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Case Report

Hantavirus infection mimicking leptospirosis: how long are we going to rely on clinical suspicion?

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Abstract

Hantavirus infections and leptospirosis can have similar clinical and epidemiological features. We present here a case study of a young farmer with fever during the post-flood leptospirosis outbreak in Anuradhapura, Sri Lanka, in 2011. He presented with a classical clinical picture of leptospirosis and was managed and notified as a case of leptospirosis. Retrospective analysis of a stored serum sample confirmed acute hantavirus infection. Diagnosis of newly identified or emerging infectious diseases such as hantavirus infection is challenging due to the lack of diagnostic facilities in developing countries. This case highlights the need for improving diagnostic facilities, educating medical staff, and conducting population-based prospective studies on hantavirus infections in Sri Lanka.

Key words: Hantavirus; Sri Lanka; acute undifferentiated fever; leptospirosis.

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Introduction

Hantaviruses are RNA viruses of the genus *Hantavirus* of the family *Bunyaviridae*. Humans acquire the disease by inhaling aerosols contaminated with urine, feces, and saliva of chronically infected rodents. Hantavirus has been reported in insectivorous families *Soricidae* and *Talpidae* [1,2] and also in bats of the families *Vespertilionidae* [3] and *Nycteridae* [4], but is still not associated with human disease.

These viruses cause two classes of severe acute febrile illnesses: hemorrhagic fever with renal syndrome and hantavirus cardiopulmonary syndrome. However, most hantavirus infections do not result in severe complications [5]. Hantavirus infections and leptospirosis often have similar clinical and epidemiological features [6]. The number of leptospirosis cases reported in Sri Lanka has significantly increased over the last decade due to improved clinical awareness and dedication of laboratory resources, though the majority of cases are

only reported based on clinical suspicion because timely diagnostics are not readily available [7]. Nevertheless, hantavirus infection as a cause of acute febrile illness is not routinely considered in Sri Lanka.

Hantavirus infection in Sri Lanka was first described by Vitarana *et al.* in 1988, whose study revealed evidence of recent hantavirus infection among 4 patients out of 248 tested [8]. All 4 had a leptospirosis-like illness and were from different parts of Sri Lanka. Furthermore, this study showed the presence of anti-hantaviral antibodies among rats (*Rattus nervogicus*) caught in Colombo harbor. Thereafter, the Medical Research Institute (MRI) of Sri Lanka detected few cases, until 1994, of hantavirus infections annually in blood samples sent for further investigation from different parts of the country. In 1991, MRI conducted a seroprevalence study in the country, excluding northern and eastern provinces. It showed human exposure in all districts other than Colombo [9]. Seventeen years later, during the 2008

outbreak of leptospirosis, Gamage *et al.* reported eight cases of previous exposure to hantavirus infection among suspected cases of leptospirosis from Peradeniya hospital, demonstrating the existence of this disease in Sri Lanka [10]. However, acute hantavirus infection has not been reported after 1994, and further studies of this illness have not been conducted in Sri Lanka in the past two decades. Furthermore, hantavirus infection, a leptospirosis mimic, is not routinely considered as a cause of acute febrile illness in Sri Lanka.

Case Report

A 31-year-old man was admitted to the Teaching Hospital Anuradhapura (THA) with a history of fever of three days’ duration in March 2011. On admission, he had arthralgia, myalgia, dyspeptic symptoms, and felt faintish. Urine output was satisfactory and there were no bleeding manifestations. He had worked in a paddy field. On admission, the patient’s temperature was 39.5°C, he looked ill, and had conjunctival injections. His heart rate was 88 beats per minute and blood pressure was 120/80 mmHg. Examination of the respiratory system and abdomen was unremarkable except for mild epigastric tenderness. A clinical diagnosis of leptospirosis was made, given the exposure history, and he was given IV C penicillin 2 million U every six hours and oral doxycycline 100 mg twice daily for five days.

With the availability of investigation results (Table 1), dengue hemorrhagic fever (DHF) was also considered as one of the differential diagnoses, and he was started on fluid management according to the national dengue management guidelines. However, penicillin and doxycycline were continued, as leptospirosis and typhus, too, could give rise to a similar situation.

Throughout the hospital stay, the patient remained hemodynamically stable. Auscultation of the lungs was normal and he did not develop hepatosplenomegaly. Urine output was approximately 1,000 mL per day. He became afebrile after seven days of symptoms.

On admission, the white cell count was normal, with neutrophil predominance (83.3%). However, neutrophil percentage gradually decreased, whereas lymphocyte percentage gradually increased over the next five days. The lowest platelet count ($54 \times 10^3/\mu\text{L}$) was recorded on day six of fever and increased thereafter. Liver transaminases remained normal except for mild elevation on admission. He was discharged home seven days after admission with oral doxycycline for a further five days.

An etiological diagnosis was not reached during the hospitalization because of lack of specific diagnostic resources. However, retrospective testing was done for leptospirosis, DHF, typhus fever, and hanta fever. As part of a study investigating the fever outbreak in Anuradhapura district following floods in the early part of 2011, these investigations were later done at the University of California San Diego School of Medicine. For leptospirosis, previously published nested PCR protocol [7] and a highly sensitive quantitative real-time PCR assay [8] was used. Dengue and hantavirus IgM/IGG was tested using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (IBL International, Hamburg, Germany). Neither leptospirosis antibodies nor DNA were detected in serum or whole blood, and dengue antibody was negative for this patient. The patient did have very high level of hantavirus IgM (Puumala) antibodies, consistent with acute infection.

Table 1. Laboratory findings on admission and during the hospital stay

| Investigation | Date | | | | | |
|-------------------------------------|-------|-------|-------|-------|-------|-------|
| | 25/03 | 26/03 | 27/03 | 28/03 | 29/03 | 30/03 |
| White cell count $10^3/\mu\text{L}$ | 5.9 | 8.2 | 8 | 8.1 | 7.2 | 6.5 |
| Neutrophils % | 83.3 | 69.5 | 68.4 | 59 | 53.5 | 51.7 |
| Lymphocytes % | 9.2 | 16.7 | 19.4 | 27 | 32 | 31.9 |
| Monocytes % | 4.0 | 7.2 | 7 | 9.1 | 8.7 | 6.3 |
| Haemoglobin g/dL | 14.1 | 14.8 | 15.1 | 14.7 | 15 | 15.9 |
| Haematocrit % | 42.8 | 46.4 | 47.6 | 46.3 | 46.8 | 49.7 |
| Platelet count $10^3/\mu\text{L}$ | 63 | 63 | 54 | 62 | 70 | 111 |
| SGOT IU/L(4-42) | 57 | | | | 45 | 40 |
| SGPT IU/L(4-27) | 36 | | | | 30 | 33 |
| Blood urea mg/dL(15-40) | 30 | | | | 18 | |
| Serum Na+ | | | | | 140 | |
| Serum K+ | | | | | 4.7 | |

Consent

Informed written consent was obtained from the patient as a part of a post-flood leptospirosis outbreak investigation. The patient gave permission to publish his details as a case report. Ethical approval for the study was obtained from the Ethics Review Committee, Faculty of Medicine and Allied Sciences, Rajarata University of Sri Lanka.

Discussion

Leptospirosis and hantavirus infections have similar clinical and epidemiological features. Any mammal or rodent could harbor *Leptospira*; therefore, *Leptospira* and hantavirus have common rodent reservoirs. In addition, DHF and typhus fever also demonstrate similar clinical features to leptospirosis. The majority of these diseases are being reported based solely on clinical suspicion because clinically relevant diagnostic facilities in Sri Lanka are not available. This can lead to a wrong diagnosis being reported, as in this case, with negative consequences for public health actions. Furthermore, there may have been severe hantavirus infections with severe complications which have been managed and reported as other febrile illnesses. As an example, during the 2008 outbreak of leptospirosis in Sri Lanka, Agampodi *et al.* confirmed less than 50% of suspected cases after testing those samples using an array of investigations [11]. Furthermore, they showed that only around 20%–30% of suspected cases were confirmed in some areas, and they hypothesized about a concurrent outbreak of a similar infection. During that particular outbreak, a number of cases had severe respiratory manifestations; those deaths were also attributed to leptospirosis, even though confirmatory tests were not done.

One of the limitations of this work is that we did not conduct the gold standard tests such as RT-PCR or the plaque reduction neutralization test (PRNT) that are recommended for confirmation of acute hantavirus infection.

Conclusions

In a tropical country like Sri Lanka, clinical presentations of febrile illnesses are mostly non-specific and classic; textbook manifestations are found in only a small percentage of cases. For disease burden estimates, control and prevention public health programs, and clinical management, the improvement of laboratory facilities to enable clinicians to provide timely diagnoses of hantavirus infection, leptospirosis, and their mimics is essential. Establishment of such

diagnostic infrastructure should be coupled with education and outreach to enhance awareness among medical practitioners of these infections with overlapping clinical and epidemiological features. We recommend prospective studies to identify the burden of hantavirus disease in Sri Lanka, with a specific focus on leptospirosis-like presentations.

Authors' contributions

SP collected the data and prepared samples, NJD designed the study interpreted the clinical data and wrote the first draft of the manuscript, SBA helped in study design, carried out all laboratory procedures, analyzed and interpreted the patient data, and helped in manuscript preparation. JMV was the major contributor in writing the manuscript. All authors read and approved the final manuscript.

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