RIFT VALLEY FEVER IN MAN

Report of a Fatal Laboratory Infection Complicated by Thrombophlebitis

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Although Rift Valley fever is a natural disease of sheep with a mortality of 50–95 per cent, it occurs also in man as an acute febrile illness, usually of such a mild character that in over 200 cases known to have occurred in British East Africa no untoward sequelae were observed (1). The purpose of the present communication is to report a case of laboratory infection—the first known instance of Rift Valley fever in America—which terminated in death.

Rift Valley fever or enzootic hepatitis occurs among sheep in the Kenya Colony of British East Africa (1, 2). Its symptoms are not striking; usually the affected animals show little more than listlessness, disinclination to feed, and progressive weakness. In older animals bloody diarrhea and thick mucoid rhinitis may also be observed. So rapid is the course that many animals are found dead without ever having been observed to be sick, and in most instances death supervenes within 24 hours after the initial sign of illness.

At autopsy the chief pathological change found is an extensive necrosis of the liver. In advanced cases, the liver is affected to such an extent that stained sections of it are scarcely recognizable as hepatic tissue. The lobules consist merely of irregular shaped masses of broken-down, faintly staining cells intermingled with polymorphonuclear and mononuclear leucocytes; the Kupffer cells can no longer be distinguished. In less advanced cases, the lobules of the liver are still distinguishable, but are studded with areas of necrosis of different sizes. About the periphery of these foci of degeneration are found parenchymatous cells containing cytoplasmic hyaline bodies similar to those described originally by Councilman (3) and more recently by Klotz and Belt (4) as occurring in the livers of human beings dead of yellow fever. Acidophilic intranuclear inclusions are found in great number, which, although usually of less definite outline and not so strongly acidophilic, resemble those associated with herpes and Virus III. In addition to the lesions in the liver, the ileum and large intestine are often the seat of a hemorrhagic enteritis associated with congestion of the mesenteric and omental vessels.

Hemorrhages in other organs, especially in the cortex of lymphatic glands and beneath the capsules of the spleen and the kidneys, are also common.

The etiological agent of Rift Valley fever has been shown by Daubney and Hudson (1) and others to be a filterable virus which invades the animal so completely that it can be recovered from almost all organs of the body. In addition to sheep, natural outbreaks have occurred among cattle and, as has been stated, spontaneous cases among human beings are common during the epizootics. The disease has been produced experimentally in monkeys, goats, cats, rats, and in several species of mice. Recovery from the disease apparently confers a lasting immunity.

Rift Valley Fever in Man

During the original investigations (1) of Rift Valley fever in Africa all four of the Europeans engaged in the work developed an acute febrile illness characterized by general malaise, joint pains, and vague abdominal tenderness. Blood taken from the workers at the height of their fever produced typical Rift Valley fever when injected into lambs. Upon inquiry it was then learned that almost every native engaged in herding sheep during the epizootic had been sick for some days and had complained of fever accompanied by severe pains throughout the body. These illnesses were considered most probably to have been attacks of Rift Valley fever. A native volunteer was then inoculated with the virus. 3 days after inoculation he developed headache and pains in the back, and, a day later, fever. Blood taken from him at this time caused Rift Valley fever when injected into lambs. Following the investigations in Africa, the virus was sent to England for further study. Soon after initiation of the work there, three laboratory workers developed the disease (2). Up to the present time the attacks in the eight individuals mentioned represent the only well observed cases of Rift Valley fever recorded in the literature. The following description of the disease is compiled from the reports of these cases.

The course of Rift Valley fever in man is much like that of a mild attack of influenza. Following an incubation period of 5 or 6 days, the patient complains of general malaise, chilly sensations, and headache. After 6–12 hours of increasing symptoms the temperature, which has been normal, rises rapidly to 102–104°F. With the onset of fever, the patient may develop chills. Pains spread into the extremities and joints; a sensation of fulness over the region of the liver may be followed by definite tenderness or even abdominal pain. Nausea and vomiting

sometimes occur, and in one instance epistaxis has been recorded. On examination the patient is found to be moderately prostrated. The face is flushed; conjunctival injection and photophobia may be present; the tongue is coated; the breath is foul. The lungs are normal, but there is definite tenderness in the epigastrium. The liver and spleen cannot be felt. Although fever and symptoms may persist as long as 10 days or no longer than 1, improvement is usually evident about the 3rd day and proceeds rapidly to recovery. In one case there was a second temperature reaction accompanied by a return of symptoms 3 days after recovery from the initial attack. At the onset of the symptoms there may be a slight polymorphonuclear leucocytosis. This gives way at about the time of appearance of fever to a leucopenia, the total white blood cell count reaching 3000–4000. The fall in the number of leucocytes is almost entirely due to a decrease in the number of the polymorphonuclear elements. The return of the leucocyte count to a normal level is slower than the clinical improvement. Despite the period of probable liver damage in Rift Valley fever in man, the bile pigments of the blood serum and urine are usually not appreciably increased in amount.

Report of Case

A pathologist, R. S., age 30 years, had been working with Rift Valley fever virus for several weeks before the onset of his illness. On the evening of December 22, 1932, he felt chilly while walking home and complained that his eyes and the calves of his legs ached. He found his subglossal temperature at that time to be 99.6°F. During the night his rest was disturbed by general malaise and pains, especially around the knees and hips. On awakening, the 2nd day of illness, his temperature was 101°F. He attempted to continue his work but had several chills during the day and felt so miserable that he took to bed. He complained at this time of a vague soreness over his abdomen, constant dull headache, and pain behind the eyes associated with slight photophobia. There was no sore throat, rhinitis, nausea, or vomiting. He was admitted to the Hospital of The Rockefeller Institute 24 hours after the onset of symptoms.

On admission, the temperature was 102.6°F., pulse 140, respirations 24. The patient was definitely prostrated by his illness but rational and cooperative. There were found on physical examination a slight injection of the throat, and a vague tenderness over the abdomen. The edge of the liver was not felt. Other than this the examination was entirely negative. The total leucocyte count at this time was 2800 per c. mm. Polymorphonuclear elements constituted 57 per cent of this; small lymphocytes 9 per cent; intermediate lymphocytes 10 per cent; monocytes 24 per cent.[1] The throat culture was negative for hemolytic streptococci and influenza bacilli, and blood cultures in infusion broth remained sterile. The urine showed a faint trace of albumin; no bile was present. A tentative diagnosis of Rift Valley fever or influenza was made.

[1] All differential counts were made on supravitally stained specimens.

In an attempt to confirm the tentative diagnosis of Rift Valley fever, 6 cc. of the patient's blood, drawn on the day of admission and kept fluid by the addition of 1 cc. of 1:1000 heparin solution, was injected intraperitoneally in 1 cc. amounts into six mice. All of the mice died within 48 hours. Their livers were free from ordinary bacteria, but showed in hematoxylin-eosin-stained sections the marked focal necrosis and acidophilic intranuclear inclusions typical of Rift Valley fever. Moreover, the disease was transmitted to other mice by means of serial passages. Blood taken from the patient on the day following admission gave similar results.

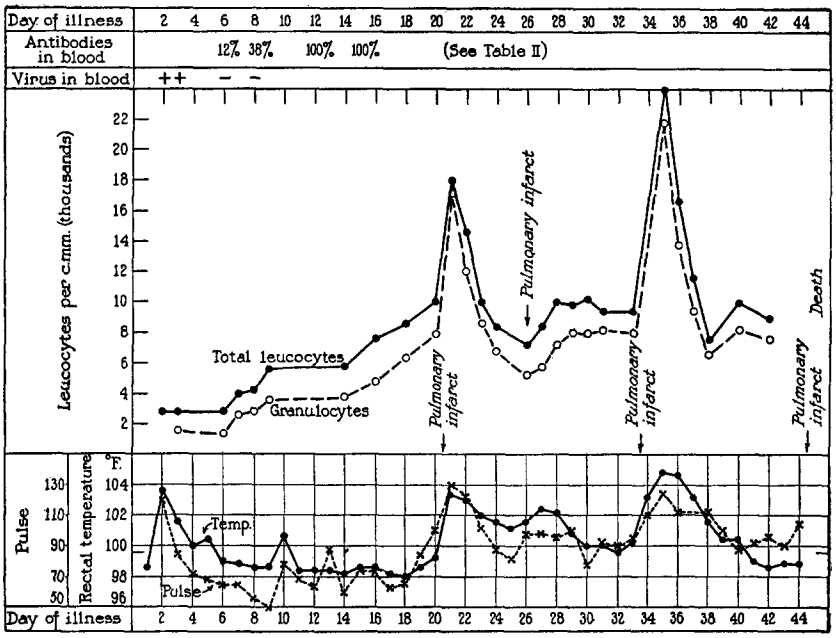

CHART 1

Consequently, the diagnosis of Rift Valley fever was confirmed. In Table I and Chart 1 are shown the results of these and subsequent tests for the presence of virus in the patient.

Almost immediately after admission the patient began to improve. The temperature, which reached a peak of 103.8°F. on the night of admission, fell promptly to normal within 24 hours (Chart 1). The symptoms, however, abated somewhat less rapidly. On the 5th day two papular areas several centimeters in diameter were observed on the right thigh and leg. They resembled in a general way isolated measles papules. After 3 days they had completely faded and since no others were observed at any time it is difficult to say whether the eruption bore

any relation to the disease. At the time of the appearance of the papules the patient developed a sore throat. The pharynx was irregularly injected and resembled the throats often seen in cases of influenza. On the following day (6th day of illness) a typical herpes simplex eruption appeared on the right side of the nose. Both this and the sore throat subsided in the next few days. During all this time the patient had been improving generally, complaining for the most part only of a constant feeling of fulness in the epigastrium which he believed was aggravated by a persistent constipation. There was a very slight and unexplained rise in temperature to a peak of 100.8°F. during the 10th day of illness.

By the 12th day of illness the patient had improved to such an extent that he was allowed to sit in a chair for a short time and on the following day was permitted to walk a short distance. Thereafter, as his strength improved, his activity was increased. On the evening of the 16th day, however, he complained of pain in

TABLE I

Tests to Determine Presence of Virus in Patient

Day of disease	Material tested	Mouse test	Result
2	Whole blood	6/6	Positive
3	" "	6/6	"
6	" "	0/6	Negative
8	" "	0/6	"
22	Sputum	0/2	"
45 (death)	Liver	0/3	"
45 (death)	Mesenteric lymph gland	0/3	"

All material was injected intraperitoneally into mice.

The denominator of the fractions signifies the total number of mice injected; the numerator denotes the number which died.

the dorsal part of the left leg. A diagnosis of phlebitis of the popliteal vein was made. The patient was returned to bed and the leg was immobilized in an elevated position. 4 days later (20th day of illness) the patient awakened with pain in the right chest which was more pronounced during deep inspiration or exhalation. Although the physical and X-ray findings in the chest were entirely negative at this time, it became apparent as conditions progressed that the patient was suffering from a small pulmonary infarct. Fever developed (103.4°F.); the leucocytes in the blood rose rapidly to 18,000 per c. mm. of which 94 per cent were granulocytes (Chart 1); dulness was apparent on percussion over the base of the right lung where the breath sounds, accompanied by many fine and coarse râles, were diminished. In the X-ray photograph made at this time there was a distinct shadow at the base of the right lung. On several occasions blood was expectorated in small amounts. In order to test for the presence of Rift Valley fever virus and

virulent pneumococci mice were injected intraperitoneally with the sputum but all remained alive and well (Table I).

During the following days the condition in the chest improved gradually until the 26th day when the patient developed a second pulmonary infarct in the right lung (Chart 1). Within a few days the patient began to improve again, but on the 34th day a third pulmonary infarct occurred, this time in the left lung. The temperature which had just returned to normal, rose rapidly to 104.4°F.; the leucocytes reached 24,200 with 90 per cent granular elements. By this time the patient had become very weak because of the repeated pulmonary insults. In spite of this fact, however, the temperature and leucocyte count again began a return to normal, and there was slow but progressive general improvement in the patient's condition. On the 38th day of illness definite signs of phlebitis in the right femoral vein developed. This caused no systemic reaction, however, and recovery seemed to be proceeding uneventfully. On the morning of the 45th day of illness, however, the patient suddenly collapsed and died within a few minutes. Death was apparently due to a large embolus in the pulmonary vessels.

At autopsy, only changes directly associated with the phlebitis and pulmonary infarcts were found. No abnormalities such as have been observed in animals dying of Rift Valley fever were seen. This is not surprising, however, since the patient died 45 days after the onset of his illness of which the acute stage occupied only the initial week. For this reason the pathological findings will be described but briefly. There were signs of a mild saphenous and femoral phlebitis. However, in the inferior vena cava where it receives the hepatic veins, there was a large thrombus branching out into the hepatic venous radicles and extending upward almost to the heart. The superior portion of this thrombus had apparently become detached, and had travelled through the chambers of the heart because it was found as an embolus in the pulmonary artery. In addition there were old pulmonary infarcts in both lungs with acute and chronic pleuritis. The liver appeared normal. Examination of the stained sections of the tissues revealed nothing unusual. Emulsions made from bits of liver and from mesenteric lymph glands were injected intraperitoneally into mice in order to test for the presence of Rift Valley fever virus. All the mice remained well (Table I).

Tests for the Presence of Antibodies in the Patient's Serum

At intervals during the course of the disease, blood was drawn from the patient in order to determine the rapidity with which antibodies to the virus are formed. To this end serum was collected on the 6th, 8th, 12th, and 15th days of illness and tested in the following manner. Decimal dilutions of infected mouse blood—ranging from 10^{-3} to 10^{-6}—were prepared. 0.5 cc. amounts of each dilution of virus were added to 1.25 cc. amounts of each specimen of serum to be tested. Without incubation, 0.7 cc. of each mixture were injected intraperitoneally into

each of two mice. The mice were observed for 2 weeks to determine the mortality rate. From the results shown in Table II it can be seen that antibodies were present in small amounts in the patient's blood as early as the 6th day and that by the 12th day had reached such a concentration that protection was afforded the mice against at least 1000 M.L.D. of the virus. These findings are in agreement with those of Findlay (2) and Broom and Findlay (5).

TABLE II

Test to Determine Presence of Antibodies in Patient's Blood

Sera	Day of disease	Virus dilution				Total	Mice protected
		10^{-3}	10^{-4}	10^{-5}	10^{-6}		
							per cent
Negative control		2/2	2/2	2/2	2/2	8/8	0
Patient's serum	6	2/2	2/2	2/2	1/2	7/8	12
" "	8	2/2	2/2	1/2	0/2	5/8	38
" "	12	0/2	0/2	0/2	0/2	0/8	100
" "	15	0/2	0/2	0/2	0/2	0/8	100

The denominator of the fractions signifies the total number of mice injected; the numerator denotes the number which died.

DISCUSSION

For purposes of discussion, the course of disease in this case may be divided into two phases—the acute illness and the period of complications. Concerning the first or acute stage, little need be said because the symptoms and signs differed in no essential detail from those previously described as characteristic of Rift Valley fever in man. In fact, with such a typical syndrome, following definite exposure to the specific virus which in turn was isolated from the blood of the patient, there can be little doubt as to the true nature of the illness. The diagnosis is further strengthened by the demonstration in the patient's blood of specific virus-neutralizing antibodies which during the early days of convalescence increased in amounts to reach a concentration capable of neutralizing at least 1000 M.L.D. of the active agent.

The phlebitis, however, which appeared during convalescence, came as an unexpected complication. The condition is not mentioned in the papers which describe the clinical course of Rift Valley fever (1, 2)

and Daubney has reported (6) that enquiries concerning its occurrence in the Rift Valley have failed to elicit any affirmative information. However, it is not altogether surprising that phlebitis should occur during convalescence from Rift Valley fever, since it has been reported following almost all other known acute infectious diseases. Its relatively high incidence in pneumonia—0.72 per cent (7)—and in typhoid fever—2 per cent (8)—is well known. In the diseases thought to be due to filterable viruses it also occurs but less frequently. Thus, phlebitis has been reported following measles (9), mumps (10), varicella (11), smallpox (12), vaccinia (13), influenza (14), and psittacosis (15). What factors predispose a patient to this complication is not known, and no attempt will be made at this time to discuss the condition further than to point out its definite though infrequent occurrence in association with most acute infectious diseases. It seems probable that should the number of cases of Rift Valley fever increase, phlebitis will again be seen as a complication in a certain percentage of them.

SUMMARY

A case of Rift Valley fever following an accidental laboratory infection, and believed to be the first instance of the disease in the Western hemisphere, is reported. Although the course of illness was otherwise quite typical, it was complicated by thrombophlebitis—a condition not previously described in association with this disease in man. Death was caused by a pulmonary embolus.

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