

Epidemic Hemorrhagic Fever† in Hubei Province, The People's Republic of China: A Clinical and Serological Study

MYRON S. COHEN, M.D.,^a * JORDI CASALS, M.D.,^b AND G.-D. HSIUNG, Ph.D.^{c,d}

^a*Department of Medicine,* ^b*Department of Epidemiology,* and ^c*Department of Laboratory Medicine, Yale University School of Medicine, Yale Arbovirus Research Unit, New Haven, Connecticut;* ^d*Virology Laboratory, Veterans Administration Medical Center, West Haven, Connecticut*

HSI-EN KWEI, M.D., CHIEN-CHING CHIN, M.D., HSIN-CHEN GE, M.D., AND CHIN-MIN HSIANG, M.D.

Hubei Provincial Medical College, Wuchang, People's Republic of China

AND

PYUNG WOO LEE, Ph.D., CLARENCE J. GIBBS, JR., Ph.D., AND D. CARLETON GAJDUSEK, M.D.

Laboratory of Central Nervous System Studies, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Maryland

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Between July 1975 and April 1980, 71 patients were admitted to the Second Attached Hospital of Hubei Provincial Medical College in Wuchang with the diagnosis of epidemic hemorrhagic fever (EHF). The clinical course among these patients was similar to that described for patients with Korean hemorrhagic fever, and hemorrhagic fever with renal syndrome of the U.S.S.R. The overall mortality was 11.2 percent. Sera obtained from some of these patients as well as from patients admitted to the First Attached Hospital of Hubei Provincial Medical College were tested against an antigen associated with Korean hemorrhagic fever and showed exceedingly high antibody titers. We conclude that EHF in Central China represents the same or a closely related disease process as Korean hemorrhagic fever.

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†A wide variety of synonyms and geographical eponyms have been adopted for an identical clinical syndrome (hemorrhagic fever with renal syndrome) and are discussed in detail by Gajdusek [2]. Epidemic hemorrhagic fever is the term used to describe this disease in the People's Republic of China.

This study represents the first report of the initiation of a collaborative exchange program in medical sciences between the People's Republic of China and the Yale-China Association.

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*Present address: Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC 27514

Address reprint requests to: Myron S. Cohen, M.D., Department of Medicine, 547 Clinical Sciences Building 229H, University of North Carolina School of Medicine, Chapel Hill, NC 27514

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INTRODUCTION

Epidemic hemorrhagic fever (EHF) is a syndrome characterized by sequential periods of fever, hypotension, oliguria, and polyuria which is often accompanied by a hemorrhagic diathesis early in the course of the illness [1,2]. During the Korean War (1950–52), this disease process represented a major source of morbidity and mortality for American armed forces [1–7]; at that time massive research efforts to define the etiologic agent were unsuccessful [4,8] although understanding of the disease [8,9] and treatment methods were improved [10].

Since that time, whereas information regarding EHF in northern Europe [3,4,11,12–14], the USSR [2,3,4,15], and Korea has become available [16,17], little is known about EHF in the People's Republic of China (PRC). Recent agreements between the governments of the PRC and the United States of America [18] have allowed investigators from this country to participate in research efforts in the PRC [19]. Between November 1979 and April 1980 one of the authors (MSC) lived and worked at Hubei Provincial Medical College and was afforded the opportunity to become involved in the management of patients with EHF [19]. (Three other of the authors [DCG, CJG, and PWL] initiated collaborative studies with Professor Z.-Y. Xu of the First Shanghai Medical School, and Professor C.-M. Hsiang of Hubei Provincial Medical College, and together established the antigenic relationship of the disease in China with that of Korea [20,21].) Subsequently, sera from the same Hubei patient population were investigated in virologic laboratories at Yale University School of Medicine, the West Haven Veterans Administration Medical Center, and the National Institutes of Health [21]. The results of these studies are included in this report.

MATERIALS AND METHODS

Patient Population

All patients admitted to Hubei Provincial Medical College's Second Attached Hospital with the diagnosis of EHF between November 1979 and April 1980 were seen and evaluated by two of the authors (MSC, HSK). Records of patients with the discharge diagnosis of EHF seen at the same facility between July 1975 and April 1980 were evaluated in collaboration with investigators and translators from Hubei Provincial Medical College.

Sera Specimens

Acute and convalescent sera were obtained from patients admitted to the Infectious Disease Ward of the First or Second Attached Hospitals of Hubei Provincial Medical College. Acute sera were collected between the fourth and seventh (mean 5.8) day of illness, whereas convalescent sera were collected between the twenty-third and thirty-ninth (mean 31) day of illness. Sera were stored at -20°C until tested, except during intercontinental transport.

Serological Tests

Hemagglutination-inhibition tests against various viral antigens associated with Murray Valley, Japanese B encephalitis, yellow fever, Omsk hemorrhagic fever, and chikungunya viruses by methods previously described [22] were performed on single and paired serum samples in the Yale Arbovirus Research Unit (YARU) laboratory, Department of Epidemiology and Public Health, Yale University School of Medicine.

Indirect immunofluorescence tests to detect antibodies against Korean hemorrhagic fever (KHF) virus were performed at the NIH laboratories where this virus and the related neuropathia epidemica antigen are available for specific antibody studies [13,14,21,27]. Two kinds of antigen preparations were used: a human lung cancer cell-line, A-549, infected with KHF virus originally isolated by Lee et al. [16] and adapted to cell culture by French et al. (personal communication), and a Wistar rat lung tissue infected with KHF virus, strain 118/AP · 7 [23]. After the addition of serial dilutions of the patient sera to acetone-fixed infected cells, slides were allowed to incubate at 37°C in a humidified chamber for 30 minutes. Then the excess serum was removed by washing with phosphate buffered saline, pH 7.2; a fluorescein conjugated antihuman IgG prepared in goat (Cappel) was added, and an additional 30 minutes' incubation was allowed. Control sera with known positive and negative antibody titers to KHF virus and two monkey sera previously shown to have high antibody titers to simian hemorrhagic fever virus were included in the same test.

RESULTS

Three cases which emphasize the spectrum of disease associated with EHF are described below. In addition, these case reports offer a view of the health care delivery system in the People's Republic of China.

Case A

Case 144599 is a 19-year-old Chinese female. She had no history of prior illness. She was employed as a field worker in a suburban commune; between November 21 and December 2, 1979, she participated in a water irrigation project near her home. She was well until December 12th when she noted the acute onset of a fever of 40°C, back pain, nausea, and vomiting. In addition she noted pain over the frontal sinuses and was observed to be slightly confused. Eleven other workers participated in the same irrigation project, but reported no problems. She was seen on the first day of her illness in the commune clinic where she was treated with IV fluids, penicillin, and streptomycin. She failed to improve and five days after the onset of her illness she was transferred to the Second Attached Hospital. On the day of transfer, her urine output was 460 cc. Over 24 hours, her axillary temperature was 38°C, but blood pressure and respiration were normal. Physical examination revealed marked facial flushing (see Fig. 1) and petechiae over the chest and in the axillae. She had conjunctivitis and eyelid edema. The remainder of the examination was unremarkable except for slight agitation. The white blood count was 24,100/mm³ with 25 percent neutrophils, 62 percent lymphocytes, 8 percent monocytes, and 5 percent atypical lymphocytes. The platelet count was 57,000/mm³. Blood urea nitrogen was 57 mg% and PTT and PT were normal. Urinalysis revealed many white blood cells, 1+ protein and red blood cells too numerous to count. The fibrinogen level was 95 mg% (normal 200–400 mg%), and an electrocardiogram was normal.

Although the patient had persistent fever, oliguria (urine output less than 500 cc/24 hours) was short-lived. She was treated with hydrocortisone 100 mg IV, phytohemagglutinin 20 mg IV, vitamin C, furosemide, ethacrynic acid, chloramphenicol, and potassium chloride. Urine output remained in the normal range until the seventh day after admission at which time polyuria developed. Polyuria lasted nine days and was managed with fluid and electrolyte replacement. Repeat laboratory examination revealed a normal hemoglobin, leukocyte count, platelet count, and urinalysis; all symptoms abated. The patient was discharged 44 days after the onset of illness and returned to her commune. Sera obtained six days after the onset of illness



FIG. 1. Case A who presented marked facial edema and flushing characteristic of EHF.

(acute) and 31 days after the onset of her illness (convalescent) were assessed for antibodies against antigens associated with KHF by the indirect immunofluorescence test (see Methods). The acute serum reacted at a dilution of 1:128 and the convalescent sera reacted at a dilution of 1:8192. The patient's sera did not react positively with any of the arbovirus antigens against which they were tested (see Results).

Comment

This patient presented with rather typical findings of EHF, although the fever phase was prolonged for 13 days. She did not have hypotension or shock but did have one day of oliguria. She subsequently had nine days of polyuria. Her confusion emphasizes the central nervous system involvement which we observed among patients with this disease; lumbar puncture was not performed. (The serological response observed will be discussed below.)

Case B

Patient 144893 was a 40-year-old Chinese female. She was well until December 15 when she noted the sudden onset of chills, fever, nausea, and myalgias. She was seen almost immediately by a "barefoot" doctor and treated with unknown medications. Four days later she was admitted to the commune hospital with the diagnosis of EHF; fluids, dextran, hydrocortisone, and bicarbonate were administered. Three days after admission to the commune hospital the patient became confused, and hypotension and oliguria developed. At that time she was transferred to the Second Attached Hospital of Hubei Provincial Medical College. On admission to that facility the temperature was 37°C, the blood pressure was 60/30 mmHg, the pulse was 140 per minute, and the patient was disoriented in all spheres. Physical examination revealed marked conjunctivitis and swelling about the eyelids. In addition blood oozed from an intravenous cutdown site in the right leg, but no other abnormalities in the physical examination were observed. Laboratory evaluation revealed a white blood count of 74,400/mm³ with 60 percent neutrophils, 12 percent lymphocytes, and 28 percent atypical lymphocytes. The hemoglobin was 13.0 g/dl; the platelet count was 63,000 per mm³. Urinalysis revealed red blood cells too numerous to count, 10–20 white blood cells per high power field, and 2+ protein. On the day following admission the patient developed respiratory insufficiency. Rales were heard at both bases and the respiratory rate was 50 per minute. In addition,

swelling about the neck was observed. Laboratory examinations at this time revealed a hemoglobin of 7.25 gm and a blood urea nitrogen of 102 mg%. The patient was treated with furosemide, vitamin C, ethacrynic acid, penicillin G, and gentamicin. Over the subsequent 24 hours the swelling about the patient's neck increased dramatically, as did her respiratory distress (see Fig. 2). She died on the fourth hospital day.

Comment

This patient had 11 days of fever, two days of hypotension and shock, and two days of oliguria. Subsequently her urine output was normal until death. Although she had only slight peripheral edema the dramatic swelling about her neck and probable pulmonary edema led to her demise. Inability to maintain fluid in the intravascular space is characteristic of EHF [2,7] and contributes to the very difficult fluid management of these patients.

Case C

Patient 145380 is a 42-year-old male worker. He had excellent health until January 11, 1980, at which time he developed fever of 38.6°C and submandibular lymphadenopathy. He was seen in the outpatient department of the Second Attached Hospital and was given a Chinese traditional medicine, tetracycline, and aspirin. Subsequently he remained stable over the next two days until he developed crampy abdominal pain and diarrhea. In addition he had nausea and vomiting; coffee ground emesis was noted. At that time he was admitted to the Second Attached Hospital. Physical examination revealed blood pressure of 70/0 mmHg, pulse of 90 per minute, and temperature of 39°C. Erythema of the pharynx was noted and the laboratory examination revealed hemoglobin of 12 g/dl, leukocyte count of 18,600 with 84 percent neutrophils and 16 percent lymphocytes. Blood urea nitrogen was 44 mg%, and potassium was slightly depressed. Gastric contents were aspirated and were 2+ positive for blood. The patient was treated with fluids, bicarbonate, and vitamin C. His abdominal pain did not resolve and on the day following admission gastroscopy was performed. This examination revealed acute diffuse gastritis without a focal ulcer. The blood pressure was stable with fluid replacement but the patient's urine output decreased dramatically on the third hospital day. Examination of the urine revealed 4+ protein, gross hematuria, and leukocytes with white blood cell casts.

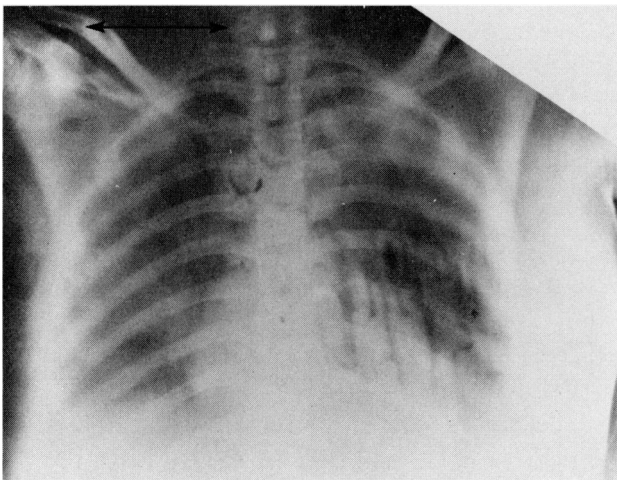


FIG. 2. Case B died of respiratory complications associated with EHF. She developed massive neck edema (outlined by arrows) shortly before her death, presumably secondary to the vascular damage associated with EHF.

Blood urea nitrogen was 72 mg% and the CO₂ combining power was slightly depressed. The patient was treated with dihydrocortisone and furosemide vice lasix. Evaluation of the coagulation status revealed a platelet count of 92,000 per mm³ and prolonged clotting time and bleeding time. In addition, the patient developed confusion and seizures which were attributed to uremia. Concomitantly the patient developed marked facial and periorbital edema about the eyelids. At that time the diagnosis of EHF was entertained. Subsequently on the fifth hospital day the patient developed polyuria which persisted more than 40 days. His other symptoms improved and all laboratory examinations returned to normal.

Comment

This case emphasizes the difficulty in making the diagnosis of EHF in the absence of a classical presentation. The patient's sequential fever, hypotension, and acute renal failure were attributed to gastritis, shock, and acute renal failure rather than considered as a single syndrome. In addition the patient's central nervous system abnormalities most probably were related to the disease process itself rather than to uremia.

Clinical Studies

Between July 1975 and April 1980, 71 patients were admitted to the First Attached Hospital with the diagnosis of EHF (Fig. 3). Eighty percent of the patients developed this illness between November and February. The age of the patients ranged from 13 to 69 with a mean of 38.0 ± 13.2 years (mean \pm standard deviation). There were 49 males and 22 females. Occupations included commune workers (46), laborers (9), students (5), administrative officials (2), teachers (2), and technicians (2); the occupation was not known for five of the patients.

The most common signs and symptoms of the illness are shown in Table 1. Whereas most symptoms were nonspecific (e.g., fever, myalgias, diarrhea), facial flushing, axillary petechiae, and conjunctival edema, often with eyelid swelling, were considered highly suggestive of EHF. Unfortunately, these latter symptoms occurred in 50 percent or less of the patients. The "three pains" of EHF—headache, orbital

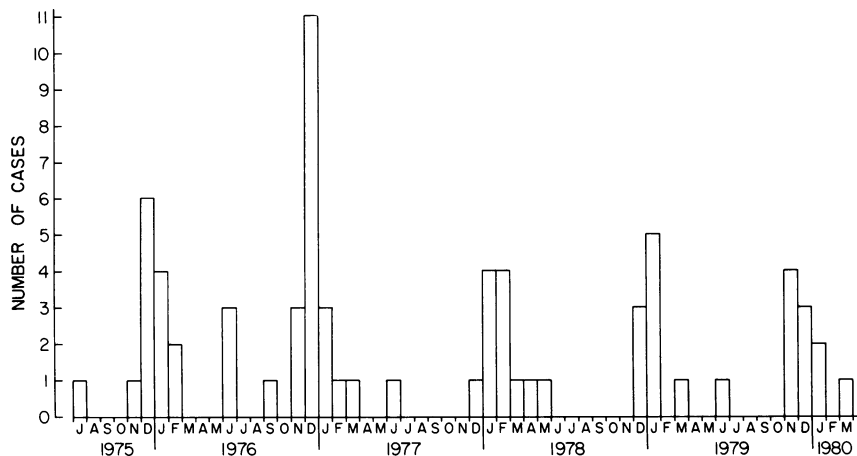


FIG. 3. Month of admission of patients with EHF to the Second Attached Hospital of HPMC, July 1975–March 1980.

TABLE 1
Signs and Symptoms Associated with EHF at the Time of Admission (Total, 71 cases)

	Number of patients	(%)
Fever	71	100
Headache	59	83
Palatal injection	58	82
Nausea	51	72
Costovertebral angle pain	49	69
Conjunctivitis	45	64
Vomiting	41	58
Axillary petechiae	40	56
Myalgia	39	55
Flushing	30	42
Weakness	30	42
Dizziness	29	41
Diarrhea	26	37
Orbital pain	24	34
Bleeding ^a	22	31
Chest Petechiae	21	30
Abdominal pain	18	25
Conjunctival edema	16	23
Ecchymosis	15	21
Blurred vision	13	18
Eyelid edema	12	17
Confusion	11	16
Abdominal tenderness	11	16
Rhonchi, wheezes	7	10
Rales	5	7
Lymphadenopathy	2	3
Ankle edema	2	3

^aBleeding from venipuncture site, gastrointestinal tract, and/or epistaxis.

pain, and back pain—were observed in 83 percent, 34 percent, and 69 percent of patients, respectively.

Regardless of the frequency of the disease in Hubei Province, the diagnosis was rarely made during the initial medical contact. As outlined in Fig. 4, although

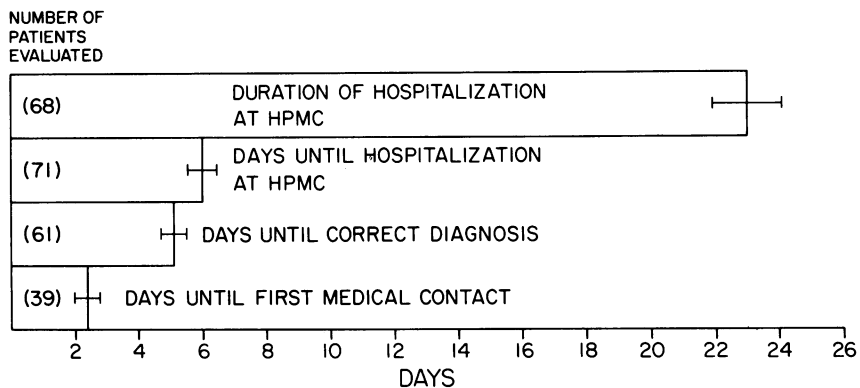


FIG. 4. The temporal sequence of events associated with EHF among patients admitted to the Second Attached Hospital are shown.

TABLE 2
The Phases of EHF among 71 Patients

Phase	No. Pts	(% total)	No. Evaluable	Duration (days)	Range (days)
Fever (>37.6°C axillary)	71	(100)	57/71	7.4 ± 3.8	2-15
Hypotension (<90/60 mm Hg)	30	(42)	29/30	1.3 ± 0.67	0.5-3
Oliguria (<500 cc urine/24 hr)	42	(59)	38/42	2.8 ± 2.1	1-10
Polyuria (>2,000 cc urine/24 hr)	64	(87) ^a	29/64 ^b	14.8 ± 8.2	1-35

^a87 percent may be lower than expected because six patients died prior to the polyuria phase and one patient remained in the hospital at the termination of this study.

^bPatients discharged with urine output greater than 2,500 cc/24 hours could not be evaluated.

patients were seen by a health worker within two or three days after onset of illness, the correct diagnosis was not entertained until the second or third visit.

The frequency and duration of the expected phases of the disease are shown in Table 2. Although 100 percent of the patients had a fever phase, hypotension and oliguria were reported in only 42 percent and 59 percent of the patients, respectively. Polyuria was observed in all patients in whom this could be evaluated.

A summary of some of the abnormal laboratory results encountered is shown in Tables 3 and 4. Ninety-two percent of the patients had leukocyte counts greater than 10,000 per mm³ at some time during the disease. Fifty percent of the patients had atypical lymphocytes on differential examination. Eleven percent of the patients had myelocytes or metamyelocytes observed in the peripheral blood smear. Platelet counts were depressed in 78 percent of the patients examined. The nadir of the platelet count occurred during the fever phase in one-third of the patients, and in the early polyuria phase¹ or polyuria phase in 44 percent of the patients. The blood urea nitrogen (BUN) was elevated during all phases of the disease. BUN was highest in the oliguria phase (73.7 ± 20.3 mg%, *n* = 15) and remained elevated during the polyuria phase (55.4 ± 22.9 mg%) in 59 patients in whom this parameter was assessed. The blood urea nitrogen returned to near normal (22.9 ± 13.21, *n* = 5) before discharge. Electrolyte abnormalities were common, as shown in Table 4, but were rarely severe. Abnormalities in the urine including hematuria, pyuria, and proteinuria were invariable findings; red and white blood cell casts were also seen on occasion.

Epidemic hemorrhagic fever was associated with severe morbidity and mortality. The mean duration of illness was 29.4 ± 11.8 days (range 3-67 days, *n* = 68) and the

¹Early polyuria refers to the state of illness wherein oliguria has resolved but polyuria has not yet ensued and urine output is normal.

TABLE 3
Laboratory abnormalities observed in 71 patients with EHF^a

Phase of Disease	Maximal BUN (mg%)	Maximal Neutrophil Count (× 10 ³ /mm ³)	Platelet Nadir (× 10 ³ /mm ³)
Fever	47.9 ± 18.7 (36) ^a	20.7 ± 14.8 (41)	70.7 ± 44.1 (28)
Hypotension	46.2 ± 13.34 (18)	16.5 ± 10.7 (7)	68.0 (1)
Oliguria	73.7 ± 20.3 (15)	25.5 ± 16.5 (4)	136 ± 75.0 (2)
Polyuria	55.4 ± 29.9 (59)	10.3 ± 4.0 (50)	102.4 ± 55.8 (38)

^aValues are expressed as the mean and standard deviation of the mean of the number of samples shown in parenthesis.

TABLE 4
Serum Electrolyte Imbalances in 71 Patients with EHF^a

Phase of Disease	CO ₂		K ⁺		Ca ⁺⁺	
	↑	↓	↑	↓	↑	↓
Fever	0/36	29/36	0/30	15/30	0/26	16/26
Hypotension	0/18	17/18	2/14	3/14	0/12	4/12
Oliguria	0/21	17/21	2/19	4/19	0/18	7/18
Polyuria	0/59	44/59	4/60	21/60	0/57	34/57

^aAn increase (↑) or decrease (↓) in serum carbon dioxide combining power (CO₂), potassium (K⁺), and calcium (Ca⁺⁺) are shown (numerator) among the patients in whom these parameters were evaluated (denominator).

Normal values are as follows: CO₂, 24–30 meq/L; K⁺, 3.5–5.0 meq/L; and Ca⁺⁺, 9–11 mg/dl (converted from Chinese units of measurement).

duration of hospitalization was 23.4 ± 10.7 days (range 1–48, $n = 68$, Fig. 1). The mortality among patients admitted to Hubei Provincial Medical College between 1975 and 1980 ranged from 4.5 percent to 30 percent per year with a mean of 11.2 percent. Circumstances associated with the death of the patients are shown in Table 5.

Serological Studies

Serum samples collected from patients hospitalized in both the First and Second Attached Hospitals were brought to the United States for testing by one of the au-

TABLE 5
Cause of Death among 8 Patients with EHF

Patient	Age	Sex	Day of Illness	Phase	Sequelae Preceding Death
1	56	M	31	polyuria	Pulmonary edema, anisocoria, persistent fever (? 2° infection); BUN 21 mg%, K ⁺ low
2	55	F	6	hypotension (shock)	Patient died immediately after transfer; past history of hypertension and nephritis; no laboratory data available
3	60	M	14	polyuria	Severe anemia, persistent leukocytosis, coma, and nuchal rigidity preceding death; BUN 100 mg%; electrolytes normal
4	46	M	13	oliguria	Anisocoria, CSF "yellow," BUN 96 mg%, Ca ⁺⁺ low
5	42	M	15	early polyuria ^a	Confusion, nuchal rigidity, anisocoria, fever, BUN 116 mg%, acidosis
6	39	M	3	hypotension (shock)	BUN 54 mg%, acidosis
7	41	M	13	?	History of hemoptysis; patient died immediately after transfer to HPMC; no laboratory data available
8	40	F	23	early polyuria ^a	Confusion and convulsions, pulmonary infiltrates and "bull neck" (see Fig. 2); BUN 98 mg%

^aEarly polyuria refers to a brief period of normal urine output which follows oliguria and precedes frank polyuria.

thors (CMH). Positive immunofluorescence was observed in A 549 cells and frozen and fixed sections of rat lung tissue infected with KHF virus strain 118 when tested by the indirect immunofluorescence technique as shown in Fig. 5. Exceedingly high antibody titers (1:4096–1:8192) were observed in convalescent serum samples obtained 19–43 days after the onset of illness (Table 6). Less marked elevation in antibody titers (1:128–1:256) were also noted in three acute phase specimens obtained 6–7 days after the onset of illness. In control experiments employing a hemagglutination-inhibition assay, low titers of antibodies directed against Japanese B encephalitis antigen (10 patients) and Murray Valley encephalitis antigen (five patients) were detected (Table 6); such low titered reactions are not considered diagnostic of recent infection with these agents.

DISCUSSION

Although specific information concerning the incidence of epidemic hemorrhagic fever in the PRC is not available, the disease occurs in at least 18 provinces [24]. Between July of 1975 and April of 1980, 71 cases of Epidemic Hemorrhagic Fever were admitted to the Second Attached Hospital of Hubei Provincial Medical College. The majority of cases occurred during the winter months between November and February. This observation differs considerably from seasonal occurrence of the disease in Korea where peaks have been observed in the summer months [4,5,25] and the late fall [4,5,17,25–27].

In this study, the disease was twice as common among men compared to women and did not occur in young children and infants. Although this pattern may relate to risk factors associated with host defenses, it is more likely that exposure of male laborers to the infectious agent accounts for this observation [26]. In other reported series with male predominance, military populations were involved [1].

The initial symptom complex of EHF was difficult to distinguish from other febrile illnesses. The subsequent full-blown picture of the disease, however, was quite characteristic. Constitutional symptoms included fever, headache, myalgia, and weakness. More specific complaints including orbital pain, conjunctivitis, axillary petechiae, facial flushing, and costovertebral angle tenderness occurred frequently, but were not seen in every case. The symptom complex observed among Chinese patients was nearly identical to that recorded among American soldiers who developed EHF during the Korean War [1] and reports of the disease from the

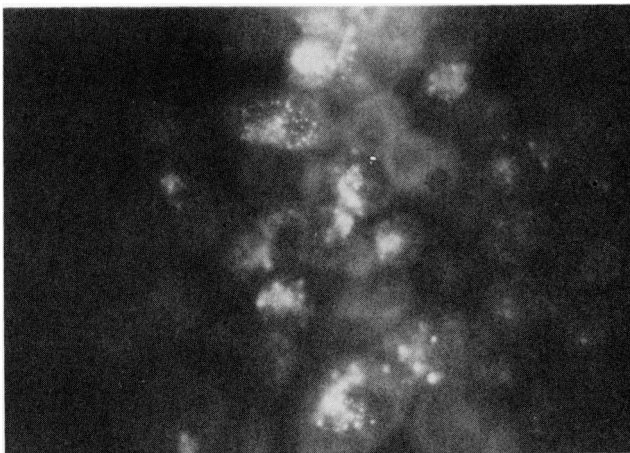


FIG. 5. An A-549 cell culture infected with KHF virus overlaid with convalescent serum obtained from patient (case A) showing positive immunofluorescence.

TABLE 6
KHF and other Viral Antibody Titers in sera obtained from Chinese EHF patients

Serum Sample	Days After Onset of Illness	Acute/Conv.	Hemagglutination-Inhibition Test ^a					FA ^b	
			JE	MVE	YF	OHF	CHIK	KHF Virus	
Paired	5	A	10	10	10	10	10	ND	
	19	C	10	10	10	10	10	ND	
	4	A	20	10	10	10	10	ND	
	35	C	20	10	10	10	10	ND	
	7	A	20	10	10	10	10	256	
	25	C	80	20	10	10	10	8,192	
	6*	A	10	10	10	10	10	128	
	31	C	10	10	10	10	10	8,192	
	Single	7	A	ND	ND	ND	ND	ND	256
		NA**	C	20	10	10	10	10	8,192
NA		C	80	10	10	10	10	8,192	
NA		C	20	20	10	10	10	8,192	
NA		C	80	20	10	10	10	8,192	
NA		C	20	10	10	10	10	4,096	
NA		C	40	20	10	10	10	8,192	
23		C	10	10	10	10	10	8,192	
43		C	20	20	10	10	10	ND	
39		C	10	10	10	10	10	ND	
36		C	10	10	10	10	10	ND	
28	C	20	10	10	10	10	8,192		

^aTested at YARU

JE, Japanese encephalitis; MVE, Murray Valley encephalitis; YF, yellow fever; OHF, Omsk hemorrhagic fever; CHIK, chikungunya; titers are expressed as the reciprocal of the highest dilution of serum that inhibited hemagglutination of red blood cells by 4-8 units of antigen.

^bTested at NIH by the indirect immunofluorescence test. Titers are expressed as the reciprocal of the highest dilution of serum giving a 2+ or greater reaction.

*Case A under results

**NA, not available

USSR [4,15,28]. The vague initial symptom complex, however, made early diagnosis somewhat difficult, and diagnosis was rarely made at the initial medical contact.

EHF among Chinese patients was characterized by phases of fever, hypotension, oliguria, and polyuria. Surprisingly, only 20 percent of the patients had a defined period of hypotension, and slightly more than half had oliguria. This observation is important because Chinese investigators attempting to improve the treatment of EHF often gauge the success of their therapy on the duration or extent of the expected phases. In particular, the absence of a phase of disease (e.g., a hypotensive period followed by polyuria with no oliguria) seemingly linked to a particular form of therapy might be used as evidence of efficacy. Few studies have been designed to include adequate control groups, and our observations would suggest that the absence of one or more of the phases of EHF is a common spontaneous occurrence. At any rate, the duration of the observed phases of the disease were consistent with earlier reports [1,15,28].

Laboratory abnormalities included leukocytosis with shift to the left, observation of atypical lymphocytes, thrombocytopenia, abnormal urinalysis (proteinuria, he-

maturia, pyuria), azotemia, and electrolyte imbalance. These abnormalities have been observed in virtually all previous studies of the disease [2,6,28]. There is no obvious explanation as to why patients develop an elevated leukocyte count during what is presumed to be a viral disease. Furthermore, regardless of leukocytosis, tissue infiltration of phagocytic cells is actually mild [7,29], suggesting that these cells may not function normally.

Increase in blood urea nitrogen was seen in virtually every patient in whom this was studied. Azotemia began to develop during the fever phase and generally reached maximal elevation during the polyuria phase. Blood urea nitrogen returned to normal in every patient who survived, which is consistent with the notion that EHF has few, if any, long-term sequelae after recovery [2]. A recent Chinese study, however, described persistent renal abnormalities as well as a variety of physical complaints among survivors [30]. Acidosis and mild hyponatremia were common electrolyte disturbances, and were undoubtedly due to the renal damage which has been described in this disease [31], as well as hypotension and fluid imbalances [6,10]. Hyperkalemia, which was seen frequently among American soldiers with EHF [6], was only rarely observed. Hypocalcemia was common during all phases of the disease and may relate to protein abnormality, kidney damage, or other mechanisms.

The cumulative mortality rate of 11.2 percent which we observed is consistent with the experience of other investigators in China [32], as well as workers in Korea [1] and the USSR [25]. Mortality in Scandinavia from a related disease, Nephropathica Epidemica, however, is rare [11]; this may relate to strain differences with regards to the virulence of the etiologic agent [12,13,14,20,21,27,28,33].

In the present study, two patients died early in the course of disease as a result of shock, whereas the remaining six patients died during the second or third week of illness during the polyuria phase. Most of the patients who died had a variety of abnormalities including azotemia, electrolyte imbalance, and central nervous system abnormality. Although in other studies concerning the cause of death in EHF, patients succumbed to the disease somewhat earlier in their course [6], the clinical circumstances surrounding death are quite similar to the present study. Besides primary shock, death has been attributed to uremia, secondary infection, pulmonary edema, brain edema, and cerebral hemorrhage [6,7,16,28]. Spinal fluids obtained from these patients have revealed mild pleocytosis with lymphocytes predominant and elevated protein [28,34]. Spinal fluids occasionally have a yellow tinge which has been attributed to azotemia, but xanthochromia or gross blood in the spinal fluid is generally not observed.

It is probable that the central nervous system abnormalities reported (which appear to be particularly common among patients who succumb to this infection) involve a combination of electrolyte abnormality, azotemia, and cerebral edema, as well as direct involvement of the brain [34]. Among autopsies of patients who died, pituitary necrosis and mononuclear infiltration of the brain were frequently observed [7,31].

Sera obtained from patients admitted to the First and Second Attached Hospitals of Hubei Provincial Medical College were examined with respect to the formation of antibodies directed against a variety of agents known to produce hemorrhagic fevers. The results of this study have been reported by Lee et al. [21] who demonstrated that all the sera tested reacted with very high titers of antibodies directed against Korean hemorrhagic fever virus antigen in the indirect immunofluorescence test and none of the sera had significant concentrations of antibodies directed against several arbovirus antigens in the hemagglutination-inhibition test. Chinese investigators have

suggested that the formation of antigen antibody complexes may actually be responsible for such abnormalities as renal damage and petechia, as well as triggering of disseminated intravascular coagulation [35]. These workers have proposed therapy directed against antibody formation [36]. Alternatively, immune sera obtained from survivors could potentially ameliorate the course of the disease as has been suggested for other hemorrhagic fevers [37].

The antigen of Korean hemorrhagic fever is prepared from the lungs of wild mice (*Apodemus agrarius*) endemic in several parts of Asia [17]. Transmission of the disease appears to occur most commonly via the nasopharyngeal route by aerosol infection, and outbreaks have occurred among animal trappers and laboratory workers exposed to infected rodents [38,39]; nosocomial transmission, however, has not been reported. Early studies designed by Soviet and Japanese investigators demonstrated that blood and urine from patients with EHF contained an infectious agent [28]. They also suggested that some of the insects harbored by wild mice could transmit the disease although more recently Lee was unable to find EHF antigen in ectoparasites collected from infected rodents [27].

Most of the patients in this study lived in the countryside area where exposure to mice is common. Eighteen percent of the patients had known travel and/or living conditions which may have increased the risk of developing EHF. These observations are in agreement with a study in China by Xu and co-workers who observed an increased incidence of EHF among adult male farm workers who slept in field shacks [26]. They concluded that exposure to an airborne agent from rodent excrements might explain their findings. KHF virus has been isolated from rodent saliva and respiratory secretions [39], from *Apodemus* mouse urine (H.W. Lee, personal communication) and from the feces and urine of *Apodemus* mice and Wistar rats experimentally infected with KHF virus (P.W. Lee, unpublished data).

In summary, this study demonstrates that the clinical course of EHF among patients in south central China is a disease similar to that described in Korea and the USSR. Furthermore, the immunological response among this population of patients strongly suggests that EHF in China is produced by the same (or closely related) agent as EHF in Korea [20,21], the USSR [17], and is closely related to the agent of Nephropathica Epidemica in Scandinavia [12,13,14,27,33,39,40]. Many questions concerning the morbidity, mortality, epidemiology, immunopathology, and therapy of EHF remain to be answered.

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