Short Report: Experience with Extrarenal Manifestations of Hemorrhagic Fever with Renal Syndrome in a Tertiary Care Hospital in South Korea

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Abstract. Reports on the clinical entity of hemorrhagic fever with renal syndrome (HFRS) have focused on acute renal failure. Data on the extrarenal manifestations are limited primarily to case reports. In this study, protean extrarenal manifestations involving the major organs occurred in one-third of patients with HFRS during various stages (i.e., febrile phase through diuretic phase). Pancreatobiliary manifestations and major bleeding occurred in 11% and 10% of patients, respectively. Cardiovascular and central nervous system manifestations developed during the febrile or oliguric phase, whereas pancreatobiliary manifestations and major bleeding were detected even in the diuretic phase. Thus, close monitoring of and additional knowledge about various extrarenal manifestations are needed.

Hemorrhagic fever with renal syndrome (HFRS) is an acute infectious disease caused by hantaviruses, which occur widely in Asia and Europe. In Korea, the main pathogenic hantaviruses are Hantaan and Seoul virus. The incidence of HFRS in civilians ranges from 2.1 to 6.6 per 100,000 person-months, and the annual prevalence in military personnel is 40–64 per 100,000 person-months, with seasonal predominance in the autumn/winter and spring.¹

HFRS shows diverse clinical manifestations, from acute influenza-like febrile illness to shock syndrome, depending, in part, on the causative virus.^{2–4} Although renal involvement is a distinctive feature of HFRS, extrarenal manifestations, including acute impairment of visual function, acute myopia, central nervous system (CNS) complications with seizures, myocarditis, and severe gastrointestinal hemorrhages, are infrequently reported in case reports and in some cases, are fatal.^{5–7} Furthermore, unfamiliarity with these clinical presentations among clinicians can cause diagnostic problems and result in unnecessary procedures.⁸ However, to date, there has been no systematic report outlining the overall scope and frequency of extrarenal manifestations of HFRS cases. Thus, we conducted this study to analyze the wide scope of the extrarenal manifestations of HFRS and to evaluate their prevalence and clinical recognition and management.

This study included 73 patients with HFRS who were admitted to Chonnam National University Hospital from 2000 to 2007. Information on age, gender, incubation period, symptoms, signs, physical and laboratory findings at the time of admission, and clinical courses was collected, based on medical records. A diagnosis of HFRS was confirmed with symptoms and signs compatible with HFRS and positive serology using an immunochromatography assay (SD Hantaan virus multi; Sewon, Korea). A single titer higher than 1:640 or 4-fold rising titers in the paired sera were deemed to be positive. Extrarenal manifestation was defined as an involvement of major organs, except the kidney, in patients without risk factors. Furthermore, extrarenal manifestations must be confirmed by laboratory, radiologic, or other diagnostic procedures. We diagnosed acute pancreatitis when edematous pancreas or extrapancreatic change/fluid collection was present on abdominal imaging,

such as computed tomography (CT) or ultrasound (US) and elevations in amylase or lipase levels greater than three times the upper limit of normal were observed.^{9,10} Acalculous cholecystitis was defined as local signs of inflammation (Murphy's sign or right upper quadrant (RUQ) pain/tenderness) and imaging findings, such as sonographic Murphy's sign, thickened gallbladder wall (> 4 mm), enlarged gallbladder (long axis diameter > 8 cm, short axis diameter > 4 cm), or pericholecystic fluid collection without gall bladder stone.¹¹ Acute cholangitis was defined as Charcot's triad (fever/chills, jaundice, abdominal pain), abnormal liver function tests, and imaging findings, such as biliary dilatation.¹² Pericarditis was confirmed by the presence of pericardial fluid on echocardiography and typical electrocardiographic changes. Myocarditis was identified on the basis of physical examination (muffled first heart sound), electrocardiographic changes (non-specific ST segment and T wave abnormalities, tachycardia, arrhythmia), elevated cardiac enzymes, and no evidence of coronary heart disease. Major bleeding was defined as a drop in systolic pressure less than 90 mm of Hg with no trauma or bleeding diathesis. Acute respiratory distress syndrome (ARDS) was defined as bilateral interstitial infiltrates with no clinical evidence of increased left atrial pressure. The diagnosis of hemophagocytic lymphohistiocytosis (HLH) was established if five of the following eight diagnostic criteria were met: fever, splenomegaly, bicytopenia (with at least two of the following: hemoglobin ≤ 9 g/dL, platelets $< 100 \times 10^3/\mu\text{L}$, and neutrophils $< 1.0 \times 10^3/\mu\text{L}$ in the peripheral blood), hypertriglyceridemia (≥ 265 mg/dL) or hypofibrinogenemia (≤ 150 mg/dL), hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy, low or absent NK-cell activity, hyperferritinemia (≥ 500 $\mu\text{g/L}$), and increased soluble plasma CD25-levels (IL-2R α chain; $\geq 2,400$ U/mL).¹³

The study group consisted of 56 men and 17 women, with men constituting 76.7% of the cases. The mean patient age was 50.3 ± 14.4 years (range, 20–82). Epidemic seasonal predominance was observed in the autumn/winter (86.3%) and spring (4.1%). In total, 64 patients (87.7%) reported a history of exposure to open air, including occupational contact (34.3%) and recreational contact (47.0%). The suspected mean incubation period of all patients was 9.6 ± 6.3 days.

The most common symptom was fever (94.5%), followed by abdominal pain (64.4%) and headache (50.7%). Physical signs included conjunctival hemorrhage (74%), flank tenderness (56.2%), and petechia (56.2%). Twenty-two patients

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(30.1%) were suffering from shock on admission. The initial mean leukocyte count was $18,120 \pm 10,134$ cells/ μ L (normal value 4,000–11,000 cells/ μ L), and the platelet count was $46 \pm 34.5 \times 10^3$ / μ L (normal value $130\text{--}450 \times 10^3$ / μ L). Mean blood urea nitrogen and creatinine levels were 42.8 ± 23.0 mg/dL (normal value < 23 mg/dL) and 3.4 ± 2.8 mg/dL (normal value < 1.2 mg/dL), respectively. Mean lactate dehydrogenase (LDH,) and aspartate aminotransferase (AST) levels were $1,108 \pm 823$ U/L (normal value 218–472 U/L) and 127 ± 112 U/L (normal value < 37 U/L), respectively. Hemodialysis was required in 13 of 36 patients who had oliguric acute renal failure. The mean length of hospital stay was 10.3 days (range, 2–41). Overall mortality was 8.2% (6/73). Major causes of death were refractory shock (2 cases), and heart failure by myopericarditis (2), occurring during the early phase of the disease. The remaining deaths were caused by acute respiratory distress syndrome (1 case) and compartment syndrome, complicated with bilateral leg edema with secondary bacterial infection and massive generalized bleeding (1).

We identified 25 extrarenal manifestations in 23 patients (Table 1). The most common extrarenal manifestation was pancreatobiliary involvement, followed by major bleeding and cardiovascular manifestations.

Eight patients manifested pancreatobiliary involvement, including acalculous cholecystitis (4 cases), pancreatitis (3), and cholangitis (1) (Table 2). There was no previous history of underlying pancreatobiliary disease in these patients. Abdominal imaging studies, including CT or US, were performed in 55 patients. Pancreatic enzymes (amylase and/or lipase) were checked in 37 patients and elevations greater than three times the upper limit of normal was observed in nine patients. All three patients with pancreatitis recovered completely with general supportive care. One patient with acalculous cholecystitis underwent percutaneous cholecystostomy.

Cardiovascular manifestations developed in four patients. Among three patients with myocarditis, one patient had concomitant pancreatitis. Two patients died of heart failure. One patient with an ejection fraction (EF) of 25% on echocardiog-

raphy had a sudden cardiac arrest. Although he recovered transiently after resuscitation, he died because of aggravation of heart failure after hydration on Day 4 of hospitalization. The other patient was admitted to the hospital complaining of chest tightness. On admission, sinus tachycardia and low voltage changes were observed on electrocardiography. Echocardiography showed moderate amounts of pericardial effusion. The patient died of sudden cardiac arrest associated with ventricular dyssynchrony on Day 3 of hospitalization. The electrocardiogram (ECG) was performed in 64 patients. Abnormal ECG findings were identified in 18 patients (28.1%). Sinus tachycardia was the most common abnormal ECG finding (9 patients), and sinus bradycardia occurred in four. Other ECG abnormalities included bundle branch block (2 cases), first degree atrioventricular block (1), and prolonged QT interval (1).

Three patients showed extrarenal manifestations in the CNS. One patient with meningitis was diagnosed by spinal tapping. A diagnostic lumbar puncture yielded clear cerebrospinal fluid, with a white blood count of 13 cells/ mm^3 with 55% neutrophils. The protein count was 57 mg/dL (normal value 20–50 mg/dL) and glucose was 55 mg/dL (normal value 40–70 mg/dL). Two patients with cerebritis or cerebral infarction were diagnosed with magnetic resonance imaging (MRI) and showed no neurologic sequela. The patient with infarction presented with dysarthria and confusion during the febrile phase and focal infarction in the right periventricular white matter was shown on the MRI conducted on admission.

Major bleeding developed in seven patients: gastrointestinal hemorrhage (5 cases), retroperitoneal hemorrhage (1), and intramural hemorrhage (1). Only one patient with gastrointestinal hemorrhage was managed endoscopically; the remainder recovered with supportive care. The patients with retroperitoneal hemorrhage recovered with hemodialysis and supportive care without surgical decompression. Intramural bleeding at the buttock developed spontaneously in one patient without any history of trauma or intramuscular injection.

Other extrarenal manifestations observed in this cohort include ARDS, compartment syndrome, and hemophagocytic lymphohistiocytosis. The patient with ARDS developed acute asymmetric bilateral pulmonary infiltration during the fourth hospital day even though he was on hemodialysis at that time and his EF, based on echocardiography, was 58%. The patient with compartment syndrome eventually died because of massive bleeding and secondary bacterial infection by methicillin-resistant staphylococcus aureus (MRSA) despite surgical decompression. One patient with HLH presented with unexplained cytopenia, coagulopathy, and hepatosplenomegaly. Bone marrow examination revealed proliferation of histiocytes with prominent hemophagocytosis. Serological tests showed a 4-fold increased titer in paired sera. The patient recovered completely with only supportive care.¹⁴

Cardiovascular and CNS manifestations developed primarily during the hypotensive and oliguric phases, whereas intramural and retroperitoneal bleeding developed during the diuretic phase. Although gastrointestinal hemorrhage and pancreatobiliary manifestations were detected during all phases, they were most common in the early diuretic phase.

This study is the first detailed report of the overall scope and frequency of protean extrarenal manifestations in HFRS. Previously, a broad spectrum of clinical conditions had been recognized in HFRS, ranging from unapparent or mild illness

TABLE 1

Extrarenal manifestations in patients with hemorrhagic fever with renal syndrome

Extrarenal manifestation	No. of patients
Pancreatobiliary	
Acalculous cholecystitis	4
Pancreatitis*	3
Cholangitis†	1
Cardiovascular	
Myocarditis*	3
Pericarditis	1
Central nervous system	
Meningitis	1
Cerebritis	1
Cerebral infarction	1
Major bleeding	
Gastrointestinal hemorrhage†	5
Retroperitoneal	1
Intramural (buttock)	1
Others	
Acute respiratory distress syndrome	1
Compartment syndrome	1
Hemophagocytic lymphohistiocytosis	1

*One case each of myocarditis and pancreatitis developed in the same patient.

†One case each of cholangitis and gastrointestinal bleeding developed in the same patient.

TABLE 2
Clinical characteristics of pancreatobiliary involvement in patients diagnosed as hemorrhagic fever with renal syndrome*

Age/sex	Symptom and sign	Laboratory findings	Abdominal imaging study (CT severity index)	Clinical diagnosis	Therapy	Outcome
55/F	Diffuse abdominal pain/tenderness	WBC = 15,800 cells/ μ L Amylase = 244 U/L Lipase = 587 U/L AST = 23 U/L ALT = 33 U/L ALP = 66 U/L T-bil = 0.56 mg/dL	CT: pancreatic tail swelling (grade B)	Acute pancreatitis	Conservative therapy	Recovery
64/M	Epigastric pain/tenderness	WBC = 17,300 cells/ μ L Amylase = 223 U/L Lipase = 468 U/L AST = 297 U/L ALT = 133 U/L ALP = 164 U/L T-bil = 1.89 mg/dL	CT: peripancreatic infiltration and minimal fluid collection (grade D)	Acute pancreatitis	Conservative therapy	Recovery
64/F	Diffuse abdominal pain/tenderness	WBC = 17,300 cells/ μ L Amylase = 144 U/L Lipase = 260 U/L AST = 82 U/L ALT = 22 U/L ALP = 77 U/L T-bil = 1.0 mg/dL	CT: diffuse pancreatic swelling and peripancreatic fluid collection (grade E)	Acute pancreatitis	Conservative therapy	Recovery
51/F	RUQ pain, Murphy's sign (+), fever	WBC = 16,500 cells/ μ L AST = 49 U/L ALT = 3 U/L ALP = 340 U/L T-bil = 5.8 mg/dL	CT: diffuse GB wall thickening (10 mm), r/o sludge in distal CBD with dilatation of biliary tract	Acute cholecystitis accompanied by acute cholangitis	Conservative therapy	Recovery
49/M	RUQ pain, Murphy's sign (+)	WBC = 17,500 cells/ μ L AST = 75 U/L ALT = 48 U/L ALP = 47 U/L T-bil = 0.6 mg/dL	US: diffuse GB wall thickening (> 5 mm)	Acute acalculous cholecystitis	Conservative therapy	Recovery
25/M	Epigastric pain, Murphy's sign (+)	WBC = 13,200 cells/ μ L AST = 173 U/L ALT = 50 U/L ALP = 127 U/L Total bil = 1.5 mg/dL	US: diffuse GB wall thickening (7 mm) CT: edematous thickening of GB wall and enlarged GB (8 $\times$ 6 cm)	Acute acalculous cholecystitis	Conservative therapy	Recovery
43/M	RUQ pain, Murphy's sign (+)	WBC = 23,600 cells/ μ L AST = 150 U/L ALT = 50 U/L ALP = 51 U/L T-bil = 1.0 mg/dL	US: diffuse GB wall thickening (5 mm) and pericholecystic fluid collection	Acute acalculous cholecystitis	Conservative therapy	Recovery
73/M	Mild RUQ discomfort, Murphy's sign (+) icteric sclera	WBC = 14,500 cells/ μ L AST = 34 U/L ALT = 16 U/L ALP = 263 U/L T-bil = 8.97 mg/dL	US: diffuse GB wall thickening (5.5 mm) CT: marked enlarged GB (13 $\times$ 7.2 cm) and infiltration in the pericholecystic fat plane	Acute acalculous cholecystitis	Conservative therapy and PTGBD	Recovery after PTGBD insertion

* Abbreviation and normal value: WBC = white blood cell count (normal value 4,000–11,000 cells/ μ L); ALT = alanine aminotransferase (normal value < 37 U/L); AST = aspartate aminotransferase (normal value < 37 U/L); ALP = alkaline phosphatase (normal value 32–117 U/L); T-bil = total bilirubin (normal value 0.2–1.3 mg/dL); Amylase (normal value 20–100 U/L); Lipase (normal value 7–60 U/L); GB = gall bladder; CBD = common bile duct; RUQ = right upper quadrant; PTGBD = percutaneous transhepatic gall bladder drainage.

to a fulminant hemorrhagic process with severe renal failure and death.^{7,15} However, the occurrence of extrarenal manifestations has received little attention. In this study, one-third of patients with HFRS showed the involvement of major organs, excluding the kidney. Thus, a comprehensive understanding of protean extrarenal manifestations would be helpful in making diagnoses and in managing patients with HFRS presenting with various types of extrarenal manifestations.

Pancreatobiliary manifestations were the most common extrarenal manifestation in this study. In a previous report, pancreatitis was presented in one-third of HFRS autopsies during the Korean conflict.¹⁶ Kim and others¹⁷ reported that gallbladder-wall thickening occurred in 43% of patients with HFRS. In fact, most patients with HFRS do complain of abdominal pain. For example, 64.4% of patients complained of abdominal pain in the current report. Among them, 17% had

pancreatobiliary diseases. Because this study was based on a retrospective chart review, we could not differentiate between abdominal pain caused by pancreatobiliary disease(s) and HFRS itself. However, patients with pancreatobiliary manifestations showed elevated pancreatic enzymes and liver function tests. Thus, in HFRS patients with abdominal pain and abnormal pancreatic or liver enzyme levels, further imaging, including CT scans or US, should be considered to evaluate the presence and severity of pancreatobiliary complications. Furthermore, extrarenal manifestation of HFRS can be indistinguishable from the clinical presentations of other infectious or noninfectious diseases, which may lead to difficulties in diagnosing HFRS. Additionally, unnecessary surgeries are often performed as a consequence of misinterpreted symptoms, especially in areas with a low prevalence of the disease.⁸ Although the two prevailing treatment options for acalculous

cholecystitis are cholecystostomy and cholecystectomy,¹⁸ all patients with cholecystitis (except one who underwent percutaneous cholecystostomy) recovered completely without intervention in this report. Because HFRS is generally a self-limiting disease, conservative treatment and close monitoring would be recommended for these patients. In Scandinavia, increasing awareness of this infection has dramatically reduced the number of unnecessary surgical interventions.

In this report, abnormal ECG findings were found in one-third of HFRS patients, with sinus tachycardia as the most common finding. These findings resolved spontaneously as the patients recovered, consistent with a previous report.¹⁹ Puljiz and others reported that all ECG alterations were transient and all patients, including three with myocarditis, recovered spontaneously. However, in our case series, two of four patients with cardiac manifestations, one with myocarditis and one with pericarditis, died during the oliguric phase. The infective forms of myocarditis are almost as numerous as the causative microbial agents. The viral diseases are represented by measles, mumps, poliomyelitis, varicella, variola, infectious hepatitis, yellow fever, psittacosis, infectious mononucleosis, epidemic hemorrhagic fever, and encephalomyocarditis.²⁰ Pathological findings support that viruses multiply within tissue cells and occasionally produce extensive vacuolar lesions in the myocardium, including interstitial infiltration and muscular fiber fragmentation. Myocarditis is known to become fatal in a few days. In some cases, even though the alarming symptoms partially disappear or a sort of convalescence is established, careful monitoring is required. When acute viral pericarditis manifests in its clinical isolated form, it is usually benign. However, clinicians must be aware that pericardial involvement is not the sole abnormality, because there may be associated myocarditis.

The frequency of CNS manifestations in HFRS ranged from 11% to 34%. The CNS signs and symptoms include disorientation, extremity restlessness, lethargy, delusions, hallucinations, manic-depressive states, schizoid reactions, motor or kinetic disturbance, and seizure, all of which can result in grave outcomes.^{21–23} Myron and others²² reported that all fatal cases showed CNS disturbances, and mortality among patients with CNS disturbances was 41%. Autopsy findings suggest that the CNS shares vascular abnormalities observed with hemorrhagic fever, including cerebral edema and hemorrhage.²¹ One patient with meningitis showed mild pleocytosis and protein elevation in the cerebrospinal fluid (CSF). A lumbar puncture was performed to exclude a diagnosis other than HFRS. Although this observation could not represent the CSF finding of HFRS, it was compatible with previous reports of meningitis caused by epidemic hemorrhagic fever.²² Late neuropsychiatric abnormalities were not identified within a group of convalescing patients.²¹

The HFRS in Korea manifests more frequently as distinct bleeding tendencies, compared with Puumala virus in Europe.²⁴ Mild mucosal bleeding in the gastrointestinal tract can be detected gastroscopically in virtually all HFRS patients.²⁵ In Korea, clinically significant hemorrhagic manifestations ranged from 10% to 30%.²⁶ In this report, major bleeding requiring endoscopy and imaging studies such as CT, was reported in seven patients. Although the pathogenesis of these hemorrhagic phenomena is not completely understood, increase in vascular permeability and vascular fragility, thrombocytopenia, defects in platelet function, and disseminated

intravascular coagulation may play a central role in causing bleeding manifestations.²⁷ Most constitutional symptoms, such as abdominal pain and headache, disappear with improvements in renal function. However, in the current report, gastrointestinal hemorrhage and pancreatobiliary complications occurred in the hypotensive, oliguric, and even diuretic phases. In particular, buttock and retroperitoneal bleeding developed after platelet recovery during the diuretic phase. Thus, hemorrhagic and pancreatobiliary manifestations should be monitored after a patient's vital signs have stabilized.

Sin Nombre virus and Andes virus frequently show pulmonary involvement, while this is an infrequent occurrence in HFRS.²⁸ Pulmonary complications were observed in only 6% of HFRS patients.²¹ However, these symptoms are of great interest because of their prominence among the causes of death. In our cohort, patients with ARDS died during the hypotensive phase. Acute compartment syndrome has been previously reported as a serious complication of viral hemorrhagic fever.²⁹ In HFRS patients, increased intracompartmental pressure may develop caused by hemorrhage between fascial sheaths and severe edema. Infection-induced HLH is often associated with systemic viral infections, particularly Epstein-Barr virus, and occasionally with bacterial, fungal, or parasitic infections. The HFRS caused by *Hantaan* and *Puumala* should also be considered as one of the underlying infectious diseases resulting in hemophagocytosis in endemic areas.^{14,30}

Detection of serum *Hantavirus* antibodies is currently the diagnostic method of choice according to criteria issued by WHO and the Centers for Disease Control and Prevention. Because the risk of hantavirus infection is higher in rural areas, a rapid and easy diagnostic test is required. The sensitivity and specificity of immunochromatographic tests detecting Hantaan virus-specific nucleocapsid antibody were 96–100% and 94–100%.³¹ Additionally, both immunoglobulin M (IgM)- and IgG-specific tests have important diagnostic value because they are able to differentiate between acute infections (IgM positive) and past infection (IgG positive). In this study, both IgM and IgG titers were semiquantitatively checked, using serial dilutions. However, Hantaan virus infection elicited the nucleocapsid-specific humoral immune response beginning 4–5 days after infection.³² Because a negative serological result for the diagnosis of HFRS may occur during the early phase of the disease, serial sampling should be performed in high-risk patients.

This study has several limitations. First, these data were collected retrospectively. Second, the rate of extrarenal manifestations may have been overestimated. Because this hospital is a tertiary referral center, patients who manifested with atypical HFRS might have been referred. Third, in this report, clinical differences according to specific hantavirus serotypes were not evaluated. Although different human pathogenic hantaviruses, including Hantaan and Seoul virus, have diverse clinical presentations in Korea, serologic cross-reactivity between serotypes leads to a positive result in tests against any of the related antigens.⁸ However, the epidemiologic history in 87.7% of exposures to open air suggests that most cases were likely Hantaan virus. Other diagnostic tests, such as the polymerase chain reaction, would be helpful in differentiating these species. Finally, we could not define the relationship between extrarenal manifestations and clinical outcomes because of the limited number of each extrarenal manifestation. Further studies, including more patients with extrarenal manifestations, are warranted to evaluate these relationships.

In conclusion, protean extrarenal manifestations can develop at various stages, from the febrile phase to the diuretic phase, in HFRS. Because they can be associated with disease severity and occur at any stage of HFRS, clinicians should be aware of extrarenal manifestations for early detection and close monitoring.

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