

## Case Report

# A case of hemorrhagic fever with renal syndrome and abnormal serum levels of ferritin, vitamin B<sub>12</sub>, and folic acid

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### Abstract

**Introduction:** Hemorrhagic fever with renal syndrome (HFRS) is a globally prevalent infectious disease caused by the hantavirus in rodents.

**Case study:** This report describes a case of a 36-year-old male presenting with elevated ferritin, vitamin B<sub>12</sub>, and folic acid deficiency during the early onset phase of HFRS. Despite normal renal function at admission, the patient exhibited persistent fever and thrombocytopenia, leading to a potential misdiagnosis of an atypical HFRS presentation. Abnormal serum levels of ferritin, vitamin B<sub>12</sub>, and folic acid served as early indicators of renal dysfunction in patients with HFRS. The patient's condition improved rapidly with a combination of vitamin B<sub>6</sub>, methyl cobalamin, and folic acid, as evidenced by a subsequent decrease in the ferritin levels, from 3000 to 600 ng/mL, on days 4 and 24, respectively, and an increase in the vitamin B<sub>12</sub> and folic acid levels to 200 pg/mL and 36.7 ng/mL, separately.

**Conclusions:** These findings suggest that ferritin, vitamin B<sub>12</sub>, and folic acid have the potential to serve as biomarkers for HFRS and play a predictive role in the diagnosis and treatment of the disease.

**Key words:** HFRS; ferritin; vitamin B<sub>12</sub>; folic acid.

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### Introduction

Hemorrhagic fever with renal syndrome (HFRS) is a rodent-borne disease caused by the hantavirus and is primarily transmitted through rodents. It is characterized by fever, bleeding, circulatory collapse with hypotension, and acute kidney injury [1]. HFRS is a global public health concern with a wide distribution. It is particularly prevalent in eastern Asia, notably in China, which has accounted for over 90% of HFRS cases worldwide in recent decades [2]. HFRS substantially burdens healthcare systems due to its impact on morbidity and mortality [3].

Hantaviruses primarily target the human endothelial cytokines that are commonly released early in HFRS, leading to the detection of high serum levels [4,5]. Ferritin is an acute-phase reactant synthesized by reticuloendothelial cells in response to viral infections such as Ebola, Epstein-Barr, human immunodeficiency, dengue, and coronavirus disease 2019 (COVID-19) [6-9]. Ferritin levels are elevated in severe HFRS cases. High serum ferritin levels hold promising potential as biomarkers for predicting disease severity and mortality [10]. Vitamin B<sub>12</sub>, also known as cobalamin, is an essential nutrient and a crucial cofactor in various biochemical reactions, including those that involve the

enzyme methionine synthase. Vitamin B<sub>12</sub> deficiency is commonly observed in patients with chronic kidney disease [11]. Folic acid is a B vitamin that occurs naturally in certain foods. It is an essential cofactor for methionine synthetase and other biochemical reactions and plays a crucial role in human health [12]. Vitamin B<sub>12</sub> and folic acid deficiencies may potentially contribute to renal anemia, and their supplementation can slow the progression of chronic kidney disease [13,14].

Here, we report a rare case of HFRS presenting with abnormal serum levels of ferritin, vitamin B<sub>12</sub>, and folic acid. Ferritin, vitamin B<sub>12</sub>, and folic acid may be promising predictors for diagnosing and treating HFRS.

### Case report

A 36-year-old male with no significant medical history was hospitalized with a fever and thrombocytopenia. On admission, the patient exhibited the following vital signs: blood pressure of 111/79 mmHg, heart rate of 106 beats per minute, and temperature of 38.6 °C. Laboratory tests revealed thrombocytopenia with a platelet count (PLT) of 49 × 10<sup>9</sup>/L (reference interval (RI): 125–350). Blood

chemistry analysis indicated an elevated C-reactive protein (CRP) level of 24.4 mg/L.

On the second day of hospitalization, the patient developed severe sepsis symptoms, including a fever of 38.7 °C. Hematological indices showed a gradual decline in platelet count (approximately  $24 \times 10^9/L$ ), along with significantly elevated inflammatory markers, such as CRP (92.2 mg/L) and procalcitonin (19.27 ng/mL). Complete clinical and laboratory results are provided in Table 1. Normal renal function, impaired liver function, and abnormal myocardial enzymes were observed. Despite negative blood culture results, the patient exhibited persistently elevated levels of CRP and procalcitonin, leading to suspicion of sepsis as a result of invasive bacterial infection. Bone marrow biopsy and hematological tumor immunophenotyping results were normal, and thrombocytopenia was attributed to immune thrombocytopenic purpura (ITP). Supportive therapy with piperacillin sodium-tazobactam sodium and Yiganling capsule were initiated, leading to subsequent clinical improvement.

On the fourth day, the patient experienced a sudden 24-hour fluid output of 800 mL. Urinalysis revealed abnormalities such as a relative density of 1.025, pH of 5.5, urobilinogen 1+ (approximately 16  $\mu\text{mol/L}$ ), urine occult blood 1+ (approximately 10 red blood cells/ $\mu\text{L}$ ), and protein 3+ (approximately 450 mg/L). Microscopic examination revealed the presence of red blood cells (0-1 cells per field at 200x magnification). Notably, despite normal renal function at this stage, the patient exhibited elevated ferritin levels, decreased vitamin B<sub>12</sub> levels, and reduced folic acid levels of approximately 3000 ng/mL (RI 4.63–204), 12.5 pg/mL (RI 5.21–20), and 0.375 ng/mL (RI 200–1100), respectively. These findings suggest that serum ferritin, vitamin B<sub>12</sub>, and folate levels may be early indicators of renal

dysfunction in patients with HFERS. The patient was administered a combination of vitamin B<sub>6</sub>, methylcobalamin, and folic acid as part of the treatment.

On the seventh day, the patient developed acute renal failure, evident through percussion of the kidney and a sudden 24-hour fluid output of 3700 mL. Blood chemistry analysis indicated increased levels of blood urea nitrogen (BUN) 19.81 mmol/L (RI 2.5–8.0) and creatinine (Cr) 957.6  $\mu\text{mol/L}$  (RI 40–106). However, the levels of inflammatory markers, including CRP (29.5 mg/L) and procalcitonin (4.04 ng/mL), were significantly decreased. Platelet count increased from 24 to  $153 \times 10^9/L$ . Based on clinical observations, the initial symptoms in the patient were characterized by fever and thrombocytopenia. Subsequently, acute kidney failure developed, leading to the potential risk of severe fluid overload. The clinical presentation strongly suggested a hantavirus infection associated with HFERS. Notably, the patient exhibited a four-stage progression: febrile, oliguric, polyuric, and convalescent, as observed during clinical assessment. A careful re-examination of the patient's history revealed exposure to rodents one month prior, leading to the identification of HFERS through a positive serological test for hantavirus infection. Supportive therapy remained the primary approach for patient care.

On the 24<sup>th</sup> day, the patient recovered and was discharged. BUN decreased gradually from 19.81 mmol/L to 6.02 mmol/L, while Cr decreased from 957.6  $\mu\text{mol/L}$  to 139.0  $\mu\text{mol/L}$ . Anemia indicators vitamin B<sub>12</sub> and folic acid levels individually increased to 200 pg/mL and 36.7 ng/mL. Ferritin levels gradually decreased from 3000 ng/mL on day four to 600 ng/mL on day 24. These indicators reflected positive improvements in the patient's condition.

**Table 1.** Clinical and laboratory features.

Features	Day 2	Day 4	Day 7	Day 24	RI	Units
PLT	24	33	153	207	125-350	$\times 10^9/L$
BUN	5.06	5.67	19.81	6.02	2.5-8.0	mmol/L
Cr	98.5	99.8	957.6	139	40-106	$\mu\text{mol/L}$
ALT	123.8	58.9	62.6	33.6	7-40	U/L
AST	198.2	94.0	49.4	20.9	9-50	U/L
CK	761.0	243.1	41.6	/	26-196	U/L
CK-MB	5.1	5.1	1.66	/	0-5	ng/mL
LDH	1102.8	687.6	127.9	/	109-245	U/L
MYO	153.4	411.1	375.9	/	0-94	ng/mL
CRP	92.2	41.7	29.5	/	0-10	mg/L
PCT	19.27	/	4.04	/	0-0.5	ng/mL
Ferritin	/	3000	/	600	4.63-204	ng/mL
Vitamin B <sub>12</sub>	/	12.5	/	200	200-1100	pg/mL
Folic acid	/	0.375	/	36.7	5.21-20	ng/mL

PLT: platelet count; BUN: blood urea nitrogen; Cr: creatinine; ALT: alanine aminotransferase; AST: aspartate transferase; CK: creatine kinase; CK-MB: creatine kinase isoform CK-MB; LDH: lactate dehydrogenase; MYO: myoglobin; CRP: C-reactive protein; PCT: procalcitonin; RI: reference interval.

## Discussion

HFRS is a rodent-borne viral disease caused by hantaviruses and is primarily transmitted through the inhalation of dust or aerosols contaminated with virus-containing rodent excretions, such as urine, faeces, or saliva [3]. The pathogenesis of HFRS involves viral infection and immune response targeting endothelial cells [15]. Excessive immune response characterized by a cytokine storm plays a central role in the development of HFRS, leading to vascular endothelial cell damage, increased capillary permeability, acute renal failure, and hemorrhage [16].

The incubation period of HFRS typically ranges from four to 45 days, with most cases manifesting within seven to 14 days. The clinical course of HFRS comprises five distinct phases: febrile, hypotensive, oliguric, diuretic, and convalescent. In severe cases, these phases may overlap, while in moderate cases, one or more phases may be absent [17]. Kidney injury and thrombocytopenia are the primary manifestations of HFRS. Acute kidney injury (AKI) is a common cause of mortality, particularly during the oliguric phase [18]. Additionally, acute thrombocytopenia serves as a significant laboratory finding throughout hantavirus infection [19]. Serologic tests, such as enzyme-linked immunosorbent assay (ELISA) for detecting IgM and IgG antibodies against hantavirus antigens, are the main diagnostic tools for suspected cases of HFRS.

The primary approach to treating HFRS is supportive care, with an emphasis on managing the clinical symptoms and manifestations of the disease. The treatment measures include antibacterial therapy, haemodialysis, fluid administration, diuretic therapy, and shock management. However, no specific antiviral treatments for HFRS are currently available. A meta-analysis was conducted to assess the clinical disease severity of hantavirus pulmonary syndrome (HPS) in ribavirin-treated patients [20]. However, the results indicated that ribavirin treatment did not significantly reduce mortality rates among patients with HPS. Besides, bivalent inactivated vaccines containing Hantaan and Seoul hantaviruses have been used in clinical practice in China. Regrettably, the protective response elicited by these vaccines has been transient [21]. Given the lack of effective antiviral therapy and vaccines, rodent control remains the primary strategy for preventing hantavirus infections.

Upon admission, the patient presented with fever and thrombocytopenia but exhibited normal renal function. Notably, the patient did not report any history of rodent exposure during the initial visit. The diagnosis of HFRS relies heavily on serological tests. However,

early-stage patients are susceptible to misdiagnosis owing to atypical clinical presentations. In this case, the patient exhibited high ferritin, vitamin B<sub>12</sub>, and folic acid deficiencies in the early-onset phase. Consequently, vitamin B<sub>12</sub> and folic acid supplementation were considered viable treatment options for the patient. Ferritin levels decreased as the patient's condition improved, and vitamin B<sub>12</sub> and folic acid levels returned to normal.

Ferritin, an essential component of the host immune system, is involved in the cellular defense against inflammatory responses [22]. A retrospective analysis involving 373 HFRS patients revealed significantly higher serum ferritin levels in severe patients (n = 108) compared to mild patients (n = 265), suggesting its potential as a prognostic marker for disease severity and mortality [10]. Additionally, a few cases reported that patients with HFRS had significantly increased serum ferritin levels [23,24]. Vitamin B<sub>12</sub> levels have been shown to enhance postoperative AKI risk stratification accuracy and enable early management of patients [25]. Folic acid supplementation improves endothelial nitric oxide synthase dysfunction [26]. The levels of vitamin B<sub>12</sub> and folic acid in the plasma of 29 HFRS patients were significantly reduced. Thus, the folic acid pathway may be a therapeutic target for treating erythropoiesis disorders in patients with HFRS [27]. Hence, vitamin B<sub>12</sub> and folic acid supplementation may serve as therapeutic interventions for HFRS patients.

## Conclusions

In conclusion, we have presented the first reported case of HFRS associated with abnormal serum levels of ferritin, vitamin B<sub>12</sub>, and folic acid. Ferritin, vitamin B<sub>12</sub>, and folic acid have the potential to serve as promising biomarkers for HFRS and predictors of treatment outcomes. Early-stage HFRS cases may pose diagnostic challenges owing to their atypical presentations, emphasising the importance of prompt diagnosis and timely therapeutic interventions for improved prognosis.

## Ethical approval

Informed consent was obtained from the patient.

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