Am. J. Trop. Med. Hyg., 82(3), 2010, pp. 371–375
doi:10.4269/ajtmh.2010.09-0669

Case Report: Severe Rift Valley Fever May Present with a Characteristic Clinical Syndrome

Summerpal S. Kahlon, Clarence J. Peters, James LeDuc, Eric M. Muchiri, Samuel Muiruri, M. Kariuki Njenga, Robert F. Breiman, A. Clinton White Jr, and Charles H. King*

Departments of Medicine, Immunology, and Pathology, University of Texas Medical Branch, Galveston, Texas; Division of Vector Borne and Neglected Tropical Diseases, Ministry of Public Health and Sanitation, Nairobi, Kenya; International Emerging Infections Program—Kenya, Centers for Disease Control and Prevention, Nairobi, Kenya; Center for Global Health and Diseases, Case Western Reserve University School of Medicine, Cleveland, Ohio

Abstract. Rift Valley fever (RVF) virus is an emerging pathogen that is transmitted in many regions of sub-Saharan Africa, parts of Egypt, and the Arabian peninsula. Outbreaks of RVF, like other diseases caused by hemorrhagic fever viruses, typically present in locations with very limited health resources, where initial diagnosis must be based only on history and physical examination. Although general signs and symptoms of human RVF have been documented, a specific clinical syndrome has not been described. In 2007, a Kenyan outbreak of RVF provided opportunity to assess acutely ill RVF patients and better delineate its presentation and clinical course. Our data reveal an identifiable clinical syndrome suggestive of severe RVF, characterized by fever, large-joint arthralgia, and gastrointestinal complaints and later followed by jaundice, right upper-quadrant pain, and delirium, often coinciding with hemorrhagic manifestations. Further characterization of a distinct RVF clinical syndrome will aid earlier detection of RVF outbreaks and should allow more rapid implementation of control.

INTRODUCTION

Rift Valley fever (RVF) virus (RVFV) is a negative sense, segmented genome RNA virus of the family *Bunyaviridae*, which was first isolated from ill sheep in the Rift Valley District of Kenya.[1] The RVFV-associated disease, RVF, was initially described in 1931 as a livestock illness of sheep and cattle and shortly thereafter, as a symptomatic human infection among pastoralists and laboratory personnel exposed to infected animal materials.[2] Numerous species of mosquitoes, particularly of the genera *Aedes* and *Culex*, can transmit the virus, and epizootics and epidemics of RVF often occur after episodes of flooding in areas where RVFV has transmitted in the past.[3] During outbreaks, aerosols of virus-containing materials can also transmit infection.[4,5] Typically, floodwater mosquito-borne viral transmission first reintroduces RVFV and causes RVF outbreaks among animals. Then, if sufficiently widespread, the epizootic will be followed by case reports of symptomatic RVF among humans.[6] There are also data to suggest the virus is transmitted at low levels between epizootic/epidemic outbreaks.[3,7] Epidemic RVF has been documented throughout sub-Saharan Africa as well as in Egypt and the Arabian Peninsula.[8–13] The spectrum of RVF symptoms ranges from a mild, self-limited illness to a potentially fatal hemorrhagic disease.[9,14–20] Various general symptoms and signs have been associated with acute human infection, and encephalitis and retinal vasculitis have been described as late RVF complications.[14,15] Although past epidemiological studies suggest a range of possible disease manifestations, these data do not suggest a distinctive clinical syndrome for RVF. Thus, disease diagnosis can be difficult for a clinician having only limited laboratory diagnostic resources.

Despite its widening geographic distribution, outbreaks of RVF usually occur in remote areas with underdeveloped health-care systems. The symptoms of RVF mimic many other endemic infections in these areas, such as malaria and other arboviral fevers.[21] Because of the explosive nature of most RVF epidemics, active study of RVFV-related human illness has been confined to brief periods of time. Human infections are often identified only after widespread livestock illness. As a result, human cases are diagnosed and observed only late in an epidemic or not diagnosed at all. These factors contribute to reporting bias and have combined to limit detailed descriptions of the natural clinical course of the disease.

From December 2006 to February 2007, an outbreak of RVF occurred in the Ijara District of Northeastern Province, Kenya.[22] Ultimately, throughout Kenya, Somalia, and Tanzania, hundreds of people were affected over this time period.[23] In Kenya, the World Health Organization reported 684 confirmed RVF cases (333 in Northeastern Province) with 155 deaths from November 30, 2006 until March 12, 2007. This RVF outbreak provided the authors with the opportunity to personally assess and fully evaluate both the early and late clinical course of acutely ill RVF patients. Below are the detailed clinical descriptions of six serologically confirmed cases of RVF in the Ijara District.

METHODS

Participants. The six patients reported here, ultimately confirmed as having RVF,[24] were evaluated and followed by serial visits in Ijara District during a 2-week period in late January 2007.

Patients were evaluated at Ijara District Hospital in Masalani, at its related Health Centers, or in their homes. All were informed of their participation in the RVF outbreak investigation through a translator, and each gave verbal informed consent to be involved in reporting and signed consent for RVFV testing, which is in accordance with ethical standards for public-health investigations as approved by the Kenya Ministry of Health (now the Ministry of Public Heath and Sanitation and the Ministry of Medical Services).

Approach. To better describe the disease course of RVF, 15 patients with suspected RVF were identified and observed at a rural hospital during the RVF outbreak. To identify RVF patients, Kenya Ministry of Health established case definitions for suspected, probable, and confirmed RVF cases.[22] A suspected case was defined as an acute febrile illness

*Address correspondence to Charles H. King, Center for Global Health and Diseases, CWRU School of Medicine, 10900 Euclid Avenue, Cleveland, OH 44106-7286. E-mail: chk@cwru.edu

(temperature greater than 37.5°C) occurring in districts with serologically confirmed RVF after December 1, 2006 and without other known cause. A probable case was defined as any suspected case with unexplained hemorrhagic manifestations, visual disturbances, or alteration of mental status. A confirmed case was defined as any suspected or probable case confirmed by presence of either anti-RVF IgM antibodies as measured by IgM capture enzyme immunoassay or RVF-specific genome detected by reverse transcription-polymerase chain reaction (RT-PCR).[24]

Procedures. Blood samples were collected, when permitted, for malaria screening [by microscopy or rapid immunochromatographic testing (ICT) cards] and for RVF laboratory confirmation. For purposes of this study, all patients were seen and examined by a single physician (S.S.K.). Consultation with physician specialists highly familiar with RVF was available during this period through a satellite-linked telemedicine system. A thorough, standardized history and physical examination was performed on consenting patients. Hospitalized patients were serially assessed at least twice a day during their disease course until discharge. Standard medical care, including other necessary history and physical exam, was administered concomitantly by local medical staff. Treatment primarily consisted of intravenous fluids and other supportive care.

RESULTS

Overall, 6 of 15 observed Ijara District patients met the criteria for confirmed RVF cases. Three were male, and three were female. The youngest was 24 years old, and the oldest was 50 years old. Their symptoms during the first three days of their illnesses are shown in Table 1. All six patients reported an initial syndrome of subjective fever and arthralgias, and five of six reported throbbing headaches as well. Arthralgia involving the proximal large joints (primarily elbows, knees, shoulders) were noted by all subjects but varied in severity. No tenderness, effusion, or pain with active or passive movement was noted on physical examination of the joints.

Headaches were described as either diffuse or frontal in location. Four of six patients reported malaise, anorexia, and subjective weight loss within the first few days of illness. Five of the six also reported nausea and vomiting with a vague mid-epigastric discomfort early in the syndrome. As shown in Table 2, later symptoms were variable as to their time of onset. Three of six patients developed scleral icterus between 5 and 21 days after the onset of illness, and a fourth patient showed icterus on day 2 of illness. Three patients developed right upper-quadrant tenderness, and one was noted to have palpable hepatomegaly on examination. Five of six developed delirium during their acute illness, often coinciding with the peak of clinical disease severity. Three of the patients developed bleeding tendencies around the time of onset of delirium. One patient died shortly thereafter; the others survived. All three males had prolonged recovery periods in which anorexia persisted and appetite was slow to return. At 1–2 weeks after resolution of acute illness, the three male patients were ambulatory but reported a poor appetite. One patient developed visual disturbances consistent with retinal vasculitis roughly 4 weeks after the initial onset of disease. No patients were found to have palpable lymphadenopathy on examination, and no cardiopulmonary abnormalities were clinically evident on exam. None of the patients complained of diarrhea, nor were they noted to have diarrhea clinically.

TABLE 2
Day of onset of advanced symptoms and signs

	Delirium	Scleral icterus/ jaundice	Right upper-quadrant tenderness	Hemorrhage	Visual change
A	8	8		8	
B	6	5	5		
C*	21	21	14	21	28
D	2	2	3		
E	4				
F†					

*Patient's timeline of events as reported before contact with health-care workers.
†Patient did not have advanced symptoms.

ILLUSTRATIVE CASES

Case 1: Hemorrhagic fever. A 40-year-old female was evaluated in her home after several days of illness. She had an 8-day history of fever, chills, malaise, large-joint arthralgias, nausea, and vomiting. After 7 days, she developed mid-epigastric discomfort and jaundice. Family members noted bleeding gums. She continued to vomit, although she did not have hematemesis. She was weak and refused to answer many questions on the day of examination (day 8 of illness). Although reported through a translator to be oriented to person, place, and time, she was lethargic and confused. She had no known ill contacts and no clear history of exposure to infected animals. On examination, she was thin and cachectic in appearance with mild subconjunctival hemorrhage. She and her family refused thorough physical examination or treatment. She expired early the next morning (day 9 of illness). Her serum sample drawn the day before physician evaluation (i.e., day 7 of illness) was positive for anti-RVF IgM and negative for RT-PCR.

Case 2: Fever, jaundice, and altered mental status. A 50-year-old male was admitted to a local hospital after failing appropriate malaria outpatient therapy with artemether-lumefantrine. A blood smear at admission showed no evidence

TABLE 1
Symptoms reported during first 3 days of illness

	Age	Gender	Fever	Headache	Malaise	Arthralgias	Anorexia	Nausea/emesis	Epigastric discomfort
A	40	Female	+		+	+		+	*
B	50	Male	+	+	+	+	+	+	+
C	25	Male	+	+	+	+	+	+	+
D	24	Female	+	+		+		+	+
E	24	Male	+	+		+	+	+	+
F	25	Female	+	+	+	+	+		

*Symptom reported at 7 days after onset of illness.

of malaria parasites. The patient was a goat herder in a nearby village and reported staying at home for the week before the onset of symptoms; he denied sick contacts or illness among his household livestock, although he did note several mosquito bites during that time. He reported 3 days of fever, severe, diffuse, throbbing headache, and mild arthralgias of the knees and elbows accompanied by progressively worsening fatigue and malaise. His hand and feet joints were not painful. He noted anorexia and subjective weight loss over that time. He developed nausea and vomiting just before admission, accompanied by a vague mid-epigastric discomfort. At admission, physical examination revealed scleral icterus, splenomegaly, and hepatomegaly. He had no evidence of joint tenderness or swelling on examination. Over a few hours, he developed right upper-quadrant tenderness, and his scleral icterus became more pronounced. He had low-grade fevers (peak of 38.2°C) and hypotension without tachycardia with systolic blood pressures in the 60–70 mmHg range. At the lowest blood pressure, 65/40 mmHg (confirmed manually in both arms), the heart rate was 88 beats per minute. Within the next 24 hours after admission, he developed subconjunctival erythema without frank bleeding as well as delirium. Aside from disorientation, his neurological exam was otherwise normal throughout the illness. One day later, his delirium and abdominal tenderness resolved, his blood pressure rose to 100/80 mmHg, and scleral icterus slowly resolved over the course of the next 2–3 days. He had a prolonged recovery period, remaining as an inpatient for 5 days total because of persistent anorexia (without nausea or vomiting) and weakness but without further complications. His serum anti-RVF IgM antibody, drawn at admission on the third day of illness, was positive. RT-PCR testing on the same blood sample was also positive.

Case 3: hemorrhagic fever and retinal vasculitis. A 25-year-old male was seen in his home during the late phase of his disease. He stated that he first became ill while tending his cattle in a remote area about 4 weeks previously. He noted that his animals had been sick before leaving home, but none were ill at the time that he became ill. He denied slaughtering any animals or handling aborted animal fetuses while tending the herd. He did report collection and consumption of raw milk from his animals. He reported a prolonged period of fever, lasting about 1 week, severe, throbbing frontal headache, arthralgias of the shoulders, elbows, and knees, nausea, and vomiting. He reported having yellow eyes, mid-epigastric discomfort, and severe right upper-quadrant tenderness, which prevented him from sleeping on his side. He also noted numerous episodes of syncope during this time and was brought to a local hospital after developing delirium and hematemesis followed by a syncopal episode. He was given supportive care in the hospital, and his symptoms improved; however, he left the hospital against medical advice after 5–6 days and returned home to his village. Within 1 week thereafter, he developed blurry vision and noted floating black spots within his visual fields. Over the subsequent 2 weeks, he slowly recovered his strength and appetite, and his vision resolved gradually to near normal throughout that time. On bilateral fundoscopic examination, he had multiple small yellow plaques/patches with mild erythema at the borders. His visual field testing was normal. His neurological exam was otherwise normal as well. During the acute phase of his illness while he hospitalized, he tested positive for anti-RVF IgM; he refused repeat blood sampling at the time of evaluation. It should be noted that his dates of illness are self-reported and were unable to be independently confirmed.

DISCUSSION

During the most recent outbreak of RVF in the Ijara District of Northeastern Province, Kenya, early recognition of the disease outbreak by astute clinicians allowed for the installation of public-health measures to stem the spread of the disease.[22–24] With a multitude of febrile tropical illnesses overlapping in geographical distribution with Rift Valley fever,[21,25,26] the disease can be difficult to identify in the early stages of an outbreak.

Several series in the past have described general symptoms associated with RVF.[9,14–20] However, for a clinician at the bedside, these descriptions are difficult to apply in recognizing disease outside of a known outbreak. The above cases illustrate the evolution of individual clinical cases. The illness in these patients was largely characterized by an early syndrome of fever, proximal large-joint arthralgias (particularly knees, elbows, and shoulders), throbbing headaches, malaise, and anorexia followed shortly thereafter by nausea, vomiting, and vague midepigastric discomfort. Only one-half of the confirmed cases had hemorrhagic manifestations (two of which were severe with hematemesis). The peak of disease severity coincided with tender hepatomegaly, scleral icterus, and delirium. This is consistent with earlier findings of hepatic necrosis noted at autopsy in two Egyptian RVF patients.[8]

Many infections with RVF virus are mild and often subclinical.[18,20] These mild cases can often be difficult to distinguish from other mild, self-limited illnesses. In particular, the symptoms of mild disease can mimic those of malaria, and in an area with a high incidence of malaria, RVF can be difficult to identify. The symptoms and geographic distribution of RVF partially overlap with those of dengue fever. RVF is less often characterized by rash, bone pain, and myalgia than is dengue fever.[9,18,27,28] Chikungunya virus, also found recently in East Africa often during times of drought,[29] is also characterized by severe arthralgias, which persists for prolonged periods of time and often involves the small, peripheral joints.[30–32] In endemic areas, after periods of flooding, RVF should be considered in patients with febrile illness and without evidence of malaria.

One patient in this series was found to have the late manifestation of retinal vasculitis. His syndrome was similar to that described in previous descriptions of ocular manifestations of disease.[14] With a small sample size, the low number of observed late complications of disease is not unexpected. Additionally, cultural and economic limitations of the healthcare system in this region may have led to an overall underreporting of late manifestations of RVF, such as encephalitis and retinal vasculitis.[14,17]

In this case series, we studied only a very small subset of RVF cases among the total that occurred during this outbreak. As with other, previously published RVF reports, there was undoubtedly some selection bias in the cases that came to our attention. However, the cases reported here were generally observed over a longer period of time with careful attention to patient history and the details of clinical presentation. The particular population studied in this single location may have manifested a specific set of RVFV infection-related symptoms because of a particular combination of genetic background in

combination with concurrent malnutrition, anemia, or chronic dehydration. Other potential comorbidities, such as malaria, schistosomiasis, typhoid fever, hypertension, congestive heart failure, tuberculosis, and peptic ulcer disease are also common illnesses treated in this region and could have affected the patients' clinical presentations.

RVF is present in many areas of sub-Saharan Africa. The conditions that favor its epidemic spread tend to exist more commonly in rural, semi-arid, sparsely populated and underdeveloped areas. All patients seen in this series were evaluated in their local milieu using evaluation techniques available to local medical staff. The focus on history and physical examination in diagnosis reflects resources available to providers in this setting—routine, laboratory serum studies (such as complete blood counts, basic chemistry, and liver-function tests), radiographic studies, and advanced supportive-care technology were unavailable. As a result, the natural disease course was followed in its natural setting.

Currently, RVF in humans is distinguished from other febrile illnesses primarily by its epidemiological association with concurrent livestock illness. With emerging data that suggest persistent interepidemic transmission,[7,33] the concurrent epizootic criterion is not sufficiently reliable in detecting human RVF. Whereas RVFV outbreaks often afflict rural sub-Saharan Africa,[12,13,34] epidemics in Egypt[8] and Saudi Arabia/Yemen[9,10] illustrate the ability for the virus to move into presently non-endemic regions and to expand the risk of human RVFV-associated disease outside of its traditionally reported geographic range. Earlier identification of disease is a key in limiting its spread and initiating appropriate treatment of RVF-afflicted patients.[35] More work will be needed in further describing the distinct manifestations of disease in humans to promote this early phase of RVF recognition.

Received November 6, 2009. Accepted for publication November 23, 2009.

Acknowledgments: Special thanks to Dr. Mohamed A. Sheikh whose commitment and gracious hospitality allowed this work to be performed in Ijara District Hospital, Northeastern Province, Kenya. Also, thanks to Public Health Officers Said Dahir and Hasan Hussein in Northeastern Province, Kenya for their invaluable assistance in navigating Ijara District and gathering data.

Financial support: Funding for these studies and their analysis was provided in part by National Institutes of Health Grants U01AI45473 and U54AI057160.

Disclaimer: The findings and conclusions of this work are the authors' own and should not be construed to represent the CDC's determination or policy.

Authors' addresses: Summerpal S. Kahlon, formerly Department of Medicine, University of Texas Medical Branch, Galveston, TX, currently, Melbourne Internal Medicine Associates, Melbourne, FL, E-mail: summerpal.kahlon@mima.com. Clarence J. Peters, Departments of Microbiology and Immunology and Pathology, University of Texas Medical Branch, Galveston, TX, E-mail: cjpeters@utmb.edu. James LeDuc, Institute for Human Infections and Immunity, University of Texas Medical Branch, Galveston, TX, E-mail: jwleduc@utmb.edu. Eric M. Muchiri and Samuel Muiruri, Division of Vector Borne and Neglected Tropical Diseases, Ministry of Public Health and Sanitation, Nairobi, Kenya, E-mails: ericmmuchiri@gmail.com and muiruri1001@yahoo.ca. M. Kariuki Njenga, Global Disease Detection Program, Centers for Disease Control and Prevention, Kenya, E-mail: Knjenga@ke.cdc.gov. Robert F. Breiman, IEIP, CDC/KEMRI, Nairobi, Kenya, E-mail: rbreiman@ke.cdc.gov. A. Clinton White Jr, Division of Infectious Diseases, Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX, E-mail: acwhite@utmb.edu. Charles H. King, Center for Global Health and Diseases, CWRU School of Medicine, Cleveland, OH, E-mail: chk@cwru.edu.

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