known cases of SEOV occur in China and the Republic of Korea [1, 2]. SEOV infections are uncommonly reported in the United States [3], where the Sin Nombre orthohantavirus (SNV) causes the majority of known hantavirus cases. As of January 2017, 728 cases of hantavirus infections have been reported to the Centers for Disease Control and Prevention (CDC), with >96% reported in the Western United States.

Humans infected with SEOV most commonly experience either no symptoms or a mild illness characterized by fever, chills, headache, nausea, vomiting, rash, and conjunctival injection. Severe disease is rare and typically manifests as hemorrhagic fever with renal syndrome (HFRS), characterized by fever, hemorrhage, and impaired kidney function, as reflected by proteinuria or microhematuria and occasionally elevated creatinine. SEOV infection in humans has a mortality rate of <1%. In the SEOV outbreak among 183 rat owners in the United States and Canada in 2017, 24 (13.1%) had *Seoul* virus antibodies, 3 (12.5%) were hospitalized, and no deaths occurred [4].

Hemophagocytic lymphohistiocytosis (HLH) is a rare immune disorder in which overactivity of white blood cells leads to hemophagocytosis and can result in death. HLH may be primary due to genetic causes or secondary due to cancers, autoimmune disorders, or infections. Although a variety of infections have been shown to cause HLH, studies have raised the possibility of HLH linked to HFRS, mostly due to PUUV- induced HFRS (*Puumala* virus) [5, 6].

Although it has been shown that wild Norway rats on the east coast of the United States can carry SEOV, it has never been noted in Washington, DC [7, 8]. This case represents a reported diagnosis of SEOV in a person residing in Washington, DC, and a case of HLH secondary to SEOV.

CASE REPORT

A 30-year-old male with no medical history presented to a Washington, DC, hospital in May 2018 with complaints of subjective fevers and myalgia for 6 days. He was evaluated at an urgent care clinic 3 days after onset of symptoms and advised to continue symptomatic management with nonsteroidal anti-inflammatory agents. He presented to the emergency department on day 6 POS (after onset of symptoms) with persistent fevers, worsening myalgia, and fatigue. He denied rash, joint pains, cough, shortness of breath, abdominal pain, and dysuria.

The patient was a resident of Washington, DC, and was employed as a maintenance worker at 2 facilities. He reported no travel outside the United States in the previous 9 years. The patient also reported no direct animal contact, known exposure to rodent excrement, or tick bites. However, he reported observing rats on the street outside his residence and outside both of his workplaces.

On admission, physical exam revealed an ill-appearing young male. Oral temperature was 39.5°C, heart rate 140 beats per minute, blood pressure 143/81 mm Hg, respiratory rate 16 breaths per minute, and oxygen saturation on room air was 97%. He had mild bilateral conjunctival injection and flushed, diaphoretic skin without a rash, jaundice, or petechiae. He was breathing comfortably with no wheezing, crackles, or rhonchi. There was no hepatosplenomegaly or lymphadenopathy. Muscles and joints were not tender to palpation. A laboratory evaluation on admission was notable for elevated hemoglobin and hematocrit, thrombocytopenia, and elevated transaminases and creatinine (Table 1). Serum white blood cell count and bilirubin were normal. Chest radiography was normal. Abdominal

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Table 1. Laboratory evaluation of a 30 year old male from Washington DC on day 6, day 10 and day 16 post onset of symptoms of Seoul Virus infection (2018)

Specimen, Analyte	On Admission POS Day 6	Midcourse POS Day 10	On Discharge POS Day 16	Range
White blood cell count, cells/mm^3	5000	14 800	7400	4000–10 800
Hemoglobin, g/dL	18.4	13.7	15.6	12.5–16.5
Hematocrit, %	55.4	40.2	46	37.5–49.5
No. of platelets/mm^3	25 000	74	316	145 000–400 000
Urea nitrogen, mg/dL	14	76	112	9–20
Creatinine, mg/dL	1.38	4.30	3.65	0.66–1.50
Creatinine kinase, units/L	768	1367	553	39–308
Aspartate aminotransferase, IU/L	209	127	21	3–34
Alanine aminotransferase, units/L	117	240	109	15–41
Total bilirubin, mg/dL	0.4	0.7	1.3	0.2–1.3

Abbreviation: POS, post onset of symptoms.

ultrasound showed enlarged kidneys bilaterally, with the left kidney measuring 13.2 cm and right kidney 12.7 cm.

Hospital Course

The patient was admitted to the medical ward for further workup. On day 7 POS, his platelets decreased to 18 000/mm^3, and he remained febrile with an oral temperature of 39.9°C. As a result of this, the Hematology and Infectious Diseases Departments were consulted to assist with further diagnostic testing. His peripheral blood smear showed megakaryocytes suggesting peripheral destruction without any evidence of a microangiopathic process or inclusion bodies. This selective destruction of platelets raised concerns for an autoimmune process, and he was started on intravenous immunoglobulin and intravenous methylprednisolone the same day. His fevers, myalgia, and fatigue resolved by day 8 POS. His platelets reached a nadir of 10 000/mm^3 before recovering, and his hemoconcentration normalized on day 8 POS. Blood urea nitrogen and creatinine peaked at 112 mg/dL and 4.95 mg/dL, respectively, by day 10 POS. Urine analysis was notable for >500 mg/dL protein and moderate blood. Serial, aerobic, and anaerobic blood cultures as well as a respiratory virus shell vial culture, were negative. Serologic and serum polymerase chain reaction testing for cytomegalovirus, Epstein-Barr virus, HIV, hepatitis A, B, and C viruses, herpes simplex virus, parvovirus B19, *Ehrlichia chaffeensis*, *Anaplasma phagocytophilum*, and *Leptospira interrogans* were negative. Computed tomography of the chest, abdomen, and pelvis showed no pertinent abnormalities. Kidney biopsy was suggestive of acute tubular damage with focal calcifications, and the interstitium demonstrated mild inflammatory infiltrate.

Triglyceride levels (on day 8 POS) and ferritin (on day 12 POS) checked in the evaluation of his thrombocytopenia were elevated: triglycerides 266 mg/dL and ferritin >40 000 ng/mL. A bone marrow biopsy performed on day 8 POS showed scattered hemophagocytic cells. His soluble interleukin-2 receptor (CD 25) level, checked on day 9 POS, was also elevated at 8820 pg/mL. At this time, the patient fulfilled 5 of 8 criteria for HLH, with fever and elevated ferritin, triglycerides, IL-2 levels, and hemophagocytotic cells in the bone marrow biopsy. He was started on standard HLH treatment with etoposide and dexamethasone.

Due to the patient's occupation in building maintenance with frequent rat sightings at 1 workplace, hemoconcentration, thrombocytopenia, and acute kidney injury consistent with HFRS, hantavirus infection was suspected, and commercial serologic testing was performed on day 11 POS (Quest Infectious Diseases Inc., San Juan Capistrano, CA). Results returned positive for both hantavirus immunoglobulin M (IgM) and immunoglobulin G (IgG) on day 14 POS. He received treatment for HLH presumed to be induced by hantavirus infection and tolerated it well. He was discharged 18 days after symptom onset with a serum creatinine of 2.3 mg/dL, normal complete blood counts, and improving transaminases.

Given the unusual nature of the patient's presentation and his possible rat exposure, the DC Department of Health (DC Health) and CDC were contacted to request further assistance with diagnostic and epidemiological surveillance. Whole-blood and serum specimens from day 11 POS that were sent to the CDC tested positive for SEOV IgM and IgG via enzyme-linked immunosorbent assay at titers of ≥1:6400. RNA extracted from patient serum tested negative by polymerase chain reaction (PCR) using a nested pan-hantavirus assay known to detect SEOV.

As a result of the reported rodent exposure and no reported exposure to pet rats, DC Health Rodent Control completed inspections of the 3 addresses where the patient had observed rats. Evidence of rats was not discovered at 2 locations, but rat feces were discovered at 1 of the patient's workplaces. At this location, it was also noted that an adjacent vacant property had a substantial rat infestation. Abatement steps were taken on the vacant property, and the patient's employer was mandated to hire a pest control company.

DISCUSSION

Our case is unique because, to our knowledge, this is the first reported case of HLH secondary to SEOV HFRS and the second hantavirus infection associated with the syndrome, with the first case reported in South Korea in 2002 secondary to Hantaan virus infection [6]. Past studies have documented that Norway rats serve as the reservoir species for SEOV in the United States and elsewhere [7, 8, 9, 10]. The 2016–2017 outbreak of SEOV associated with exposure to pet rats was the first time that SEOV had been linked to the pet rat population in the United States. Whole-genome sequencing of outbreak specimens revealed a closer linkage to the Cherwell strain, a strain of SEOV from infected pet rats in the United Kingdom [3, 11]. It was not possible in our case to genetically characterize the SEOV strain as PCR testing was negative. This was expected as the specimen was collected 11 days after the patient's onset of illness. Furthermore, as the SEOV strain could not be isolated from the patient, DC Health did not attempt to capture wild rats for surveillance testing.

Our case illustrates the ongoing risk of SEOV infection to people who may be exposed to wild rat infestations in occupational or other peridomestic settings, highlighting the importance of rodent control measures. Although uncommon, there have been a number of SEOV cases in the last 2 years in the United States, and SEOV should be considered in the differential diagnosis of patients presenting with an undifferentiated febrile illness with renal injury and a possible history of recent rodent exposure. This case also demonstrates that SEOV should be included among the etiologies of HLH and suggests that such cases would be expected to respond to standard HLH treatment.

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