Hantavirus pulmonary syndrome: Report of four Alberta cases

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IN MAY 1993, THE FIRST CASES OF HANTAVIRUS PULMONARY SYNDROME (HPS) were reported from the Four Corners region of the southwestern United States including New Mexico, Arizona, Colorado and Utah (1). As of February 1, 1995, 103 cases have been reported in 21 states with an overall mortality of 52% (personal communication). The first confirmed cases in Canada were documented in British Columbia between February and June 1994 (2).

In 1994, following media reporting of the American HPS cases, a patient who had been admitted to an Edmonton hospital in 1990 with adult respiratory distress syndrome of unknown etiology wrote to local physicians requesting that his case be reviewed regarding a possible diagnosis of HPS. Stored serum was positive for immunoglobulin (Ig) M antibodies to hantavirus. Within the next three months, two further cases were recognized. Epidemiological investigations led to the discovery of a fourth case. We present a description of the clinical courses of the four Alberta cases.

CASE PRESENTATIONS – CASE ONE

On June 17, 1990 a 42-year-old soldier was admitted to his local hospital with a one-week history of progressive sore throat, rhinorrhea, dry cough, fever, myalgias and dyspnea. In the seven days before becoming unwell, he had been sta-
tioned at a rural camp site, where there had been spraying of biological insecticide. He had also driven a diesel powered tank in which he had been exposed to exhaust fumes. There was no history of recent foreign travel. He later admitted to sharing his tent with deer mice.

Following admission, he was found to be hypoxicemic with bilateral interstitial infiltrates on chest x-ray. He was treated with intravenous erythromycin and, as he developed progressive respiratory failure, was intubated and transferred to an Edmonton tertiary care hospital for intensive care.

On examination he had a temperature of 37.7°C, blood pressure 92/50 mmHg and pulse 88 beats/min. Examination of the chest revealed bibasilar crackles. Fraction of inspired oxygen (FiO2) of 1.0 was required to maintain adequate oxygenation.

Admission laboratory findings are listed in Table 1. Peripheral smear showed neutrophil leukocytosis with increased band forms and a low platelet count.

A provisional diagnosis of atypical pneumonia was made, with a differential diagnosis of acute insecticide poisoning or hypersensitivity pneumonitis.

Following transfer to the intensive care unit (ICU), the patient was ventilated with progressively higher requirements of inspired oxygen and positive end-expiratory pressure. He was treated empirically with intravenous erythromycin, cefuroxime and streptomycin. Cardiac monitoring via a Swan Ganz (Edwards Laboratories, Division of Baxter, California) catheter revealed a pulmonary capillary wedge mean pressure of 25 mmHg, mean arterial pressure of 62 mmHg, cardiac index of 3.28 L/min/m2 and systemic vascular resistance index of 1170 dynes/sec/cm–5/m2. Several pneumothoraces were drained. Bronchoscopy revealed no gross abnormalities.

By day 5 of admission, the patient’s oxygenation had improved. By day 7, chest x-ray also showed marked improvement, and FiO2 had decreased to 0.45. After this initial improvement, oxygenation once again deteriorated and he became hemodynamically unstable requiring inotropic support. Chest x-ray showed bilateral air space consolidation and he was given intravenous piperacillin and tobramycin as empirical treatment for presumed nosocomial pneumonia.

An open lung biopsy on day 12 showed chronic diffuse alveolar injury and hyaline membranes consistent with adult respiratory distress syndrome of probable viral etiology.

Intravenous methylprednisolone was commenced on day 13 at 1 g intravenously daily for three days. By day 14, he had again improved with FiO2 reduced to 0.6. Chest x-ray still showed bilateral air space consolidation.

On day 17, a tracheostomy was performed. On day 22, increasing purulent secretions and an elevated temperature with new alveolar consolidation on chest x-ray prompted a second diagnosis of nosocomial pneumonia. He was treated for Escherichia coli isolated from sputum. His ICU stay was further complicated by the development of a large pulmonary embolus, which required thrombolysis.

He was weaned from the ventilator on day 73, when his main problems included generalized weakness due to loss of muscle mass and mild peripheral neuropathy of undetermined etiology. Pulmonary function tests before discharge on day 81 revealed a restrictive defect with reduced diffusing capacity.

Bronchoscopy specimens from early admission were negative on direct microscopic examination and culture for acid-fast bacilli, fungi and bacteria including legionella. Silver stain for Pneumocystis carinii was negative. Serology for in-

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**TABLE 1**

Admission laboratory values of four Alberta cases

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal range</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute leukocyte count (x10⁹/L)</td>
<td>5.0-10.0</td>
<td>24.8</td>
<td>40.4</td>
<td>5.5</td>
<td>12.4</td>
</tr>
<tr>
<td>Absolute neutrophil count (x10⁹/L)</td>
<td>2.0-7.5</td>
<td>11.41</td>
<td>26.6</td>
<td>NA</td>
<td>9.18</td>
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<tr>
<td>Absolute band count (x10⁹/L)</td>
<td>&lt;0.8</td>
<td>5.95</td>
<td>Nil</td>
<td>2.69</td>
<td>0.12</td>
</tr>
<tr>
<td>Absolute myeloblasts/myelocytes (x10⁹/L)</td>
<td>0</td>
<td>1.24</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Absolute lymphocyte count (x10⁹/L)</td>
<td>1.5-4.0</td>
<td>4.46</td>
<td>7.2</td>
<td>1.26</td>
<td>1.98</td>
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<tr>
<td>Hematocrit</td>
<td>0.38-0.5</td>
<td>0.52</td>
<td>0.47</td>
<td>0.47</td>
<td>0.5</td>
</tr>
<tr>
<td>Platelet count (/mm³)</td>
<td>150,000-440,000</td>
<td>79,000</td>
<td>17,000</td>
<td>89,000</td>
<td>43,000</td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>135-150</td>
<td>124</td>
<td>130</td>
<td>133</td>
<td>139</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>53-106</td>
<td>90</td>
<td>165</td>
<td>76</td>
<td>132</td>
</tr>
<tr>
<td>Prothrombin time INR</td>
<td>0.8-1.2</td>
<td>0.8</td>
<td>1.9</td>
<td>1.0</td>
<td>NA</td>
</tr>
<tr>
<td>Partial thromboplastin time (s)</td>
<td>26-37</td>
<td>33.5</td>
<td>81</td>
<td>33.9</td>
<td>NA</td>
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<td>PaO₂ (mmHg)</td>
<td>75-105</td>
<td>55</td>
<td>130 (FiO₂ 1.0)</td>
<td>44</td>
<td>43.2</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>24-32 (23-28)</td>
<td>34</td>
<td>13</td>
<td>32</td>
<td>25.1</td>
</tr>
<tr>
<td>Aspartate aminotransferase (µmol/L)</td>
<td>10-40</td>
<td>100</td>
<td>174</td>
<td>84</td>
<td>55</td>
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<tr>
<td>Creatinine kinase (µmol/L)</td>
<td>20-130</td>
<td>NA</td>
<td>582</td>
<td>1323</td>
<td>164</td>
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<tr>
<td>Lactate dehydrogenase (µmol/L)</td>
<td>100-225</td>
<td>1493</td>
<td>1295</td>
<td>1061</td>
<td>219</td>
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<tr>
<td>Urine red blood cell count</td>
<td>100-200</td>
<td>NA</td>
<td>1-2</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Urine white blood cell count</td>
<td>5-10</td>
<td>NA</td>
<td>1-2</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Urine protein</td>
<td>1+</td>
<td>NA</td>
<td>2+</td>
<td>24 h &gt;3 g/L</td>
<td></td>
</tr>
</tbody>
</table>

*Room air unless stated; FiO₂ Fraction of inspired oxygen; INR International normalized ratio; NA Not available*
flamiviruses A and B, adenovirus, herpes simplex virus, acute and convalescent tularemia and mycoplasma were all negative. Cytology revealed atypical alveolar cells.

A retrospective diagnosis of HPS was made in 1994 by testing for hantavirus antibodies. Both IgM antibodies from stored serum and IgG antibodies from fresh serum were positive for Sin Nombre virus at titres greater than 1:1600 by enzyme immunoassay (EIA). Lung tissue from the original open lung biopsy was also positive by immunohistochemical staining for hantavirus (personal communication).

**CASE TWO**

A 55-year-old male was transferred to an Edmonton hospital from a rural hospital on October 4, 1994. One week before transfer, he had developed fever, nausea, vomiting, diarrhea and a nonproductive cough. On October 2, he was seen at the emergency department of his local hospital where he was treated with intravenous fluids for a presumed gastroenteritis and discharged home.

The following day he was admitted to the same hospital after presenting with worsening respiratory symptoms. Chest x-ray showed patchy left lower lobe consolidation, and he was started on intravenous penicillin and erythromycin. He had a pulse rate of 104 beats/min, temperature of 38.1°C, blood pressure was 90/60 mmHg and body temperature was 39.9°C, pulse rate was 118 beats/min, respiration rate was 28 breaths/min. Chest examination revealed crepitations at the right lung base.

On examination after transfer, he was diaphoretic with diffuse skin mottling. Pulse rate was 130 beats/min, blood pressure was 90/60 mmHg and body temperature was 38.5°C. He had pinpoint pupils, scleral edema and a palpable left submandibular lymph node. Chest examination revealed coarse, diffuse crackles.

Laboratory findings are shown in Table 1. Peripheral smear showed leukocytosis with atypical lymphocytes. Chest x-ray revealed extensive air space consolidation. HPS was included in the differential diagnosis of atypical pneumonia.

Following admission, the patient was started on cefazidime, erythromycin and pressor agents. Bronchoscopy revealed a diffusely inflamed and bronchospastic airway with no endobronchial lesions. After initially appearing to stabilize, his condition deteriorated rapidly with hypotension unrespon-

tive to intravenous fluids and pentastarch. He received a total of 24 L of fluid during admission.

He developed severe metabolic acidosis (serum lactate rising to 20.4 mmol/L) unresponsive to sodium bicarbonate, coagulopathy with prothrombin time international normalized ratio rising to greater than 7, partial thromboplastin time to 129 s and renal dysfunction with serum creatinine rising to 312 µmol/L. He died 30 h following admission.

Postmortem examination was limited to a liver biopsy due to concerns regarding biosafety. Histology showed mild steatosis and prominent hepatic congestion with mild reactive changes in the hepatocytes.

Bacterial cultures from bronchoscopy specimens grew mixed oropharyngeal flora and small amounts of yeast as well as *Hafneai alvei*. Direct fluorescent antibody testing and cultures for *Chlamydia pneumoniae*, *Legionella pneumophila*, adenovirus, parainfluenza virus and cytomegalovirus were negative. Cytology was negative for malignant cells and *P. carinii*. Cultures for *Mycoplasma pneumoniae* and acid-fast bacilli were also negative. Serology for *M. pneumoniae*, *C. pneumoniae* and *L. pneumophila* were also negative.

The diagnosis of HPS was subsequently confirmed with positive IgM antibodies to Sin Nombre virus by EIA.

**CASE THREE**

On October 19, 1994, a 32-year-old farmer was admitted to a local hospital. Since the spring of that year, he had been intermittently unwell, with several episodes of fever and influenza-like illness. Three days before admission, he developed a fever to 39.9°C, chills, rigors and neck stiffness. He was admitted with a diagnosis of febrile illness of unknown etiology and treated with acetaminophen and cephalaxin. Admission chest x-ray was normal.

Due to persistently elevated temperature and lack of clinical response to empirical antibiotic therapy, he was transferred to an Edmonton hospital on October 21. Chest x-ray before transfer showed increased linear markings in the hilar regions and fluid in the fissures. When seen in the emergency department, he complained of a bifrontal headache, nonproductive cough and dysuria. Past history was noncontributory.

On initial examination after transfer, he was diaphoretic. Temperature was 39.9°C, pulse rate was 118 beats/min, blood pressure was 140/50 mmHg and respiratory rate was 28 breaths/min. Chest examination revealed crepitations at the right lung base.

Laboratory findings on admission are summarized in Table 1. Peripheral smear showed moderate thrombocytopenia with a shift to the left in polymorphs and a few reactive lymphocytes. Chest x-ray showed worsening bilateral interstitial infiltrates.

Further inquiry determined that in the two months before becoming unwell, the patient had had repeated exposure to mice and their nests and droppings during his farm work. HPS was suspected.

He received intravenous erythromycin and cefuroxime and oxygen by mask. During the course of the evening, he be-
came progressively more dyspneic and developed hemoptysis. Arterial blood gases on 10 L of oxygen by mask showed \( \text{PaO}_2 \) of 48 mmHg, \( \text{PaCO}_2 \) of 31 mmHg and oxygen saturation of 86%. He was transferred to the ICU and intubated. In the early hours of the following day, he developed tension pneumothorax, requiring chest tube placement. Bronchoscopy did not show any gross abnormalities. By the following morning, he required an \( \text{FiO}_2 \) of 1.0 and inotropic support.

His oxygen saturation deteriorated to 84% on an \( \text{FiO}_2 \) of 1.0 and he developed worsening pulmonary infiltrates. He received intravenous methylprednisolone 1 g at 14:30 h. Six hours later, he had improved with an oxygen saturation of 91% on an \( \text{FiO}_2 \) of 1.0. He developed lactic acidosis with serum lactate peaking at 3.3 mmol/L, which was treated with intravenous bicarbonate. Intravenous ribavirin was started.

The patient improved progressively over the next few days, with \( \text{FiO}_2 \) decreased to 0.5 by day 4; he was off all inotropes by day 5. White blood cell count peaked at 9.7x10^9/L with a marked left shift and serum creatinine at 145 \( \mu \text{mol/L} \). Antibiotics were discontinued after negative culture results were obtained. He received three doses of methylprednisolone 1 g intravenously daily and a five-day tapering course of intravenous ribavirin.

On day 7, the patient was successfully extubated with chest x-ray showing almost complete resolution of infiltrates. He was discharged from hospital seven days later.

Bronchoscopy results from admission showed negative direct fluorescent antibody testing for legionella, chlamydia, parainfluenza and adenovirus. Direct examination and cultures for bacteria, fungi and mycobacteria were negative as was silver stain for \( P \text{carinii} \). Two sets of blood cultures, serology for human immunodeficiency virus and mycoplasma IgM antibodies were negative as was cytology for malignant cells.

When seen at follow-up six weeks later, the patient was diagnosed with hypertension and was started on antihypertensive agents. He was noted to have a strongly positive family history for hypertension. Pulmonary function tests were normal and complete blood count and serum creatinine had normalized.

A diagnosis of HPS was confirmed two weeks later by positive serum IgM antibodies to Sin Nombre virus with a titre greater than 1:1600 by EIA.

**CASE FOUR**

A 42-year-old farmer with a past history of hypertension was admitted to a community hospital on October 21, 1994 with headache and stiff neck. He had been well until three weeks before admission when he developed increasing shortness of breath, orthopnea and productive cough. He denied fevers or chills. His symptoms settled after a week and he remained well until two days before admission when he developed sudden onset of chills with left chest heaviness and nausea.

He indicated that a neighbour had recently been admitted to an Edmonton hospital with HPS (case 3). The patient had also been repeatedly exposed to mice during farming activities. This included the cleaning of a hot water tank that had become infested with mice and the feeding of cattle in barns where the presence of numerous mice was noted.

On admission, the patient had a temperature of 39.6°C and blood pressure of 230/130 mmHg. He had discontinued antihypertensive medication for eight months for financial reasons. Initial laboratory findings are listed in Table 1. Chest x-ray on October 21 was reported as normal. Repeat chest x-ray on October 24 showed right middle lobe atelectasis. He required oxygen by mask and was treated with oral ciprofloxacin and captopril.

He was transferred to an Edmonton hospital on October 29 for further assessment of renal dysfunction and ‘pneumonitis’. He was admitted with diagnoses of accelerated hypertension and atypical pneumonia.

Past history was noncontributory. He had not smoked for 20 years.

On admission, temperature was 37.0°C, pulse 92 beats/min, blood pressure 138/102 mmHg. Examination of the chest revealed a few diffuse crackles. His liver edge was palpable and he had mild bilateral pedal edema.

Laboratory findings included an absolute leukocyte count of 11.1x10^9/L with 55% neutrophils and 2% bands, hemoglobin 169 g/L and platelet count 193,000/mm^3. Serum creatinine was 113 \( \mu \text{mol/L} \). \( \text{PaO}_2 \) was 51 mmHg with \( \text{PaCO}_2 \) 26 mmHg. Aspartate aminotransferase was 124 \( \mu \text{mol/L} \) and lactate dehydrogenase 657 \( \mu \text{mol/L} \). Urinalysis showed no red blood cells, zero to two white blood cells and trace protein. Chest x-ray on October 29 showed patchy bronchopneumonia in the right lower lobe and a small right pleural effusion. Sputum for routine bacterial culture showed no growth. After transfer, he remained afebrile throughout hospitalization.

He was treated with antihypertensive agents and discharged five days later following resolution of his respiratory symptoms and control of his blood pressure. Before discharge, oxygen saturation on room air was 94%.

Based on the patient’s clinical condition following transfer, HPS was not suspected and was diagnosed retrospectively after epidemiological investigations. Stored serum was reactive for IgM antibodies to Sin Nombre virus by EIA.

**DISCUSSION**

Before the initial reports of HPS in the United States, all known hantavirus infections were collectively called hemorrhagic fever with renal syndrome (3); this term includes the syndromes referred to as nephropathica epidemica in Scandinavia and epidemic hemorrhagic fever in Asia. These syndromes consist of predominantly renal and hemorrhagic complications, but a few cases have been described with co-existing or primarily pulmonary pathology (4). Since the recognition of HPS, a few retrospective cases of hemorrhagic fever with renal syndrome have been identified in the mainland United States (5). HPS has been characterized by a predominance of respiratory symptoms (6). The typical picture is one of rapidly developing noncardiogenic pulmonary edema. Recent reviews and case reports have summarized the clinical and epidemiological findings (7-9).

The etiological agent of HPS in the southwest United States
A case control study carried out by the Centers for Disease Control and Prevention (CDC Atlanta, Georgia) suggested that the combination of four symptoms (myalgias, dizziness, cough, nausea/vomiting) and three laboratory findings (hematocrit, platelet count and bicarbonate level) applied to patients with fever, tachypnea and nonlobar radiographic infiltrates accurately differentiated patients with HPS from control subjects. These findings require further validation. No rapid diagnostic test is available.

Normal or elevated systemic vascular resistance and normal or reduced cardiac output have been reported as typified by case 1. These findings are in contrast to the changes seen with bacterial sepsis. Chest x-ray findings include significant interstitial edema with progression to airspace disease within 48 h in the majority of patients. Pleural effusions are also commonly seen.

Subclinical and mild disease is said to be uncommon. In more than 500 residents of the Four Corners area who were asymptomatic or had mild illness, specific hantavirus antibody prevalence was 1% (22). Case 4 experienced a milder form of disease and his presentation was complicated by coexisting accelerated hypertension. With the non-specificity of initial symptoms and physical signs, the diagnosis may be difficult with only a history of exposure to deer mice or mouse droppings to hint at the diagnosis.

Once HPS is recognized, optimal management consists of prompt control of hypoxia, which can deteriorate rapidly, the early use of inotropic agents and avoidance of excessive fluid administration (6,8). Ribavirin is an antiviral drug that inhibits the replication of several hantaviruses. Prospective double-blind clinical trials of ribavirin in China in patients with hemorrhagic fever with renal syndrome demonstrated a sevenfold reduction in mortality among treated patients (23). The CDC carried out an open label trial of intravenous ribavirin in patients with suspected HPS. A review of the results did not demonstrate a clear benefit and the trial was terminated (14). The CDC is no longer advocating its use but randomized controlled trials have yet to be performed.

Although hypertension has been associated with other hantaviruses (24), it has not been reported as a complication of HPS. The development of hypertension in case 3 may have been associated with this disease but his family history of hypertension makes essential hypertension more likely.

Various activities have resulted in HPS infection, including planting or harvesting field crop, occupying previously vacant barns or outbuildings, cleaning barns or other outbuildings, disturbing rodent-infested areas while hiking or camping, inhabiting dwellings with indoor rodent populations and residing in or visiting areas with increased rodent density (25,26). All our cases had documented exposure to deer mice.

Finally, given the significant presence of the reservoir host for HPS in Canada, it is likely that more cases will be identified. As eradication of the primary host is neither feasible nor advisable (25), it is important to reduce human contact with potentially infected rodents. Interim guidelines to reduce the risk of infection have been published by the CDC (25) and adapted by Canadian authorities (16).
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REFERENCES