Rift Valley fever hepatitis complicated by disseminated intravascular coagulation and hepatorenal syndrome

Tarig S. Al-Khuwaitir, *MRCP(UK), ABIM,*
Abdurahman M. Al-Moghairi, *MBBS, MRCP (I),*
Safia M. Sherbeeni, *MBBS, MRCP(UK),*
Abdullah S. Al-Ghamdi, *MBBS.*

Bunyaviridae named after a town in Africa are known to cause disease in both animals and humans.[1] The illness on a large part mild in humans can cause a lethal hemorrhagic syndrome sometimes complicated by hepatorenal syndrome (HRS).[2] The viral infection once confined to the African continent now poses a threat to farmers and travelers in the Southern region of Kingdom of Saudi Arabia (KSA).[1] We describe a typical case of Rift Valley fever (RVF) virus in a farmer of Gizan who died with the severe form of the illness, his presentation, diagnosis and the management problems of a disease associated with a public fear of unknown infection in our society.

A 70-year-old male from Gizan, KSA presented to the accident and emergency department of Riyadh Medical Complex, Riyadh, in September 2000 with fever, loose motions and frequent vomiting for the last 3 days from his arrival in Riyadh via plane. The fever was not associated with rigors and increased at night, the motions were passed painless amounted to a frequency of 4-5 times a day and were watery and not accompanied by bleeding. Vomiting occurred only with food intake and was associated with nausea. Upon systemic enquiry he reported occasional episodes of wheezing in cold weather from childhood but had no other complaint. His past medical and surgical history were unremarkable. He had no known allergies and currently was on no medication. The patient was a farmer and married with 2 children who are all alive and well. He occasionally visit his son in Riyadh, but had never traveled outside the Kingdom and particularly had not been to Africa. One of his sheep recently had succumbed to the RVF virus and also his neighbors stock had been affected by the disease.

The physical examination revealed a febrile, thin build, elderly male, in no distress, with a temperature of 37.5^{o}C, with a blood pressure of 110/70 mm Hg, a regular pulse of 84 beats per minute and a respiratory rate of 18 breaths per minute. He had no lymphadenopathy, no jaundice and had no signs of chronic liver disease. There was no skin rash or lower limb edema. Examination of the chest revealed expiratory wheezes in both lung fields and on examination of the central nervous system, fundal examination was normal and only a mild tremor of his outstretched hands but no flapping was observed. The cardiovascular and abdominal examination were unremarkable. Urinalysis was normal. Laboratory tests showed a white cell count of 2.6 x10 per cubic millimeter with a differential of 73% neutrophils, 0.4% eosinophils, 1.3% basophils, 5.1% monocytes and 20.2% lymphocytes and a hemoglobin of 10 g/dl, hematocrit of 30.7, mean cell volume (MCV) of 75.1, mean corpuscular hemoglobin (MCH) of 26.2 and a platelet count of 42. The erythrocyte sedimentation rate was 45 mm on the first hour and the serum electrolytes were showing urea of 5.2 mmol/l, creatinine 79 µmol/l, sodium 143 mmol/l, chloride 110 mmol/l, a potassium level of 3.2 mmol/l indicating hypokalemia and a random glucose level of 6.8 mmol/l. Liver function tests revealed an aspartate aminotransferase (AST) of 11106 u/l, alanine aminotransferase (ALT) of 4321 u/l, alkaline phosphatase (ALP) of 79 u/l, total bilirubin of 21 µmol/l, total protein of 62 g/l and an albumin of 31 g/l. Amylase level was 59 u/l. Cardiac enzymes showed a lactate dehydrogenase (LDH) of 10480 u/l and a creatine phosphokinase (CPK) of 288 u/l with normal creatine kinase isoenzyme containing M and B subunit fraction. His coagulation profile revealed a prothrombin time of 38.3 seconds, partial thromboplastin time of 65.4 seconds with an international normalized ratio of 2.78. Three thick and thin films for malaria parasite were reported as negative. Stool analysis revealed many pus cells, no occult blood and no ova or parasites detected. Sputum, urine, stool, aerobic and anaerobic blood cultures were reported as negative. Serology for *Brucella* abortus and melitensis was negative, a Widal test was negative, indirect hemagglutination antibody for *Echinococcosis* weakly positive.

Screens for hepatitis A, B, C and HIV 1 and 2 were negative. Electrocardiogram revealed a normal sinus rhythm with inferolateral T wave inversion. Chest radiograph showed a right hilar calcified lymph node and a trachea deviated to the right, plain x-ray of the abdomen showed a calcified lesion in the liver region (**Figure 1**). Ultrasound of the abdomen showed a calcified cyst most likely hydatid in the left liver lobe. Computed tomography of the abdomen confirmed the finding as well as normal liver and spleen size.

As the patient fulfilled the diagnostic criteria for a possible RVF infection he was admitted in an isolation ward with barrier nursing, which had been prepared following an alert by the Ministry of Health as regard to possible cases of RVF reaching the capital city of Riyadh, despite the quarantine measures commenced by government agencies. The

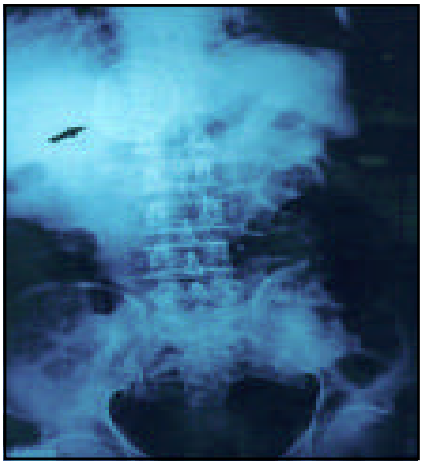

Figure 1 - Plain erect abdominal radiograph showing a calcified hydatid cyst in left lobe of liver in a Gizani farmer.

ward staff was given twice daily N, N-diethyl-3-methylbenzamide (DEET) containing mosquito repellent and the ward was sprayed twice daily with a commercial insecticide. He was given gentamicin 80 mgs intravenously stat dose, ceftriaxone 2 gms intravenously once daily and metronidazole 500 mgs intravenously 3 times a day in addition to intravenous fluids in the form of dextrose 5% per saline 0.9% at 100 ml per hour, vitamin K orally in a dose of 10 mg daily and lactulose 10 ml orally 3 times a day. In the evening of the day of admission he was reexamined and found to be fully oriented, ambulant, with no evidence of bleeding from any orifice, yet his complete blood count revealed thrombocytopenia of 15 and he was transfused 6 units of platelets then took his dinner and had an uneventful night. On the second day of admission, he remained afebrile fully oriented with a mild tremor in the outstretched hands, a few expiratory wheezes and loose motions now associated with some mucus. The AST had risen to 14547, ALT 5275, ALP remained normal with 91, total bilirubin 27, LDH 10480. Prothrombin time of 36.8 seconds and a partial thromboplastin time of 78.6 seconds with a INR 2.6, fibrinogen level 1.37g/l (normal range: 2-4 g/l) and D-Dimer level >400 (normal range: <250). Fresh frozen plasma (FFP) 3 units were administered and a bone marrow aspiration and biopsy performed and sent for microscopy and culture. Serology and culture for RVF virus was arranged. On the morning of the third day of hospitalization the patient developed a coarse flapping tremor but remained conscious, alert, oriented and ambulant. No lymphadenopathy or rashes were noted. He had developed a hemorrhagic lesion at the left side of his tongue but was not bleeding actively. Mild dependent edema was noted. Abdominal examination revealed tenderness in the right upper quadrant. The complete blood count revealed pancytopenia with a white blood count of 1.6, neutrophils of 73%, a hemoglobin of 9.4, MCV of 75, MCH of 23 and a platelet of 25. Bone marrow aspiration was reported as a dry tap. Creatinine had risen to 173 µmol/l. The arterial blood gases showed a metabolic acidosis with a pH of 7.273, PCo_2 33.8 and HCO_3 15.2. A nephrology consult was made in anticipation of a developing HRS. In the afternoon of the third day of hospitalization the patient became anuric and creatinine had risen to 561. Furosemide 60 mg intravenously and sodium bicarbonate 8.4% 50 ml intravenously each one dose were given a strict input output chart commenced with fluids restricted to 2 liters per day. At that point he was clinically compensated. He had a cardiorespiratory arrest in the early morning of his fourth hospital day just prior to transfer to the intensive care unit. The relatives declined post-mortem liver biopsy.

In the absence of a post-mortem examination the exact cause of death could not be ascertained. Rift Valley fever antigen and IgM antibody were subsequently reported as positive, ribavirin had been ordered but could not be acquired prior to his death. The virus known as RVF virus belongs to the *Phlebovirus genus*, one of the 5 genera in the family of *Bunyaviridae*.[1] It causes several pathogenic syndromes in human beings including an acute febrile illness, hemorrhagic fever, hemorrhagic fever with hepatitis and infection of the nervous system and ocular disease.[2] The mortality rate for hemorrhagic fever with hepatitis reaches 36%, however, overall mortality rate is less than 1%.[1] The virus is contracted by direct handling of infected animals and consumption of their products, mosquito bites and inhalation of infectious aerosols and hence poses an occupational hazard for farm workers and related professions, laboratory and medical staff and a health risk for travelers to endemic areas.[1] After introduction into the body the virus moves to the draining lymph nodes, where it replicates; and from there it spreads throughout the body to the critical organs such as the spleen, liver and brain.[1] It gains entry into the cell via endocytosis and uses the host's replicative machinery to transcribe its RNA which is eventually translated in the cytoplasmic ribosomes, the assembled virions are then accumulated in the Golgi apparatus and exocytosis disseminates them further.[1] Though infecting many different organs, the liver is one of its prime targets and there lays its propensity for causing death via inducing a hemorrhagic fever and the lethal acute form of the HRS.[1] The liver upon light microscopy reveals mid zonal hyaline changes leading to necrosis and bodies resembling the Councilman bodies of yellow fever.[2] Our patient, who was a farmer, fulfilled the US centers for disease control case definition of RVF most likely contracted the illness from his animals and had a severe affection to the liver. In

this case, the remarkable clinical signs was the complete absence of severe hepatic encephalopathy right up to the time of the patient's sudden demise. Nausea and vomiting occurred in a great proportion of patients 91.5% in the recent outbreak in Gizan the southern region of KSA and loose motions in 43%.[2] Our patient's liver failure progressed at a rapid pace. The management problems, which we faced, compromised an inciting viral infection leading to hepatitis, was the development of disseminated intravascular coagulation (DIC) with the parallel development of HRS. Options to combat the inciting viral invader are limited to convalescent serum or the rare antiviral medication ribavirin.[1] This broad spectrum antiviral drug is a triazole nucleoside first synthesized in 1970 resembling the structure of guanosine.[3] Existing in the cell primarily in the triphosphate form it has 3 proposed mechanisms of antiviral action including potent inhibition of inosine 5'-monophosphate dehydrogenase activity, inhibition of guanosine triphosphate-dependent capping of the 5'end of viral messenger ribonucleic acid (mRNA's) and direct inhibition of RNA polymerase complex all resulting in inhibition of viral replication.[3] In rodents and monkeys infected with RVF virus, ribavirin therapy resulted in reduced mortality with the only important side effect in humans being a manageable reversible anemia, no resistance to ribavirin was demonstrated.[3] Although dispensed through the center for disease control in Atlanta, Georgia, USA we did not have enough time to procure it. Disseminated intravascular coagulation was the second problem faced in our patient. Even though etiologies vary they share on one common factor, which is the consumption of coagulant factors. These were replenished by FFP in our patient who did not exhibit severe external or internal bleeding tendency. Chuansumrit et al[4] in Thailand used an interesting new approach for 2 cases of Dengue hemorrhagic fever. Recombinant factor VII (rFVIIa) was given for liver failure in conjunction with DIC and control of bleeding was achieved. However, the patients had more severe manifestations of hemorrhage and prolonged shock. Other novel approaches include the administration of antithrombin III concentrate and activated protein C concentrate as the final common pathway of activation of DIC is mediated by cytokines which depress the inhibitory mechanism of both antithrombin III and protein C. Controlled trials of these new strategies are awaited. The general consensus however, that is the cornerstone of DIC management is vigorous treatment of the underlying disorder, which in this case could not be dealt with in a timely fashion. Type 1 HRS occurred as a terminal event in our patient and could not be remedied. Hepatorenal syndrome is a specific form of renal failure in severe liver disease. It is a functional event causing decreased renal perfusion and especially in the renal cortex.[5] The diagnosis is based on exclusion of other conditions causing renal insufficiency.[5] Two types were distinguished: 1) Type 1 with a rapid and progressive increase of serum creatinine, which is observed within days and without orthotopic liver transplantation carries a poor prognosis with a mortality rate of 95% within a few weeks. 2) Type 2 is characterized by a moderate and stable reduction in kidney function.[5] Orthotopic liver transplantation (OLT) is the only effective and permanent treatment for patients with HRS.[5] However, recently 2 other options have received attention, first was the transjugular intrahepatic portosystemic stent-shunt (TIPS) that provides long term renal function and probably survival benefits in the majority of non-transplantable cirrhotics with HRS. It works by reducing the acidity of the renin-angiotensin and sympathetic nervous systems in cirrhotic patients with type 1 HRS. Second was long term administration (1-3 weeks) of analogs of vasopressin (ornipressin and terlipressin) or other vasoconstrictors together with plasma volume expansion with albumin, which reportedly were associated with a dramatic improvement in circulatory function and normalization of serum creatinine concentration in patients with severe HRS.[5] In our patient with combined liver and renal failure, both standard hemodialysis and the newer continuous renal replacement therapies have been found to help maintaining fluid, electrolyte and acid base balance.[5] Extra corporeal purification techniques would have been useful in our patient if available prior to his renal failure as they remove hepatic toxins and help in the replacement of clotting factors in liver failure without kidney dysfunction. According to our knowledge, our patient was one of the few infected people who were able to come to Riyadh despite the announcement of the discovery of the RVF epidemic in Southern region of Saudi Arabia and the subsequent quarantine measures implemented by the government through the Ministry of Health.[2] This case demonstrates that with proper isolation and standard body fluid precautions a RVF patient can be cared for with minimal risk to hospital personnel. Although it is a mild illness with many subclinical cases the hepatic form of the disease occurred in 88% in those with severe illness.[2]

Inasmuch as the culprit is the RVF virus, ribavirin should be at the ready to study its clinical efficacy should a second epidemic occur to prevent the dire consequences of this illness in our population.

Received 29th October 2003. Accepted for publication in final form 20th December 2003.

From the Department of Medicine, Riyadh Medical Complex, Riyadh, Kingdom of Saudi Arabia. Address correspondence and reprint requests to Dr. Tarig S. Al-Khuwaitir, Department of Medicine, Riyadh Medical Complex, PO Box 3847, Riyadh 11481, Kingdom of Saudi Arabia. Tel. +966 (1) 4783446. Fax. +966 (1) 4783446. E-mail: Tarig_AlKhuwaitir@hotmail.com

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Breast cancer during pregnancy and lactation

Abdul-Wahed N. Meshikhes, *MBChB (Dublin), FRCSI,*
Mohammed A. Al-Mubarek, *MBBS, SBGS,*
Ahmed A. Al-Tufaif, *MBBS.*

Pregnancy associated cancer is a cancer that is diagnosed during pregnancy or within a year after.[1-3] Although its incidence is relatively rare,[1] it is the most common malignancy encountered in pregnant women. It is seen in approximately 0.03% of pregnancies and only 1-2% of overall breast cancers is diagnosed during pregnancy or lactation.[2] In recent years, gestational breast cancer seems to be occurring with increasing incidence,[3] but clinicians often tend to attribute breast symptoms and signs to the physiological breast changes of pregnancy or lactation. The matter is further complicated by breast engorgement as pregnancy advances hiding any breast solid lumps. It is not surprising therefore that the breast cancer during pregnancy or lactation has the reputation of 'bad prognosis' mainly due to late presentation and delayed diagnosis which is very common.[1]

We report 3 cases of gestational breast cancer that were encountered by the authors over a year period (1998) and discuss the diagnostic dilemma and modern management options.

The first case was a 38-year-old Saudi female who was 8 month pregnant presented with 3 month history of left breast lump and intermittent bloody nipple discharge. She started menarche at the age of 13 years and denied any past history of benign breast diseases or oral contraceptive pill. There was no family history of malignant breast disease. Clinical examination revealed an irregular hard lump (3x3 cm) in the subareolar area of the left breast with no palpable axillary or supraclavicular lymph nodes. Fine needle aspiration cytology (FNAC) showed infiltrating ductal carcinoma. She underwent left simple mastectomy and axillary clearance together with cesarian section (CS) and tubal ligation at the same time. Histology revealed grade II infiltrating ductal carcinoma with 2 of the 11 level I nodes were positive for malignancy. She later underwent adjuvant chemoradiation and remained well with no evidence of locoregional recurrence 34 months later (**Table 1**).

The second case was a 40-year-old Saudi female who has been lactating for 10 months presented with a left breast lump of one week duration. There was no history of breast pain or nipple discharge and denied any past history of benign breast disease. There was no family history of breast cancer. Clinically, there was a 2x3 cm irregular left breast mass, in the upper outer quadrant with no palpable axillary lymphadenopathy. Mammography revealed suspicious opacity in the left breast but bone scan and ultrasonography showed no bone or liver metastases. Fine needle aspiration cytology showed suspicious of malignancy. She underwent a wide excision and left axillary clearance. Histopathology showed grade II medullary carcinoma and 2 out of 20 axillary lymph nodes were malignant. She later underwent systemic chemotherapy and radiation to left breast and declared disease free 30 months later (**Table 1**).

The third case was a 32-year-old Saudi female who has been lactating for 5 months presented with a month history of a right breast lump. There was no history of nipple discharge or past history of any benign breast diseases. There was no family history of breast carcinoma. Clinically, there was an irregular right breast mass (5x3 cm) in the upper inner quadrant with palpable right axillary lymph nodes. She underwent right simple mastectomy and axillary clearance. Histology showed grade II infiltrating ductal carcinoma with 15/18 lymph nodes were positive. Postoperative adjuvant therapy was given but was lost to follow up 6 months after surgery (**Table 1**).

Contrary to the general belief, pregnancy does not appear to have an adverse effect on the disease process nor there is a solid evidence to implicate pregnancy or lactation as etiological factors. The reputation of 'bad prognosis' associated with pregnancy associated breast cancer is greatly attributed to late presentation and delayed diagnosis which is very common.[1] Therefore, it is not surprising to encounter axillary lymph node involvement in 70-80% of operable breast lesions diagnosed during pregnancy, mainly due to delayed