


# Acute Pancreatitis and Leukemoid Reaction as the Presenting Manifestation of Hemorrhagic Fever with Renal Syndrome: A Case Report

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**Background:** Hemorrhagic fever with renal syndrome (HFRS), caused by Orthohantavirus hantaanense (HTNV) infection, is characterized by a range of symptom including fever, hemorrhage, and renal impairment. Acute pancreatitis and leukemoid reaction associated with HFRS have been less frequently reported.

**Case Presentation:** A 20-year-old male presented with fever, dizziness, and gastrointestinal symptom, which progressed to acute pancreatitis and leukemoid reaction. Despite initial treatment, his condition worsened, necessitating transfer to a tertiary care facility. Upon admission, the patient exhibited signs of organ dysfunction, and laboratory tests confirmed leukocytosis and thrombocytopenia, with imaging suggestive of pancreatitis. HTNV antibody test results were positive.

**Discussion:** This case illustrates the complexity of diagnosing HFRS when the disease presents atypically. The symptom that are shared with other conditions can lead to misdiagnosis. Treatment of HFRS patients requires a multidisciplinary approach, with particular attention to the timing and type of therapy to manage complications effectively.

**Conclusion:** This report emphasizes the importance of recognizing atypical presentations of HFRS and the benefits of a prompt and comprehensive treatment strategy. Early diagnosis and a tailored therapeutic approach are crucial for improving patient outcomes in such rare and complex cases. The case underscores the necessity for clinicians to be vigilant for secondary symptom of HFRS, particularly in high-incidence regions, and the role of early diagnosis and treatment in improving outcomes.

**Keywords:** hemorrhagic fever with renal syndrome, hantavirus, acute pancreatitis, leukemoid reaction

## Introduction

Hemorrhagic fever with renal syndrome (HFRS) is an acute zoonotic disease caused by Orthohantavirus hantaanense (Hantaan virus, HTNV) infection, that is characterized primarily by fever, shock, hemorrhage, and kidney damage. HTNV primarily uses rodents as its main carrier of infection and spreads to humans through rodent blood, urine, faeces, and aerosols.<sup>1,2</sup> HTNV has broad tissue tropism and directly damages vascular endothelial cells, resulting in increased vascular permeability and decreased barrier function of the vascular wall, leading to vascular leakage and plasma extravasation.<sup>3</sup> Furthermore, HTNV infection can trigger strong innate and adaptive immune responses that collectively lead to multiorgan dysfunction.<sup>4</sup>

The typical clinical manifestations of HFRS patients include the “three pains” (headache, eye pain, and lower back pain), the “three redness” (redness of the face, neck, and upper chest), capillary congestion, and hemorrhagic signs. The course of HFRS can be divided into five stages: fever, hypotensive shock, oliguria, polyuria, and restoration.<sup>3,5</sup> Owing to endothelial damage and the inflammatory response, HFRS leads to multiorgan dysfunction, including pulmonary edema, cardiac insufficiency, cerebral hemorrhage and acute renal failure. Gastrointestinal damage in HFRS often presents as

nausea, vomiting, and abdominal pain, whereas pancreatic damage is rarely reported. Hematological damage primarily manifests as mild leukocytosis, thrombocytopenia, and lymphopenia, with leukemoid reaction being uncommon. Recently, the emergency department of Xiangya Hospital admitted an HFRS patient presented primarily with acute pancreatitis combined with leukemoid reaction. The patient's medical history, clinical manifestations, auxiliary examinations, and treatment process are summarized below.

## Case Presentation

The patient is a 20-year-old male who, four days prior (on June 3, 2024), experienced fever and dizziness without any obvious cause from Hunan province of China. His body temperature fluctuated between 36.5 °C - 38.6 °C, followed by abdominal pain, bloating, lower limb soreness, nausea, and vomiting. Abdominal computed tomography (CT) at the local hospital indicated acute pancreatitis. Despite treatment, his symptom progressively worsened, accompanied by a decrease in blood pressure and reduced urine output, leading to his transfer to our hospital. The patient said that there were some wild mice roaming around in his home.

On admission, physical examination revealed: a body temperature 36.5 °C, respiratory rate of 25 breaths per minute, pulse of 115 beats per minute, blood pressure of 84/52 mmHg, acute physiology and chronic health evaluation (APACHE II) score of 12, sequential organ failure assessment (SOFA) score of 8. The patient exhibited clear consciousness, and a distressed facial expression. Scattered wet rales were heard in both lower lungs, and the heart rate was 115 beats per minute with a regular rhythm and no obvious murmurs. The abdomen was flat without significant tenderness or rebound pain, the bowel sounds were normal, there was no shifting dullness, and there was no significant edema in the extremities. Laboratory tests revealed the following results: a complete blood count showed a white blood cell count (WBC) count of  $57.6 \times 10^9/L$ , a neutrophil count of  $39.9 \times 10^9/L$ , 2% promyelocytes and late promyelocytes, a monocyte count of  $8.4 \times 10^9/L$ , a lymphocyte count of  $8.3 \times 10^9/L$ , 7% atypical lymphocytes, and a platelet count of  $24.0 \times 10^9/L$ . Liver function tests indicated an albumin level of 25.9 g/L, an alanine aminotransferase (ALT) level of 25.9 U/L, an aspartate aminotransferase (AST) level of 129.1 U/L, and a direct bilirubin level of 3.6  $\mu\text{mol/L}$ . Renal function tests revealed a creatinine (Cr) concentration of 273  $\mu\text{mol/L}$  and a blood urea nitrogen (BUN) of 16.2 mmol/L. Cardiac enzymes revealed a lactate dehydrogenase (LDH) level of 1379 U/L, creatine kinase (CK) level of 2813.3 U/L, and myoglobin level of 841.2  $\mu\text{g/L}$ . Amylase levels were 59.8 U/L in the blood and 282.1 U/L in the urine. Urinalysis indicated proteinuria (++) and hematuria (+++) (Table 1).

An abdominal CT scan (June 6 2024) revealed pancreatic swelling with peripancreatic exudate and perirenal fluid accumulation, highly suggestive of pancreatitis, along with a small amount of fluid in the abdominal and pelvic cavities (Figure 1a). Bone marrow aspiration (June 7 2024) revealed active hyperplasia, increased segmented neutrophils in the granulocyte series, normal erythroid hyperplasia, increased atypical lymphocytes, and platelet clusters. The peripheral blood smear revealed increased white cell distribution, and increased numbers of band cells, monocytes, and atypical lymphocytes, with visible myelocytes and erythroblasts (Figure 2a and b). HTNV antibody test results were positive for both IgM and IgG (June 11 2024). The treatment included fasting, empiric anti-infective treatment with meropenem, and supportive care, such as the inhibition of pancreatic enzyme secretion. The patient's urine output decreased, and on the evening of the sixth day of illness, he developed polypnea and dyspnea. Arterial blood gas analysis revealed a significant decrease in arterial oxygen pressure and oxygenation index, for which high-flow nasal cannula oxygen therapy (FiO<sub>2</sub> 40%, 30 L/min) and intermittent renal replacement therapy were administered. The patient's laboratory test results during the treatment are summarized in Table 1. The APACHE II and SOFA scores are shown in Table 2, and the dynamic changes in the WBC count, platelets count, and pancreatic injury markers levels are shown in Figure 3.

On the 13th day of illness, the patient experienced a significant increase in urine output and a notable relief of dyspnea. High-flow nasal cannula oxygen therapy was switched to nasal cannula oxygen therapy at FiO<sub>2</sub> 2 L/min. Laboratory tests revealed improvement: the WBC count was  $6.8 \times 10^9/L$ , the platelet count was  $78 \times 10^9/L$ , and the Cr concentration was 444.4  $\mu\text{mol/L}$  (Table 1). Compared with previous scans, a follow-up abdominal CT scan (June 14 2024) showed reduction in pancreatic swelling and decreased peripancreatic and perirenal exudation compared to previous scans (Figure 1b). On the 15th day, the patient's condition improved, and he was discharged from the hospital. The stages and duration of the patient's illness are illustrated in Figure 4.

**Table 1** The Changes of Laboratory Parameters During Patient's Hospitalization

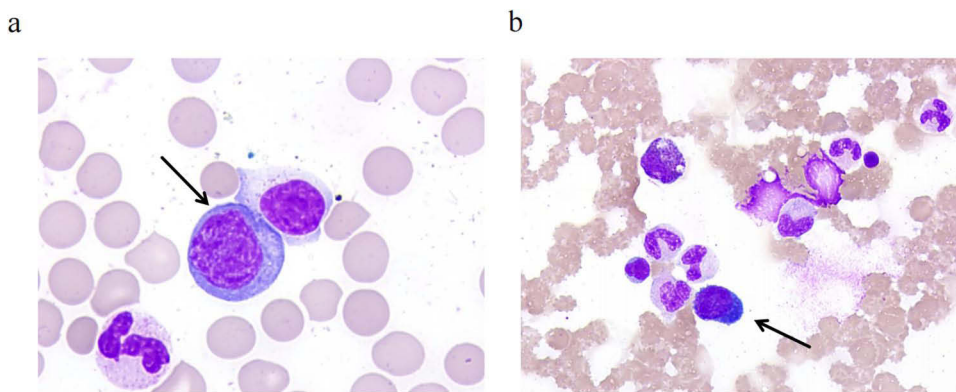
	Reference range	Day 4 POS	Day 5 POS	Day 6 POS	Day 7 POS	Day 8 POS	Day 9 POS	Day 10 POS	Day 12 POS	Day 13 POS	Day 15 POS	Day 42 POS
WBC ( $10^9/L$ )	3.5–9.5	57.6	55.4	43.5	28.8	17.7	–	9.1	6.8	6.6	5.6	8.6
Neu ( $10^9/L$ )	1.8–6.3	39.9	33.3	24.2	18	10.6	–	4.9	4	3.8	3	5.1
RBC ( $10^{12}/L$ )	4.3–5.8	5.91	4.42	3.54	3.65	3.44	–	3.37	3.16	3.24	3.2	3.91
PLT ( $10^9/L$ )	125–350	24	15	20	29	28	–	54	78	108	163	234
Mono ( $10^9/L$ )	3.0–10	8.4	10.2	4.4	4	2.6	–	1.5	0.9	0.6	0.6	0.6
Lym ( $10^9/L$ )	1.1–3.2	8.3	11	14.4	6.4	4.2	–	2.4	1.7	2	1.9	2.6
Ab Lym (%)	<2	7	5	5	5	–	–	–	–	–	–	–
CRP (mg/L)	0–6	–	64.7	–	–	–	–	29.5	–	–	–	–
AST (U/L)	15–40	129.1	94.7	82.5	63.5	–	28	25.5	33.3	35.1	39.5	21.4
ALB (g/L)	40–55	25.9	24.2	25.3	26.6	26.5	26.8	26	27.6	33	35.3	47.7
LDH (U/L)	120–250	1379	1083	–	834	653	538	–	–	–	390	–
CK (U/L)	50–310	2813.3	1439.1	–	189.6	125.3	65.3	–	–	–	98.1	–
Myo (U/L)	<70	841.2	599.3	–	198.6	239.4	151.9	–	–	–	55.8	–
AMY (U/L)	35–135	59.8	–	–	–	–	252	316.4	388.5	407.1	302.8	82.5
LPS (U/L)	13–60	–	–	–	–	–	158.8	189.6	291	298.6	185	40.6
Cr ( $\mu\text{mol/L}$ )	41–111	273	433.1	629.9	653.2	–	453.9	628.4	444.4	369	149.6	70
APTT(s)	22.3–32.5	43.4	–	–	30	–	28.2	–	27.2	28	27.4	–
D-D (mg/L)	0–0.5	0.72	–	–	4.96	–	2.19	–	2.16	3.6	4.36	–
PaO <sub>2</sub> / %FiO <sub>2</sub>	>300	538	486	78	74	91	93	285	298	333	–	–

**Abbreviations:** POS, post of symptom; WBC, white blood cell; Neu, neutrophil; RBC, erythrocyte; PLT, platelet; Mono, monocyte; Lym, lymphocyte; Ab Lym, Abnormal lymphocyte; CRP, C-reactive protein; PCT, procalcitonin; AST, aspartate aminotransferase; ALB, albumin; LDH, lactate dehydrogenase; CK, creatine kinase; Myo, myoglobin; AMY, amylase; LPS, lipase; Cr, creatinine; APTT, activated partial thromboplastin time; D-D, D-dimer; PaO<sub>2</sub>/%FiO<sub>2</sub>, oxygenation index.

At a follow-up on the 42nd day of illness, the patient's urine output had returned to normal, and routine blood examination revealed a WBC count of  $8.6 \times 10^9/L$  and a platelet count of  $234 \times 10^9/L$ . Renal function tests revealed a BUN of 2.46 mmol/L and a Cr of 70  $\mu\text{mol/L}$ , and amylase and lipase levels had returned to normal. HTNV IgG and IgM antibodies were negative (July 14 2024). Abdominal CT scans (July 14 2024) revealed that the swelling of the



**Figure 1** Abdominal computed tomography scans on day 3 POS. (a), day 12 POS (b), and day 42 POS (c). (a) Acute pancreatitis was accompanied by significant pancreatic swelling, peripancreatic and perirenal effusion, left arrow point perirenal effusion, right arrow point peripancreatic effusion; (b) A improvement in pancreatic, peripancreatic and perirenal changes, the arrow point peripancreatic effusion improvement; (c) Pancreatic and peripancreatic changes were nearly to the normal, the arrow points pancreas.



**Figure 2** The abnormal lymphocytes in Peripheral blood and bone marrow. (a) Peripheral blood smear, the arrow points abnormal lymphocytes. (b) bone marrow smears, the arrow points abnormal lymphocytes. The smears were stained with Wright's stain (×1000).

pancreatic body and tail improved, with almost complete absorption of peripancreatic and perirenal exudate and resolution of the pleural and abdominal effusions (see Figure 1c).

### Discussion

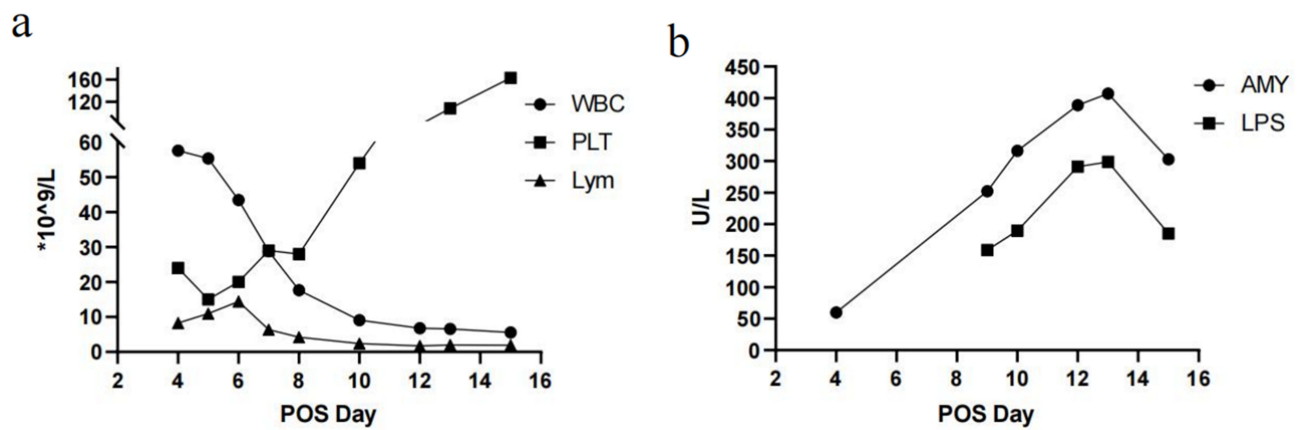
This case reports the successful treatment of a patient with HFRS who presented primarily with acute pancreatitis (AP) and leukemoid reaction. The main symptom of this patient were fever, abdominal distension, and lower back pain at the onset, and he was subsequently admitted to our hospital for “fever and abnormal blood count investigation”. Despite the absence of typical clinical manifestations of “three rednesses and three pains” clinical manifestations and no clear epidemiological history, we rapidly diagnosed this case as HFRS. For the AP, treatment included fasting and the use of somatostatin to inhibit pancreatic enzyme secretion. For the leukemoid reaction, bone marrow aspiration and smears were conducted to determine the cause, platelet transfusion was administered to increase platelet counts, and empirical anti-infection treatment with meropenem was given. For acute renal failure, continuous renal replacement therapy was provided. Through timely and accurate diagnosis and comprehensive treatment, the patient’s condition was effectively controlled. His WBC and platelet count gradually returned to normal, the pancreatitis-related radiographic findings improved, and his renal function recovered. This case highlights the importance of multidisciplinary comprehensive treatment in the management of HFRS.

In recent years, AP has been increasingly recognized as a rare but severe complication of HFRS, that is closely associated with disease severity and mortality. Notably, diagnosing AP in HFRS patients can be challenging, as both conditions share common symptom and signs, such as nausea, vomiting, and abdominal pain, which can easily lead to a missed diagnosis of HFRS.<sup>6,7</sup> Unlike general pancreatitis, the initial symptom of HFRS-related AP usually included fever, thrombocytopenia, and oliguria.<sup>8,9</sup> Other laboratory results, such as the WBC count, platelet count; amylase, bilirubin, and Cr levels; activated partial thromboplastin time; and blood calcium levels, may vary during hospitalization.<sup>7,10</sup> Studies have identified several independent risk factors for the occurrence of AP in HFRS patients, including a history of alcohol consumption, a high lymphocyte percentage, high proteinuria, high levels of fibrinogen degradation products, low levels of D-dimer, age, and the time from symptom onset to hospital admission.<sup>11,12</sup>

**Table 2** The Changes of APACHE II Score and SOFA Score

	Day 4 POS	Day 6 POS	Day 10 POS	Day 15 POS
APACHE II score	12	17	8	6
SOFA score	8	12	8	2

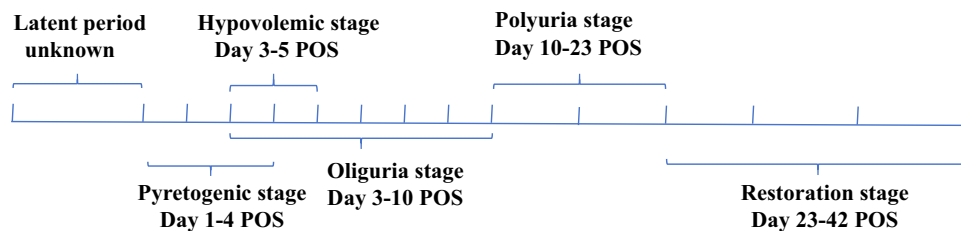
**Note:** APACHE II score: acute physiology and chronic health evaluation, aggregate score of 71, score ≥15 classified as serious, score <15 classified as non-critical; SOFA score: sequential organ failure assessment, aggregate score of 24, score ≥2 diagnosed as sepsis.



**Figure 3** Dynamic changes in WBC, PLT, Lym, AMY and LPS levels during hospital admission.

**Note:** (a) ● represent WBC, ■ represent PLT, ▲ represent Lym, (b) ● represent AMY, ■ represent LPS.

**Abbreviations:** WBC, white blood cell; PLT, platelet; Lym, lymphocyte; AMY, amylase; LPS, lipase.



**Figure 4** The date change of clinical stages of HFRS.

**Abbreviations:** POS, post of syndrome.

Additionally, the occurrence of AP is independently associated with increased mortality in HFRS patients.<sup>7</sup> The mechanism of injury in HFRS-related AP likely involves hantavirus-induced swelling of vascular endothelial cells, which prompted the release of large amounts of cytokines, the activation of immune cells, and a complement-mediated inflammatory cascade, that ultimately leads to pancreatitis.<sup>13,14</sup> Studies have shown that high levels of viral replication in microvascular endothelial cells do not cause cytopathic effects but lead to microvascular leakage. These findings suggest that hantaviruses disrupt the endothelial cell barrier by inducing vascular endothelial growth factor and downregulating VE-cadherin.<sup>15</sup> The present patient had upper abdominal distension and pain upon admission, with tenderness on palpation and hypoactive bowel sounds. On the 4th day after onset, blood amylase levels were normal (59.8 U/L), AST was 129.1 U/L, and ALT was normal. However, abdominal CT had already revealed pancreatic swelling and peripancreatic exudation, accompanied by elevated inflammatory and infection markers such as CRP and PCT. After treatment for pancreatitis with fasting, somatostatin, and proton pump inhibitors, the patient's blood amylase and lipase levels peaked on the 13th day of illness, whereas his AST levels had decreased to normal values. These findings suggest that the indicators of pancreatic injury related to HFRS peak approximately two weeks after symptom onset, which is consistent with reports by Kilit, Liu, and Yang.<sup>16-18</sup> Interestingly, before reaching the peak of pancreatic injury, by the 12th day of illness, the patient's abdominal CT showed improvement in pancreatic swelling and peripancreatic exudation. In Liu's case report, a comparison of abdominal CT scans taken on the 5th and 15th days of illness showed significant improvement in pancreatic swelling and peripancreatic and perirenal exudation by the 15th day. Similarly, in Yang et al's case, a comparison of abdominal CT scans on the 4th, 6th, and 14th days of symptom revealed that the pancreatic swelling and peripancreatic exudation significantly worsened by the 6th day but markedly improved by the 14th day.<sup>16,17</sup> These imaging changes were similar to those in the current case, indicating that the imaging findings of HFRS-related AP improves significantly approximately two weeks after onset. Therefore, the deterioration of imaging associated with HFRS-related AP occurs earlier than the increase in serum amylase and lipase, and imaging improvement also precedes

the decrease in AMS and LPS. This may serve as a key point in differentiating HFRS-related AP from AP caused by other etiologies.

Reports of HFRS patients with concurrent leukemoid reaction apart from AP are rare. HTNV primarily affects the blood system, causing both decreased platelet counts and impaired function, which can lead to bleeding and thrombosis, closely correlating with disease severity.<sup>19,20</sup> In this case report, the patient experienced a significant progressive decline in platelets after symptom onset and maintained low levels during the febrile, hypotensive, and oliguric phases. Platelet counts normalized by the 13th day of symptom, aligning closely with the findings of Rao et al.<sup>21</sup> Previous studies have suggested that platelet reduction and dysfunction in HFRS patients may result from activation, consumption, and subsequent exhaustion.<sup>22</sup> However, recent research has indicated that Puumala virus (PUUV) does not directly interact with platelets or megakaryocytes or affect platelet generation, activation, maturation, or aggregation. Instead, PUUV indirectly promotes platelet sequestration in the circulation by infecting endothelial cells and enhancing immune-mediated thrombus formation, which may exacerbate platelet dysfunction and depletion.<sup>23</sup> On the other hand, in the early stages of HFRS, patients typically present with normal or decreased WBC counts, which may subsequently increase significantly around 3rd-4th day, albeit with fewer occurrences of leukemoid reaction. In this case, the patient's WBC count was remarkably elevated at  $57.6 \times 10^9/L$  on the 4th day after symptom onset. The number of lymphocytes in the peripheral blood was notably increased, and this was accompanied by the presence of abnormal lymphocytes in both the bone marrow and the peripheral blood. The neutrophil-to-lymphocyte ratio (N/L) was as high as 4.8, which could easily lead to misdiagnosis as acute leukemia. Notably Nusslag et al reported a correlation between the N/L ratio at admission in HFRS patients and hospital stay duration, as well as changes in the serum Cr concentration.<sup>24</sup> Generally, in the early stages, virus-induced leukocytosis may be associated with innate immune responses that aid in virus clearance or control at low levels. In the middle to later stages, adaptive immune responses mediated by various lymphocytes begin to play an active role.<sup>25</sup> Tomas found that in acute PUUV-HFRS patients, HTNV infection activates neutrophils in the blood through endothelial cells, leading to significant increases in myeloperoxidase, neutrophil elastase, and interleukin-8 (IL-8) levels, but no direct evidence that PUUV directly activates neutrophil granules was reported.<sup>26</sup> Additionally, an increase in monocytes during the acute phase of HFRS also contributes to neutrophil activation.<sup>27,28</sup> Tang conducted monocyte phenotypic analysis on blood samples from 85 HFRS patients and reported that the downregulation of CD226 inhibited the expression of HLA-DR/DP/DQ and CD80, thereby promoting immune evasion of PUUV.<sup>29</sup> Hepojoki et al found that HTNV directly activates B lymphocytes, leading to the production of polyclonal IgG and free light chains, which may be associated with acute kidney injury.<sup>30</sup> Previous studies have linked increased free light chains to pulmonary diseases.<sup>31</sup> During in vitro experiments, Zhang et al discovered that IL-15 produced by HTNV-infected umbilical vein endothelial cells induces bystander activation of CD8<sup>+</sup> T cells through NKG2D, which may mediate cytotoxic effects on virus-infected endothelial cells during HFRS and contribute to endothelial cell damage.<sup>32</sup> Researchers have also reported that free DNA in the serum of HFRS patients (possibly from apoptotic or necrotic cells) may contribute to abnormal leukocytosis.<sup>33</sup> Thus, the leukemoid reaction caused by HTNV infection likely results from the combined effects of virus-induced innate and adaptive immune responses, abnormal activation of neutrophils and monocytes, direct activation of B/T lymphocytes, and the presence of free DNA in the serum. However, further research is needed to clarify the specific mechanisms involved.

HFRS might pose a global public health threat, particularly in Asia and Eastern Europe.<sup>2,5</sup> The population transmission of HFRS is prone to occur in high-incidence areas during high-incidence seasons. Once the diagnosis is missed, misdiagnosed, or the treatment is delayed, it could augment the complexity of treatment and medical costs. It is acknowledged that the prevalence of HFRS is closely associated with the habitat of rodents.<sup>2,3</sup> Environmental management measures, such as rodent control and habitat clearance, are typically requisite to control the HFRS epidemic. These measures are frequently costly and challenging to implement comprehensively. Once this case was diagnosed, it was reported to the public health system of Hunan Province, and the local health system carried out an epidemiological investigation and evaluation at the place of its residence. Hence, early diagnosis is conducive for public health workers to initiate prevention and control measures for HFRS promptly. It is also advantageous for public health departments to assess the epidemic trend timely and take precautionary measures in advance. Moreover, it can provide effective health education to the public and enhance the community's awareness and ability to respond to the disease. At the same time, it

assists in establishing an effective disease surveillance system to guarantee that the epidemic can be identified in the early stages, appropriate control measures can be adopted in a timely manner, the poor prognosis of individual cases can be mitigated, and the outbreak of a larger-scale epidemic can be precluded. The main limitation of this case is that neither the nested PCR nor PCR was performed to determine the species/variant of hantavirus, which would be helpful for studying the epidemiology of HFRS in this area.

## Conclusion

In summary, this case report presents a rare case of HFRS in which the primary feature was AP combined with leukemoid reactions. Through epidemiological observation, meticulous clinical observation, comprehensive physical examinations, and targeted laboratory tests, we were achieved early diagnosis and promptly initiated multidisciplinary comprehensive treatment. The successful management of this case underscores the importance for clinicians to maintain a high degree of vigilance and diagnostic acumen when confronted with atypical symptom. Particularly in regions with a high incidence of HFRS, health care providers should pay closer attention to secondary symptom that might otherwise be overlooked, as these could serve as early indicators of HFRS.

## Abbreviations

HFRS, hemorrhagic fever with renal syndrome; HTNV, Orthohantavirus hantaanense (Hantaan virus); APACHE II, acute physiology and chronic health evaluation; SOFA sequential organ failure assessment; WBC, white blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr creatinine; BUN blood urea nitrogen; LDH, lactate dehydrogenase; CK creatine kinase; CT, computed tomography; POS, post of symptom; AP, acute pancreatitis.

## Ethics Approval and Informed Consent

Consent for this case report was obtained from the patient and approved by the clinical ethics committee of Xiangya Hospital, Central South University (IRB{C}NO202407013).

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## Disclosure

The authors report no conflicts of interest in this work.

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