Ordinary contact appears to be very low. History of tick bite, believed to be occurring, although the infectivity of the virus by it is transmitted either through bite of the tick vector, Nairovirus) and often causes severe viral hemorrhagic fever. It is transmitted either through bite of the tick vector, mainly Hyalomma spp., or via direct contact with blood or tissues of viremic animals or humans. Human-to-human transmission is believed to be occurring, although the infectivity of the virus by ordinary contact appears to be very low. History of tick bite, high-risk occupations, having contact with livestock, living in a rural area and older age are risk factors identified by investigators for acquisition of CCHF. Meat consumption is not usually a risk factor for CCHF. A wide variety of vertebrates like cattle, goats, donkeys, horses, etc., along with smaller wild life species like hares and hedgehogs act as a reservoir for the virus. CCHF has the potential to cause community acquired and nosocomial outbreaks. Healthcare workers are at increased risk of transmission of CCHF infection while taking care of patients with CCHF. There are several reports of nosocomial outbreak with high mortality among hospital staff.

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First Crimean-Congo Hemorrhagic Fever Outbreak in India

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Abstract

Crimean-Congo hemorrhagic fever (CCHF) has not been reportedly previously from India. Initial clinical features of dengue fever and CCHF are similar and it is very difficult to differentiate and diagnose CCHF. Common clinical features of CCHF include; high grade fever with chills, headache, body ache, myalgia, vomiting, abdominal pain, weakness and bleeding from multiple sites. Laboratory investigations showed cytopenia, raised prothrombin time (PT) and activated partial thromboplastin time (aPTT), raised creatinine phosphokinase (CPK) and lactic dehydrogenase (LDH) as well as altered liver and renal functions. Patients with above symptoms can rapidly progress to bleeding from multiple sites and death compared to dengue fever. It is crucial to recognize CCHF at early stage to institute ribavirin treatment and also to prevent nosocomial spread of disease to healthcare workers. We are describing first four cases of recent CCHF outbreak in Ahmedabad.

Introduction

Crimean-Congo hemorrhagic fever (CCHF) virus is an enveloped RNA virus of the family Bunyaviridae (genus Nairovirus) and often causes severe viral hemorrhagic fever. It is transmitted either through bite of the tick vector, mainly H. Armeghada. The infection affects the reticuloendothelial system and activates cytokine cascades in the body. This leads to increased vascular permeability in the victims, ultimately culminating in hemorrhage, shock and multi-organ failure. The average case fatality rate is 30-50%, but mortality rates from 10% to 80% have been reported in various outbreaks. After early reports from Crimea, Russia in 1944, it has been reported from more than 30 countries in Africa, Asia, Southeast Europe and the Middle East. During the last decade, new outbreaks have been recorded in countries including Pakistan, Iran, Senegal, Mauritania, Bulgaria, Albania, Kosovo, Turkey and the Ukraine as well as southwestern regions of the Russian Federation. CCHF virus is endemic in 23 out of the 30 provinces of Iran. CCHF is endemic in Pakistan and multiple healthcare associated outbreaks have been reported since the detection of the first case in 1976. CCHF cases in Pakistan have mainly occurred in the months of October and November, which roughly corresponds to the Islamic festival of Eid-ul-Azha, celebrated on days 10 to 13 of the last month of each lunar calendar year, when large flocks of sacrificial animals are brought into the cities from the rural areas of Pakistan. CCHF has not been reported from India. We are reporting first documented outbreak of CCHF in India from Ahmedabad, western India.

Cases

Case 1: Index Case

A 32 years old woman, housewife, had come to Shalby hospital...
on 31st December 2010 with chief complaints of high grade fever prior to 4 days, severe bodyache – 2 days, abdominal pain -2 days, Nausea and vomiting 2 days and breathlessness one day. Patient was admitted for the same in private nursing home and treated with Antibiotics and supportive therapy. Investigation showed platelet count of 5000/cmm. Dengue serology was negative. Further work up showed platelet count: 12800/cmm, WBC 1910/cmm, LDH 23,349 IU/L, CPK total: 45 U/L, s. creatinine: 1.6mg%, blood urea: 63mg/dl, SGPT: 2,184 U/L, S. Na: 125meq/l, S. K: 5 meq/l, prothrombin time (PT) 2.6 INR and activated partial thromboplastin time (APTT) 200s/28, random blood sugar: 336mg/dl. Ultrasound abdomen was normal except mild hepatomegaly and bilateral pleural effusion. Malaria, dengue antigen and serology were negative. Patient was treated with antibiotics (Ceftriaxone), proton pump inhibitors and IV fluid.

On the day 2, patient had stable hemodynamic but started irrelevant talking and became restless. She had decreased urine output which responded to fluids and diuretics. She continued to have low platelets (14,500/cmm), leucopenia (3,040/cmm), and creatinine increased to 2.3 mg% with development of acidosis (bicarbonate: 13.5meq/l). LDH was 27,357 U/L at this stage. Workup for TTP and Lupus was negative.

On day 3, patient worsened clinically and developed respiratory distress for which she required endotrachial intubation and mechanical ventilatory support. She started bleeding from oral and nasal cavity. Blood reports showed; SGOT; 15286 U/L, Blood urea; 83.2 mg%, creatinine; 2.8 mg%, Alkaline Phosphatase: 226 IU/L, Hb: 7.92 g%, WBC: 4,490/cmm, sodium: 137meq/l, Potassium: 5 meq/L, SGPT: 3,633 IU/L, Bilirubin:16.2 mooml/L, Uric acid: 12.8 mg%, Ammonia: 64micromol/L, bilirubin – 4.7mg%, procalcitonin-8, ABG showed metabolic acidosis, viral markers-negative, HIV-negative. In view of low platelets (33,400/cmm), markedly elevated PT (INR 2.64)/APTT (>200) and very low fibrinogen (80mg/dl), blood products [Platelet rich concentrate (PRC), fresh frozen plasma (FFP), cryoprecipitate] were given along with supportive care. Patient deteriorated rapidly and developed cardio-respiratory arrest in 4 hours after intubation. Patient was revived with cardiopulmonary resuscitation. She was started on vasopressors and 1 gm Methylprednisolone. Despite support, she remained hypotensive and died next day early morning.

CCHF was not suspected in her case and therefore was not tested. Retrospectively, she was thought to have had CCHF

**Case 2**

A 25 years, unmarried female nursing staff working in ICU was admitted with high grade fever with headache, bodyache, nausea, vomiting with upper abdominal pain since 3 days. Her illness started after 7 days of death of index case. She was involved in care of index case, who died of hemorrhagic fever. On admission, temperature was 99.6 F and vitals and physical examination were normal. Her laboratory work up showed Hb: 12.5 gm%, WBC: 5,370/cmm, DC 85/13/1/L, Platelet count: 80,400/cmm. Her test for malaria, dengue antigen and serology were negative. Her blood urea: 37mg%, s. creatinine: 1.3mg%, SGPT: 93 IU/L, SGOT: 394 IU/L, PT-INR: 1.59, aPTT: 102/29, CPK total: 928 U/L, LDH: 8194 U/L, serum ferritin: 1,36,720 ng/ml. ECG and CXR were normal. Patient remained stable on day 2 and shifted to isolation room. Investigation showed Hb: 13gm%, WBC: 5620/cmm, Platelet counts: 59,100/cmm, Creatinine 1.0 mg%, S. proteins: T: 5.7 gm%, electrolytes were normal. Her blood sample was sent to national Institute of virology (NIV) Pune for viral PCR for unknown hemorrhagic fever. She developed hematuria and hemoptysis next day with mild confusion state and restlessness with stable vital parameters. Her laboratory work up showed WBC: 5,430/cmm, Platelets: 34,600/cmm, PT INR: 1.05, aPTT: 72/29, fibrinogen: 80. RFT and electrolytes were normal. LDH: 11031 U/L, CPK total: 1120 U/L, SGPT: 453 IU/L, SGOT: 14,457 IU/L, Procalcitonin: 0.3 and dengue/HIV/ HBsAg/HCV serology were non-reactive. She continues to have hematuria, hemoptysis and bleeding per vagina on next day with mild confusion. Her platelet dropped to 15,200/cmm. She started getting fresh bleeding from every site; including alveolar hemorrhage. She required ventilatory assistance and vasopressor. She died on 5th day. She received antibiotics and supportive care during course of illness and also received Ribavirin for one day before she died due to hemorrhage and shock. Her RT-PCR report from NIV Pune confirmed Crimean-Congo hemorrhagic fever virus.

**Case 3**

A 32 years male, non-smoker, non-alcoholic patient weighing 83kg was admitted with history fever with righrs, bodyache, arthralgia and occasional vomiting since last 3-4 days. He is the husband of case 1. His vital data and physical examination was normal except icterus and mild epigastric tenderness. He had no significant past history of medical or surgical illness. He chews pan-massala. His wife died of undiagnosed viral hemorrhagic fever before 9 days of his symptoms.

His available laboratory investigations one day before admission showed hemoglobin 14.8g%, WBC: 2640/cmm, Platelet: 47,300/cmm, PT: 16.3/9.0 with 1.7 INR, aPTT: 48/28. urea: 32mg%, creatinine: 1.7mg%, electrolytes were normal. Bilirubin: Total: 3.38mg%, Direct: 2.18, Indirect: 1.2, SGPT: 222 IU/L, SGOT: 195 IU/L, alkaline phosphatase: 123 U/L, S. proteins: T 7.7gm%/Albumin: 4.9gm%/globulin: 2.8gm%, LDH: 1921 U/L, CRP: 2.63 mg% (<1 mg%), and PCT < 0.5. His dengue antigen and malaria was negative. He was admitted in isolation ward suspecting unusual hemorrhagic fever as his wife died of undiagnosed hemorrhagic fever and attending nursing staff of hospital was also admitted with features of similar hemorrhagic fever at another hospital. Patient was started with hydration (PO and IV), ceftriaxone 1gm q12h, along with carnirot PO 3gm/day and oral sodium bicarbonate tablets, vitamin E and B-complex. Patient was give loading dose of capsule ribavirin 2 gm followed by 1.2gm QDS for 4 days and then 600mg QDS to complete 10 days. Patient tolerated Ribavirin well except nausea and vomiting. He showed rapid symptomatic improvement following Ribavirin. His fever disappeared and marked improvement in bodypain and myalgia after 48 hours of starting treatment. His blood sample collected on the 3rd day of hospitalization was sent to NIV Pune came positive for CCHF virus. His follow-up laboratory reports are shown in Table 1.

Patient was closely monitored for hemorrhagic complications. Patient was not transfused platelets/ FFP or cryoprecipitates as there was no evidence of mucocutaneous bleeding. Hospital course remained uneventful and patient was discharged on 10th day.

**Suspected case:** Attending doctor in ICU of first case also had similar viral hemorrhagic fever and he also died after 6 days of hospitalization in third hospital. His blood was not tested for CCHF. Chronology and outcome of all 4 patients are shown in Fig. 1. Case 1, 2 and 3 are as described above and suspected case was not tested for CCHF.
CCHF, a tick borne viral hemorrhagic fever, is highly contagious and associated with high mortality (more so in patient with nosocomially acquired infection) with rate ranging from 10-50%,1,10,24-26

Clinical features of patients with CCHF are like any other viral infection and include high grade fever with chills, headache, body ache, arthralgia and vomiting. They have leucopenia, thrombocytopenia, elevated ALT and AST, elevated CPK, LDH and prolong PT and aPTT. Overall clinical and laboratory parameters are overlapping with other commonly found endemic infections like dengue fever, complicated P. falciparum malaria and leptospirosis. Few but significant differences were observed between CCHF and Dengue in present case series; mainly being early as well as rapid thrombocytopenia, early and severe rhabdomyolysis leading to renal failure. These findings though are seen in the other hemorrhagic fever cases, they are less common and late as compared to CCHF.

Treatment of CCHF include isolation of suspected patients to prevent nosocomial spread of the virus and supportive treatment in form of adequate hydration of a patient to ensure good urine out put, as virus commonly causes rhabdomyolysis and renal failure. Patients with coagulopathy, thrombocytopenia and active bleeding should receive appropriate blood component replacements to correct coagulation and platelet abnormalities.

Unlike other viral hemorrhagic fever, early antiviral therapy using Ribavirin can provide a good outcome in CCHF. Therefore it is important to diagnose CCHF in early stage. However other hemorrhagic fever like Dengue is more common and endemic in Gujarat, Western India. Also there is significant overlap of presentation, clinical scenario and lab abnormalities between the two. These lead to either complete non-suspicion of CCHF or the late diagnosis of it, at which stage Ribavirin therapy may not be effective. Early and definite diagnosis of CCHF requires either viral isolation by culture or PCR from blood or tissue and exclusion of other more common viral, bacterial and parasitic infections. However specific viral culture and PCR tests are not available routinely except in the most specialized centers, making the entire situation more complex. History including that of tick bite, meat handling, travel or residence to endemic region and contact with blood or infected secretion from CCHF infected patient along with exclusions of other common infections by doing appropriate tests may help clinician to make a probable diagnosis.

In our report, total 4 patients, 2 suspects and 2 confirmed cases were involved. Chronology of onset of symptoms and death were shown in figure 1. Index patient died on 4th January. Suspected case developed symptoms after 2 days of the index case and died on 7th day. The third patient (Case 2) developed symptoms 7 days after death of first patient and died on 7th day.

Fourth case (case no. 3) developed symptoms 9th day after death of the first case and he recovered with supportive care and ribavirin and is alive. When he presented with fever, body ache, arthralgia and occasional vomiting of four days durations along with leucopenia, thrombocytopenia, raised liver enzymes and bilirubin, raised CPK total, raised serum ferritin, raised PT and aPTT, mildly altered serum creatinine and negative dengue antigen, we suspected uncommon viral hemorrhagic fever, as his wife died before 9 days of unknown hemorrhagic fever illness in another hospital. The doctor and a nurse (case number 2 and 3), who were involved in care of his wife, had similar presentation with fever and hemorrhagic manifestations. Doctor died and nurse was admitted with hemorrhagic fever. Clinical manifestations and laboratory parameters of the three patients (index case, doctor and nurse) who died of unknown hemorrhagic fever were similar to those seen in CCHF. With the available information, we strongly suspected CCHF in the fourth patient, and started treating him with oral ribavirin (2 gm loading dose followed by 1200mg q6h for next 6 days) empirically. At the same time, blood sample was sent to National Institute of Virology (NIV), Pune for reverse transcriptase polymerase chain reaction (RT-PCR). He also received intravenous and oral fluid along with other supportive treatment (vitamin E, carnitine, sodium bicarbonate, multivitamin). Patient had symptomatic improvement after 48 hours of starting treatment, laboratory parameters showed decreasing total WBC and platelet count and
raised CPK (total) and aPTT. S. creatinine, LDH, PT improved and eventually became normal. Patient didn’t bleed from any site despite persistent thrombocytopenia. Subsequently, CCHF was confirmed by the positive RT-PCR. Our series is the first to report an outbreak of CCHF from India. Mortality was high as CCHF was never seen or reported in our geographic area and therefore not suspected in the first three cases. Fourth patient did survive and he was started on empiric ribavirin treatment while waiting for the definite report of RT-PCR for CCHF. While observational studies and case reports support the use of ribavirin treatment in CCHF, clear benefit of ribavirin in the treatment of CCHF is not well established in meta-analysis due to lack of sufficient evidence. Oral ribavirin is found to be effective in vitro, though a clear benefit as far as the decrease in the viral load and improved outcome has not been seen. We do believe though that ribavirin therapy did help our patient. We also strongly advocated isolation and universal precaution to stop further spread of the outbreak.

Low platelet count, raised AST, ALT, CPK and LDH levels, and prolonged PT, aPTT are associated with poor prognosis. Patients who died in our reports (Case 1, 2 and suspected case) also had markedly elevated ALT, AST, LDH, CPK and PT and aPTT.

Conclusions
Ours is the first case series reporting and describing clinical profile of patients involved in the outbreak of CCHF from India. Certain factors like low platelet count, raised AST, ALT, CPK and LDH levels, and prolonged PT, aPTT were associated with poor prognosis. Ribavirin therapy may be helpful and should be started early in suspected cases. Overall, case fatality rate was higher as early cases were not suspected of having CCHF due to prior nonexistence in this geographical area. Outbreak does cause serious concerns due to high infectivity, high mortality rate and its potential for endemicity leading to possibility of future outbreaks. Clinicians should isolate and strictly follow barrier nursing care for undiagnosed hemorrhagic fever patients to reduce nosocomial transmission.

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References
Nodular Regenerative Hyperplasia of Liver—A Rare Cause of Portal Hypertension in Patients of Rheumatoid Arthritis


Abstract
Nodular regenerative hyperplasia of liver (NRHL) is a rare entity and is infrequently associated with collagen vascular disease. Clinically patients present with recurrent abdominal pain, non-specific symptoms of underlying systemic disease and signs of portal hypertension. This entity is usually diagnosed by MRI and liver biopsy. Prognosis is usually good.

Introduction
Nodular regenerative hyperplasia is a rare entity and generally is encountered in association with collagen vascular disease. Clinically patients present with recurrent abdominal pain, nonspecific systemic symptoms and signs of portal hypertension such as ascites, bleeding esophageal varices or splenomegaly.

Diagnosed by MRI and liver biopsy. As with other forms of noncirrhotic hypertension, the prognosis is usually better than that of patients with portal hypertension due to cirrhosis. Portal diversion is useful in relieving symptomatic portal hypertension.

Case Report
A 35 year old female, a known case of rheumatoid arthritis, presented with progressive fullness of abdomen since the last 10 days. Presently there was no history of joint pain, swelling, skin rash, jaundice, vomiting, abdominal pain or any other systemic complaint. Clinical examination showed patient was febrile with the temperature of 101°F with tachycardia. Patient was severely pale, with a swan neck deformity in both hands and a dental abscess. Abdominal examination showed splenomegaly, 14 cm from costal margin, without hepatomegaly and free fluid. Investigation showed Hb 7.8 gm%, Total WBC count 1200/cumm, Total platelet count 85,000/ cumm. Peripheral smear examination showed neutrophil 57%, lymphocyte 36%, eosinophil, 7%. There were no abnormal cells and the platelets were reduced on smear. Bone marrow biopsy showed reactive hyperplasia of all three cell lines, otherwise normal study. Anti-CCP(Cyclic citrullinated peptide) antibody was positive. Rheumatoid factor and anti cardiolipin antibody were negative. Liver function tests showed, total protein 6 gm%, serum Albumin 3% gm, total bilirubin 0.6 mg%, direct 0.1 mg%, AST 38 IU, ALT 24 IU, ALP 255 IU and prothrombin time13 sec with an INR of 1.3. Doppler ultrasound showed, liver was 11 cm with altered echotexture, spleen 25 cm with dilated portal vein and absent phasicity. Upper G I endoscopy upto second part of duodenum was normal. Viral and auto-immune markers were negative with serum ceruloplasmin of 36.

MRI of Abdomen
Findings in MRI of abdomen were as shown in Figs. 1 and 2.

Liver Biopsy (Fig. 3)
Nodular Regenerative Hyperplasia (NRH), Regenerating nodules but absence of fibrous septa HE stain 100x.

With all this clinical information and investigation a final diagnosis of rheumatoid arthritis with nodular regenerative hyperplasia of liver with portal hypertension and splenomegaly with hypersplenism and dental abscess was made and the patient was treated with tooth extraction and antibiotics. She was alright after 10 days of therapy. She is on regular follow up and she has no recurrent infection. She has been told that she may require elective splenectomy for hypersplenism.

Discussion
Nodular regenerative hyperplasia is a rare entity and generally is encountered in association with other diseases like collagen diseases (rheumatoid arthritis, Felty syndrome, progressive systemic sclerosis, systemic lupus erythematosus, polymyalgia rheumatica, polyarteritis nodosa), hematologic diseases (myeloproliferative disorders, lymphoproliferative disorders, idiopathic thrombocytopenic purpura), glomerulonephritis, metabolic diseases, endocrine disorders (lymphocytic thyroiditis, diabetes mellitus) and lymphomas. It has an equal predilection in both sexes and can occur in all age groups and races. The disease can be described as hepatocellular nodule formation

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