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Case Report

Pathology Section

Diagnosis of a Fatal Rickettsial Infection in a 44-Year-Old Male

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ABSTRACT

Rickettsial infections are an emerging public health concern in many parts of India with several undiagnosed or misdiagnosed cases. Despite its widespread prevalence in India, lack of suspicion, nonspecific signs and symptoms, and absence of widely available sensitive and specific diagnostic test contributes to a high fatality rate. This is a case study of a 44-year-old male patient with a severe Rickettsial infection that turned fatal. Aim of this case study is to highlight the importance of timely diagnosis of Rickettsial infections which in this case could have saved the patient's life.

Keywords: Acute kidney injury, Hepatitis, Molecular diagnostics, Multiple organ dysfunction, Septicaemia

CASE REPORT

A 44-year-old male resident of Mumbai (Maharashtra, India) who was on a visit to Benaras (Uttar Pradesh, India) presented with a history of high grade fever with chills and cough/cold since one week. While in Benaras, the patient took treatment from a private doctor without much relief. The patient was then admitted to a local hospital in Benaras with acute febrile illness with thrombocytopenia (TCP; platelets: 70000) and liver dysfunction (Serum glutamic-pyruvic transaminase or SGPT: 243; Bilirubin: 3.8/2.0). In addition, the patient also complained of breathlessness. Rapid Malarial Test was found to be negative. Patient got discharge against medical advice and travelled back to Mumbai the next evening. He had one episode of Generalised Tonic-Clonic Seizure (GTCS) at the airport and was immediately admitted to the hospital.

On admission, patient was found to be in poor general condition. He was conscious but restless, irritable and confused, and was not following verbal commands. He had no pallor or edema but had petechial rash all over the trunk and leg. There was no evidence of loss of consciousness, limb weakness, haematuria, shortness of breath or chest pain. The patient had leukocytosis (WBC: 15000) and TCP (platelets: 35000). He was icteric with deranged liver enzymes (Serum glutamic oxaloacetic transaminase or SGOT: 219; SGPT: 112; Bilirubin: 5.9/4.0). His creatinine had also increased to 2.7 from 1.0 the previous day and his Disseminated Intravascular Coagulation (DIC) profile showed elevated levels of Fibrin Degradation Products (FDPs) (>80<160) and Fibrinogen (443.80). He had no history of hypertension, diabetes mellitus, tuberculosis, bronchial asthma, or addiction to alcohol or tobacco. Patient was shifted to the ICU and put on anti-epileptics, antibiotics (Monocef), and steroids.

Blood and urine samples were also sent for culture and sensitivity. Ultrasound of the pelvis and abdomen only showed mild hepatomegaly with gall bladder wall edema and mild splenomegaly. Chest X-ray showed that both lungs and costophrenic angles were clear. Mild cardiomegaly was seen. Plain Computed Tomography (CT) scan of the brain showed suspicious blurring of the grey-white matter differentiation in both occipital poles which was likely artefactual. Other than this, everything else was normal in the brain CT.

On Day 2 of admission, the patient was extremely restless with altered sensorium. He was electively intubated and sedated/paralysed. Patient had tachycardia (152 bpm) and hypotension was present so he was put on Norad. He had acute kidney injury with high serum creatinine and decreased urine output so patient was advised Sustained Low-Efficiency Dialysis (SLED). SLED was given for six hours which the patient tolerated well. TCP was still positive (25000) and he was hyponatremic (128). Rapid Malarial Test, Dengue IgM and NS1, Leptospira, Hepatitis B Surface Antigen (HBsAg), Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) were negative. As the patient was not responding to Monocef, Meropenem and Acyclovir (the latter for suspected viral encephalitis) were added to the treatment regimen. In view of the petechiae and suspicion of a Rickettsial infection, Doxycycline was also added. Herpes Simplex Virus (HSV) serology was ordered. As blood and urine cultures were still negative, a blood sample was sent that evening for screening for pathogens that could potentially cause a Central Nervous System (CNS) infection (iGenetic Comprehensive CNS Panel; See [Table/Fig-1].

Bacteria	Viruses
Streptococcus pneumoniae	Herpes Simplex Virus 1 & 2
Listeria species	Cytomegalovirus
Hemophilus influenzae	Varicella Zoster Virus
Neisseria meningitidis	Human Herpes Virus 6
Treponema pallidum	Adenovirus
Rickettsia species	Enterovirus
Acid fast bacilli	Japanese Encephalitis Virus
Mycobacterium tuberculosis Complex (MTC)	Mumps Virus
	Epstein Barr Virus
Non-Tuberculous Mycobacteria (NTM)	**Fungi**
	Cryptococcus neoformans

[Table/Fig-1]: iGenetic Comprehensive CNS panel.

At the same time, Endotracheal (ET) secretion was sent for the iGenetic Atypical Pneumonia Panel See [Table/Fig-2]. The patient required Norad at high dose overnight.

iGenetic Atypical Pneumonia Panel
Mycoplasma pneumoniae
Chlamydia pneumoniae
Legionella pneumophila
Pneumocystis jiroveci

[Table/Fig-2]: iGenetic Atypical Pneumonia Panel.

On the third day, the fever continued despite treatment with antibiotics and antivirals. Anti-malarials were also started. Due to elevated creatinine (3.1) and decreased platelets (30000 on Day 3), there was suspicion of Thrombotic Thrombocytopenic Purpura (TTP).

However, there was no evidence of haemolysis, schistocytes were negative and haemoglobin levels were between 12.7 and 14.9. Hence, TTP was ruled out. HSV-1&2 IgM and IgG were negative. Within 24 hours, the results of the molecular tests showed that the blood sample was positive for *Rickettsia* spp while the ET secretion was negative for pathogens causing atypical pneumonia. The PCR test confirmed that the sepsis and all other symptoms in the patient were due to Rickettsiosis.

Meanwhile, during the day, the patient's serum creatinine had climbed to 3.1, so SLED was administered and administration of IvIg was also considered. About 2 hours later, patient was hypotensive so Inj Vasopressin was started and Inj Norad increased while SLED was terminated. However, at about 7.20 pm, patient went into brady arrest followed by asystole. Cardiopulmonary Resuscitation (CPR) was started as per American Heart Association (AHA) protocol. Medications were administered and CPR was continued for 20 minutes. Asystole was noted, the pupils were dilated/fixed and Non-Reactive to Light (NRTL). CPR was stopped at 7.39 pm and patient was declared dead at 7.40 pm. Cause of death was declared as septicaemia with Multiple Organ Dysfunction Syndrome (MODS).

DISCUSSION

Rickettsial infections are prevalent throughout the world except Antarctica. Cases of such infections have been reported in India for several decades. It is widely prevalent across many states like Maharashtra, Tamil Nadu, Karnataka, Kerala, North east states and in north states like Jammu and Kashmir, Uttaranchal, Himachal Pradesh and Haryana [1-5]. In India, scrub typhus, spotted fever and Indian tick typhus caused by *R. conori* are the most prevalent of Rickettsial diseases. Eleven outbreaks of Rickettsial infections were reported between 2000 and 2011 [6]. There are limited studies conducted on the prevalence of Rickettsial infections in India with one study reporting CNS involvement in 26% of the cases with scrub typhus [7]. *Rickettsia* can cause a wide range of diseases from mild, self-limiting to severe, life-threatening infections depending on host factors, Rickettsial species involved, and type and timing of treatment [8]. [Table/Fig-3] shows various species of *Rickettsia* causing infection and wide range of symptoms [9-18].

Infection	Symptoms
Rickettsia conorii	Skin rash, fever, arthromyalgia, increased inflammatory markers, hepatic cytolysis and anicteric cholestasis, bilateral uveitis [9].
Rickettsia parkeri	Fever, chills and eschar [10].
Rickettsia africae	Fever, headache, eschar, maculopapular rash [11].
Rickettsia sibirica mongolotimonae	Fever, chills, dizziness, weakness, eschar with regional lymphangitis, generalised faint maculopapular rash, leukopenia, thrombocytopenia, deranged liver enzymes [12].
Rickettsia aeschlimannii	High-grade fever, left knee monoarthritis, sore throat, asthenia, increased inflammatory markers, acute hepatitis, elevated prothrombin time, mild thrombocytosis [13].
Rickettsia conorii and *Mycobacterium tuberculosis*	High grade fever, myalgia, headache, multiple seizures, altered sensorium, tachycardia, eschar, shock, aspiration pneumonia [14].
Rickettsia typhi	Sudden fever of unknown origin, persistent nocturnal headache, myalgias, arthralgias, diarrhea, hypersomnia, generalised fatigue, maculopapular rash on arms, thighs, buttocks, back, thorax and abdominal region, leucocytosis [15].
Rickettsia typhi	Scleral icterus, fever, arthralgias, headache, eye pain with movement, stiff neck, excessive thirst, back pain, nausea, leukocytosis, thrombocytopenia, elevated liver enzymes [16].
Rickettsia conorii	Fever, myalgia, headache, discrete erythematous macular rash, swelling of ankle joints, myocarditis, Acute Respiratory Distress Syndrome (ARDS) [17].
Rickettsia felis	Fevers, retro-orbital headaches, nausea, vomiting, pancytopenia, increased inflammatory markers, elevated liver enzymes, non-itchy maculopapular rash [18].

[Table/Fig-3]: Case studies showing that Rickettsial infections can cause a wide range of diseases [9-18].

In fact, Rickettsial disease can be confused with a variety of viral (measles, enteroviral exanthems, dengue, infectious mononucleosis), protozoal (malaria), bacterial (meningococcemia, typhoid, leptospirosis, toxic shock syndrome, scarlet fever) and collagen vascular diseases (Kawasaki disease, other vasculitis). Neurological manifestations including dizziness, drowsiness, disorientation, tinnitus, photophobia, delirium, meningismus and visual disturbances all are seen more commonly with typhus group rickettsioses. Rash is considered as hallmark of Rickettsial infection, but might not be seen on every patient [6]. This infection can be treated with antibiotics but the greatest challenge to clinicians is the difficulty in diagnosing these infections early in their clinical course when antibiotic therapy can be most effective. Most physicians do not consider *Rickettsia* in their differentials [1].

Immunofluorosence assay (IFA) is considered the gold standard for serologic testing of Rickettsial diseases. However, the absence of standardised antigens, conjugates, and threshold levels defining a positive result make it difficult to use and interpret [19]. Molecular diagnosis by Polymerase Chain Reaction (PCR) and Enzyme-Linked Immunosorbent Assays (ELISA) are also widely used diagnostic techniques. In addition, the Weil-Felix test is also used where Proteus antigens shared with *Rickettsia* are used for detecting *Rickettsial* antibodies in the patient.

In this case, Molecular diagnosis using the iGenetic Comprehensive CNS Panel implicated *Rickettsia* as the causative factor of septicaemia in the patient. Rickettsial infections commonly cause fevers with chills, exanthems, thrombocytopenia, hyponatremia, liver dysfunction, nausea, vomiting, abdominal pain, encephalitis, hypotension, acute renal failure, and respiratory distress. The patient showed a majority of these symptoms. Although the serological tests for *Rickettsia* were not done in this patient, the symptoms and the confirmatory PCR test point to the fact that the patient suffered from septicaemia caused by *Rickettsia* followed by multiorgan failure and ultimately succumbed to the illness.

Rickettsial illnesses are difficult to diagnose early because of non-specific symptoms that often mimic benign viral illness. In cases that are not promptly diagnosed and appropriately treated, fatality rates are as high as 30-45% due to multi-organ dysfunction [19]. In this case, the diagnosis came too late for the patient.

CONCLUSION

The present case study points to the importance of considering *Rickettsia* in the differentials in hepatic dysfunction especially when accompanied by one or more of the symptoms observed in this patient i.e., petechiae, TCP, hyponatremia, AKI, respiratory distress and CNS symptoms. In most cases, diagnosis of a Rickettsial infection relies on serological tests that are positive only in the second week of illness (at the earliest) in these infections. Consequently, the diagnosis may come only after the patient has recovered or died. PCR-based tests are positive in the first 7-10 days and if done early in the illness could have potentially saved this patient's life.

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