Case Report

# A Nonfatal Case of Dobrava Hantavirus Hemorrhagic Fever with Renal Syndrome Combined with Hantavirus Cardiopulmonary Syndrome

**Shemsedin Dreshaj, Lindita Ajazaj, Nderim Hasani, Bahrije Halili, Albina Ponosheci, Xhevat Jakupi[1]**

Prishtina University Clinical Center Faculty of Medicine, University of Prishtina, Infectious Diseases Clinic, [1]Institute of Public Health, Prishtina, Kosovo

## Abstract

Among hantaviruses (HTNV), 22 are known as pathogenic for humans. HTNV can cause two clinical entities: hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome or hantavirus cardiopulmonary syndrome (HCPS). In most countries of Eastern Europe as well as in Kosovo, HTNV infection is presented mainly as HFRS. Here, we report a 20-year-old man with HFRS and HCPS caused by Dobrava hantavirus strain, successfully treated in Intensive Care Unit of Infectious Diseases Clinic, University Clinical Center of Kosovo. In HFRS endemic areas, patients with acute respiratory distress syndrome need to be evaluated for Dobrava hantavirus strain as a possible causative agent.

**Keywords:** Dobrava hantavirus, hemorrhagic fever with renal syndrome, hantavirus cardiopulmonary syndrome, Kosovo

## Introduction

Based on the epidemiological findings and clinical characteristics, hantaviruses (HTNV) (Bunyaviridae family) can cause hemorrhagic fever with renal syndrome (HFRS) or hantavirus cardiopulmonary syndrome (HCPS) (respectively hantavirus pulmonary syndrome [HPS]).[1,2] HCPS was first recognized in 1993 in the Four Corners region of the southwestern United States.[3] Based on the available data, HCPS-causing viruses show a rapid disease course with serious pulmonary symptoms[1,4-8] with a 40% case-fatality rate (CFR).[1,2] There is growing evidence that HFRS and HCPS partly overlap.[6,9] In patients with HFRS, respiratory symptoms are frequent and are linked to Puumala virus (PUUV) infection.[2,6,10] In areas where both PUUV and Dobrava virus (DOBV) circulate, more than half of HFRS patients present with abnormal pulmonary X-ray findings and transient EKG changes, mostly in the oliguric phase.[11] In Kosovo, each year, we treat several sporadic cases of HFRS, and every fourth or 5th year, epidemic features present with different clinical forms of the HTNV disease.[12] Over 30 years, we have evidenced only one confirmed case that developed severe HCPS. Here, we report a case of a 20 yearold male with HFRS and HCPS caused by Dobrava-Belgrade hantavirus, successfully treated in the Department of Infectious Diseases.

Access this article online

Quick Response Code:

Website: www.jgid.org

DOI: 10.4103/jgid.jgid_12_17

## Case Report

At the end of April 2014, a previously healthy 20 yearold male living in a rural area (near Ferizaj, Kosovo) developed a febrile illness for 8 days before admission (the patient consent form has been obtained) Two days before hospitalization (day 6 postsymptom onset [PSO]), he developed diarrhea with dark stools, dark urine, conjunctival injection (cherry eyes), and severe malaise [Figure 1a]. Laboratory tests on admission day (day 8 PSO) showed anemia with thrombocytopenia, elevated blood urea nitrogen (BUN) and creatinine, high C-reactive protein, high procalcitonin, elevated aspartate aminotransferase, alanine aminotransferase, and creatine kinase (CK). Initial chest X-ray was unremarkable. On hospital

**Address for correspondence:** Prof. Shemsedin Dreshaj, Prishtina University Clinical Center, Faculty of Medicine, University of Prishtina, Infectious Diseases Clinic, Prishtina, Kosovo.
E-mail: shemsedin.dreshaj@uni-pr.edu



**How to cite this article:** Dreshaj S, Ajazaj L, Hasani N, Halili B, Ponosheci A, Jakupi X. A Nonfatal Case of Dobrava Hantavirus Hemorrhagic Fever with Renal Syndrome Combined with Hantavirus Cardiopulmonary Syndrome. J Global Infect Dis 2018;10:22-5.

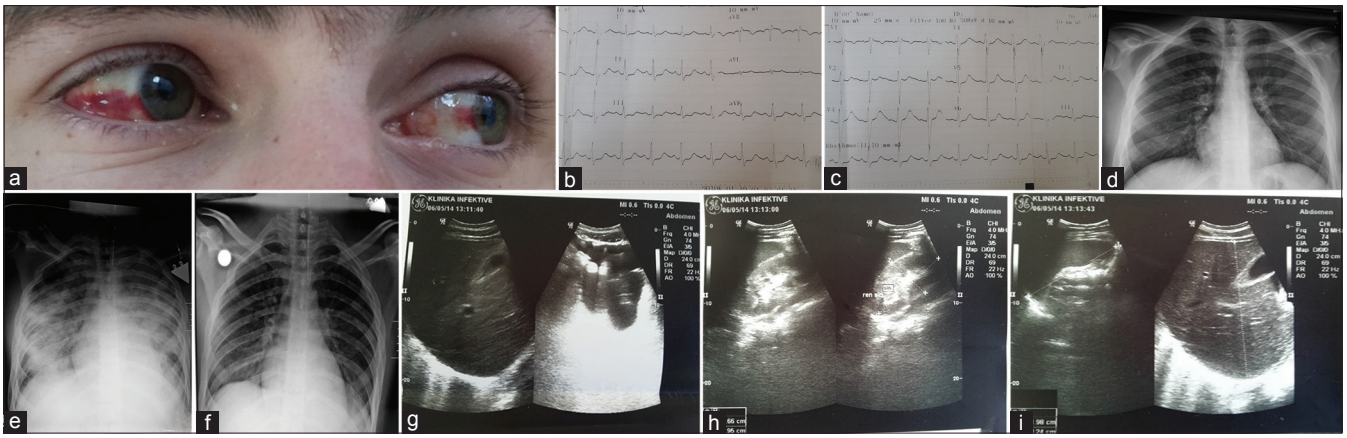


**Figure 1:** Clinical and radiological findings in the reported case: (a) Cherry eyes; (b and c) electrocardiogram (present 2 mm ST depression in $D_2$, $D_3$, and a VF on day of hospitalization in Intensive Care Unit [POS 11]). (d) Radiography on hospitalization (POS 8) (normal chest). (e) Radiography (POS 11) (bilateral lung damage). (f) Radiography (POS 17) (four days after intubation present complete lung resolution). (g-i) Ultrasonography presenting enlarged liver (182 mm), enlarged spleen, acute renal inflammation, and abdominal-free liquid

day 2 (day 9 PSO), BUN and creatinine increased rapidly, and the patient became anuric, with hypertension and bradycardia. Renal replacement therapy was initiated and continued until day 52 PSO. On hospital day 4 (day 11 PSO), the disease was complicated with agitation and high fever, and the patient became tachy dyspneic and developed acute severe respiratory distress. Chest X-ray showed extensive bilateral infiltrates and enlarged heart shadow with rapid improvement by day 15 PSO [Figure 1d-f]. EKG (day 11 PSO) showed sinus rhythm 114 b/min, with 2 mm ST depression on lead II, III, and aVF suggesting acute coronaritis [Figure 1b and c]. Abdominal ultrasound presented enlarged liver (182 mm), acute renal inflammation, and abdominal-free liquid [Figure 1g-i]. In addition, laboratory tests presented acute kidney injury and acute lung injury [Table 1]. The patient was intubated and mechanically ventilated; intravenous ampicillin, ribavirin, and crystalloid infusions were commenced immediately on arrival to the Intensive Care Unit. The critical respiratory phase lasted 7 days, contrary to the renal phase that lasted 15 days, after which urine output increased entering polyuric phase. Ventilation support was weaned off after 11 days. On day 25 PSO, the patient was transferred to the Infectious Disease department, and after 44 hospital days (day 52 PSO), the patient was discharged in good clinical condition; still with mild anemia, elevated BUN, and creatinine, but without the need for dialysis. After a 2-year follow-up, the patient still had mild anemia and findings of CK disease.

Initial diagnosis of HFRS was made on the day of hospitalization by rapid antihantavirus test (immunochromatography SD, INCCE (IgG and IgM positive for entire Hantan viruses group, Standard Diagnostics, Republic of Korea).

Next day, serum sample has been tested for the presence of antibodies against Hantavirus Dobrava/Hantaan IgG/IgM, with ELISA following the manufacturer's instructions (Progene, Germany), at the National Institute of Public Health of Kosovo, Prishtina. Specific IgM and IgG antibodies against Dobrava/Hantaan virus were detected. The Line Hanta plus IgG, Ig*M in vitro* test for detection of IgM, and/or IgG antibodies against the Hantavirus serotypes Puumala, Sin Nombre, Hantaan, Dobrava, and Seoul was used. Following manufacturer's instructions (Mikrogen Diagnostik, Germany), serotyping is possible using the recommended Line HantaPlus IgG test. Based on instructions for result interpretation from the producer, IgM antibodies were reactive on Dobrava, Hantaan, and Seoul HTNV, and IgG antibodies were more reactive on Dobrava compared to Hantaan and were negative to other hantavirus serotypes. RT-PCR from a blood sample was negative for HTNV, tested by commercial test (Primerdesign UK). Following information gained through serological tests, infection with Hantavirus Dobrava could be taken into consideration [Table 2].

Written informed consent from the patient who participated in this study was obtained.

## Discussion

The HTNV cause vascular leak by injuring the endothelial vascular cells resulting in capillary leak.[1,2] The form of clinical presentation depends directly on the localization of the process, causing tubulointerstitial damage in the renal system or pulmonary edema with perialveolar infiltration and pleural effusion.[1,2,7,13] The severe form of HFRS has a CFR of 5%–15%, whereas HCPS has a much higher CFR, 40%.[1,2,7] Viral strain seems to be determinant key for the organ tropism and the diseases.[7,14] In patients with HFRS, respiratory symptoms appear more frequently and are especially linked to PUUV infection.[9,10] In areas where both PUUV and DOBV are circulating, half of HFRS patients present with abnormal pulmonary X-ray findings and transient EKG changes, mostly in the oliguric phase.[11] Contrary to adult acute respiratory distress syndrome (ARDS) seen in systemic infections and systemic noninfectious diseases, respiratory failure in HCPS usually resolves within a few days and is

**Table 1: Laboratory findings in the patient with hemorrhagic fever with renal syndrome and hantavirus cardiopulmonary syndrome in the Intensive Care Unit**

| Specimen | On admission (PSO 8) | Day 4 (PSO 11) ICU day 1 | Day 7 (PSO 14) ICU day 3 | Day 11 (PSO 18) ICU day 7 | Day 15 (PSO 22) ICU day 11 | Day 18 (PSO 25) ICU day 17 | Reference range |
|---|---|---|---|---|---|---|---|
| WBC | 8.3 | 11.8 | 14.3 | 13.9 | 16.6 | 6.7 | 4.5-12 |
| Neutrophils | 85.5 | 88.9 | 85.1 | 92.7 | 71.7 | 64.4 | 50-70 |
| Lymphocytes | 9.8 | 7.4 | 12.1 | 5.5 | 26.2 | 31.6 | 20-40 |
| RBC | 2.9 | 2.93 | 3.7 | 3.85 | 3.05 | 3.51 | |
| Hemoglobin | 8.9 | 9.1 | 11.3 | 11.6 | 9.7 | 11.0 | 12-16 |
| Hematocrit | 26.3 | 26.5 | 33.7 | 35 | 28.5 | 31.8 | 34-54 |
| Platelets | 128 | 156 | 208 | 185 | 195 | 238 | 150-400 |
| Sodium | 125 | 121 | 144 | 129 | 133 | 125 | 136-145 |
| Potassium | 4.4 | 4.1 | 4.3 | 4.1 | 3.3 | 4.0 | 3.7-4.7 |
| BUN | 22.6 | 27.3 | 12.4 | 28.4 | 31.7 | 24.0 | 3.3-6.6 |
| Creatinine | 660 | 624 | 533 | 625 | 679 | 496 | 40-101 |
| AST | 51 | 17 | 18 | 44 | 23 | 19 | <42 |
| ALT | 32 | 18 | 19 | 32 | 31 | 22 | <42 |
| PCT | 15.89 | 23.79 | 6.29 | | | 2.3 | <2 |
| CRP | 365 | 356 | 256 | | | 96 | >6 |
| LDH | 967 | | | | | 287 | 200-480 |
| pH | 7.4 | 7.25 | 7.35 | 7.38 | 7.43 | 7.42 | 7.35-7.45 |
| $pCO_2$ | 34 | 68 | 40 | 35 | 33 | 32 | 32-45 |
| $pO_2$ | 85 | 44 | 163 | 51 | 85 | 78 | 72-104 |
| $HCO_3$ | 25 | 35 | 22.1 | 20.7 | 22 | 23 | 22-26 |
| Diuresis (/mL) | 200 | 540 | 1100 | 1800 | 2500 | 4500 | |

BUN: Blood urea nitrogen, WBC: White blood cell, RBC: Red blood cell, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, PCT: Procalcitonin, PSO: Postsymptom onset, ICU: Intensive Care Unit, LDH: Lactate dehydrogenase

**Table 2: Laboratory assays used in diagnosis**

| Test | Hantaan | Puumala | Dobrava | Seul | Sin Nombre | Leptospira |
|---|---|---|---|---|---|---|
| Rapid test immunochromatography | Positive | Positive | Positive | Positive | Positive | Negative |
| ELISA | | | | | | |
| IgM | Positive | Not tested | 4.01 (poz. >2.0) | Not tested | Not tested | Negative |
| IgG | Positive | Not tested | 2.97 (poz. >1.5) | Not tested | Not tested | Negative |
| Western blot | | | | | | |
| IgM | +++ | Negative | +++ | +++ | Negative | Not tested |
| IgG | + | Negative | ++ | Negative | Negative | |
| PCR | Negative | Negative | Negative | Negative | Not tested | Not tested |

PCR: Polymerase chain reaction; + : very low intensity (lower than cut-off band); +: low intensity (equivalent to the cut-off band); ++: high intensity (higher than the cut-off band); +++: very strong intensity.

followed by a polyuric phase, as our case demonstrates.[1] With increasing contact between humans and the natural host for HTNV, the spreading of these viruses can be easier and can be responsible for the pulmonary syndrome in all endemic areas.[14]

## Conclusion

In endemic areas, hantavirus infection should be considered in the differential diagnosis of acute respiratory distress in previously healthy adults with acute renal failure, hemorrhagic syndrome, fever, leukopenia, thrombocytopenia, and a history of possible exposure. We wish to point out that the lung involvement during HFRS is frequent, and ARDS may also be encountered in Europe, which is usually caused by the PUUV of the Hantavirus genus but does not rule out Dobrava strain, as in our case.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

## References


1. Manigold T, Vial P. Human hantavirus infections: Epidemiology, clinical features, pathogenesis and immunology. Swiss Med Wkly 2014;144:w13937.
2. Clement J, Maes P, Van Ranst M. Hemorrhagic fever with renal syndrome in the new, and hantavirus pulmonary syndrome in the old world: Paradi(se) gm lost or regained? Virus Res 2014;187:55-8.
3. Nichol ST, Spiropoulou CF, Morzunov S, Rollin PE, Ksiazek TG, Feldmann H, *et al.* Genetic identification of a hantavirus associated with an outbreak of acute respiratory illness. Science 1993;262:914-7.
4. Murgue B, Domart Y, Coudrier D, Rollin PE, Darchis JP, Merrien D, *et al.* First reported case of imported hantavirus pulmonary syndrome in Europe. Emerg Infect Dis 2002;8:106-7.
5. Rovida F, Percivalle E, Sarasini A, Chichino G, Baldanti F. Imported hantavirus cardiopulmonary syndrome in an Italian traveller returning from Cuba. New Microbiol 2013;36:103-5.
6. Atkinson B, Jameson LJ, Bovill BA, Aarons EJ, Clewlow J, Lumley S, *et al.* A non-fatal case of hantavirus cardiopulmonary syndrome imported into the UK (ex Panama), july 2014. J Clin Virol 2015;67:52-5.
7. Avšič-Županc T, Saksida A, Korva M. Hantavirus infections. Clin Microbiol Infect 2015. pii: S1198-743X(15)00536-4.
8. Duchin JS, Koster FT, Peters CJ, Simpson GL, Tempest B, Zaki SR, *et al.* Hantavirus pulmonary syndrome: A clinical description of 17 patients with a newly recognized disease. The Hantavirus Study Group. N Engl J Med 1994;330:949-55.
9. Vaheri A, Henttonen H, Voutilainen L, Mustonen J, Sironen T, Vapalahti O, *et al.* Hantavirus infections in Europe and their impact on public health. Rev Med Virol 2013;23:35-49.
10. Vollmar P, Lubnow M, Simon M, Müller T, Bergler T, Alois P, *et al.* Hantavirus cardiopulmonary syndrome due to Puumala virus in Germany. J Clin Virol 2016;84:42-7.
11. Puljiz I, Kuzman I, Markotić A, Turcinov D, Matić M, Makek N, *et al.* Electrocardiographic changes in patients with haemorrhagic fever with renal syndrome. Scand J Infect Dis 2005;37:594-8.
12. Dreshaj S, Ahmeti S, Ramadani N, Dreshaj G, Humolli I, Dedushaj I, *et al.* Current situation of Crimean-Congo hemorrhagic fever in Southeastern Europe and neighboring countries: A public health risk for the European Union? Travel Med Infect Dis 2016;14:81-91.
13. Rasmuson J, Andersson C, Norrman E, Haney M, Evander M, Ahlm C, *et al.* Time to revise the paradigm of hantavirus syndromes? Hantavirus pulmonary syndrome caused by European hantavirus. Eur J Clin Microbiol Infect Dis 2011;30:685-90.
14. Klempa B, Avsic-Zupanc T, Clement J, Dzagurova TK, Henttonen H, Heyman P, *et al.* Complex evolution and epidemiology of Dobrava-Belgrade hantavirus: Definition of genotypes and their characteristics. Arch Virol 2013;158:521-9.