

Hantavirus cardiopulmonary syndrome: a report of two cases

Síndrome cardiopulmonar por hantavírus: relato de dois casos

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ABSTRACT

Infection with hantavirus, from the family *Bunyaviridae*, causes hantavirus cardiopulmonary syndrome (HCPS) in the Americas. This highly lethal anthroozoonosis afflicts preferentially individuals in rural areas and is transmitted by aerosol of excreta from infected wild rodents. The aim of this study is to report the almost simultaneous occurrence of two cases of HCPS in the municipality of Jataí, state of Goiás, Brazil.

Key words: hantavirus; hantavirus infections; hantavirus pulmonary syndrome.

INTRODUCTION

The hantavirus cardiopulmonary syndrome (HCPS) was first reported in the United States, during an outbreak among Navajo Indians in 1993^(1, 3). In the same period, Brazil also confirmed cases of hantavirus infection in the municipality of Juitituba, state of São Paulo. Since then, HCPS has been described from Canada to Patagonia. It is classified as an emergent disease and a serious public health problem^(4-6, 11, 16).

In Brazil, hantaviruses Juitituba, Araraquara, Laguna Negra-like, Castelo dos Sonhos and Anajatuba have been described as causative agents of HCPS^(5, 9). Wild rodents host the virus, and each hantavirus strain is associate to a specific type of rodent of the *Sigmodontinae*^(1, 6) subfamily. From 1993 to 2012, HCPS was reported in different regions of Brazil, with the greatest number of cases in the South (565), followed by regions Southeast (456), Central-West (395), North (88) and Northeast (14). A total of 1,573 confirmed cases, showing lethality of 40%⁽²⁾.

As most viroses exhibit inespecific symptoms, the definite diagnosis must be established by differential laboratory tests, such as the serologic immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA), or the molecular methods^(7-9, 15). However, the medical team may reach a diagnosis suggestive of hantavirus infection based on clinical data and epidemiological background, taking into account the rapid evolution of the disease, whose treatment must be immediate. The objective of this work is to report the occurrence of two cases of HCPS in Jataí, in order to discuss the potential seriousness of the disease, underlining the importance of an early differential diagnosis.

CASE 1

A 29-year-old married male pig farmer of mixed race, resident in a rural area of Jataí (but born in Montes Altos, state of Maranhão), who had a smoking history, and was seemingly healthy before admission, went into the emergency ward of

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Centro Médico de Saúde Serafim de Carvalho (CMSSC) at 12h of August 31, 2012 with a 5-day history of symptoms. He presented sweating, cough, malaise, blood pressure of 80 × 60 mmHg and axillary temperature of 38.8°C. He also reported chest pain and adynamia. Medication was immediately administered and a chest radiograph was obtained. Based on his clinical picture of serious bilateral pneumonia with septic shock, the diagnostic hypotheses were dengue fever, leptospirosis, hantavirus infection, or influenza A subtype H1N1.

Just after admission, the patient presented intense dyspnea, saturation of peripheral oxygen (SpO₂) of 74% (after 20 minutes, SpO₂ of 82%) and heart rate of 140 beats per minute (bpm). He was put on an oxygen mask with reservoir bag delivering oxygen at 10 l/min, and treated with Rocefin®, Claritromicina® and Tamiflu®. The required laboratory tests and their results are

shown in the **Table**, where it is possible to observe that practically all analysed parameters differed from reference values. The patient was then referred to the intensive care unit (ICU).

Upon admission to the ICU, the patient's clinical state worsened, with intense dyspnea, sweating, cough that produced large amounts of yellow secretion, and lowered level of consciousness. SpO₂ of 73%. Before intubation, a reservoir mask was put on the patient, who was sedated with Dormonid®, alongside 2 ml of Fentanil®. Chest radiograph showed bilateral diffuse pulmonary infiltrate with ill-defined opacity in the upper third of the lung (image not shown). At 20h45, the patient's condition was even worse and he suffered a cardiac arrest. Cardiopulmonary resuscitation was performed with chest compression and intravenous drug administration. The patient died at 21h.

TABLE – Patients' laboratory data required at hospital admission

Laboratory tests	Case 1	Case 2	Reference ranges
Hematocrit	57%	40%	41%-51%
Platelet count	58,000	286,000	143 × 10 ³ /mm ³ to 450 × 10 ³ /mm ³
Hemoglobin	19.3	13.8	14 to 18 g/dl
White blood cell count	15,300	5,700	4.5 × 10 ³ /mm ³ to 10 × 10 ³ /mm ³
Neutrophil count	11,934	3,021	2,295/mm ³ to 6,000/mm ³
aPTT	39.15	-	22.7 to 31.8 s
PT	15.80	-	10 to 14 s
PT	1.38	-	1.00 to 1.08 INR
γ-GT	136	-	5 to 38 U/l
Na	129	-	136 to 145 mmol/l
K	3.2	-	3.5 to 5.1 mmol/l
CK-MB	40.2	-	0 to 25 U/l
AST	162	124	11 to 39 U/l
ALT	88	80	11 to 45 U/l
pH	7.09	-	7.32 to 7.42
PO ₂	47.7	-	80 to 100 mmHg
PCO ₂	46.2	-	36 to 46 mmHg
Bicarbonate	13.8	-	22 to 26 mmol/l
O ₂ SAT	68.9	-	> 90%
Creatinine	1.42	0.63	0.40 to 1.30 mg/dl
Urea	26	33	15 to 42 mg/dl
Creatine phosphokinase	711	-	26 to 189 U/l
Blood culture	-	Absence of anaerobic Mφ	Negative growth of Mφ
Hantavirus serology	IgM positive	IgM positive	Negative
Dengue serology	IgM Negative	IgM Negative	Negative
Leptospirosis serology	-	IgM Negative	Negative
Yellow fever serology	IgM Negative	-	Negative
HIV serology	Negative	-	Negative

Bold type indicates results outside reference ranges.

aPTT: activated partial thromboplastin time; PT: protrombin time; PT (INR): protrombin time (international normalized ratio); γ-GT: gamma-glutamyltransferase; CK-MB: creatine kinase MB-fraction; AST: aspartate transaminase; ALT: alanine transaminase; O₂SAT: oxygen saturation; Mφ: microorganism; IgM: Immunoglobulin M; HIV: human immunodeficiency virus.

CASE 2

A 32-year-old married male pig farmer of mixed race, ex-smoker, resident in the rural area of Jataí (but born in Pancas, state of Espírito Santo), searched medical care at CMSSC on September 25, 2012, three days after the onset of symptoms (fever, myalgia, arthralgia, headache, chest pain, cough, hypoxia, and acute respiratory failure) (Figures 1 to 4). The patient came from the same place as Case 1 patient, and was involved in several risk activities associated with hantavirus infection: deforestation; wood chopping; cleaning sheds, warehouses, store rooms; among others. He also reported direct or indirect contact with rodents. Several laboratory tests were carried out (Table) and treatment with Tamiflu®, Amplacilina® and Rocefin® was administered.



FIGURE 1 – Chest radiographic image of Case 2 patient at hospital admission



FIGURE 2 – Chest radiograph of Case 2 patient on day 3. A slight pulmonary edema with bilateral alveolar-interstitial infiltrate is observed



FIGURE 3 – Chest radiograph of Case 2 patient on day 4. The image reveals a diffuse pulmonary edema with dense alveolar-interstitial infiltrate

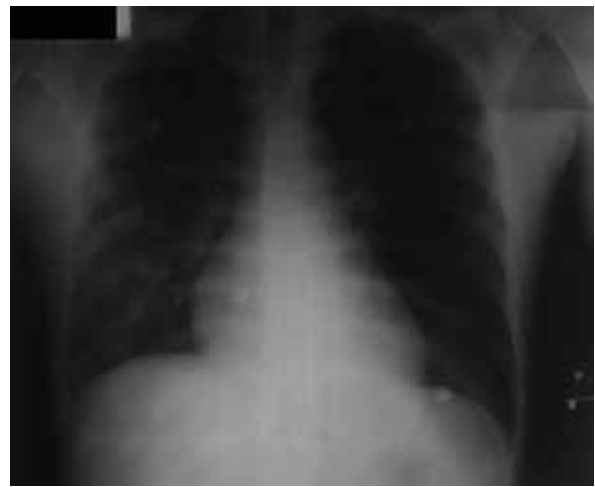


FIGURE 4 – Chest radiographic image of Case 2 patient on day 6, showing regression of the bilateral alveolar-interstitial infiltrate

Due to the worsening of the patient's clinical status, evolving to severe dyspnea, fever, chest pain, besides alterations in pulse, oxygenation, blood pressure and gasometry, he was referred to UCI, and mechanically ventilated. After a 9-day hospital stay, clinical improvement took place and laboratory results returned to normal ranges, as the patient entered the convalescent phase.

DISCUSSION

The patients in this study presented clinical pictures similar to those of acute respiratory distress syndrome (ARDS). Supportive treatment (like respiratory supports, the use of antibacterials and Tamiflu®) is the absolute indication for ARDS of any suspected etiology⁽¹⁴⁾. Thus, given the possible severe evolution, immediate intervention is required: one should not wait for laboratory results to act.

Because HCPS presents as a clinical condition similar to ARDS^(18, 20, 21), Ketai *et al.*⁽¹²⁾ sought to determine if radiographs of HCPS and ARDS patients could distinguish between these two clinical conditions. Their hypothesis was confirmed, however, accuracy is increased by the use of serial radiographs and more highly trained professionals. Besides, according to chest X-rays, interstitial pulmonary edema was observed in most HCPS patients, being a less common finding in ARDS⁽¹¹⁾.

The suspicion of HCPS involves several clinical, epidemiological and laboratory parameters. The non-specific symptomatology, or prodromal phase, culminates with the onset of fever, intense headache, myalgia and abdominal pain⁽⁴⁻⁶⁾; whereas in the cardiopulmonary phase we can observe dry cough, tachycardia, tachydyspnea, and hypoxemia. As a consequence, a differential diagnosis is necessary to distinguish hantavirus infection from other diseases, such as leptospirosis, influenza, dengue fever, yellow fever or several pneumonias⁽⁴⁻⁷⁾. One of the methods usually employed is chest radiograph, which has been of help in the diagnostic suspicion of hantavirus disease and in the prognosis of patients with HCPS^(10-13, 17, 18, 20, 21). However, confirmation is obtained principally by means of IgM serology^(8, 21).

Figueiredo *et al.*⁽⁵⁾ have analysed the laboratory aspects of confirmed cases of HCPS, in which they verified high hematocrit levels (> 55%), leukocytosis (> 15,000/mm³) and thrombocytopenia in most of the patients. On the other hand, in some individuals these altered laboratory parameters did not correlate well, as in Case 2, which presented hematocrit of 40% and low platelet count of 83,000/mm³, verified days after admission.

The serological assay ELISA for hantavirus detects the presence of specific antibodies in samples. In Brazil, the antigen used in the ELISA is the N recombinant protein of Araraquara virus. This method, as well as the molecular methods, presents high specificity and sensibility^(8, 15), but not all laboratories have support or demand to employ it, so suspicious samples are referred to reference laboratories⁽¹⁹⁾. Notifiable diseases, such as hantavirus disease, need a quality diagnosis reference system, with samples being referred to central laboratories of Fundação Oswaldo Cruz (FIOCRUZ), Instituto Evandro Chagas (IEC) and Instituto Adolfo Lutz (IAL). In spite of the adequate procedures involving the diagnosis of acute hantavirus infection, the results obtained by

these centers are jeopardized from failure to establish an early diagnosis still at hospital, what could improve patients' survival.

Pathogenesis of HCPS involves hiperresponsiveness of the immune system. Hantaviruses have been shown to have tropism for certain endothelial cells of pulmonary capillaries, through β_3 integrin receptors, also present on platelets. By the viral infection of these cells, there are stimuli to the secretion of chemokines. These attract CD8⁺ lymphocytes that, when activated, stimulate the secretion of tumor necrosis factor (TNF) and interleucin-1 (IL-1), which have systemic action, activating endothelial cells and inducing macrophages to secrete more chemokines. In the of cytokine cycle, large amounts of TNF are produced, resulting in shock^(6, 10, 13).

Gavrilovskaya *et al.*⁽⁹⁾ have recently evaluated the role of cytokine vascular endothelial growth factor (VEGF) in the pathogenesis of HCPS during the acute phase. Their observations confirm that hantavirus-infected endothelial cells are hiperresponsive to the effects of VEGF, considering that inhibition of β_3 integrin, which normally restricts VEGF-directed capillary permeability, is blocked by viral infection. Besides, VEGF is induced in hypoxic conditions, disrupting endothelial adherens junctions, increasing vascular permeability and, consequently, causing pulmonary edema.

In this study, the immediate search for medical help, associated to the clinical and epidemiological data of early suspicion of hantavirus infection in the second patient probably contributed to his convalescent outcome. We highlight the necessity of supplying the population with further information on the adoption of prophylactic measures against hantavirus disease. We also draw attention to the importance of an early diagnosis, what will contribute to the adequate clinical management of HCPS.

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RESUMO

A infecção por hantavírus, família Bunyaviridae, provoca a síndrome cardiopulmonar por hantavírus (SCPH) nos países da América. Ela é uma antroponose, de elevada letalidade, que tem acometido preferencialmente indivíduos em contato com o meio rural, sendo transmitida por aerossóis a partir das excretas dos roedores silvestres infectados. O objetivo deste estudo foi relatar a ocorrência, quase que simultânea, de dois casos de SCPH ocorridos no município de Jataí, Estado de Goiás, Brasil.

Unitermos: hantavírus; infecções por hantavírus; síndrome pulmonar por hantavírus.

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