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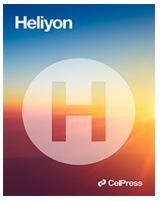

Case report

Characteristics of the Hantaan virus complicated with SARS-CoV2 infection: A case series report

Han-Dong Zhao [a], Jian-Wu Li [b], Ze-Kun Wang [c], Hong-Bo Qian [d], Kui Fu [e], Hong-Li Liu [f,*]

[a] *Central Laboratory of Virology, Shaanxi Provincial Hospital of Infectious Diseases, The Eighth Hospital Affiliated to Medical College of Xi'an Jiaotong University, Xi'an, 7100613, China*
[b] *Department of Infectious Diseases, Shaanxi Provincial Hospital of Infectious Diseases, The Eighth Hospital Affiliated to Medical College of Xi'an Jiaotong University, Xi'an, 710061, China*
[c] *Department of Radiology, Shaanxi Provincial Hospital of Infectious Diseases, The Eighth Hospital Affiliated to Medical College of Xi'an Jiaotong University, Xi'an, 710061, China*
[d] *Clinical Laboratory Center, Shaanxi Provincial Hospital of Infectious Diseases, The Eighth Hospital Affiliated to Medical College of Xi'an Jiaotong University, Xi'an, 710061, China*
[e] *Section of Science and Education, Shaanxi Provincial Hospital of Infectious Diseases, The Eighth Hospital Affiliated to Medical College of Xi'an Jiaotong University, Xi'an, 710061, China*
[f] *Clinical Laboratory Center, Xi'an People's Hospital (Xi'an Fourth Hospital) Guang-Ren Hospital Affiliated to Xi'an Jiaotong University Health Science Center, Xi'an, 710004, China*

A R T I C L E I N F O

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A B S T R A C T

Background: Coinfection poses a persistent threat to global public health due to its severe effect on individual-level infection risk and disease outcome. Coinfection of SARS-CoV2 with one or more pathogens has been documented. Nevertheless, this virus co-infected with the Hantaan virus (HTNV) is rarely reported.

Case summary: Here, we presented three cases of HTNV complicated with SARS-CoV2 infection. Not only the conditions including general clinical manifestations, immune and inflammation parameters fluctuation presented in the single infection of HTNV or SARS-CoV2 can be found, but also the unexpected manifestations have attracted our attention that presented as more symptoms of HTNV infection including exudative changes in both lungs and an amount of bilateral pleural effusion as well as bilateral kidney enlargement rather than typical viral pneumonia in SARS-CoV2 infection. Fortunately, the conditions of patients gradually return to normal which is beneficial from the antiviral treatment, hemodialysis, and various supportive therapies including anti-inflammation, liver and gastric mucosa protection.

Conclusion: Unexpected manifestations of coinfection patients present herein may be associated with multiple factors including virus load, competition or antagonism among antigens, and the susceptibility of target cells to the various pathogens, even though the pathogenesis of HTNV and SARS-CoV2 remains to be elucidated. Given that these two viruses have posed a profound influence on the socioeconomic, healthcare system worldwide, and the threat of coinfection to public health, it is warranted for clinicians, public health authorities, and infectious disease researchers to have a high index of consideration for patients co-infected with HTNV and SARS-CoV2.

* Corresponding author.
E-mail address: liuhongli1965@163.com (H.-L. Liu).

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1. Introduction

The world has experienced several epidemics and pandemics that have injured thousands to millions of lives. Although advances in diagnosis, monitoring, and treatment, we are still threatened by established and emerging pathogens. HFRS, an infectious disease that can be induced by the Hantaan virus (HTNV) with a manifestation of fever, hemorrhage, renal impairment, and thrombocytopenia, and the causative agent of this disorder was first recognized in Korea in 1978 and mainly prevalent in Europe and Asia [1]. Unexpectedly, decades after the discovery of HTNV, a novel coronavirus that was first identified in China and finally named severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) has alarmed the world. It is the causative agent of COVID-19 and has garnered increasing attention worldwide for influencing over 200 counties [2]. Although the underlying mechanism of SARS-CoV2 infection remains to be elucidated, owing to the large genetic diversity and frequent recombination of its genomes coupled with the frequent interaction between the human-human and human-animal. Coinfection of SARS-CoV2 with other pathogens is becoming an issue that needs to be seriously considered and poses a challenge for clinicians to make a precise diagnosis timely [3].

Indeed, the prevalence of coinfection among COVID-19 patients was reported, and the co-pathogens including bacteria (*Streptococcus pneumoniae, Staphylococcus aureus, Klebsiella pneumoniae*), and viruses (influenza viruses, human immunodeficiency virus) have been confirmed [4]. However, given the profound influence of HFRS and COVID-19 on public health, as well as the coinfection of these two disorders was rarely documented. Accordingly, we presented the characteristics of three coinfection cases that primarily showed unexpected clinical manifestations, even though symptoms that are similar to the single infection of HFRS and COVID-19 were also found. These findings will be an indication for clinicians and may provide new insight into the underlying mechanism of patients co-infected with HFRS and COVID-19.

2. Methods

2.1. Leukocytes, platelets, and C-reactive protein measurement

Flow cytometry, electrical impedance, and latex agglutination were performed to test the levels of leukocytes, platelets (PLT), and C-reactive protein (CRP) with Mindray CAL 8000 system (Mindray Medical Co., Ltd, Shenzhen, China) according to the manufacturer's protocol.

2.2. Creatine, uric acid, urea, LDH, α-HBDH measurement

To isolate the serum, 3 mL of venous blood was drawn from patients and then incubated in a 37 °C water bath for 10 min followed by a centrifugation (3000 rpm, 5 min). the concentrations of creatinine (Cr), uric acid (UA), urea, lactate dehydrogenase (LDH), and α-hydroxybutyrate-dehydrogenase (α-HBDH) were determined by conventional methods, using a Mindray BS800 system (Mindray Medical Co., Ltd, Shenzhen, China) according to the manufacturer's protocol.

2.3. HTNV antibody examination

The colloidal gold method was used to conduct serological tests for immunoglobulin (Ig)M and IgG against HTNV (Bosheng Biotechnology Co., Ltd, Xiamen, China). Mix 100 μL of sample diluent with 2 μL of EDTA-K2-anticoagulated plasma. Pipette 70 μL of the mixture onto a test board and incubate for 20 minutes as instructed by the manufacturer. The assay's sensitivity was 96.71%, and its specificity was 98.72%.

2.4. Lymphocytes detection

Lymphocyte levels, including $CD3^{+}$T cells, $CD4^{+}$T cells, $CD8^{+}$T cells, B, and NK cells, were measured using an IMK Kit (Becton Dickinson, Franklin, NJ, USA) as directed by the manufacturer. To begin, combine 50 μL of EDTA-K2-anticoagulated plasma and 20 μL of reagent in a TruCount tube (Becton Dickinson, Franklin, NJ, USA) and incubate in the dark for 15 minutes. After adding 450 μL of lysing buffer, the sample was incubated in the dark for 10 minutes. All samples were analyzed with the FACSCanto Clinical software (Becton Dickinson, Franklin, NJ, USA).

2.5. APTT, PT, and Fib measurement

2 mL of venous blood was aspirated into a tube containing sodium citrate, followed by centrifugation at 3000 rpm for 10 min to separate the plasma. The Mindray ExC810 system (Mindray Medical Co., Ltd, Shenzhen, China) measured activated partial thromboplastin time (APTT), prothrombin time (PT), and fibrinogen (Fib) levels following the manufacturer's protocol.

2.6. IL-6 measurement

3 mL of venous blood was drawn from the patients into a tube containing sodium heparin. The tube was then incubated in a 37 °C water bath for 10 minutes before being centrifuged at 3000 rpm for 5 minutes. The level of interleukin-6 (IL-6) was measured using a

Table 1
Timeline of the disease course.

Case	Dayofhospitalizatio	Leukocytes	PLT	CRP	$CD3^+$Tcells	$CD3^+CD4^+$Tcells	$CD3^+CD8^+$Tcells	Bcells	NKcells	APTT	PT	Fib	Cr	Urea	UA	IL − 6	LDH	α − HBDH
case 1	Day 1	6.25	148	3.8	455	107	88	170	64				80.3	1.67	365.5	3.2	293.4	244.9
	Day 3	4.94	214	1.3	250	64	50	72	28	29.43	11.6	1.99	75	2.59	304.2			
	Day 4	4.56	237	0.9				72	53				81.2	2.26	296	1.5		
	Day 9	4.39	285	0.8	901	404	309	105	65				79.9	4.16	304.5		281.2	218.7
case 2	Day 1	15.49	74	22.77	1023	464	374	135	82	39.64	12.76	3.67	470.8	31.75	652.5	25.11	431	311
	Day 2	18.14	76	20.46						33.83	13.06	3.36	446.3	30.76	629.4			
	Day 3	11.46	93	33.23	465	204	150	52	30	34.17	11.98	5.15	518.3	33.98	762.5	77.47	526.1	412.5
	Day 4	7.1	133	32.52						35.39	11.28	6.36	426.39	28.56	620.39			
	Day 5	5.88	176	29.08									201.25	13.35	464.86			
	Day 8												107.8	8.31	465			
	Day 9	7.79	268		996	478	352	89	76	27.71	12.1	5.44	85.1	7.54	394.5	2.3	136	95.1
	Day 10												76.87	6.43	346.42			
case 3	Day 1	44.89	24	24.38	255	107	88	30	14	53.13	12.23	2.6	373.3	24.84	604.5	136	676.2	535.8
	Day 2	32.39	28	40.41						51.65	12.26	3.65	455	29.53	750.3			
	Day 3	21.12	48	92.36	387	159	104	65	38	43.46	12.41	3.33	427.4	27.29	651.5			
	Day 4	15.75	72	89.34						42.6	12.13	4.28	439.5	35.6	826.51	132.3	658.1	526.3
	Day 5	10.94	110	47.8	550	264	150	72	53				291.9	25.04	610.21			
	Day 6	9.86	142	16.38									178.84	13.81	397.36	23.6		
	Day 7												169.53	11.49	419.45			
	Day 8												131.9	6.17	346	8.2	125.3	90.6
	Day 9												126.48	6.57	317	4.3		
	Day 11	9.6	306	4.2	1025	453	348	116	97	33.11	12.77	3	103.7	3.82	226.7			

Leukocyte (normal range 3.97– 9.15 $\times$ 10^9/L), PLT: platelets (normal range 85–303 $\times$ 10^9/L), CRP: C-reactive protein (normal range 0–10 mg/L), $CD3^+$ T cell (normal value 690–2540 cell/μL), CD3 + CD4 + T cell (normal value 410–1590 cell/μL), CD3 + CD8 + T cell (normal value 190–1140 cell/μL), B cell (normal value 90–660 cell/μL), NK: Natural killer cell (normal value 90–590 cell/μL). APTT: Activated partial thromboplastin time (normal range 24–38 sec), PT: Prothrombin time (normal range 10–15 sec), Fib: Fibrinogen (normal range 2–4 g/L), Cr: creatinine (normal range 70–115 μmol/L), urea (normal range 1.7–8.3 mmol/L), UA: Uric acid (normal range 202–416 μmol/L), IL-6: interleukin-6 (normal range 0–55.5 pg/mL), LDH: lactate dehydrogenase (normal range 109–245 U/L), α-HBDH: alpha hydroxybutyrate dehydrogenase (normal range 90–182 U/L).

Maccura I3000 automatic chemiluminescence immunoassay analyzer (Maccura Bio Co., Ltd, Sichuan, China) according to the manufacturer's instructions.

2.7. SARS-CoV-2 assays

The nasal and throat swab of patients was stored in the tube that contained the preservation solution, and then 300 μL solution was pipetted into the panel followed by the SARS-CoV-2 RNA extraction with polymerase chain reaction magnetic bead method according to the manufacturer's instructions. After that, 20 μL extraction solution was mixed with amplification reaction solution (12 μL), enzyme mixture (4 μL), and ORF1ab/N reaction solution (4 μL) with a total volume of 40 μL for each tube. The PCR was performed according to the manufacturer's instructions (Bio-Germ Medical Technology Co., Shanghai, China). The assay sensitivity and specificity were 100 % and 99.23 %, respectively.

3. Case series presentation

3.1. Case 1

3.1.1. Main symptoms and history of illness

A 42-year-old male without a history of health problems was referred to the Department of Infectious Disease of our hospital on December 16, 2022. The patient lived in an HFRS epidemic area located in the western of the Guanzhong region of Shaanxi province and has not been vaccinated for the HFRS and COVID-19. Six days before admission, he fell ill with fever, headache, sore throat, and general discomfort.

3.1.2. Physical examination, laboratory examinations, and imaging examinations

The initial finding at admission included a body temperature of 36.5 °C, pulse rate of 86 beats per minute, respiratory of 18 beats per minute, blood pressure of 118/77 mmHg, and slight flushing of the face. Laboratory examination during hospitalization indicated leukocytosis, elevated levels of lactate dehydrogenase (LDH), and alpha hydroxybutyrate dehydrogenase (α-HBDH). Furthermore, thrombocytopenia, and renal dysfunction with elevated levels of urea, uric acid, and creatine were also found (Table 1). The serological test for HTNV immunoglobulin M (IgM) and IgG was positive. Of note, she also tested positive for COVID-19 nasal and throat swabs. Chest computer tomography (CT) scan showed bilateral pleural effusion and pericardial effusion. Besides, liver edema was also found, despite the abnormality of bilateral renal, perirenal fascia, and peritoneal which can be found in typical HFRS patients was not observed (Fig. 1A and B). Meanwhile, examination on day 3 of hospitalization showed dramatically declining levels of lymphocytes, $CD8^+$ T cells, and NK cells which indicated a weak immune response (Table 1).

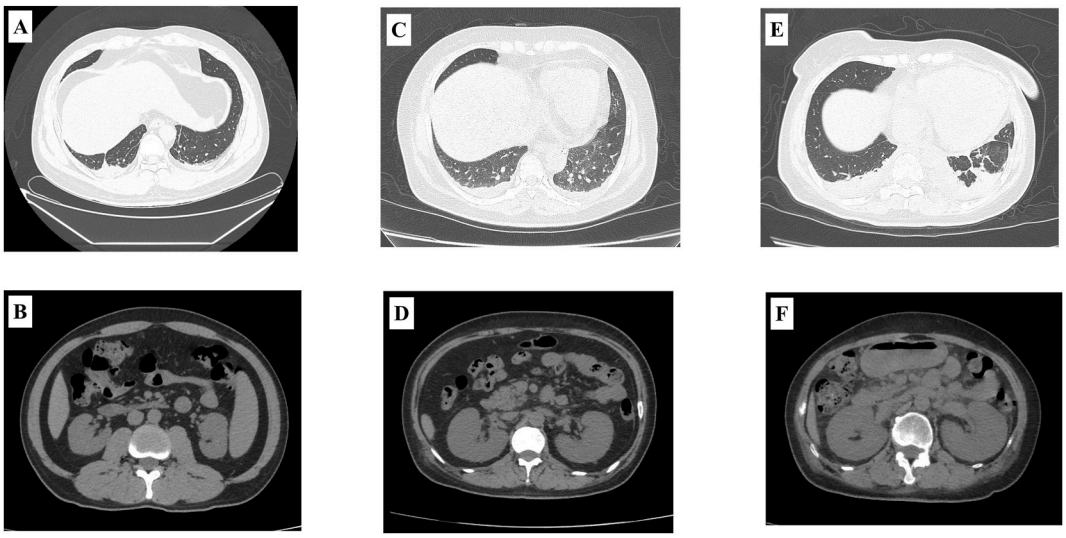

Fig. 1. Imaging findings of the patient in HFRS complicated with COVID-19.
The examination showed case 1 with bilateral pleural effusion, and pericardial effusion. Besides, liver edema was also found (A–B). Chest and abdominal computed tomography showed a small amount of bilateral pleural and pericardial effusion, bilateral kidney enlargement, perirenal fascial edema, and a small amount of exude in case 2 (C–D). In addition, significant exudative changes in both lungs and an amount of bilateral pleural effusion, bilateral renal edema, perirenal fascial edema, and a small amount of exudate, together with abdominal exudate was observed in case 3 (E–F).

3.1.3. Treatment

The patient received antiviral treatment by ribavirin (20 mL/0.5 g) via intravenous coupled with Xiyampin (a traditional Chinese medicine, 250 mL/250mg) for clearing heat and relieving cough [5]. Reduced glutathione (100 mL/2 g) and Compound glycyrrhizin (a traditional Chinese medicine, 100 mL/160 mg) for hepatoprotection [6], Ilaprazole sodium (100 mL/10 mg) for protecting the gastric mucosa, vitamin C (250 mL/2 g) and vitamin B6 (250 mL/200 mg), which clinically used for adjuvant therapy, was also applied in the first two days of admission. Given the patient would probably suffer comorbidities including hemorrhage, multiple organ insufficiency, cerebral edema, brain herniation, respiratory failure, and heart failure, and coinfection of COVID-19 may also worsen the outcome of the individual. Thus, the patient was transferred to the isolation ward of the intensive care unit on the third day of admission and continued to receive corresponding treatment as mentioned above until the seventh day of hospitalization. Beneficial from a system treatment, the conditions of patient was stabilized and transferred to the general ward at the nineth day of hospitalization.

After ten days of hospitalization, the patient was discharged with a body temperature recovered to the average level, renal and liver conditions turned to normal. Noteworthy, even though the patient has no discomfort in the heart, the LDH and α-HBDH were still higher than normal levels, with a value of 281.2 U/L and 218.7 U/L, respectively. Thus, we recommended he should pay attention to his situation and follow up, nevertheless, the patient was not compliant as suggested.

3.2. Case 2

3.2.1. Main symptoms and history of illness

A 54-year-old female was referred to the Department of Infectious Disease of our hospital on December 12, 2022. The patient has no other history of health problems except for undergoing extracorporeal lithotripsy for "kidney stones" in 2013 and "cholecystectomy" for "acute cholecystitis" in 2021. She lived in an HFRS epidemic area located in the central of the Guanzhong region of Shaanxi province and has not been vaccinated for the HFRS and COVID-19. Five days before admission, she fell ill with nausea, vomiting, and diarrhea. Three days prior to admission, her urine output was decreasing (<100 ml/day).

3.2.2. Physical examination, laboratory examinations and imaging examinations

The initial clinical finding showed a body temperature of 36.2 °C, pulse rate of 80 beats per minute, respiratory of 20 beats per minute, and blood pressure of 121/85 mmHg with no congestion and flushing on the face and neck. Laboratory tests indicated thrombocytopenia, leukocytosis, and renal dysfunction with an abnormal value of urea, uric acid, and creatine. Meanwhile, over-expression of LDH and α-HBDH was also found (Table 1). The serological test for HTNV-IgG and IgM was positive. Notably, a nasal and throat swab for SARS-CoV-2 RNA was also positive. An elevated level of IL-6 was observed (peak value 77.47; normal value 0–5.5 pg/ml). Chest CT showed a small amount of bilateral pleural effusion and pericardial effusion. Abdominal CT revealed bilateral renal edema, perirenal fascial edema, and a small amount of exudate (Fig. 1C and D).

3.2.3. Treatment

The patient was treated by ribavirin (20 mL/0.5 g) via intravenous together with the supportive treatment including Xiyampin (250 mL/250mg), Reduced glutathione (100 mL/2 g), Compound glycyrrhizin (100 mL/160 mg), Ilaprazole sodium (100 mL/10 mg), vitamin C (250 mL/2 g) and vitamin B6 (250 mL/200 mg) at the first day of admission. Although the patient did not suffer severe viral pneumonia, the progressive oliguria still attracted our attention. In view of the patient coinfected with HFRS and COVID-19, she was transferred to the isolation ward of the intensive care unit. Indeed, on the second, fourth and fifth days of hospitalization, the patient received hemodialysis owing to renal failure, thereafter, antiviral coupled with supportive treatment was continually conducted as before, which is stopped at the eighth day of hospitalization.

After ten days of hospitalization, the clinical values of the patient gradually returned to normal and was discharged from the hospital. After that, she was not re-tested again as clinician suggested, for no more uncomfortable was complaint.

3.3. Case 3

3.3.1. Main symptoms and history of illness

A 58-year-old female who has no history of health problem was admitted to the Department of Infectious Disease of our hospital with a fever. She lived in an HFRS epidemic area located in the central of the Guanzhong region of Shaanxi province and has not been vaccinated for the HFRS and COVID-19. Three days before admission, she fell ill with a fever, headache, and orbital pain.

3.3.2. Physical examination, laboratory examinations and imaging examinations

The initial physical examination showed a body temperature of 38.3 °C, pulse rate of 80 beats per minute, respiratory of 19 beats per minute, and blood pressure of 120/68 mmHg. Meanwhile, slight congestion of the face and neck was also found. Laboratory examination indicated thrombocytopenia, leukocytosis, and renal dysfunction presented as an abnormality of urea, uric acid, and creatine. Furthermore, elevated level of LDH and α-HBDH was also observed (Table 1). The serological test for HTNV-IgM was positive. Otherwise, nose and throat viral swabs for SARS-CoV-2 infection were also confirmed. In addition, overexpression of IL-6, which reflects the emergence of inflammation, was also found (peak value 136; normal value 0–5.5 pg/ml). Chest CT showed significant exudative changes in both lungs and a small amount of bilateral pleural effusion. Additionally, abdominal CT showed bilateral renal edema, perirenal fascial edema, and a small amount of exudate, together with abdominal exudate (Fig. 1E and F).

3.3.3. Treatment

The patient was received corresponding treatment including ribavirin (20 mL/0.5 g) Xiyampin (250 mL/250 mg), Reduced glutathione (100 mL/2 g), Compound glycyrrhizin (100 mL/160 mg), Ilaprazole sodium (100 mL/10 mg), vitamin C (250 mL/2 g) and vitamin B6 (250 mL/200 mg) with a duration of three days from admission.

Despite a symptom of severe viral pneumonia was not found in the patient, take into account coinfection and possible comorbidities, she was transferred to the isolation ward of the intensive care unit. Actually, the patient received hemodialysis on the fourth day of the hospitalization owing to acute renal failure. Furthermore, conductions of platelet transfusion were also performed to improve the thrombocytopenia. Adjuvant therapies were continually intervened for the corresponding purpose including ribavirin (20 mL/0.5 g) for anti-viral, Compound glycyrrhizin (100 mL/160 mg) for hepatoprotection, and Ilaprazole sodium (100 mL/10 mg) for protecting the gastric mucosa, which last four days after hemodialysis.

The patient's condition gradually stabilized and she was discharged after fourteen days of hospitalization. The follow-up examination two weeks later indicated that the situation of the patient was steadily improving with no further illness.

4. Discussion

It has been more than fifty years since the discovery of HTNV, and mounting evidence has shown that HFRS is emerging as an increasing threat to human health [7]. Although vaccination has greatly reduced the prevalence of this disorder, hundreds of thousands of lives still be injured every year worldwide [8]. Unfortunately, COVID-19, an infectious disease that outbreak in 2019, has posed another threat to human lives, global economic security, and the healthcare system. Meanwhile, the coinfection of COVID-19 with one or even more disorders is another serious concern issue. Actually, over one-sixth of the global human population is estimated to be affected by coinfection [9]. Mounting evidence suggests that coinfection may influence the spread of the disease infection at the population level and is associated with higher mortality and a worse outcome of the disease [10,11].

Although coinfection of SARS-CoV-2 with pathogens including bacteria, and viruses has been documented, there is limited knowledge on coinfection of COVID-19 with HFRS caused by HTNV [4]. Given the several similarities shared between HFRS and COVID-19, the coinfection of these two disorders has greatly attracted our attention. As reported, HTNV was first isolated from the lungs of infected striped field mice and humans can be infected via inhalation of aerosols [12]. Furthermore, the clinical manifestation of HFRS is non-specific flu symptoms including fever, headache, and fatigue [1]. Meanwhile, WHO reports that SARS-Cov2 transmission is dependent on respiratory droplets and contact routes, and the common symptom of COVID-19 is fever, cough, and fatigue which are similar to HFRS [2]. Indeed, all of these can also be found in coinfection cases presented herein, and pose a challenge for clinicians to distinguish timely. Furthermore, it had been shown that immune-mediated mechanisms, in particular, T cell activation in the acute phase, are involved in the pathogenesis of HFRS, and pathological damage caused by disorders of the immune regulation may also attributable to the onset of HFRS [13]. Besides, adaptive immune responses were found to be essential for SARS-Cov2 virus clearance [14,15]. Noteworthy, a declined levels of T lymphocytes and their subgroup, B and NK cells were observed in coinfection patients presented herein (Table 1), it is contrast to the previous study that an elevated level of $CD8^+$ T cells was found in the HTNV infection patients [16], and further confirmed the profound immunosuppressive abilities of SARS-CoV2 on the immune responses [14]. Interestingly, elevated levels of IL-6 were all found among the patients in HFRS, COVID-19, and the coinfection cases presented in this paper. Meanwhile, overexpression of cytokines is considered to be associated with the poor therapeutic outcome of COVID-19 as well as the severity of HFRS [17,18]. Although the relationship between the severity of coinfection patients discussed herein and the IL-6 expression is rarely reported, with regard to the IL-6 play a vital role in inflammation, immune response, in particular, it induces the differentiation of naïve $CD4^+$ T cells and $CD8^+$ T cells as well as the transformation of activated B cells into antibody-producing cells, the key role of IL-6 plays in the course of the coinfection will not be obscured. Interestingly, it has been documented that IL-6 can also induce a various acute-phase proteins such as the CRP [19], and the elevated levels of the latter were found in all cases presented herein, of which the underlying mechanism deserves to be further elucidated.

Noteworthy, severe pulmonary involvement has been reported in the course of HFRS, and studies show that both lung and heart are affected during the acute phase of HFRS [20,21]. Importantly, pneumonia is a typical symptom of COVID-19 and acute myocardial injury can also be found ranging from the asymptomatic elevation of cardiac troponins to fulminant myocarditis and circulatory shock in COVID-19 patients [22]. This was confirmed more clearly in the coinfection cases present herein, which are presented as elevated levels of LDH, α-HBDH. Unexpectedly, chest and abdominal CT has shown a symptom of HFRS including exudative changes in both lungs and an amount of bilateral pleural effusion as well as bilateral kidney enlargement rather than typical viral pneumonia presented in COVID-19 patients. Although the underlying mechanisms of COVID-19 and HFRS infection remain to be elucidated, the amount of evidence may provide a clue for these findings in coinfection patients. SARS-Cov2 has been shown to use the angiotensin-converting enzyme 2 (ACE2) receptor for cell entry, the latter has been found in various organs and cells including the small intestine, kidney, and vascular endothelium [23]. Notably, endothelium are believed to be the primary targets of hantaviruses, and organs composed of these cells can be severely affected such as kidneys [24]. Thus, it seems indicated that the phenomenon found on the CT may result from the competitive or antagonistic effects between the SARS-Cov2 and HTNV. In addition, it may also be associated with the viral load, given the coinfection patients enrolled in this paper is in the acute phase of HFRS, and a mild course of COVID-19 with a presumed BA.5 variant based on timing [25]. Therefore, the hantavirus load may be higher than that of SARS-Cov2, and making a profound effect on the corresponding organ than the latter, despite this is need to be further confirmed. Furthermore, apart from the potential relationship between the SARS-Cov2 and HTNV aforementioned, the difference in susceptibility of endothelium to these antigens may be another induction. Thus, it can be speculated that in a condition of a certain number of target cells, HTNV may bind more advantageously to the receptor expressed on the surface of the target cells than SARS-Cov2, coupled with the more susceptibility of target cells to the HTNV,

leading to the co-infected patients presented with more manifestations of HFRS rather than those of COVID-19.

Although the cases presented herein is rare reported and may provide a further insight for evaluating the possibility of co-infection of SARS-Cov2 and HTNV, there were still some limitations. First, this paper is a series case report with a limitation of sample size and lack of control group, despite it is inherent in case report to some extent. It is warranted to collect more cases for further investigations to broader the generalizability of the findings and would present a clear picture for researchers and readers. Second, given the retrospective nature of case report, the availability of data and variety of methodology is limited coupled with potential for selection bias involving the age, gender, regions of patients, all of which should be considered and remains to be optimized in coming studies. Last but not least, considering that the influence of COVID-19 pandemic on the diagnosis and admission of patients, and the absence of data on long-term outcomes in this report, it restricts the understanding of the chronic effects or long-term outcomes of co-infections presented herein.

5. Conclusions

The features of HFRS and COVID-19 have been well documented. However, the characteristics of patients co-infected with HFRS caused by HTNV and COVID-19 were rarely reported. Here, we reported three cases of coinfection mentioned above.

Not only the conditions including general clinical manifestations, immune and inflammation parameters fluctuation presented in the single infection of HFRS or COVID-19 can be found, but also a distinctive phenomenon in the coinfection patients was also observed, which is presented more symptoms of HFRS rather than COVID-19. It may be related to multiple factors including the virus load, competition or antagonism among antigens, and the susceptibility of target cells to the various pathogens. Admittedly, there is a long way to go before the underlying mechanism of cases presented herein is elucidated. However, coinfection of COVID-19 and HFRS should deserve to be a seriously concerned issue, and the early examinations involving the specific serological tests and imaging examinations would contribute to the timely diagnosis, in particular, the patients present a non-specific symptom. Overall, a precise diagnosis relies on a series of information collection involving history of health, epidemiology, physical examination, and specific examinations, furthermore, pour an insight into the specific symptoms, tract route, immune response and underlying pathogenesis will contribute to the precise diagnosis.

Ethics statement

This study was reviewed and approved by Shaanxi Provincial Hospital of Infectious Diseases, The Eighth Hospital Affiliated to Medical College of Xi'an Jiaotong University Ethics Committee, with the approval number: 23-2-84.

All participants/patients (or their proxies/legal guardians) provided informed consent to participate in the study.

All participants/patients (or their proxies/legal guardians) provided informed consent for the publication of their anonymised case details and images.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Han-Dong Zhao: Writing – original draft, Data curation. **Jian-Wu Li:** Visualization, Investigation. **Ze-Kun Wang:** Software, Resources. **Hong-Bo Qian:** Supervision. **Kui Fu:** Supervision. **Hong-Li Liu:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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