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A Case Report of Suspicious Epidemic Hemorrhagic Fever

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INTRODUCTION

A 22 years old man was admitted to the University Hospital on February 1, 1961. His chief symptoms were high fever and bilateral chest-pain. Those days before admission, he had developed high fever (40.5°C), headache, bilateral chest-pain, non-radiating dull pain in the left upper abdominal region, diarrhea three times a day and severe general fatigue. Dr. Tamura, who examined the patient first, detected leucopenia and sent the patient to our hospital under the tentative diagnosis of malignant influenza or acute hepatitis.

Physical findings on admission

The patient's weight and nutritional state were moderate and no wound or scar could be found on the skin. No hemorrhage or abnormal pigmentation were detected. Objectively, no abnormal signs were noted in the eye balls, pupils or the pupilary reaction to light. The face and facial expression seemed quite normal. Cervical and other lymph nodes could not be palpated. The pulse was strong and regular with a frequency of 120/min. The patient seemed slightly dyspnoeic with a respiratory rate of 30/min. The blood pressure was 130-70 mmHg. The body temperature was 39.5°C. The oral cavity was normal except for slight redness and swelling of both tonsils. Breathing was almost normal but slightly rough on auscultation. The heart sound was distinct. Moderate tenderness was noted in the epigastric area, but no resistance could be proved. The liver, spleen and kidneys could not be palpated.

Laboratory findings on admission

Urine: albumin trace, sugar (—)
urobilinogen slightly increased
Gmelin's reaction (—)
Sediment: red blood cells 0-1-1
white blood cells 5-6-5
epithelial cells 1-2-1
cast 1-1-0

Erythrocyte sedimentation rate: 2mm/1hr., 12mm/2hrs.

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Blood: red blood cells 500 × 10^4/mm^3
white blood cells 12,000/mm^3
hemoglobin 100% (Sahli)

Culture of Bacteria
arterial blood (−)
feces, salmonella (−) shigella (−)

Serological tests
ASLO 166 T.U., CRP 1+

A conclusive diagnosis could not be established from the clinical signs and symptoms of the patient and treatment started under possible diagnoses of malignant influenza, infectious hepatitis, pancreatitis, acute glomerulonephritis or some other infectious disease.

The day after admission, i.e. the 5th day after the onset of fever, the patient fell into a state of shock, and the blood pressure fell to 70-0 mmHg.

Oliguria and anuria followed the shock, manifesting the figure of acute renal failure or lower nephron nephrosis. Though the patient soon recovered from the circulatory shock, the renal failure continued and death ensued on the 7th day after admission.

Clinical course

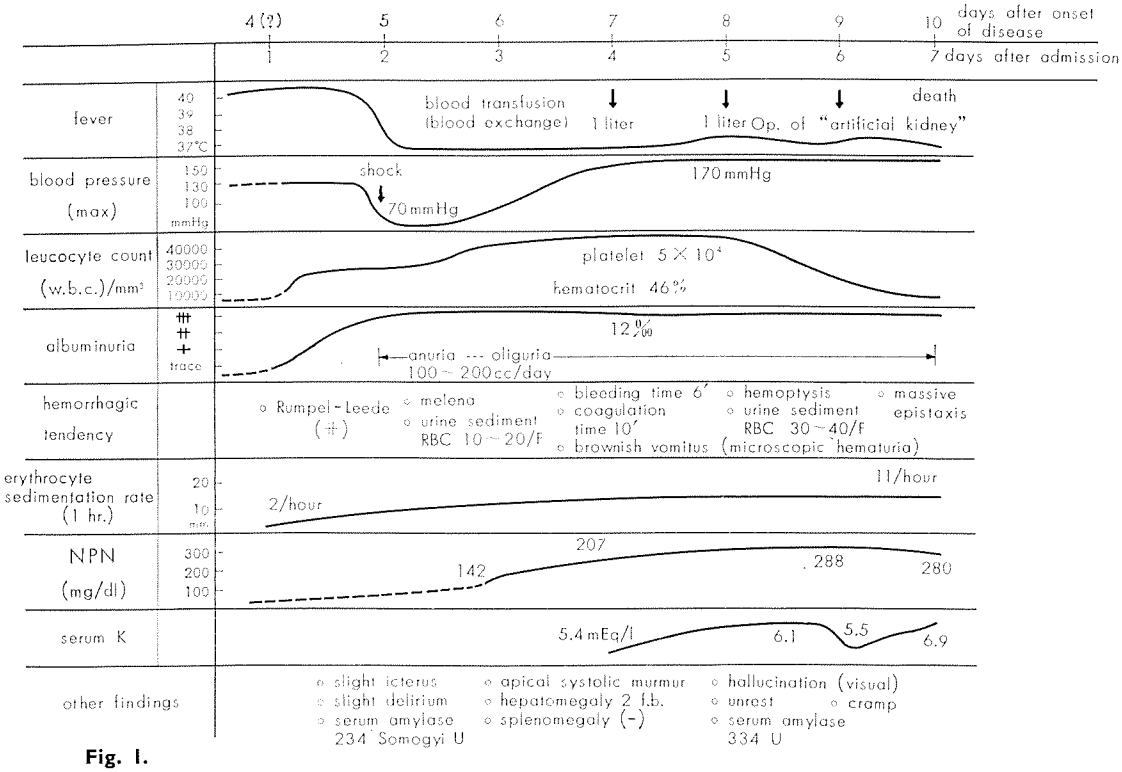


Fig. 1.

As shown in figure 1, on the 5th day after the onset of the disease, the body temperature returned to normal, accompanied by shock with manifestations of anuria, leucocytosis, a hemorrhagic tendency and marked increase in albuminuria, all of which suggested acute uremia with possible impairment of the heart, liver and kidneys.

The results of laboratory examinations after the patient's hospitalization were as follows.

Laboratory examinations

1) Erythrocyte Sedimentation Rate

4th day:	2 mm/hr.	10th day:	11 mm/hr.
	12 mm/2hr.		26 mm/2hr.

2) Blood Examinations

	5th day	7th day	↓	9th day
rbc	600×10^4	697×10^4	blood	372×10^4
Hb	100 %	94 %	exchange	58 %
wbc	16,800	43,600		15,800
N Seg.	68 %			Seg. 63 %
N Stab.	2 %			Stab. 4 %
E	1			1
B	0			0
L	19			20
M	10			7
				Metamyelo. 2
				Virocyte 3
hematocrit		46 %		32 %
platelets		5×10^4		8×10^4

3) Urine Examination

	4th day	5th day	7th day	8th day
albumin	trace	+++	+++(12%)	+++
sediment rbc	0~1~1	10~20	20~25	30~40
sediment wbc	5~6~5	1~2~2	2~3~3	3~5~3
sediment cast	1~1~0	4~5~5	4~5~4	1~2~2
sediment epithelia	1~2~1	2~3~2	2~3~4	3~5~4
sediment others		fibrinous membrane		
urobilinogen	slightly increased		(—)	
Gmelin's reaction	(—)		(+)	
sugar	(—)	(—)	(—)	(—)

4) Liver Function Tests

	6th day	9th day
Total protein	7.6 g/dl	6.8 g/dl
Albumin	3.8	4.0
Globulin	3.8	2.8
A/G	1.0	1.4
Gros	1.7	1.7
Cobalt	R_6	R_7
C.C.F.	24 hrs. (+++)	24 hrs. (+++)
Icteric index	33	21
Kunkel		8 U
T.T.T.		4 U
Takada's reaction		(±)
H.v.d. Bergh		direct (+) indirect (+)

5) Chemical Examinations of Blood

	6th day	7th day	9th day (before the op. of artificial kidney)
Na		136 mEq/l	134 mEq/l
K		5.4	6.1
Cl		99	110
Ca			9.2 mg/dl
NPN	142 mg/dl	207 mg/dl	278 mg/dl
Urea N			173
Amino N			9
Uric acid			17
Creatine			22
Creatinine			17.6
Glucose			164
Cholesterol			136
Ester-chol.			69
Amylase	234 Somogyi U		486 S.U.
Acid phosphatase pH. 4.5 pH. 6.8			 0.8 Bod. U. 1.9
Alkaline phosphatase			2.4
CO_2			15 mEq/l

6) Immunoserological Tests

	5th day	9th day			
CRP					
ASLO	166 T.U.	166 T.U.			
Waaler-Rose		28 dils.			
RA		(—)			
Candida aggl. test		40 dils.			
Serological test for syphilis		(—)			
Widal, Weil-Felix		antigen	O-aggl. titer	H-aggl. titer	Vi
		typhoid	0	0	0
		paratyphoid A	0	0	
		B	0	0	
		OX19	0		
		OXK	160 dils.		
		OX2	0		

Culture of arterial blood and feces did not reveal any bacteria as a causative agent.

7) Serum Electrophoresis

	7th day
Total protein	7.0 g/dl
Albumin	46.5 %
Total globulin	53.5
α-glob.	10.8
β-glob.	10.9
γ-glob.	31.8

8) Endocrinological Test (9th day)

The test was performed with parenteral administration of ACTH and Prednisolone.

Urinary	
17-KS	0 mg/day
17-OHCS	10.3

9) Chest X-Ray (taken in the ward)

6th day and 9th day

Nothing particular, except enlargement of the cardiac shadow between 6th and 9th day.

10) ECG Findings

6th day

↓

9th day

right side type, ST II, III, aVF, depression Tv_5, V_6 flat

11) Artificial Kidney (Feb. 6)

	before	after	next day
NPN	278 mg/dl	288	280
Amylase	486 Somogyi U		334
Na	134 mEq/l	135	133
K	6.1 mEq/l	5.5	6.9
Cl	110 mEq/l	96	96

Feb. 3

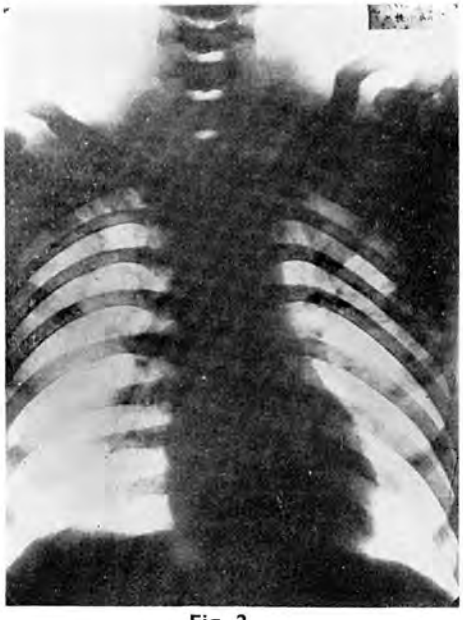


Fig. 2.

Feb. 6

Fig. 3.

Chest X-ray: No abnormal findings on admission (feb. 3), but marked cardiac enlargement is noted 3 days later.

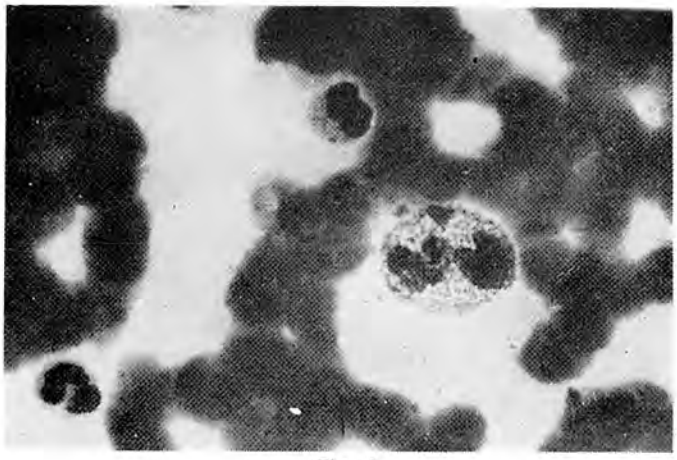


Fig. 4

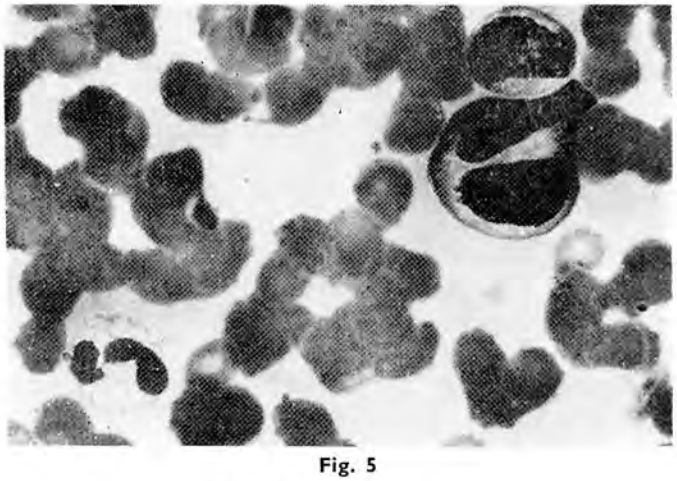


Fig. 5

Peripheral Blood Picture

Fig. 4 Note the presence of eosinophils. Eosinophilic cells did not disappear in this case
Fig. 5 Note two abnormal leucocytes (top right)

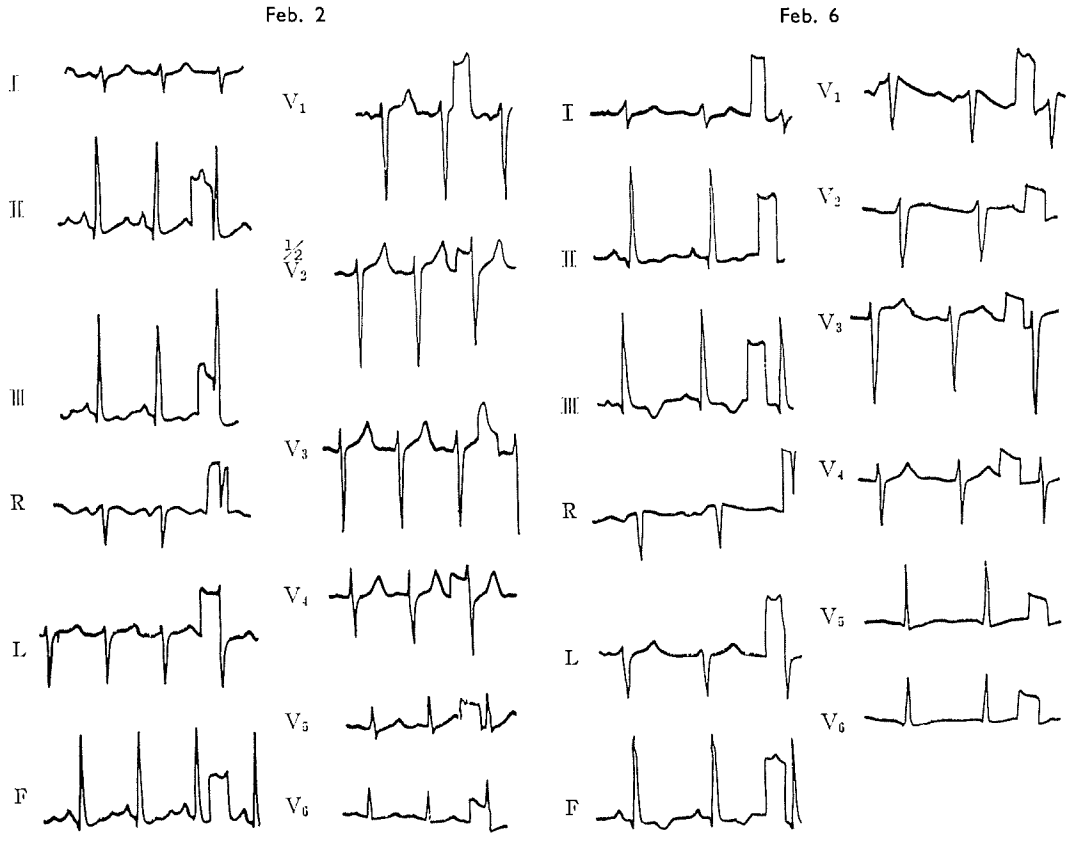
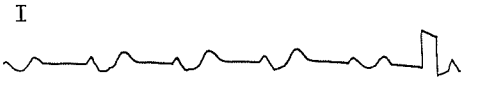


Fig. 6



ECG 5 minutes before death
Patient died at 4: 35 p.m., Feb, 7, 1961

ST depression and a flat T are found on ECGs of Feb. 2 and 6. Between Feb. 2 and 6 the T wave changed markedly. The ECG of Feb. 2 does not show bradycardia, but sinus tachycardia of 120 min.. Tachycardia is regarded as a sign of poor prognosis in this disease.

Treatment

The treatment was initially for a septicemic disease of unknown etiology and various antibiotics such as Chloramphenicol and Erythromycin propionate were given. After the occurrence of shock, many vasopressor drugs were given and fluid transfusion was begun, combined with ACTH and Prednisolone administration. As a result, the patient recovered from the shock within 5 hours and the blood pressure returned from 70/0 to the normal level of 100/50mmHg. However, oliguria

or anuria (the daily urine volume was 100-200 ml) did not improve although the patient recovered from shock. Additional impairments of the heart, liver and kidney further complicated the clinical picture of the disease.

Treatment with antibiotics, adrenocortical hromones and vitamins as well as fluid transfusion, which was adjusted by laboratory data, failed to prevent the appearance of hypertension and hyperkalemia due to renal failure. No beneficial effect could be obtained in the level of NPN or other end products in the blood by blood exchange of a total of 2 liters in 2 days.

Our last attempt was made on February 2. With the help of urologist, an "artificial kidney" operation with an electrodialyzer was performed, but the patient died on the next day after the operation. The results of laboratory examinations before and after the operation are summarieed in the table, and show some improvement in hyperkalemia.

The operation for an "artificial kidney" required the transfusion of 1,400 ml of blood, 16 liters of electrodialyzer and several hours. A large amount of heparin used to prevent coagulation of blood circulating outside the body seemed to aggravate the hemorrhagic tendency of the patient.

This case followed a very acute course with only 10 days from its onset till death, so that thorough examinations and a definite diagnosis could not be achieved before death. However, much was learnt from this case and very important clinical experiences were gained in the short period of illness. Detailed pathological findings at autopsy are reported elsewhere in this volume by Professor Okano of Osaka University.

DISCUSSION ON DIAGNOSIS

As stated above, a 22 years old patient had a fulminant course, high fever of over 40°C for the first 4 days and sudden crisis and shock, leading to anuria and death due to renal failure. It took only ten days from the onset of the disease to death.

Clinical manifestations of fever, tonsillitis, albuminuria and the terminal uremic state were suggestive of acute glomerulonephritis, but the slight degree of albuminuria before shock and absence of hypertension, edema and the characteristic "edematous pale face" did not support such a diagnosis.

The high fever was suggestive of infections, especially bacterial sepsis. If this was the case, the shock may be explained as Waterhouse-Friderichsen's syndrome, the etiology of which is adrenal hemorrhage caused by meningococcal septicemia.

However, certain clinical observations, and laboratory data throughout the whole course did not support a diagnosis of septicemia. These included (1) absence of focus or wound of infection for entrance of causative agent. (2) no bleeding in the skin or mucous membrane, such as is usually encountered in septicemia, though a hemorrhagic tendency was noted in the later stage. (3) absence of splenomegaly. (4) normal erythrocyte sedimentation rate even during period of high fever. (5)

marked leucocytosis as in the leukemoid reaction even after the fever subsided. (6) absence of parallelism between fever and general condition. (7) survival of shock, as in Waterhouse-Friderichsen's syndrome and death from uremia several days later. (8) no evidence of bacteria in circulating blood. (9) incompatible findings of no fever and abundant albuminuria in later stage with focal nephritis of septicemia. Moreover, antibiotic administration was ineffective.

Infectious hepatitis and acute pancreatitis were also taken into consideration because of the fever, slight icterus, epigastralgia and elevation of serum amylase, but these diagnoses were excluded on the basis of other conflicting data.

Another disease with a clinical course and symptoms closely similar to those reported here is an epidemic disease prevalent in 1938 in North Eastern Manchuria (the Northern part of present China). This disease was studied in detail and named "epidemic hemorrhagic fever" by a medical group in the former Japanese army. According to Kitano,[1] the causative agent is a virus and the route of infection is not from man to man, but from a kind of tick to man via a wild rodent as the vector. Thus the disease is almost entirely limited to humid grassland where these animals are habitual residents. In the Korean War of 1951, many American soldiers near the line of latitude 38 N. suffered from a febrile disease of unknown etiology. Marked injection of the bulbar conjunctivae with slight icterus in these cases was suggestive of Weil's disease, but spirochaeta could not be detected. Finally, it was found that the disease was the same as the epidemic fever described by former Japanese army doctors. It was reported[3] that 314 patients with this desease were sent from Korea to an Army Hospital in Osaka. The disease has been described in text-books by Cecil and by Harrison.

The illness begins abruptly with high fever and headache, lumbago, nausea and vomiting. The headache is rather characteristic, i.e. retrobulbar pain. The patient, therefore, has an agonized expression with narrowed eyes, injection of the conjunctivae and cutaneous flush about the face and neck. He looks sun-burnt and exhausted.[5]

Injection of the pharyngeal mucosa and abdominal pain in various areas are frequent symptoms and Hullinghorst[8] regarded the latter as due to retroperitoneal gelatinous edema.

Fever rises to over 40°C in most cases, remains high for 3-4 days and then suddenly subsides accompanying a marked fall of blood pressure. Anuria or oliguria follows in the next 1-2 days.

Severe albuminuria appears before or after shock, but it disappears during the convalescent stage of polyuria.

Red and white blood cells and casts can be observed in urine sediments, though not always in large quantity. Solid fibrinoid material is occasionally seen in the urine. Kitano and Nagayama[1] reported that it is of diagnostic aid to measure fibrin formation when the serum and urine of the patient are mixed. Ganong et al.[5] reported the presence of large oval mononuclear cells and fatty material in the patient's urine.

The hemorrhagic tendency is partly due to thrombocytopenia, but mainly to impairment of the capillary walls. This appears a few days after the onset of illness (the 3rd day of illness according to Kitano) and petechia generally appears on the soft palate and in the conjunctivae, pre- and postaxillary folds, scapular and other cutaneous areas subjected to mild trauma.

In severe cases, emesis, melena and epistaxis occur. A positive Rumpel-Leede reaction is observed even in the absence of purpura on the skin.

As the disease progresses, various parenchymatous organs are impaired and hepatomegaly with slight edema as well as heart-enlargement with bradycardia develop. However, if splenomegaly is present, some complication must be considered.[1)]

The blood picture is rather characteristic of the disease. Clinical laboratory data show first leucopenia and later marked leucocytosis, of which Kitano[1)] reported a maximum of 88,000 and Ganong[5)] a maximum of 93,000. Neutrophils constitute the largest percent of the increase with young abnormal leucocytes. Eosinophilic leucocytes do not disappear in this disease though eosinopenia is observed in most severe diseases. Polycytemia is noted in the early stage, sometimes with erythroblastosis.

A normal erythrocyte sedimentation rate is characteristic of this disease although it is a severe infectious disease.

The general condition of the patient becomes more serious after the fever subsides and this is a characteristic of the illness differentiating it from sepsis and other infections.

Although the clinical course and laboratory data of the reported case agree closely with those of epidemic hemorrhagic fever, the following points are rather inconsistent with the diagnosis and have made us hesitate in making a definitive diagnosis;

(1) Absence of injection of the conjunctiva and characteristic expression of the face in our case.

(2) Hemorrhagic tendency or purpura was not observed until the 3rd day of the illness and appeared near the end stadium.

(3) Enlargement of the heart was noted, but bradycardia was absent.

(4) Although the type of fever, shock, urinary findings (albuminuria and fibrin mass), blood picture and lack of coincidence between the fever and the peak of the disease all point to a diagnosis of epidemic hemorrhagic fever, there have been no previous reports on the occurrence of the disease in Japan and the occurrence of a disease like this, which was first found in the fields of North Manchuria and needs a special vector for its spread, in a big city like Osaka is questionable.

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