

*Prikazi bolesnika/
Case reports*

HAEMORRHAGIC FEVER WITH RENAL
SYNDROME AND DIABETES MELLITUS –
Case report

HEMORAGIJSKA GROZNICA SA
BUBREŽNIM SINDROMOM I DIJABETES
MELITUS - *Prikaz slučaja*

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Key words

haemorrhagic fever with renal syn-
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virus.

Ključne reči

hemoragijska groznica sa renalnim sin-
drom, dijabetes melitus, Beograd virus.

Abstract

Introduction. Haemorrhagic fever with renal syndrome is acute infectious disease, zoonosis, comes in endemic and epidemic form. It is caused by RNA virus from genus Hantavirus of Bunyaviridae family. Clinical feature advances through 5 stages: febrile phase, hypotensive phase, oliguric phase, diuretic phase and convalescent phase. Fever, bleeding and acute renal failure develop in all patients. Severity of the disease depends on the virus species that causes it.

Case Report. A 31 year old patient was admitted to the hospital due to fever, vomiting and diarrhea, 20 days after military activity. On physical examination he was found to have conjunctival hyperemia, somnolence, arterial hypotension, oliguria. He was transferred to the intensive care unit. Due to worsening of acute renal failure and anuria hemodialysis treatment was started. Acute heart failure developed, after several days, together with respiratory failure, necessitating mechanical ventilation. ELISA assay confirmed acute infection with Belgrade virus. Diabetes mellitus developed during treatment, requiring insulin treatment. Percutaneous kidney biopsy was performed twice. Respiratory function recovered after treatment but kidney failure grade III remained.

Conclusion. We presented the case of severe form of haemorrhagic fever with renal syndrome, caused by Belgrade virus. Disease complications were heart and respiratory failure and de novo Diabetes mellitus. Haemorrhagic fever with renal syndrome should be suspected in patients with positive epidemiological data and typical clinical feature, establish diagnosis and start treatment as soon as possible.

INTRODUCTION

Haemorrhagic fever with renal syndrome (HFRS) is acute infectious diseases, zoonosis, with endemic and epidemic characteristics (1). It is caused by RNA virus from genus Hantavirus of Bunyaviridae family (2). Typical clinical manifestation consists of fever, bleeding and acute renal failure (3). The reservoirs of Hantavirus are small mammals, mostly vole, field and house mouse, brown and black rat and shrews. Virus is excreted from the host in saliva, feces and urine. People are incidentally infected either by inhalation of aerosols or by ingestion of contaminated water and food. Three epidemiological types are recognized: rural type (typical for our country), urban type and laboratory infections (3,4).

Genus Hantavirus consists of several distinct species; the most common are Hantaan, Puumala, Belgrade/Dobrava and Seoul (1). Hantaviruses shown tropism to vascular endothelium of the kidney, heart, lung, lymphoid organs, rarely central nervous system (5,6). The disease is divided into 5 stages: febrile phase, hypotensive phase, oliguric phase, diuretic phase and convalescent phase. Acute renal failure usually develops in oliguric phase. Pulmonary edema, arterial hypertension with encephalopathy, cardiac arrhythmia and cerebral coma could complicate the course of the disease (3,5,6). Minority of patients develop chronic complications: chronic renal failure, arterial hypertension, hypopituitarism and infertility (7). Diagnosis is obtained considering epidemiological data, typical clinical feature, laboratory analysis and serologic assays, mostly the enzyme-linked immunosorbent assay (ELISA assay) (3,4,8). Kidney biopsy can be performed, in selected cases, showing picture of tubulointerstitial nephritis (4,9,10).

Rapid diagnosis and early hospital treatment predict better outcome. Daily hemodialysis are recommended if serum creatinine is raised above 400 $\mu\text{mol/l}$ (4,7,8). There is no specific treatment, but regarding several clinical trials ribavirin treatment should be initiated in the first 5 days which could reduce morbidity and mortality (11,12). Health education of soldiers, campers and workers with increased professional risk are very important (8,13). Vaccination against Hantavirus is accepted in China for high risk professions, but is not accepted in western countries (4,14).

Case report

A male patient, military person, 31 years old, is admitted to the hospital, 20 days after military exercise, due to fever 40°C, nausea, abdominal pain, vomiting and diarrhea, with worsening in the next few days and development of oliguria. Physical examination revealed injection of the conjunctiva, facial flush, somnolence, and arterial hypotension 100/70 mmHg. He was transferred to intensive care unit in Military Medical Academy (MMA). Laboratory

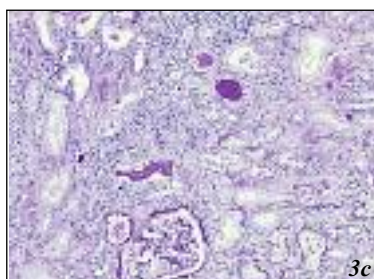
analysis showed low platelet count 13x10⁹/L, leucocytosis 20x10⁹/L, hyperviscosity syndrome (hemoglobin 196 g/L, hematocrit 0.56), serum creatinine (Cr) 200 $\mu\text{mol/l}$, lipase 300 U/L VS. 160 U/L. Due to rapid progression of renal failure (Cr 830 $\mu\text{mol/l}$), hyperkalemia 7.5 mmol/L, anuria and hypervolemia, hemodialysis treatment was initiated next day. ELISA assay confirmed positive IgM and IgG antibody to Belgrade virus. After 4 days heart failure developed (brain natriuretic peptide (BNP) 4400 pg/ml (BNP < 100 pg/mL – heart failure unlikely), probably due to hypervolemia, together with respiratory failure which required mechanical ventilation for 4 days. Severe coagulation abnormalities were verified – decreased antithrombin III, protein C and S, factor IX and X, increased international Normalised Ratio, activated partial thromboplastin time and D dimer.

Patient was treated with antibiotics, fresh frozen plasma, cryoprecipitate, hemodialysis (18 procedures). Respiratory function and diuresis recovered after therapy, but renal failure remained. Diuretic phase was prolonged to 4 weeks. Ultrasound examination of kidneys showed 11,5 cm longitudinal diameter, increased echogenicity of parenchyma (14 mm thickness), with hypoechoic halo, normal finding of the pancreas. (Pictures 1 and 2)



Pictures 1. Right kidney and Pictures 2. Left kidney

Diabetes mellitus developed during hospitalisation, requiring insulin treatment. Due to slow decrease of Cr level and proteinuria 1 gr/24h, percutaneous kidney biopsy was performed, after the patient general condition got better. The



Pictures 3a, 3b and 3c Light microscopy.

final histopathological finding (light microscopy and immunofluorescence microscopy) confirmed chronic tubulointerstitial nephritis. (Pictures 3 a,b,c)

After 58 days, patient was discharged from hospital, in good condition, diuresis was 4L, Cr 409 $\mu\text{mol/l}$, Hgb 88 g/L. During follow-up, due to urethral stricture (complication of urinary catheter placement), urethrotomy and several urethral dilations were performed, with good outcome. Three months later, control percutaneous kidney biopsy was performed, histopathological finding was unchanged. One year later, laboratory analysis improved, serum Cr 204 $\mu\text{mol/l}$, Hgb 120g/L, kidneys were smaller on ultrasound examination, 9 cm longitudinal diameter and with slightly hyperechoic parenchyma. Due to diabetes mellitus patient is receiving insulin treatment.

DISCUSSION

Taking all this into consideration, we suspected HFRS. ELISA assay confirmed acute infection with Belgrade virus, which causes severe form of the disease (2,3). Complication of the disease was acute heart and respiratory failure. What we want to emphasise with this case report is the development of de novo diabetes mellitus requiring insulin treatment, due to virus pancreatitis. Patient had normal glycemia before (data are taken from routine blood check performed twice annually). Acute pancreatitis, as rare complication of the HFRS, is published in the literature, but there are no published cases of HFRS with de novo developed Diabetes mellitus, so far (15,16,17,18).

Soon after hospital admission hemodialysis treatment started, in the beginning performed daily, according to the guidelines. Early hemodialysis treatment is associated with better disease outcome (7,8). Despite intensive hemodialysis, Cr level was decreasing slowly and diuretic phase was prolonged, complicated with hyperkalemia. Total 18 hemodialysis procedures were performed, which is much higher than

average number (5-6) of hemodialysis procedures performed in 148 patients with HFRS, treated in Clinic for Nephrology MMA, year 1989 to 2015. We performed percutaneous biopsy due to slow decrease in Cr, proteinuria and suspected glomerular disease (9,19,20). But histopathology report confirmed chronic tubulointerstitial nephritis.

It is not always easy to establish the diagnosis despite typical clinical feature. Differential diagnosis included: leptospirosis, measles, rubella, acute poststreptococcal glomerulonephritis, Henoch-Schönlein purpura, hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. Occurrence of fever, petechiae and ecchymosis after staying in country or farm favors HFRS. Serologic assays should be performed immediately, especially ELISA assay. Presence of specific anti – hantavirus IgM or 4x raised specific anti-hantavirus IgG antibody confirms acute infection (3,4,8).

CONCLUSION

In our patient with hemorrhagic fever with renal syndrome, clinical feature was complicated with heart and respiratory failure and de novo diabetes mellitus. Severity of the disease in these patients is dependent on the first place of the Hantavirus species. Belgrade virus, isolated form in our patient, is associated with severe form of the disease. Therefore, early established diagnosis of HFRS, hospital treatment in the intensive care unit and hemodialysis treatment are prognostic factors for better disease outcome.

Sažetak

Uvod: Hemoragijska groznica sa bubrežnim sindromom je akutno infektivno oboljenje, iz grupe zoonoza, endemskog i epidemijskog karaktera. Uročnik oboljenja je RNA virus iz roda Hantavirusa i familije Bunyaviridae. Kliničku sliku karakteriše pet faza: faza febrilnosti, hipotenzije, oligurije, poliurije i rekonvalescencije. Kod svih bolesnika je prisutna febrilnost, hemoragija i akutna bubrežna insuficijencija, a težina kliničke slike zavisi od soja virusa koji je izazvao oboljenje.

Prikaz slučaja: pacijent star 31 godinu, dvadesetak dana nakon vojne vežbe hospitalizovan zbog febrilnosti, uz povraćanja i dijareju. U fizikalnom nalazu dominira hiperemija konjunktiva, somnolencija, hipotenzija i oligurija. Premešten je u jedinicu intenzivne nege. Zbog brze progresije akutne bubrežne insuficijencije i anurije započeto hemodijalno lečenje. Nakon nekoliko dana razvija se akutna kardijalna dekompenzacija sa respiratornom insuficijencijom, što je zahtevalo sprovođenje mehaničke ventilacije. ELISA testom potvrđena akutna infekcija Hantavirusom, soj „Beograd“. Tokom lečenja razvija se i dijabetes melitus, uz potrebu za insulinskom terapijom. U dva navrata učinjena perkutana biopsija bubrega. Respiratorna funkcija se nakon lečenja oporavlja uz zaostajenje bubrežne insuficijencije gradus III.

Zaključak: Prikazan je teški slučaj hemoragijske groznice sa bubrežnim sindromom, koji je izazvao Hantavirus soj „Beograd“. Klinička slika je komplikovana akutnom kardijalnom dekompenzacijom, respiratornom insuficijencijom i razvojem de novo dijabetes melitusa. Kod bolesnika sa pozitivnom epidemiološkom anamnezom i tipičnom kliničkom slikom, trebalo bi posumnjati na hemoragijsku groznicu i što pre postaviti dijagnozu i započeti lečenje.

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