

Hemorrhagic Fever with Renal Syndrome Complicated by Acute Pancreatitis, High Intraocular Pressure, and Pulmonary Involvement: a Case Report

Xinran Yang^{1,*}, Chenglin Yu^{2,*}, Yixin Chen¹, Bin Nian³, Min Chai¹, Dilimulat Maimaiti⁴, Dahai Xu¹, Xiuxian Zang¹

¹Department of Emergency Medicine, The First Hospital of Jilin University, Changchun, Jilin, 130000, People's Republic of China; ²Department of Emergency Medicine, Yanbian University Hospital, Yanji, Jilin, 133000, People's Republic of China; ³Department of Ultrasonography, Yanbian University Hospital, Yanji, Jilin, 133000, People's Republic of China; ⁴Department of Emergency Medicine, Seventh Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang, 830054, People's Republic of China

*These authors contributed equally to this work

Correspondence: Dahai Xu; Xiuxian Zang, Department of Emergency Medicine, The First Hospital of Jilin University, No. 1 Xinmin Street, Chaoyang District, Changchun, Jilin, 130000, People's Republic of China, Tel +86-15043032548; +86-13596097922, Email xudahai0319@jlu.edu.cn; zangxx@jlu.edu.cn

Abstract: Hemorrhagic fever with renal syndrome (HFRS), a naturally occurring epidemic disease, is primarily caused by hantaviruses. It frequently involves the lungs and is characterized by symptoms such as fever, hemorrhage, and renal failure. However, the occurrence of acute pancreatitis (AP) in HFRS patients can be neglected, and high intraocular pressure (IOP) is exceedingly uncommon. In this report, we discuss the case of a 30-year-old male who presented with fever, nausea, vomiting, and abdominal pain. Physical examination revealed extremity petechiae rashes and elevated IOP. Laboratory tests indicated coagulopathy and renal failure. A computed tomography scan confirmed AP. Further testing revealed a positive anti-hantavirus IgM antibody. The patient received supportive care, fluid hydration, hemofiltration, mannitol, brinzolamide, and brimonidine to reduce IOP. Three days post-admission, the patient developed shortness of breath and chest pain. Subsequent chest computed tomography revealed pulmonary edema and bilateral pleural effusion. Treatment included oxygen supply, respiratory support, and thoracentesis, with continued hemofiltration. The patient recovered, regaining normal pulmonary and renal functions and normalized IOP. This case underscores the importance of comprehensive evaluations and vigilant monitoring in HFRS patients, particularly measuring IOP in those with visual complaints, to save lives and reduce morbidity.

Keywords: hemorrhagic fever with renal syndrome, acute pancreatitis, high intraocular pressure, pulmonary edema

Introduction

Hantaviruses (HTNV) infection can cause hemorrhagic fever with renal syndrome (HFRS). Mainland China has the highest incidence of HFRS in the world.¹ HTNV can directly destroy the infected cells, with subsequent intrinsic and adaptive immune responses and massive cytokine releases to cause multi-organ damage. In addition to fever, hemorrhage, and renal failure, the lung is the most commonly affected organ.² Approximately one-third of affected patients could have five typical progressive stages: fever, hypotension, oliguria, polyuria, and convalescence. Acute pancreatitis (AP) is an infrequent yet severe complication of HFRS. HFRS patients with AP carry high mortality rates.³ Due to the atypical clinical presentations of AP, early diagnosis of AP could be a challenge. In addition, HTNV can rarely involve the eyes to cause myopia, intraocular pressure (IOP) changes, conjunctival bleeding, and intraretinal hemorrhage.⁴ Both AP and eye involvement can be misdiagnosed in patients with HFRS. Delayed treatments can cause severe outcomes. Concurrent AP and increased IOP with HFRS have never been reported previously. Here, we reported a young man with HFRS who had AP, increased IOP, and pulmonary complications. We describe his management, review the previous relevant literature, and share our experience here.

Case Presentation

On July 18, 2023, a 30-year-old male presented to the emergency department of the First Hospital of Jilin University, China, reporting a series of symptoms. He experienced intermittent fever with chills for two days, accompanied by nausea, vomiting, and abdominal pain with diarrhea for the same duration. Additionally, he suffered from blurred vision for one day.

Three days prior, the patient developed chills and fever, reaching a temperature of 39.0 °C. He sought treatment at a local clinic, where he received an unspecified antibiotic, which resulted in minimal improvement. Two days prior to the presentation, he began to experience severe nausea, vomiting, abdominal pain, and intense diarrhea (15–20 episodes per day). The following day, the patient noticed blurry vision and sought care at our hospital. He did not report any other significant personal or family medical history.

At the emergency department, the vital signs were temperature 37.0 °C, blood pressure 131/90 mmHg, heart rate 140 times/min, respiratory rate 12 times/min, and oxygen saturation (SpO₂) 95% (with nasal cannula on 3 L/min oxygen supply). The physical examination revealed an ill-looking young man with generalized abdominal tenderness but with no rebound tenderness, mild muscle rigidity, and petechiae rashes on both arms and legs. The eye examination showed visual acuity of counting fingers at 1 meter, bilateral conjunctival injection, and equal and round pupils reactive to light. The optic disc had a clear boundary and normal blood vessels, with no apparent retinal abnormality (Figure 1). The posterior optical coherence tomography examination reported bilateral rough macular retina (Figure 2). Ultrasound revealed hypoechoic dark areas in peripheral walls in both eyes, with sparse dot echo in the right eye vitreous and middle and low dot echo in the left eye vitreous (Figure 3A and B). In addition, the IOP were 27 and 35 mmHg in the right and left eyes, respectively.

The laboratory tests reported white blood cell count $34.7 \times 10^9/L$, hemoglobin 204 g/L, platelet count $10 \times 10^9/L$, aspartate aminotransferase 209.7 U/L, alanine transaminase 151.0 U/L, D-dimer 14.3 mg/L, thrombin time 113.0 s, activated partial thromboplastin time 51.1 s, prothrombin time 13.6 s, international normalized ratio 1.23, fasting plasma glucose 0.79 g/L, blood urea nitrogen 12.3 mmol/L, creatinine 188.4 $\mu\text{mol/L}$, urinary protein 3+, urinary erythrocytes 1133.9 /high power field, urinary erythrocyte count 6299.7 /UL, and normal lipid profile. In addition, the blood amylase and lipase levels were 40.2 U/L (normal range 35.0–135.0 U/L) and 52.2 U/L (normal range 0.0–67.0 U/L), respectively. An abdominal computed tomography (CT) scan showed AP with peripancreatic fluid accumulation (Figure 4A). A chest CT scan showed clear lungs (Figure 5A and B). He was admitted into the emergency intensive care unit (EICU) for further management. After admission to the EICU, additional blood tests showed positive anti-hantavirus IgM antibody and negative 2019-nCoV RNA, human immunodeficiency virus, hepatitis virus, and syphilis antibody. We made the diagnosis of HFRS, AP, and eye involvement with increased IOP in this patient.

The patient received intravenous fluid hydration, antacid (esomeprazole 40 mg twice a day), and octreotide (0.2 mg, three times a day) with ulinastatin (100,000 IU, three times a day) to inhibit pancreatic enzyme secretions.^{5–7} In addition, prothrombin complex, vitamin K1 (10 mg once a day), fibrinogen, recombinant human thrombopoietin, and plasma and platelet transfusion were given to correct the coagulopathy. Glycyrrhizic acid (250 mL once daily) was given for liver

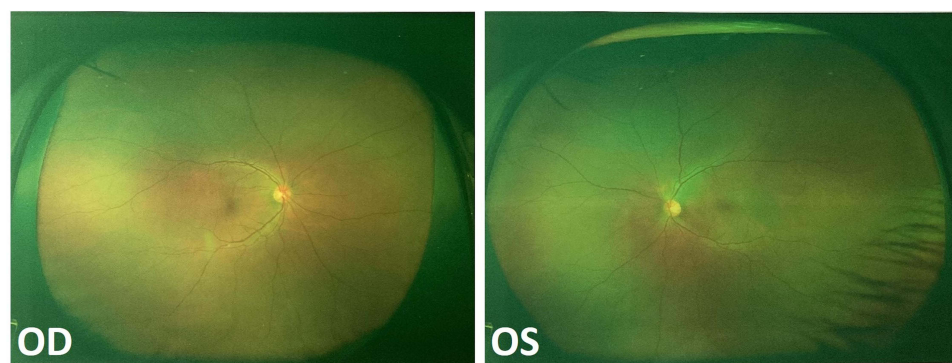


Figure 1 Fundus examinations showed clear boundaries and normal blood vessels in the optic disc, with no apparent retinal abnormality. OS, left eye; OD, right eye.

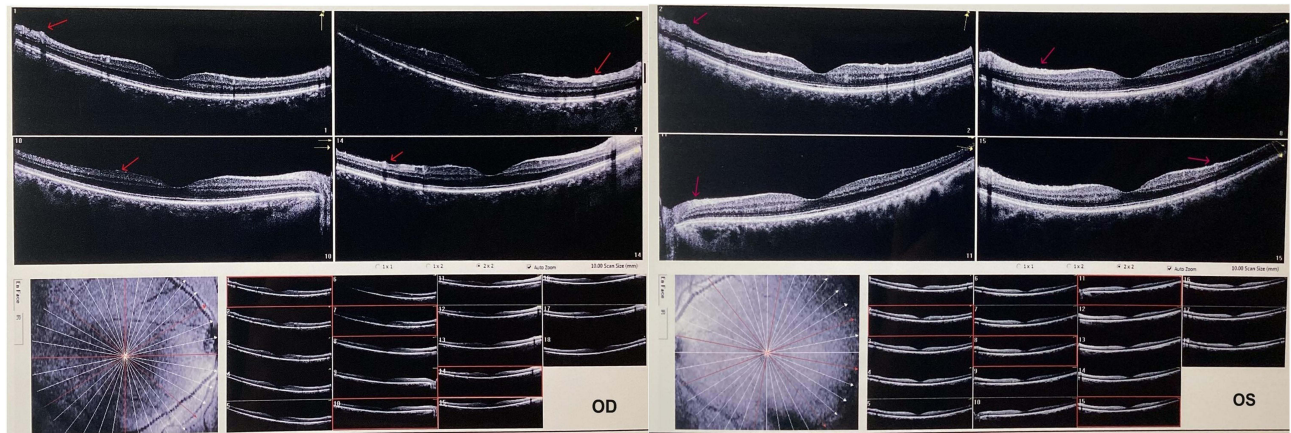


Figure 2 Optical coherence tomography examination on day 1. OS, left eye; OD, right eye. In images in each eye, pictures in the lower left corner are tomography examinations at different angles, with the results in the right lower corner. The upper four pictures are enlarged representative angles. The red arrows show the rough areas.

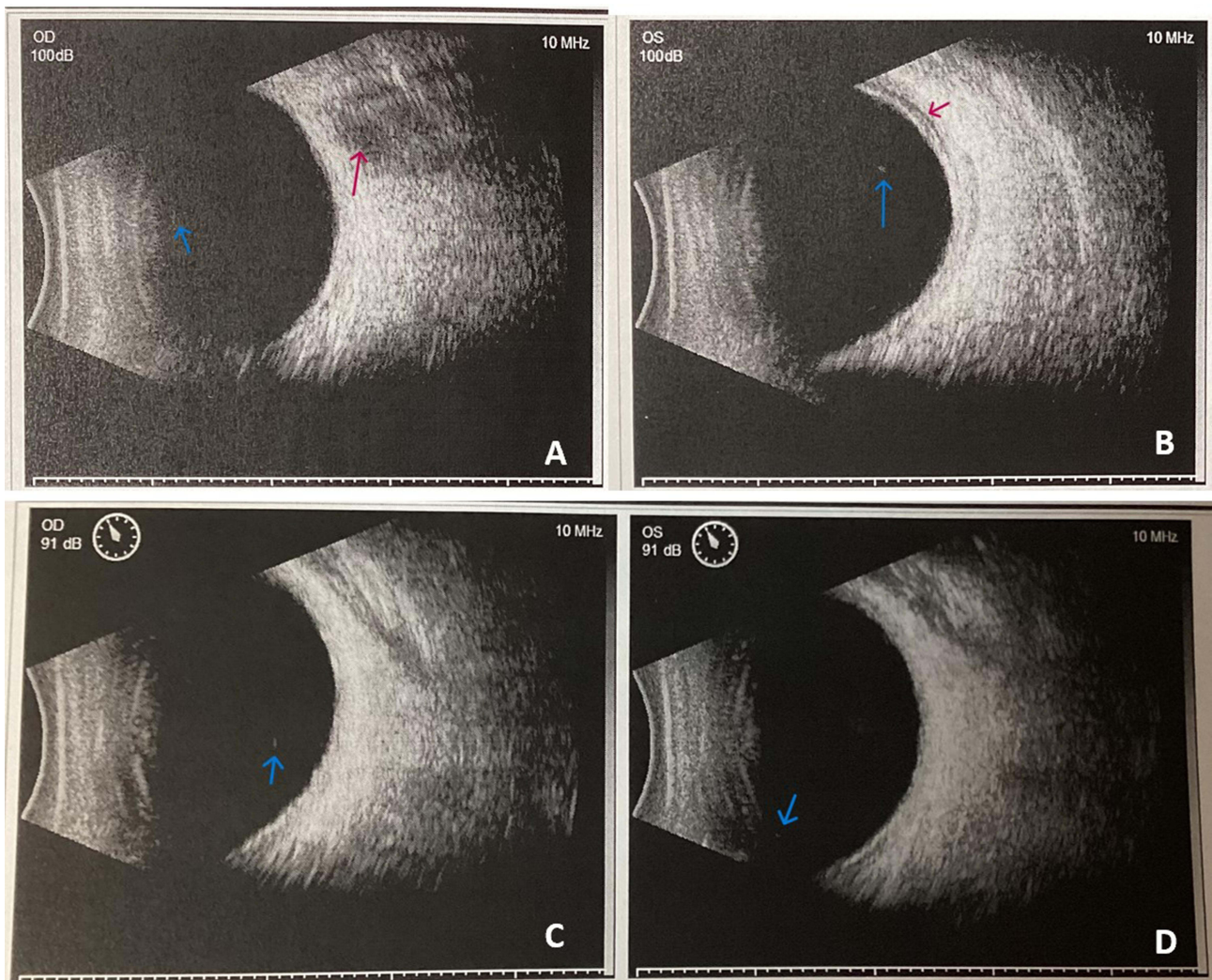


Figure 3 Ocular ultrasound examinations on days 1 (**A** and **B**) and 6 (**C** and **D**). Red arrows show the hypoechoic dark areas in the peripheral spherical walls of both eyes. Blue arrows show the punctate echoes in the vitreous humor. OD, right eye. OS, left eye.



Figure 4 Abdominal computed tomography scans on day 1 (A), day 3 (B), and day 11 (C). (A) acute pancreatitis with peripancreatic fluid accumulation. (B) a marked increase in peripancreatic fluid accumulation and exudation, (C) pancreatic and peripancreatic changes are markedly improved.

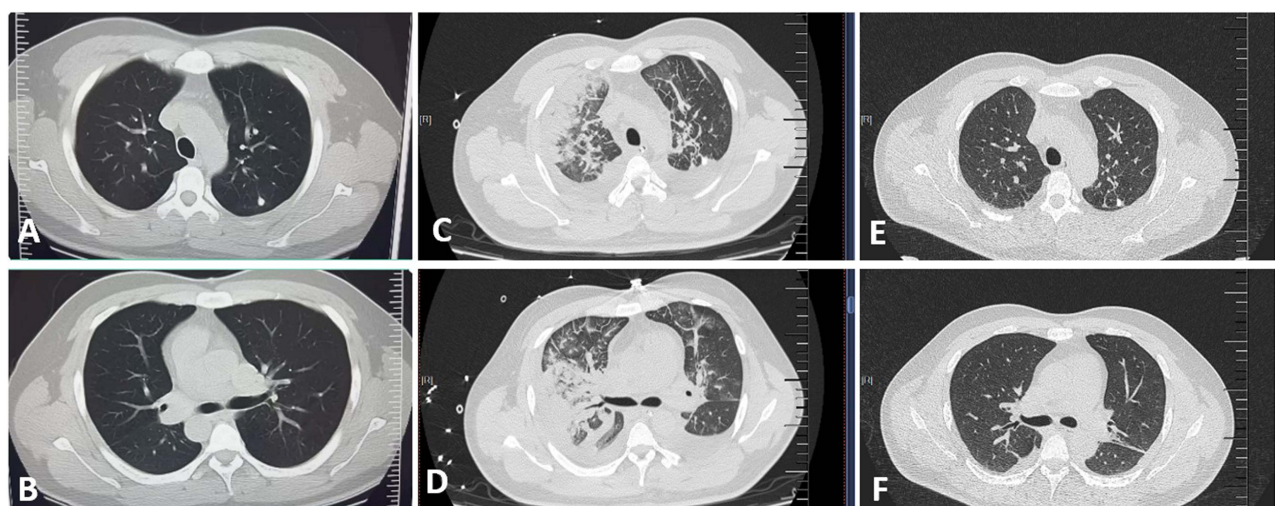


Figure 5 Chest computed tomography scans on day 1 (A and B), day 3 (C and D), and day 11 (E and F). (A and B) clear lungs. (C and D) bronchitis, bilateral lung inflammation, interlobular septal thickening, bilateral pleural effusions. (E and F), a marked improvement in inflammation and reduced pleural effusion.

protection.^{8,9} At the same time, the patient received intravenous mannitol (250 mL, once), brinzolamide (3 times a day), and brimonidine (3 times a day) eye drops to lower the IOP.

On day 3, the patient reported chest tightness, shortness of breath, worsened abdominal pain, and decreased 24-h urine output to 320 mL. A repeat abdominal CT scan showed a marked increase in peripancreatic fluid accumulation (Figure 4B). In addition, a chest CT scan showed interstitial pulmonary edema and bilateral pleural effusion (Figure 5C and D). Oxygen supplementation (high-flow nasal cannula with oxygen concentration 60% at a flow rate 40 L/min) was provided. Thoracentesis was performed to drain the pleural effusion. The laboratory test indicated a creatinine level increased to 607.3 $\mu\text{mol/L}$, and the amylase and lipase levels also increased to 41.3 U/L and 80.3 U/L, respectively. Fortunately, hepatic function and coagulation improved significantly. The platelet count was also increased to $63 \times 10^9/\text{L}$. Given the benefits of hemodiafiltration to reduce creatinine, eliminate inflammatory factors, and accurately control the fluid balance in the body, we decided to perform continuous hemodiafiltration on him. On hospital day 6, the IOP decreased to 13 and 14 mmHg in the right and left eyes, respectively, and blurry vision resolved (Figure 3C and D). His abdominal pain gradually resolved, but serum creatinine increased to reach a peak of 963.1 $\mu\text{mol/L}$ on hospital day 7. After continuous hemodiafiltration for an additional 22 h, the creatinine decreased to 471.5 $\mu\text{mol/L}$.

On day 11 after the hospital admission, a repeat CT scan showed significantly improved pancreatic inflammation and peripancreatic fluid accumulation (Figure 4C) and resolved bilateral pleural effusion (Figure 5E and F). We continued the regular hemodialysis for him due to renal insufficiency. On the 25th day of the hospital admission, the patient's condition

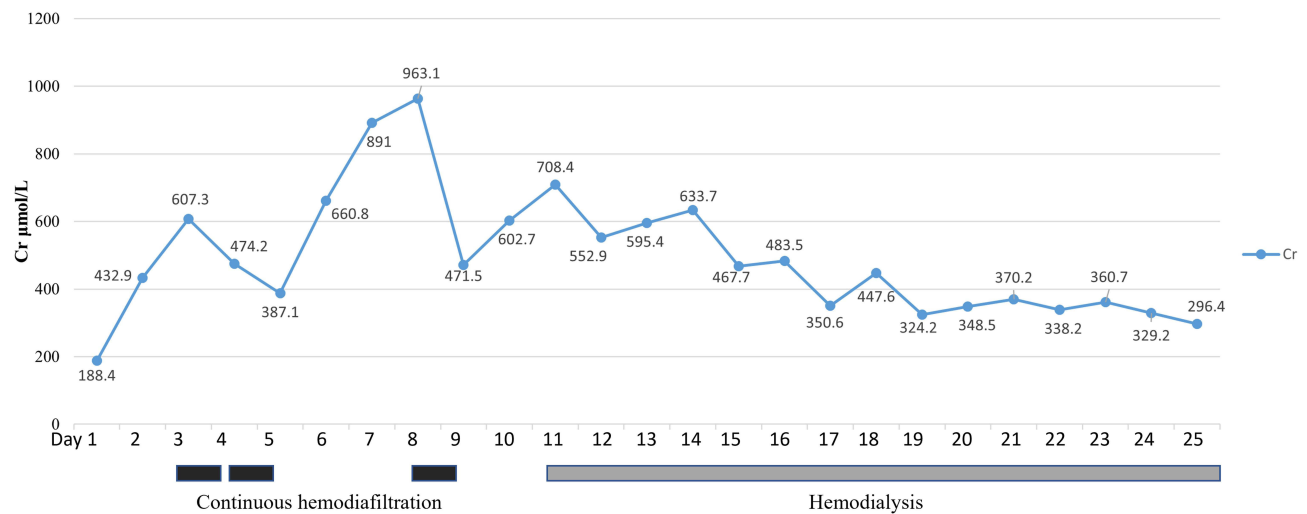


Figure 6 Dynamic change of the serum creatinine level ($\mu\text{mol/L}$) during the hospital admission. The continuous hemodiafiltration was performed for three sessions on days 3, 4, and 8 for 13, 12, and 10 h, respectively. Routine hemodialysis was initiated on day 11.

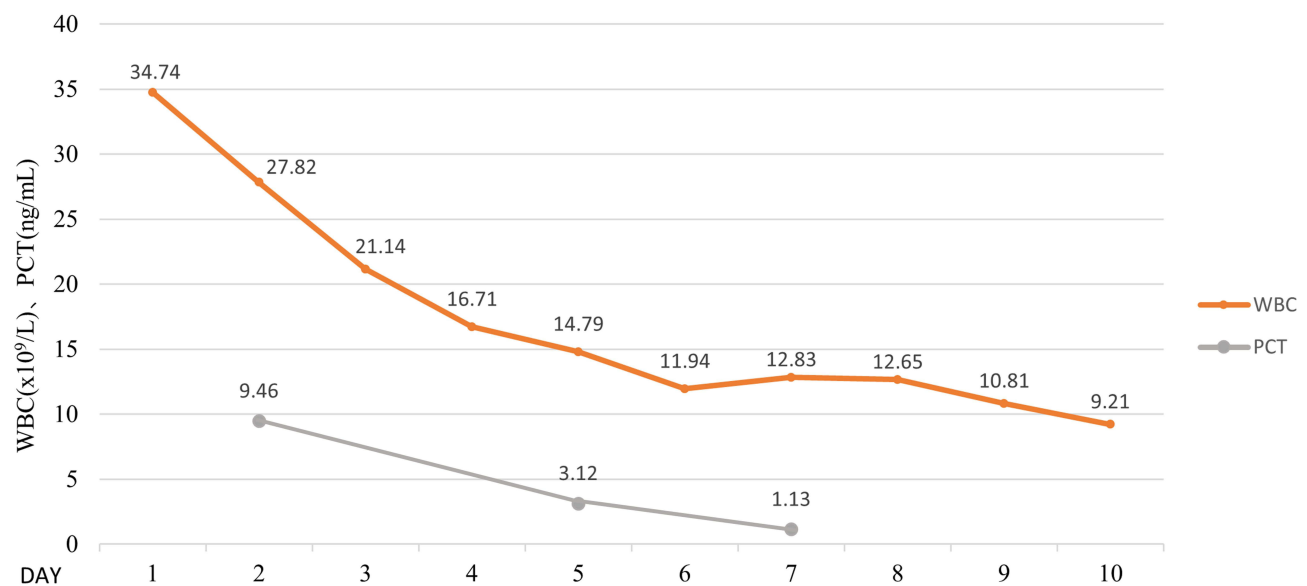


Figure 7 Dynamic changes in blood white blood cell (WBC) count and procalcitonin (PCT) level during hospital admission.

was stable, with no blurry vision. He was discharged from the hospital and instructed to follow up in the clinic for routine hemodialysis. The dynamic change of the serum creatinine level, white blood cell count, and procalcitonin levels during hospital admission is shown in Figures 6 and 7.

Discussion

HFRS is a rodent-borne disease primarily found in rural and forested areas. Our patient, who worked in a forest, presented with symptoms indicative of HFRS, including fever, petechiae rashes, coagulopathy, and renal failure. The diagnosis of HFRS was confirmed by detecting specific anti-HTNV IgM antibodies in the blood. Further evaluations revealed AP and increased IOP. The patient was treated successfully with appropriate interventions. The concurrent manifestation of AP and increased IOP in an HFRS patient, as observed in this case, has not been previously reported. This case serves as a reminder to clinicians of the importance of thorough evaluations in patients with HFRS, particularly the measurement of IOP in cases involving eye complaints, to reduce morbidity and mortality.

The diagnosis of HFRS relies on a recent exposure history, clinical presentations, and a serological result of HTNV IgM antibody. The underlying pathophysiology is vascular endothelial damage, increased capillary permeability, and coagulopathy.¹⁰ The severity and course of HFRS are determined primarily by the extent of increased permeability in infected endothelial cells.¹¹ Since HFRS can cause multiple organ failures, it is necessary to acquire a comprehensive evaluation of extrarenal syndromes to diagnose and treat these patients.¹² Currently, there is no established specific treatment protocol available for HFRS. Antiviral therapy with ribavirin was attempted at the early stage of the disease but with controversial results. The primary treatment for HFRS and AP is supportive care. Hemodialysis offers precise control of volume load, solute clearance, and cytokine and inflammatory mediator removal, which can significantly decrease the mortality rate.¹³

AP is an inflammatory response that activates endogenous pancreatic enzymes within the pancreas. Recently, some researchers have identified AP as a neglected and severe consequence of HTNV infection. During the HTNV infection, the patient can have capillary congestion and focal hemorrhages in the pancreas, with massive cytokine release, finally leading to pancreatitis. Therefore, HFRS patients with abdominal symptoms should be ruled out AP.

Our patient had eye involvement with increased IOP and blurry vision. Previous studies have shown that most HFRS patients with eye involvements presented with low IOP,¹⁴ although high IOP with glaucoma was occasionally reported.¹⁵ The elevation of IOP in HFRS patients might be due to the enhanced endothelial permeability and vascular leakage inside the eyes, which could be a pathological indicator for systemic small-vessel impairment and plasma leakage, signifying disease severity. Additionally, high IOP may contribute to headache and gastrointestinal symptoms in HFRS patients. The treatments are correction of coagulopathy and medications to decrease IOP. The IOP in these patients requires close monitoring to avoid permanent visual loss.

Pulmonary involvement is commonly observed in patients with HFRS. Factors such as thrombocytopenia and capillary leakage are believed to contribute to pulmonary complications.¹⁶ Recommended treatments include fluid restriction, oxygen therapy, respiratory support, diuretics, and hemodialysis.¹⁷ Initially, our patient had normal chest imaging; however, he developed respiratory symptoms, including pleural effusion and pulmonary edema, three days post-admission. This underscores the necessity for vigilant monitoring of HFRS patients during treatment to promptly identify any development of additional organ system failures throughout the disease course.

Conclusions

In conclusion, this case highlights a rare presentation of HFRS characterized by high IOP and multi-organ system failure. Comprehensive evaluation and close monitoring, with repeated assessments, particularly IOP measurement in patients presenting with eye complaints, are crucial for life-saving interventions and reducing morbidity in patients with HFRS.

Abbreviations

AP, acute pancreatitis; Cr, creatinine; EICU, Emergency intensive care unit; HFRS, Hemorrhagic fever with renal syndrome; HTNV, Hantaviruses; IOP, intraocular pressure; PCT, procalcitonin; SpO₂, oxygen saturation; WBC, white blood cell.

Data Sharing Statement

The datasets generated and analyzed during the present study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was approved by the ethics committee of The First Hospital of Jilin University. All procedures performed in studies involving human participants were per the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The patient has provided written informed consent to have the case details and accompanying images published.

Consent for Publication

The patient has provided written informed consent to have the case details and accompanying images published.

Acknowledgment

We thank Medjaden Inc. for assisting in preparing this manuscript.

Funding

There is no funding to report.

Disclosure

The authors declared no potential conflicts of interest for the research, authorship, and/or publication of this study.

References

1. Zou LX, Chen MJ, Sun L. Haemorrhagic fever with renal syndrome: literature review and distribution analysis in China. *Inter J Infect Dis*. 2016;43.
2. Romero MG, Anjum F. Hemorrhagic fever renal syndrome. *Statpearls*. Treasure island (fl): Statpearls publishing; 2023.
3. Guo Q, Xu J, Shi Q, Du B. Acute pancreatitis associated with hemorrhagic fever with renal syndrome: a cohort study of 346 patients. *BMC Infect Dis*. 2021;21(1):267. doi:10.1186/s12879-021-05964-5
4. Mehta S, Jiandani P. Ocular features of hantavirus infection. *Indian J Ophthalmol*. 2007;55(5):378–380. doi:10.4103/0301-4738.33827
5. Guo H, Chen J, Suo D. 奥曲肽联合乌司他丁治疗急性重症胰腺炎临床疗效及安全性分析 [Clinical efficacy and safety of ulinastatin plus octreotide for patients with severe acute pancreatitis]. *Zhonghua Yi Xue Za Zhi*. 2015;95(19):1471–1474. Chinese.
6. Li ZF, Xu MY, Zhang DH, Gao TT, Gao Z, Li H. Effects of ulinastatin combined with octreotide on blood coagulation function, inflammatory factors and amylase in patients with severe acute pancreatitis. *J Biol Regul Homeost Agents*. 2020;34(6):2147–2151. doi:10.23812/20-362-L
7. Meng L, Wu Z, Zhang H. Effect of ulinastatin combined with octreotide on serum endothelin, endotoxin levels and immune function in acute pancreatitis. *J Coll Phys Surg Pakistan*. 2019;29(1):90–92. doi:10.29271/jcpsp.2019.01.90
8. Gao W, Zhao Y, Guo L, et al. Comparative effectiveness of glycyrrhizic acid preparations aimed at improving liver function of patients with chronic hepatitis B: a network meta-analysis of 53 randomized controlled trials. *Phytomedicine*. 2023;116:154883. doi:10.1016/j.phymed.2023.154883
9. Liu X, Tian X, Ma Z, et al. Efficacy and safety of glycyrrhizic acid preparation treating comorbid liver injury in COVID-19: a systematic review. *Front Pharmacol*. 2022;13:1003697. doi:10.3389/fphar.2022.1003697
10. Fan H, Zhao Y, Song FC. Acute pancreatitis associated with hemorrhagic fever with renal syndrome: clinical analysis of 12 cases. *Renal Failure*. 2013;35(10):1330–1333. doi:10.3109/0886022X.2013.828187
11. Puca E, Harxhi A, Pipero P, et al. Pancreatitis in patients with hemorrhagic fever with renal syndrome: a five-year experience. *J Infect Develop Countries*. 2017;11(11):900–903. doi:10.3855/jidc.9567
12. Liu T, Yang W, Li K, Guo S, Tian M, Fang X. Hemorrhagic fever with renal syndrome complicated with acute pancreatitis and capillary cholangitis: a case report. *Infect Drug Resist*. 2022;15:6755–6761. doi:10.2147/IDR.S386273
13. Wang WJ, Zhao J, Yang JS, Liang MM, Ni MY, Yang JH. Clinical analysis of patients with acute pancreatitis complicated with hemorrhagic fever with renal syndrome and acute biliary pancreatitis. *Medicine*. 2020;99(5):e18916. doi:10.1097/MD.00000000000018916
14. Hautala N, Kauma H, Vapalahti O, et al. Prospective study on ocular findings in acute Puumala hantavirus infection in hospitalised patients. *Br J Ophthalmol*. 2011;95(4):559–562. doi:10.1136/bjo.2010.185413
15. Cho IH, Chang JH, Choo EJ. Bilateral simultaneous angle-closure glaucoma associated with septic condition of Korean hemorrhagic fever (KHF). *J Glaucoma*. 2015;24(1):81–83. doi:10.1097/IJG.0b013e318287ac5d
16. Rasmuson J, Andersson C, Norrman E, Haney M, Evander M, Ahlm C. Time to revise the paradigm of hantavirus syndromes? Hantavirus pulmonary syndrome caused by European hantavirus. *Eur J Clin Microbiol Infect Dis*. 2011;30(5):685–690. doi:10.1007/s10096-010-1141-6
17. Jiang H, Huang C, Bai X. Expert consensus on the prevention and treatment of hemorrhagic fever with renal syndrome. *Infect Dis Immu*. 2022;2(4):224–232. doi:10.1097/ID9.0000000000000054

Infection and Drug Resistance

Dovepress

Publish your work in this journal

Infection and Drug Resistance is an international, peer-reviewed open-access journal that focuses on the optimal treatment of infection (bacterial, fungal and viral) and the development and institution of preventive strategies to minimize the development and spread of resistance. The journal is specifically concerned with the epidemiology of antibiotic resistance and the mechanisms of resistance development and diffusion in both hospitals and the community. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/infection-and-drug-resistance-journal>