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Hantavirus infection in British Columbia: An atypical case history and epidemiological review

A patient presenting with uncharacteristic symptoms was eventually found to have hantavirus pulmonary syndrome.

ABSTRACT: Although diagnosed infrequently, hantavirus infections do occur in British Columbia. Hantavirus pulmonary syndrome has a crude mortality rate of approximately 40% to 50% and is typically characterized by fever, chills, and myalgias followed by an abrupt onset of respiratory distress and hypotension, often requiring ventilation. In 2002, a case of hantavirus pulmonary syndrome with uncharacteristic presentation was diagnosed in a 46-year-old male from the Okanagan region. This case highlights the need for physicians to be aware of such atypical case histories, the epidemiological and laboratory investigations required, and the epidemiology of hantavirus infection in British Columbia, including modes of transmission and common risk factors for disease. Physicians should also be aware of the national and BC case definition, specimen collection procedure, differential diagnoses, clinical management, and the importance of case reporting.

Case history

In early July 2002, a 46-year-old male presented to an emergency department complaining of epigastric discomfort followed by significant vomiting and intense right upper quadrant pain. He was admitted to hospital and within 2 days developed drenching night sweats and mild breathlessness, headache, but no diarrhea. Initial X-rays indicated interstitial pneumonitis with bilateral effusions; oxygen saturation was 84% on room air but improved with administration of supplemental oxygen (94% on 4 L O_2). The patient developed a cough by his fourth day in hospital and fine course crackles were present throughout both lung fields. Some bilateral chest pain was present but this was not typical of pleuritic pain. The patient's highest recorded temperature was 38.1°C on day 2, with fluctuation between 36°C and 38°C. His BUN and creatinine levels were initially normal, but he went into transient renal failure (maximum creatinine 260). His liver function studies were normal except for a GGT of 160 (normal range 12–50 U/L). His WBC count was normal at 6.18, with 3.40 polymorphonuclear leukocytes and 0.19 bands, but the smear showed rare nucleated red cells and immature granulocytes, which were considered to be abnormal. Similarly, many of the lymphocytes were abnormal in appearance. His initial hemoglobin count was 166 but on rehydration fell to 115. His platelet count was 90 000 at presentation, fell to 65 000 2 days later, and then slowly recovered. His chest X-ray ultimately revealed interstitial edema with small pleural effusions.

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Diagnostic investigation

Initial workup concentrated on the cause of the patient's severe abdominal pain. An ultrasound demonstrated a gallstone and cholecystitis; upper endoscopy and colonoscopy failed to demonstrate a significant lesion. Within 2 days of hospitalization, laboratory tests were requested for respiratory pathogens, including *Chlamydia* species, *Legionella* species, *Mycobacterium tuberculosis, Mycobacterium pneumoniae,* and Sin Nombre virus, a species of hantavirus. A fourfold decrease was observed in immunoglobulin M antibodies to Sin Nombre virus from acute to convalescent sera (1:1600 to 1:400) with a concomitant rise in immunoglobulin G antibodies (1:600 to 1:>6400). Sera were nonreactive to antibodies for other respiratory pathogens.

This case eventually proved to be an example of atypical presentation of hantavirus pulmonary syndrome (HPS). Although elevated, fever did not reach 38.3°C, the recognized threshold in HPS patients. Chills and myalgias, common to most HPS patients, were noted only on a single day. Respiratory distress was mild with minimal cardiopulmonary involvement; the predominant symptom was severe abdominal pain. In this case, as in about 80% of cases of HPS, the platelet count was below 150 000 units.[1] The combination of atypical lymphocytes, notably increased band cells (and even myelocytes, metamyelocytes, and promyelocytes), and thrombocytopenia in the setting of pulmonary edema is strongly suggestive of a hantavirus infection.[1] While less typical, abdominal pain, nausea, and vomiting are considered frequent manifestations of HPS (see **Table 1**), suggesting that hantavirus infection should be considered in the differential diagnosis of individuals presenting with gastrointestinal complaints, particularly when these complaints are accompanied by radiological evidence of bilateral diffuse infiltrates.

Table 1. Symptoms of hantavirus pulmonary syndrome, with symptoms from case under discussion highlighted.

Most frequent	Frequent	Other
Fever	Headache	Shortness of breath
Chills	Nausea	Dizziness
Myalgia	Vomiting	Arthralgia
	Abdominal pain	Back or chest pain
	Diarrhea	Sweats
	Cough	
	Malaise	

Source: US Centers for Disease Control and Prevention. www.cdc.gov/ncidod/diseases/hanta/hps/noframes/phys/clinical.htm (accessed 19 August 2003).

The classic presentation of HPS includes relatively nonspecific early symptoms and a febrile prodrome lasting 3 to 5 days. Fever is usually accompanied by chills and myalgias. Less frequently, the patient presents with headache, dizziness, nonproductive cough, nausea, vomiting, abdominal pain, and diarrhea. Indications of upper respiratory tract disease, including sore throat, rhinorrhea, sinusitis, and ear pain, are usually absent.[1] Cough and tachypnea do not usually develop until day 7 and signal the onset of pulmonary edema and hypoxia, usually requiring mechanical ventilation. This is accompanied, in some patients, by severe myocardial depression, which can progress to sinus bradycardia with subsequent electromechanical dissociation, ventricular tachycardia, or fibrillation. Following the febrile and cardiopulmonary phases of the disease, spontaneous diuresis occurs, resulting in clearance of the pulmonary edema fluid and resolution of fever and shock.

Epidemiological investigation

Based on the US national HPS case registry, the incubation period of Sin Nombre virus is estimated to range from 9 to 33 days, with a median of 14 to 17 days.[2] Other estimates place the outer range of the incubation period at 6 weeks.[3] In the case under discussion, a face-to-face interview was conducted using a standardized national questionnaire to assess potential exposures and risk factors for disease.

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Exposure assessment. At the time of illness, the patient resided in a mobile home on a large rural property in southern BC. Two years earlier, the mobile home had been infested with mice. To address the problem, the

mobile home had been set on concrete blocks, particleboard had been used to close off the space from the ground to the floor of the home, and poison had been placed in this crawl space. No rodents had been seen on the premises since the initial infestation.

In mid-May, approximately six weeks before symptom onset, the patient was hired to clean the top floor of a barn on the property. The floor of this barn had been unused for nearly 10 years following the closure of a chicken farming operation. The chicken feeders were still intact and required removal. Some of these still contained leftover chicken feed and rodent droppings. The floor of the barn was covered with a layer of sawdust and chicken manure so thick that the inward-swinging upper doors of the barn could not be opened to ventilate the area before cleanup. The patient worked to remove debris for approximately 2 hours a day for 3 days. The environment was not wetted and became extremely dusty. As protection during cleanup, the patient wore yellow nylon work gloves (cloth-type, not rubber) and a dust mask. The barn doors were eventually freed and the area ventilated. The property owner also installed a fan on the top floor of the barn in an attempt to dissipate the dust.

In early May, 2 months before symptom onset, the patient had also turned on his water pipes, which involved crawling under the mobile home to reach the tap. Additional activities during the 6-week incubation period included hiking in the forested area of the farm property and four 1-day fishing trips during which he was not exposed to fishing huts or cabins. Besides cleaning out the barn, the patient had worked pruning branches at a nearby orchard for 3 days in early May. Cleanup of the barn, an unventilated area showing clear evidence of rodent infestation, was the most likely source of exposure, considering the degree of exposure and length of the incubation period. While the patient did wear some protective gear, a dust mask offers insufficient protection against the aerosolized droplets known to transmit hantavirus.

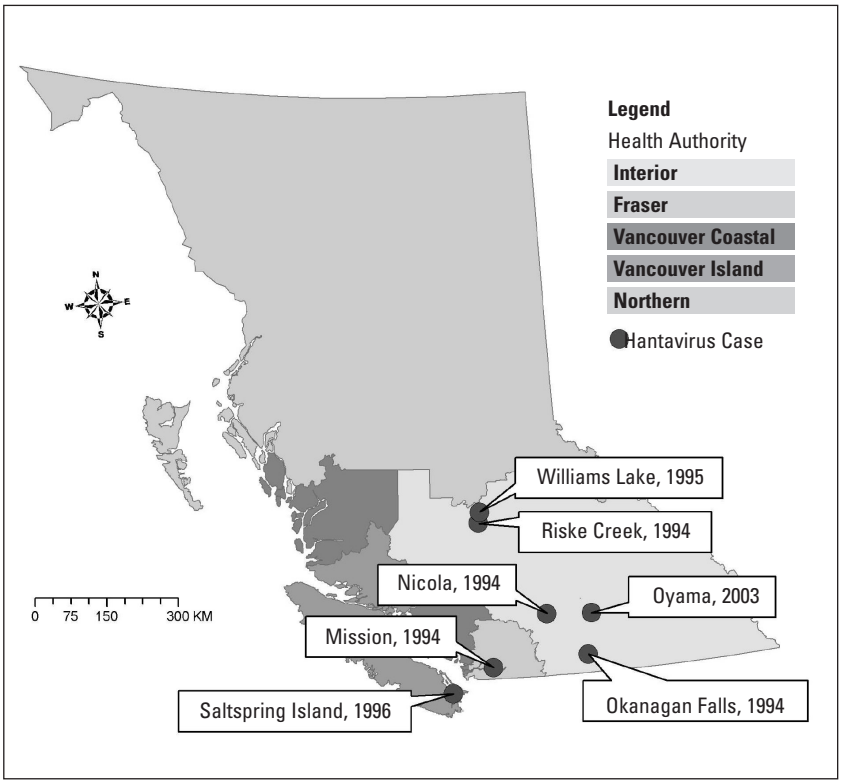

Figure. Geographic distribution of BC cases of hantavirus pulmonary syndrome, 1994–2002.

Rodent trapping. Rodent trapping was carried out over a 2-night period, from 18 September to 20 September 2002, using 82 Sherman traps. Traps were set inside and around the patient's home as well as inside and outside the barn where cleanup activities were performed. Traps were emptied each morning and the rodents caught were speciated and dissected. A total of 29 rodents (23 deer mice, 3 squirrels, 3 rats, and 1 shrew) were trapped. Blood samples were collected from each rodent and tested for the presence of immunoglobulin G antibodies against Sin Nombre virus.

One mouse serum had a titer of 1:400, indicating exposure to Sin Nombre virus. The remaining 28 specimens had titers of <1:100, suggesting that they were not infected with Sin Nombre virus. The positive mouse was trapped from the barnyard on 19 September 2002. No mice were caught from traps placed inside the patient's mobile home.

Environmental assessment. An environmental assessment examined the rodent-proofing around the barn and mobile home and identified activities to reduce the likelihood of future rodent exposure. As cleanup had not been completed, advice was provided

on safe methods to clean up the upper floor of the barn. The owner was advised to wear protective gear during cleanup including disposable coveralls, rubber boots or shoe covers, rubber gloves, protective goggles, and an appropriate mask (negative-pressure respirator with HEPA filter or a powered air purifying respirator with HEPA filters). It was advised that the barn be ventilated for several days before cleanup was to begin and that the heavy layer of sawdust covering the floor be wetted. This was to be accomplished with a fogging or misting machine in a manner that would not disturb infectious particles if present. Potentially infective materials removed from the upper floor of the barn along with personal protective gear used in cleanup were to be burned or deep-buried on site. Baseline serology was requested on all individuals involved in cleanup procedures in the event that infection developed after cleanup.

The patient submitted a claim to the Workers' Compensation Board of British Columbia based on the information obtained during epidemiological investigations and the claim was eventually approved.

Epidemiology of Hantavirus

HPS was first recognized in 1993 during an outbreak in the Four Corners region of the United States, an area bordered by parts of New Mexico, Arizona, Colorado, and Utah. Although hantavirus was then considered an emerging disease, retrospective analyses point to serological evidence of infection in the United States dating back to 1959. In Canada, HPS was first recognized in BC in 1994 as a result of active surveillance; subsequent investigation identified earlier cases, the earliest of which occurred in Alberta in 1989. Between 1989 and 1999, 32 laboratory-confirmed cases were identified in Canada.[4] To date, cases have been restricted to the western provinces of BC, Alberta, Saskatchewan, and Manitoba. Alberta has identified over 60% of reported cases (20/32).[4] This westerly case distribution parallels that observed in the United States; cases tend to occur in less densely populated areas of both countries. Since 1994, BC has reported seven cases of HPS (**Figure**) from largely rural areas of the province, ranging from the Okanagan Valley in the south to Williams Lake in the north. Between 1996 and 2002 no HPS cases were reported in BC. While it is known that changes in climate and rodent population dynamics may contribute to peak or trough years, this complete absence of reported cases is more likely due to inadequate disease recognition and surveillance. This is especially likely given that throughout this time period Alberta continued to report cases. **Table 2** compares BC and Canadian case fatality rates and age and sex distribution for HPS cases reported between 1989 and 1999. Higher case fatality rates in BC may reflect unstable estimates due to small sample size or the large proportion of BC cases occurring in 1994 and 1995, soon after the discovery of the virus in North America when recognition of HPS was often delayed.

Some seasonality seems to exist with HPS infections. Most BC

Table 2. Descriptive epidemiology of hantavirus pulmonary syndrome.

	BC (1994–2002) (n=7)	Canada[4] (1989–1999) (n=32)
Mean age (range)	40 years (31 to 47 years)	39 years (15 to 62 years)
Percentage of males infected	71%	60%
Case fatality rate	57%	38%

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patients experienced onset of illness during the spring, particularly during the month of April (3/7). Canadian data suggest a bimodal seasonal distribution with peaks occurring in the spring and late fall.[4]

Although present in North America, HPS is reported almost three times more often in countries of South and Central America, particularly Brazil, Argentina, and Chile.[5] HPS is not known outside of the Americas. Other viruses of the genus Hantavirus cause a spectrum of illness collectively referred to as hemorrhagic fever with renal syndrome, present in Europe, Asia, and the Middle East. This illness is clinically distinct from HPS.

The viruses causing HPS are primarily transmitted to humans through inhalation of aerosolized rodent urine and feces. Infectious airborne particles may be generated during human activities that disturb contaminated soil, litter, or nesting materials.[5] Another rare but potential route of transmission involves direct inoculation through the bite of an infected mouse, as the virus is known to be present in mouse saliva. Other theoretical routes of infection include ingestion of food contaminated with rodent excreta and exposure of nasal or oral membranes to contaminated hands. Although person-to-person transmission has never been reported in North America, molecular evidence of person-to-person transmission was documented in an HPS outbreak in Argentina in 1996.[6] The species of hantavirus involved in this person-to-person outbreak, Andes virus, has not been associated with human illness in Canada. Animals, ticks, mosquitoes, and other biting arthropods are not known to carry the disease.

Each species of hantavirus is typically associated with a single rodent host species. BC cases of HPS are related to the Sin Nombre virus, whose primary environmental reservoir is the deer mouse *(Peromyscus maniculatus),* commonly found throughout British Columbia. The deer mouse's propensity for entering human habitations and surrounding buildings is an important factor in transmission. Serological and genetic studies conducted on deer mouse populations in Canada have identified infected mice in all provinces except Prince Edward Island and Nova Scotia.[4] The absence of human cases in easterly provinces may be the result of the intensity of surveillance combined with geographic differences in rodent and human behaviors.

While most infections have been associated with known exposure to rodents, not all infected patients have reported contact with rodents, their droppings, or nesting materials. However, higher rodent densities have been demonstrated in and around case homes compared with control homes.[7] In Canada, 34% of HPS cases were likely infected during domestic activities and 25% had farm-related exposures.[4] High-risk domestic activities include cleaning up mouse-infested areas, especially closed or confined rooms without adequate ventilation. This may include activities such as opening up cabins or outbuildings after a period of disuse or cleaning up barns, garages, or storage areas containing machinery or farm equipment. While some HPS infections are clearly a direct result of occupational exposure,[8] serological studies of high-risk occupation groups in areas known to harbor infected rodents have not demonstrated seropositivity.[9] Despite one report of person-to-person nosocomial transmission in Argentina, transmission of hantavirus in hospital settings has not been confirmed. No immunoglobulin G antibodies were detected in 67 health care personnel in Chile exposed to patients with HPS.[10] Another study found no increased risk of exposure to hantavirus, measured by the presence of immunoglobulin G and immunoglobulin M antibodies, in hospital workers exposed to HPS patients versus those with no patient contact.[11]

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Case definition and sample collection

To satisfy the national and BC case definition, a confirmed case of hantavirus requires laboratory confirmation coupled with clinical signs of illness (see **Table 3**). If you suspect a case of HPS, collect 7 mL of blood (clotted in a red-top tube) while the patient is febrile, and before starting any antiviral therapy. Specimens should be submitted for hantavirus antibody testing with relevant clinical and epidemiological information and all specimens must be transported to the BC Centre for Disease Control laboratory according to Transport of Dangerous Goods regulations. A convalescent specimen is required 2 to 4 weeks after collection of the first specimen.

Differential diagnoses

There are many diseases with symptoms similar to hantavirus pulmonary syndrome. The most important part of diagnosis is to consider the possibility of hantavirus infection. Several exposure, clinical, and laboratory features are particularly suggestive of hantavirus. Although failure to elucidate a likely exposure is well described, the vast majority of cases, including all those diagnosed in BC, have had a strong history of exposure to rodents or rodent droppings. Any patient with community-acquired pneumonia, particularly among those who reside in or have visited the BC Interior, should be asked about such exposures. Some exposures are as obvious as that of the patient described here, while others may be more subtle, including simply being in a place where rodents or their droppings might be present.

Typically, the clinical course of HPS is different from most cases of respiratory disease. Patients usually have several days of mild symptoms with few or no respiratory symptoms, and then become febrile and over 1 to 3 days develop acute symptoms and findings suggestive of noncardiogenic pulmonary edema and respiratory insufficiency. Unlike many cases of severe community-acquired pneumonia, the vast majority of cases do not involve underlying diseases. In an attempt to better distinguish between HPS and similar illnesses, a US study followed 135 patients with adequate specimens who were suspected of having hantavirus infection; eventually, 30 patients received a laboratory-confirmed diagnosis of hantavirus while 105 persons did not.[12] Those with hantavirus were significantly more likely to complain of myalgias (85% versus 61%, OR 3.6) throughout their initial illness, of nausea prior to hospitalization, and of both nausea and diarrhea at time of hospitalization.[12] They were significantly less likely to complain of respiratory symptoms at the onset of their illness: cough in 23% versus 72%, dyspnea in 8% versus 60%, and chest pain in 4% versus 30%.[12]

Typical laboratory features include hemoconcentration, a marked left shift on blood smear (usually with a normal total white cell count), a decreased platelet count, and hypocapnia. Radiological studies typically show bilateral diffuse infiltrates more suggestive of acute respiratory distress syndrome than pneumonia.

In the US study referred to above, an alternative diagnosis was made in 55 of the 105 patients without hantavirus, and a vast number of infective and noninfective causes were identified. The 1999 document "Hantavirus in the Americas: Guidelines for Diagnosis, Treatment, Prevention and Control" (www.paho.org/English/HCP/HCT/EER/hantavirus-americas.htm) provides additional information on hantavirus diagnosis and management.

Table 3. National and BC case definition for hantavirus pulmonary syndrome.

A confirmed case requires both laboratory confirmation and clinical signs of illness.

Laboratory confirmation of infection:

- Detection of hantavirus-specific IgM antibodies or a fourfold or greater increase in hantavirus-specific IgG antibody titers
  Or
- Detection of hantavirus-specific ribonucleic acid sequence by polymerase chain reaction in an appropriate clinical specimen
  Or
- Detection of hantavirus antigen by immunohistochemistry

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Clinical signs of illness:

- Febrile illness (temperature >38.3°C oral) requiring supplemental oxygen
  And
- Bilateral diffuse infiltrates (may resemble acute respiratory distress syndrome)
  And
- Illness that develops within 72 hours of hospitalization in a previously healthy person
  Or
- Unexplained illness that results in death, followed by an autopsy examination demonstrating noncardiogenic pulmonary edema without an identifiable specific cause of death

Clinical management

Since there is no curative treatment for HPS, management is supportive. A high index of suspicion is required at the outset so that a correct diagnosis can be made. Since the respiratory symptoms are secondary to an immune-mediated diffuse increase in capillary permeability of the pulmonary microvasculature, efforts to optimize fluid balance to avoid fluid overload are important, as are provision of adequate oxygenation and hemodynamic monitoring. Since HPS is uncommon

among those with respiratory complaints, even in areas where hantavirus is common, most patients will require antimicrobials for possible sepsis. Doxycycline will be needed if the epidemiological history suggests insect or rodent exposure and possible tularemia, plague, erhlichiosis, or rickettsiosis.

Case reporting

Although not likely to affect the course of treatment, laboratory confirmation and reporting of HPS cases are important from a public health standpoint. Regular diagnosis allows surveillance for changes in the epidemiology of the disease (i.e., increased number of cases and increases in atypical clinical presentations such as the case described here). Case reporting also allows monitoring for geographic expansion of the disease to areas of the province previously not known to harbor infected rodents. Ultimately, collection of surveillance information allows an accurate portrayal of disease risk in the province and identifies changes over time. Additionally, by characterizing the risk factors for disease (obtained through case investigations of laboratory-confirmed cases) preventive messages can be targeted to those most at risk.

Competing interests

None declared.

Acknowledgments

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