

## Case Report

# Renal and Extrarenal Manifestation of Hemorrhagic Fever with Renal Syndrome

Ermira Muco<sup>1\*</sup>, Arta Karruli<sup>1,3</sup>, Ahmet Duraku<sup>2</sup>, Neada Hoxha<sup>1</sup>, and Pellumb Pipero<sup>1</sup>

<sup>1</sup>Unit of Infectious Diseases, University Hospital "Mother Teresa", Albania

<sup>2</sup>Unit of Nephrology Diseases, University Hospital "Mother Teresa", Albania

<sup>3</sup>Department of Precision Medicine, University of Campania "L. Vanvitelli", Italy

**\*Corresponding author**

Ermira Muco, Department of Infectious Diseases, Tirana, Street of Dibra, No 370, University Hospital, "Mother Teresa", Albania, Tel: 355698238587

**Submitted:** 26 September 2022

**Accepted:** 17 October 2022

**Published:** 19 October 2022

**ISSN:** 2373-9282

**Copyright**

© 2022 Muco E, et al.

OPEN ACCESS

**Keywords**

• Hemorrhagic fever; Acute renal failure; Hypertransaminasemia; Albania

**Abstract**

**Background:** Hantaviruses are a large group of RNA viruses that belong to the genus Hantavirus, family Bunyaviridae. This pathology has a wide clinical spectrum from mild to moderate forms to fulminant hemorrhagic. Albania as well as Bulgaria, Greece and the former Yugoslavia have severe forms of the disease.

**Case presentation:** We presently report a case of a 44-year-old men resident of Tirana city who was hospitalized at the UHC of Tirana. He had history of traveling sixteen days before to the Albanian Alps. He complained of diarrhea with blood content, nausea, vomiting, abdominal pain, headache, fever, myalgia since three days. The physical findings included hypotension, tachycardia, tachypnea, hyperemia of the face and Murphy's sign. The first laboratory examinations showed hemoconcentration, decrease in platelet count, renal and hepatic alterations as well as increased of pancreatic enzymes. He was transferred to the intensive care unit due to severe alteration in vital parameters. Urine analysis showed proteinuria of 6.61 g/liter/24 h and he had increase in creatinine 12.9 mg /dL and urea 207 mg /dL. The situation precipitated to oligoanuria, severe hypotension, dyspnea. The patient underwent hemodialysis sessions. ELISA IgM and IgG antibodies for anti-Hantavirus resulted positive. The patient was successfully treated with antiviral and supportive treatment and was discharged in good clinical conditions 39 days after the onset of this severe illness.

**Conclusions:** Hemorrhagic fever with renal syndrome shows a very diverse clinic. So by knowing its clinic well and getting complete epidemiological information, we can diagnose it quickly and accurately.

**INTRODUCTION**

Hantaviruses are a large group of RNA viruses that belong to the genus Hantavirus, family Bunyaviridae. Rodents are the reservoirs of most of these viruses. There are five hantaviruses circulating in Europe such as Puumala, Dobrava-Belgrade, Tula, Saarema and Seoul. However, we can say that only two of them (Puumala and Dobrava-Belgrade) are the causes of human infection. It is precisely the Dobrava virus that causes HFRS, this serious viral disease in Albania [1]. Two syndromes are caused by hantaviruses: haemorrhagic fever with renal syndrome (HFRS) as observed in Asia, Europe and recently in Africa, and the hantavirus cardiopulmonary syndrome (HCPS) as observed in the New World [2]. Haemorrhagic fever with renal syndrome was first described in the 1930s as hemorrhagic nephrosonephritis in far eastern Russia and Tula fever in European Russia, while viral origin was proved by passages in volunteering in 1940 [3]. However, the disease may have existed in Asia for at least the last 1000 years, as there is a meaningful description of hemorrhagic fever associated with renal syndrome in a Chinese medical textbook written from the 960s AD. During the Korean War more than 3,000 military troops contracted a hemorrhagic disease that resulted in renal failure, shock and death in 10-15% of cases. The causative agent of this epidemic was isolated in 1976 from the rodent *Apodemus Agrarius* and in 1978 from the

sick. This agent was named the Hantaan virus, from the Hantaan River that flows near parallel 38 across the Korean Peninsula. The antibody study showed a close link between this disease, HFRS in the USSR, epidemic nephropathy in Scandinavia, and epidemic hemorrhagic fever in China and Japan. Therefore, the WHO working group meeting in Tokyo in 1982, decided that all these pathologies be named: "Hemorrhagic fever with renal syndrome" [4]. Hemorrhagic fever with renal syndrome is an endemic zoonosis in our country. The first clinical case of this viral disease was described by infectious disease clinicians as Eltari et al in 1987 [5]. Our country has such a complex ecology that favors the existence of different species of rodents that harbor hantaviruses. Rodents are the primary hosts of Hantaviruses. Large amounts of viruses are excreted mainly through the saliva, urine, feces of infected rodents *Apodemus Agrarius*. Exposure to them leads to human infection and subsequent development of the disease. People are the ultimate hosts of this chain of transmission. There are also ecological and climatic factors that affect the circulation of viruses in nature. It is this mode of transmission and exposure that makes us say that lifestyle is a key risk factor in infections from this virus. So although the disease affects both sexes, it has the highest prevalence in men for the high risk of exposure. This pathology has a wide clinical spectrum from mild to moderate forms to fulminant hemorrhagic ones with symptoms that develop one to two weeks after exposure to infectious material.

The first symptoms include fever, chills, headache, myalgia or nausea followed by kidney damage to acute renal failure, liver or other organ damage. Albania as well as Bulgaria, Greece and the former Yugoslavia have severe forms of the disease. And out of 150,000 people hospitalized with HFRS worldwide, 3% -10% of them die each year [6]. The severity of the disease varies depending upon the virus causing the infection. Hantaan and Dobrava virus infections usually cause severe symptoms, while Seoul, Saaremaa, and Puumala virus infections are usually more moderate [7]. In the only complete clinical study of Rista et al on this pathology in our country, it was observed that 24.2% of patients ended up under hemodialysis and there was a considerable mortality rate, going up to 9.09% [1]. Diagnosis for hantavirus infections is based on serology (ELISA IgM and IgG tests for the detection of specific IgM and IgG antibodies), PCR, immunochemistry and virus culture. Prevention of this infection takes on an absolute value. We can say that the discovery of a vaccine would be the best form of prevention, which is almost impossible due to the heterogeneity of top of viruses.

## CASE PRESENTATION

A 44-year-old men resident of Tirana city, the capital of Albania was hospitalized at the UHC of Infectious Diseases Tirana, Albania. The signs and symptoms were diarrhea (it occurring more than 10 times/day and often bloody diarrhea), nausea, vomiting, abdominal pain, headache, fever 40°C and myalgia since three days. Our patient had history of traveling to the Tropoja, located in the Albanian Alps. Sixteen days before he had been there for vacation, while he had gone to the forest and cut down some wood. On the epidemiological anamnesis our patient confirmed the presence of rodents there. Initially physical signs included hypotension 85/45 mm/Hg, tachycardia 114/min, tachypnea 20/min, hyperemia of the face and Murphy's sign. The first laboratory examinations showed hemoconcentration (Red blood cells  $6.5 \times 10^6$ /uL, Hematocrit 56.6, Hemoglobin 19.4), slight decrease in platelets (Platelet count 128 K/uL), renal and hepatic alterations (Aspartate aminotransferase 149 U/L, Alanine aminotransferase 61 U/L, Lactate dehydrogenase 532, Azotemia 83.4 mg/dl, Creatinine 2.74 mg/dl) as well as increased pancreatic enzymes such as Amylase (489U/L). Blood group tested was 0 positive. He was transferred to the intensive care unit due to severe vital parameters alteration. In the following days the condition worsened both clinically and in terms of laboratory examinations (Tables 1,2). Urine analysis displayed a nonselective proteinuria with a total loss of 6.61 g/liter/24

h. Abdominal echography showed hepatomegaly, fluid around the gallbladder and in the right phrenicocostal sinus as well as gallbladder wall thickness > 5-6 mm. Lung x-ray showed the presence of bilateral pleural effusions. The situation precipitated towards oligoanuria, less than 100 ml / day, deep hypotension, dyspnea. The patient had a marked increase in renal parameters (creatinine 12.9 mg /dL; urea 207 mg /dL). The patient underwent hemodialysis sessions during the oliguric phase. In the intensive care unit, he underwent a rather complex treatment that included fluids, electrolyte (sodium, potassium, chloride), antagonists of the H<sub>2</sub> receptors, oxygen, antibiotic, vasoactive agents, fresh frozen plasma, antiviral drug (ribavirin). Ribavirin was administered orally for 7 consecutive days at the dose recommended by WHO (30 mg/kg as an initial loading dose, then 15 mg/kg every 6h for 4 days, and then 7.5 mg/kg every 8h for 6 days). Hantavirus infection was confirmed by serology ELISA IgM and IgG antibodies anti-Hantavirus. We had these results in the first search, on the seven day of hospitalization, IgM 3.087 (0.8-1.1) and IgG 1.593 (0.8-1.1) and in the second research, on the ninth day of hospitalization, IgM 2.889 (0.8-1.1) and IgG 1.669 (0.8-1.1). The results of antinuclear antibodies, antismooth-muscle antibodies, anti HAV/HBV/HCV were negative as well as serological analysis of Leptospira, Salmonella, Rickettsia and Brucella. Toxic hepatitis was excluded. Blood and urine cultures were negative. The patient was successfully treated with supportive management and antiviral. The patient was finally left the hospital in good clinical conditions 39 days after the onset of his severe illness.

## DISCUSSION

Just as various authors have written about this pathology, also clinicians of Albania have tried to study and describe it. The first clinical case of this viral disease was described by infectious disease clinicians as Eltari et al in 1987 [5]. From that time onwards, this puzzle continues to be completed. Thus we mention the study of Rista et al on epidemiological, clinical, therapeutic data of HFRS in the Albanian population or the study of Puca, Qyra et al that speak of particular clinical manifestations [1,8,9]. Hemorrhagic fever with renal syndrome is endemic in our country. Cases with Hemorrhagic Fever with Renal Syndrome in Albania are caused by Dobrava strains. Our country has such a complex ecology that favors the existence of different species of rodents that harbor hantaviruses. It is a small country with mountainous geography as for the most part it rises in the mountains and hills, being surrounded by the Albanian Alps in the

**Table 1:** Laboratory data of clinical tests.

Laboratory data	Reference range	D0	D2	D7	D9	D12	D17	D21	D27	D33	D39
Red blood cells	4.2-6.3M/uL	$6.5 \times 10^6$	$6.99 \times 10^6$	$3.14 \times 10^6$	$2.55 \times 10^6$	$3.36 \times 10^6$	$3.14 \times 10^6$	$2.51 \times 10^6$	$2.71 \times 10^6$	$2.75 \times 10^6$	$3.23 \times 10^6$
Hematocrit	37-51%	56.6	65.1	28.4	23.5	30.5	29.1	22.6	24.8	25.4	29.4
Hemoglobin	12-18g/dL	19.4	20.9	9.6	9.9	10.4	9.4	7.6	8.5	8.7	9.8
Platelet count	140-440K/uL	128	106	99	145	570	478	543	601	321	241
White blood cells	4.1-10.9K/uL	3600	8100	10100	11700	10300	4400	3400	4200	4400	4500
Monocytes	0.1-24%	4.5	4.6	9.1	9.9	9.6	6	6.4	6.1	7.9	6.2
Granulocytes	37-92%	83.5	80.8	75.5	77.4	75.7	66	50	45.3	48.8	49.4
Lymphocytes	10-58.5%	12	14.6	15.4	12.7	14.7	26	43.6	48.6	43.3	44.4

**Table 2:** Laboratory data of biochemical tests.

Laboratory data	Reference range	D0	D2	D7	D9	D12	D17	D21	D27	D33	D39
Aspartate aminotransferase	0-35U/L	149	295	89	81	67	45	38	36	38	28
Alanine aminotransferase	0-45U/L	61	114	25	22	20	13	14	29	32	31
Total bilirubin	0.3-1.2 mg/dl	0.7	1.1	1.2	0.9	1.3	0.8	0.9	1.1	0.8	1.2
Glycemia	74-106mg/dl	148	136	121	103	99	98	89	111	106	100
Azotemia	10-43mg/dl	83.4	117.4	204.8	203.6	184.3	207.3	205.7	160.9	101.2	58.5
Creatinine	0.7-1.4mg/dl	2.74	5.2	10.38	11.92	11.24	12.94	8.65	4.38	2.15	2.02
Lactate dehydrogenase	125-250U/L	532	644	805	602	553	430	263	226	205	209
Creatine phosphokinase	0-171 U/L	608	699	638	566	455	423	355	345	236	240
Total proteins	6.6-8.8g/dl	5.4	4.9	5.3	5.8	5.6	5.8				
Amylase	(28-100 U/L)	489	678	544	355	267	230	194	103	78	75

north, Sharr mountains in the northeast, Skanderbeg Mountains in the center, Korab mountains in the east, Pindi Mountains in the southeast and mountains of Ceraun in the southwest. Our patient had history of traveling to the Tropoja, which is located on the banks of the Valbona river between the Albanian Alps in northeastern Albania. He had gone to the forest in the alpine area to cut wood. In a study of Rista et al, 88% of the patients were male and 48.5% of patients were from Northeast Albania [1]. Lifestyle has a key role as a risk factor in infections from this virus, mentioning here professions such as shepherds, lumberjack, farmer or activities such as outdoor camping in forest areas with the presence of rodents. Our case showed the clinic in June. Apparent seasonal distribution, with most cases occurring in the summer months is observed [10]. The presence of this pathology more in men is more understandable, as heavy work outside the home in fields or forests is done by males. Our patient had an incubation period of 13 days. Usually the incubation period for HFRS is two to four weeks, ranging from a few days to nearly two months [11]. Temperature and chills are important symptomatic elements. This disease is characterized by kidney damage, which is manifested by increased values of urea and creatinine, oliguria to anuria or immediate renal insufficiency that requires urgent intervention with hemodialysis. Our case had considerable renal impairment, which was seen from the high values of urea (207.3) and creatinine (12.94). He underwent several hemodialysis sessions. In addition to renal manifestations, our patient also presented extrarenal ones. The extrarenal manifestations were pancreatobiliary involvement; gastrointestinal hemorrhages, rhabdomyolysis and pulmonary manifestations. Gastrointestinal symptoms of this disease can cause difficulties in diagnosis at the beginning of HFRS [10]. Acute pancreatitis with the most common symptom being that of abdominal pain as well as with the increase of enzymes (amylase), is a clinical manifestation described by Puca et al [12]. Liver disorders, like hepatomegaly and elevated liver transaminases and bilirubin have been frequently diagnosed in HFRS patients [13]. Our patient had only increased transaminases but no increase in bilirubin. Among the laboratory disorders of our patient, the low protein values and the high LDH values were noticeable. Hypoproteinemia possibly due to protein leakage through the vessel wall and high levels of serum lactate dehydrogenase (an indicator of cell death) are important indicators of the severity of disease [14]. Our patient had increased values of hemoglobin

(19.4 g/dL) and hematocrit (56.6%) since hospitalization. Increased hemoglobin and hematocrit values are the result of dehydration, which comes from endothelial dysfunction with extravasation due to increased vascular wall permeability. These increased values correlate well with disease severity. In cases of neurological symptoms, realization of MRI head will show PRES syndrome, a pathology that is not very common [15]. Diagnosis was based on the clinical, epidemiological findings and the serological positive confirmation for IgM Hantavirus by enzyme-linked immunosorbent assay and immunofluorescence assay IFA. Hantavirus infection was confirmed by serology ELISA IgM and IgG antibodies anti-Hantavirus. We had these results in the first search, on the seven day of hospitalization, IgM 3.087 (0.8-1.1) and IgG 1.593 (0.8-1.1) and in the second research, on the ninth day of hospitalization, IgM 2.889 (0.8-1.1) and IgG 1.669 (0.8-1.1). This test was performed in the Laboratory National Reference, at the Institute of Public Health. The role of Public Health Institute in the serological diagnosis of this pathology was very important. This pathology is a serious clinical condition that requires treatment and specialized support. Treatment consisted of supportive therapy with antibiotic, saline infusions, electrolytes, antipyretics, oxygen therapy as well as antiviral therapy. Ribavirin was administered orally for 7 consecutive days at the dose recommended by WHO (30 mg/kg as an initial loading dose, then 15 mg/kg every 6h for 4 days, and then 7.5 mg/kg every 8h for 6 days). The patient finally left the hospital in good clinical conditions 39 days after the onset of his severe illness. In their study Rista et al talk about an average hospital stay at  $15.7 \pm 6.9$  days [1]. Of course, our patient showed a very complex clinic with the involvement of several organs and the hospital stay was much longer. He was treated in the Infectious Diseases Service, Tirana University Hospital Center, as the only tertiary center in Albania. Prevention of this infection takes on an absolute value as described in this report [16]. Information of the population and appropriate measures by the relevant units will make it possible to reduce the spread of the virus, in the absence of an effective vaccine. People should be informed to avoid contact with feces or rodent urine as well as to keep rodent populations as far away from their homes as possible.

## CONCLUSION

Hemorrhagic fever with renal syndrome shows a very diverse clinic. So by knowing its clinic well and getting complete

epidemiological information, we can diagnose it quickly and accurately.

## CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

## REFERENCES

1. Elvana Rista, Arben Pilaca, Ilir Akshija, Ariol Rama, Endri Harja, Edmond Puca, et al. Hemorrhagic fever with renal syndrome in Albania. Focus on predictors of acute kidney injury in HFRS. *J Clin Virol.* 2017; 91: 25-30.
2. Kruger DH, Schonrich G, Klempa B. Human pathogenic Hantaviruses and prevention of infection. *Hum Vaccin.* 2011; 7: 685-93.
3. Boris Klempa, Evgeniy A. Tkachenko, Tamara K. Dzagurova. Hemorrhagic Fever with Renal Syndrome Caused by 2 Lineages of Dobrava Hantavirus, Russia. *Emerg Infect Dis.* 2008; 14: 617-625.
4. World Health Organization. Geneva 1985. Viral Haemorrhagic Fevers. Report of a WHO Expert Committee. Technical Report Series 721.
5. E Eltari, M Nuti, I Hasko, A Gina. Haemorrhagic fever with renal syndrome in a case in northern Albania. *Lancet.* 1987; 2: 1211.
6. Menelaos Papadimitriou. *Kidney International. Nephrology Forum. Hantavirus nephropathy Aristotelian University, Hippokratia General Hospital, Thessaloniki, Greece.* 1995; 48: 887-902.
7. HW Lee, G van der Groen. "Hemorrhagic fever with renal syndrome." *Prog Med Virol.* 1989; 36: 62-102.
8. Edmond Puca, Arjan Harxhi, Pellumb Pipero, Elda Qyra, Gentian Stroni, Ermira Muco, et al. Pancreatitis in patients with hemorrhagic fever with renal syndrome: A five-year experience. *J Infect Dev Ctries.* 2017; 11: 900-903.
9. Qyra E , Puca E , Harxhi A, et al. Hemorrhagic Fevers with Renal Syndrome Presenting with Pregnancy Interruption. *Journal of Microbiology and Infectious Diseases.* 2017; 07: 198-201.
10. Tatjana Avšič Županc, Miša Korva, Alemka Markotić. HFRS and Hantaviruses in the Balkans/South-East Europe. *Virus Res.* 2014; 187: 27-33.
11. Heymann DL, editor. *Control of Communicable Diseases Manual 19th Edition* ed. Washington, DC: American Public Health Association; 2008.
12. Edmond Puca, Arben Pilaca, Pellumb Pipero, Dhimiter Kraja, Entela Y Puca. Hemorrhagic fever with renal syndrome associated with acute pancreatitis. *Virol Sin.* 2012; 27: 214-217.
13. A Markotić, ST Nichol, I Kuzman, AJ Sanchez, TG Ksiazek, A Gagro, et al. Characteristics of Puumala and Dobrava infections in Croatia. *J Med Virol.* 2002; 66: 542-51.
14. Menelaos Papadimitriou. *Kidney International. Nephrology Forum. Hantavirus nephropathy Aristotelian University, Hippokratia General Hospital, Thessaloniki, Greece.* 1995; 48: 887-902.
15. Ermira Muco, Amela Hasa, Arben Rroji, Arta Kushi, Edmond Puca, Dhimiter Kraja, et al. Posterior Reversible Encephalopathy Syndrome in a Patient with Hemorrhagic Fever with Renal Syndrome. *Case Rep Infect Dis.* 2020; 2020: 1017689.
16. European Centre for Disease Prevention and Control. Prevention measures and communication strategies for hantavirus infection in Europe.