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RESEARCH ARTICLE

Zika Virus Infection with Fatal Secondary Hemophagocytic Lymphohistiocytosis Syndrome as an Atypical Presentation

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ABSTRACT

Rationale: **Zika virus (ZIKV) is an uncommon tropical viral illness caused by a flavivirus transmitted by mosquitoes such as dengue virus, West Nile virus and yellow fever virus. Clinical manifestations of Zika virus infection are usually milder in nature. It usually presents with a self-resolving triad of fever, rash and polyarthralgia. There are very few case reports of severe or lethal cases.**

Patients concern: **66 years male patient was admitted with an acute febrile illness for 5 days and underwent evaluation for multiple organ dysfunction. He was diagnosed with Zika virus infection which was confirmed by polymerase chain reaction. He had rapid clinical deterioration with coagulopathy, resistant hypotension, multi- organ dysfunction with secondary Hemophagocytic Lymphohistiocytosis Syndrome (sHLH). He died within 72 hours of presentation.**

Diagnosis: **Zika virus infection with secondary HLH syndrome.**

Interventions: **The patient was admitted to the intensive care unit (ICU). He had multi-organ dysfunction and required mechanical ventilation, sustained low efficiency dialysis (SLED), vasopressors, steroids, intravenous immunoglobulin, antibiotics and supportive treatment.**

Outcomes: **The patient succumbed to his illness within 72 hours of admission.**

Lessons: **Zika infection though considered a mild illness, can rapidly evolve into a severe form of disease and can be lethal. There is a need for increased clinical awareness and watchfulness for such atypical presentations of ZIKV infection.**

Keywords: Atypical presentation, secondary Hemophagocytic Lymphohistiocytosis Syndrome, Zika serology, Zika virus.

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1. Introduction

Zika virus belongs to the family *Flaviviridae*, genus *Flavivirus*, and is a vector borne virus transmitted by *Aedes* mosquitoes. It may be transmitted to humans via multiple routes—primarily transmitted by bite of an infected mosquito besides other modes of transmission including perinatal, in utero, sexual (including vaginal, anal, and oral sex), blood product transfusion, organ transplantation and laboratory exposure [1]–[3]. ZIKV infection is usually a self-limited illness, mild in nature, presenting with a triad of fever, maculopapular rash polyarthralgia and sometimes bilateral conjunctivitis [4]. ZIKV is known to be associated with pregnancy complications such as fetal loss, still birth, preterm birth and congenital microcephaly among women infected during pregnancy, as well as various neurologic complications including Guillain-Barré syndrome [5]. The lethal potential of acute ZIKV infection has been reported in some case reports [6]–[8] and case series [9].

In 2018, Jaipur experienced a Zika virus infection outbreak limited to the Shastri Nagar area, with the first laboratory confirmed case of Zika virus disease being reported on September 21, 2018. A total of 159 individuals

tested positive for ZIKV infection in further house-to-house surveys of the area around the index case. However, all cases had mild to asymptomatic infection except for the index case which was admitted for a neurological disorder and tested positive for ZIKV infection [10]. Since then, no cases of ZIKV infection have been reported in Rajasthan. Here, we present detailed clinical and diagnostic reports and management of an adult presenting with fever, polyarthralgia, a few loose stools, and extreme weakness on day 5 of febrile illness. He rapidly deteriorated with hypotension and multi-organ dysfunction and developed secondary HLH syndrome. ZIKV was the only pathogen identified after an extensive diagnostic work-up. He succumbed to febrile illness on day 8. We intend to emphasize the need for increased awareness of atypical and severe presentations of acute ZIKV infection and to develope a practice to perform a fever panel test including multiple viruses in such cases.

2. Method and Results

2.1. Case Presentation

A 66 years male patient attended triage in Fortis Escorts Hospital, Jaipur, on 20/11/2024 at 2.30 PM with complaints of fever with chills, intermittent, from 16/11/24. It was associated with marked body-aches and polyarthralgia limiting mobility so much that he was moved on a stretcher during triage. He was administered non-steroidal anti-inflammatory drugs (NSAID) for fever and aches. He also had a few loose and black stools, 1–2 episodes of non-bilious vomiting, extreme weakness, shortness of breath and decreased urine output from the early morning of 20/11/24. The patient had hypertension as a co-morbidity. During triage he was febrile with 101.2°f, heart rate 123/mt., blood pressure 84/58 mm Hg, Respiratory rate 32/minute, SpO2 96% on ambient air, GCS E4v5M6, bilateral conjunctiva suffused, severely dehydrated and lungs clinically clear with vesicular breathing. His arterial blood gas showed a pH of 7.272, pO2 of 48.4 mm Hg, pCO2 of 27.7 mm Hg, sodium level of 113 meq/L, base excess of (-) 13 mmol/Bicarbonate 12.4 mmol/L, and lactate 8.4 mmol/l suggesting compensated metabolic acidosis. He was admitted to the medical intensive care unit for further management. The patient was resuscitated with fluid and further evaluated. He was started on Inj. Doxycycline, azithromycin and oseltamivir tablets have been empirically used to treat tropical febrile illness(s) and influenza. A comprehensive polymerase chain reaction (PCR) pyrexia panel was performed, which include a real-time PCR (RT-PCR) test for chikungunya virus, dengue virus, Leptospira species, Plasmodium species, Rickettsia species, Salmonella species, West Nile virus, and Zika virus. His initial laboratory results showed elevated inflammatory markers, leukocyte count, procalcitonin, lactic dehydrogenase (LDH), natriuretic peptide, Troponin T, transaminases, severe thrombocytopenia, azotemia (acute kidney injury), dyselectrolytemia, and mild hyperbilirubinemia. The results of the investigations are present in Table I.

A non-contrast computed tomography (NCCT) scan of the thorax showed a thin rim of bilateral pleural effusion and multiple parenchymal bands with patchy ground glass opacities in the right upper lobe, right middle lobe and both lower lobes, with overall features suggestive of infective etiology (Figs. 1 and 2).

His dengue NS1 serology (card test) was positive, but later, ELISA and PCR tests were negative. Abdominal Ultrasound showed mild hepatosplenomegaly with increased periportal echogenicity, mild gall bladder wall edema, and grade 1 renal parenchymal changes (Figs. 3 and 4). His 2-dimensional echocardiography findings were unremarkable.

The patient was catheterized and required noninvasive ventilation support (NIV) for type 2 respiratory failure and Inj. Meropenem was administered along with supportive care. The patient had persistently low blood glucose levels and required continuous dextrose infusion. He was oliguric, with 410 ml urine output in 24 h on 20/12/2024 and Inj. Torsemide infusion was administered. He also had mild hemoptysis. On 21/11/2024, in the morning, he was started on vasopressors for hypotension. Sustained low-efficiency dialysis (SLED) was done on 21/11/2024 night. He remained febrile and had rapid deterioration with multi-organ dysfunction, a further drop in platelet count, and increased azotemia and transaminitis. 1-unit single donor platelet (SDP) was given on 21/11/2024 in the evening. A tentative report of a pyrexia panel with unequivocal results for ZIKV was received on 21/11/2024 in the evening with other viruses and species negative as mentioned earlier. A repeat sample was sent for confirmation.

Thus, the possibility of sHLH was considered. He had markedly raised D-dimer, serum Ferritin, transaminases, fever, hepatosplenomegaly and with deteriorating condition he was given pulse methylprednisolone (MPS) and intravenous immunoglobulin (IVIG) as per protocol for sHLH [10]. On 22/11/2024 he developed atrial fibrillation for which amiodarone was administered. Government Health authorities were informed of the possible ZIKV infections. He had worsening shock, metabolic acidosis, high lactate levels, nil urine output (20 ml on 22/11/2024), labored breathing, rising D-dimer, ferritin, and transaminases. Mechanical ventilation was performed in the evening on 22/11/2024, and a second session of SLED was also performed. On 22/11/2024 the PCR pyrexia panel was confirmed to be positive for Zika virus. Blood cultures, urine culture, endotracheal secretion culture, and influenza virus panel were negative. However, he succumbed to his illness on 23/11/2024 at 3 AM despite the best possible efforts. Autopsy was not done. Fig. 5 shows a schematic representation of the patient's history and clinical course of the disease.

A report from the state virology referral lab, Jaipur (Rajasthan) was also reported to be positive for ZIKV by real-time PCR (RT-PCR) from urine and blood samples on 22/11/2024 and further confirmed later by ICMR NIV, Pune (India) on 25/11/2024 for ZIKV RT-PCR positive on samples of plasma, serum, urine of 22/11/2024, and plasma and serum samples of 23/11/2024. Viral loading was not performed, as the test was not available.

TABLE I: Hematology and Biochemistry Parameters

	Reference range	20/11	21/11	22/11
C Reactive Protein	0–5 mg/L	337.9	–	273.2
D Dimer	< 255 ng/ml DDU	–	15300	18600
Ferritin	13–150 ng/ml	–	52450	>50000
Blood urea nitrogen	6–20 mg/dl	38	41	40
Serum creatinine	0.5–0.9 mg/dl	3.25	3.51	3.8
Uric acid	3.4–7 mg%	7.6	7.5	8.0
Hemoglobulin	13–17 gm/dl	14.2	11.2	11.7
Hematocrit	40%–50%	43.3	32.7	35.0
Total Leucocyte count	4–10 × 10^3/cmm	15.90	14.7	17.80
Platelets count	150–410 × 10^3/cmm	70	65	75
SGOT	<32 U/L	297	648	6175
SGPT	<32 U/L	112	244	2457.4
Serum total bilirubin	upto1.2 mg/dl	1.63	1.47	2.57
Serum bilirubin direct	< or = 0.30 mg/dl	1.32	–	2.06
Serum alkaline phosphatase	40–129 U/L	190	–	362
Serum total protein	6.6–8.7 gm/dl	5.8	–	5.0
Serum albumin	3.97–4.94 gm/dl	3.3	–	2.5
GGT	5–36 U/L	108	–	194
LDH	135–225 U/L	1234	–	11064
PT-INR	<1.40	–	1.59	1.79
aPTT		–	–	63.2
S. Amylase	28–100 U/L	–	–	1789
S. Lipase	13–60 U/L	–	–	44.1
S. Triglycerides	<150 mg%	–	153	100
Procalcitonin	<0.046 ng/ml	5.87	–	–
B type natriuretic peptide	< or =125 pg/ml	6855	–	–
CK MB	0.30–6.22 IU/L		–	6.3
Creatine phosphokinase	39–308 U/L	248	–	1005
Troponin T	<14p g/ml	18.1	–	252.7
Serum calcium	8.8–10.2 mg%	–	–	8.0
Serum magnesium.	1.6–2.6 mg/dl	–	–	2.0
Serum phosphorus.	2.5–4.5 mg%	–	–	3.8

Note: SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamate pyruvate transaminase; GGT: Gamma glutamyl transpeptidase; LDH: Lactic dehydrogenase; PT-INR: Prothrombin time – International ratio; aPTT: Activated partial thromboplastin time; CK-MB: Creatine kinase – myocardial band.

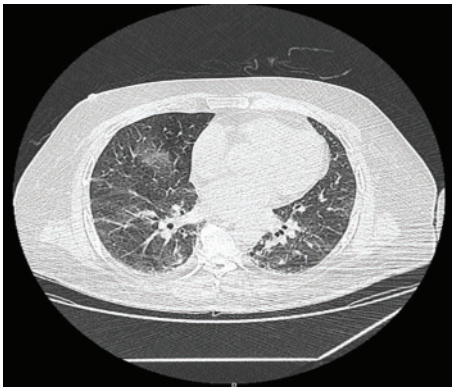

Fig. 1. NCCT chest axial view show thin rim of bilateral pleural effusion, multiple parenchymal bands and patchy ground glass opacities in right lung and left lower lobe.

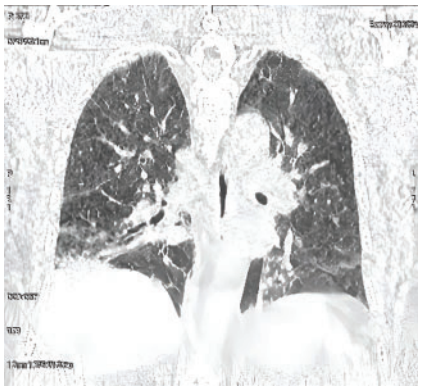

Fig. 2. NCCT chest coronal view show thin rim of bilateral pleural effusion, multiple parenchymal bands and patchy ground glass opacities in right lung and left lower lobe.

3. Discussion

ZIKV infection leads to clinical manifestations in 20–25 percent of individuals [11]. The illness is usually mild, and the symptoms settle within two to seven days. Immunity to reinfection occurs following a primary infection. Severe disease requiring hospitalization is uncommon, and case-fatality rates are low [12]. ZIKV infection is generally not considered an alarming illness and much less a life-threatening pathogen, until very recently. However, many reports of life-threatening ZIKV infections have been published in the literature since 2016, when the first ZIKV-related death was reported [12]. In this

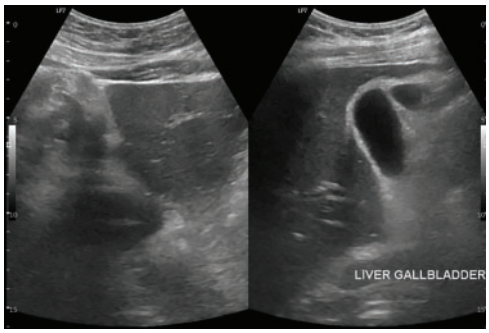

Fig. 3. Ultrasonography of patient showing mild hepatomegaly and mild GB wall edema.

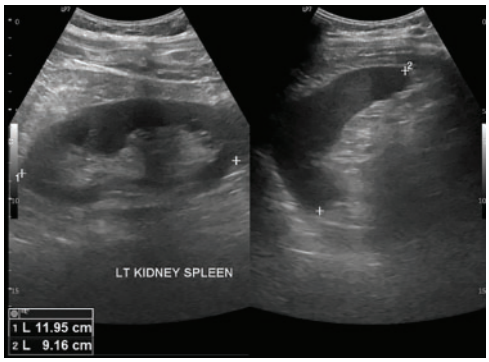

Fig. 4. Ultrasonography of patient showing mild Splenomegaly.

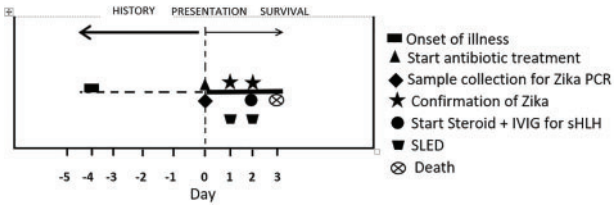

Fig. 5. Schematic representation of patient's history and clinical course of the disease.

case report, we describe a fatal case of ZIKV infection that presented with severe illness with a rapidly deteriorating course and development of sHLH syndrome. There are very few reports on sporadic lethal cases of ZIKV infection, including two case series of three cases each, a case report on the severe and lethal presentation of ZIKV infection, and a systematic review [6], [9], [13]. However, none of the patients had the sHLH syndrome. Strikingly, many of these patients with fatal ZIKV infection had a septic presentation and rapid progression, similar to this case. Many of the patients had additional co-morbidities. However, co-morbidities, age, and viral load are risk factors, and the role of these variables in the progression to death has not been established. Furthermore, in this systematic review, it was reported that in these cases, the time of evolution and the clinical picture were similar to those of other arboviruses [12]. Our patient had hypertension as a co-morbidity and was underwent regular treatment. Reports from Brazil, Guadeloupe—Martinique and Venezuela on severe and lethal cases of Chikungunya virus infection describes similar septic and progressive presentations in patients of similar age group and co-morbidities [13]–[15]. In report from Brazil on 68 cases of fatal chikungunya, 45.5% had no co-morbidity, suggesting that chikungunya infection can lead to patient death even in the absence of an underlying medical condition [13]. Fig. 1 shows the temporal evolution of the case from the time of onset, time of sampling and confirmation of ZIKV infection, interventions performed, and death. The course of the illness appears similar to that of other arboviruses, such as dengue and chikungunya, and other possible explanations, such as co-infections, co-morbidities (except controlled hypertension), and treatment errors were excluded.

An important step along the evolution to death in fatal Zika cases is the ability of ZIKV to disseminate to multiple tissues not only in immunocompromised but even in immunocompetent non-human primates [12]. This could help elucidate the involvement of multiple organ systems in fatal cases. An important limitation in completely confirming a causal relationship between ZIKV infection and fatal outcome is the presence of co-infection. It had been suggested that prior infection with dengue virus may cause antibody -dependent enhancement of ZIKV infection and thereby increased virus replication in host with effects on virulence [16]. In the present case, the patient's serology (card test) for Dengue NS1 antigen was initially positive. However, a simultaneous negative confirmatory ELISA test for Dengue NS1 and negative RT-PCR for dengue virus rules this out. Similarly, other common viral pathogens and arboviruses were ruled out using the RT – PCR-based pyrexia panel. He also tested negative for HIV and bacterial or fungal infections. Mild hemoptysis in our patient suggests the hemorrhagic potential of ZIKV infection, as seen in dengue infection.

There are reports of a positive association between high viral loads, increased virulence and severe fatality, as observed in dengue and chikungunya viral illnesses. High viral loads, increased replication rates, and delayed viral clearance have been observed in cases transitioning from mild to severe illness [17], [18]. It seems interesting to hypothesize that high viremia could play a role in disease progression. However, viral load and sequencing could not be performed because of their non-availability.

The link between ZIKV infection and severe disease remains to be determined; however, the possibility of an exaggerated immune response of the host causing hyperinflammatory syndrome remains unclear. Laboratory results show evidence for the activation of acute and innate immunity, as is seen in severe cases of dengue and chikungunya viral infection. Intravascular cytokine storm/sHLH syndrome in severe cases of dengue fever is known. It is possible that a similar mechanism is involved in severe cases of ZIKV infection. sHLH is a hyper inflammatory syndrome with up regulation of inflammatory cytokine and can occur after strong immunologic activation by systemic infection with various infections such as viruses, bacteria, fungi and/or protozoa infections, besides malignancy, auto-immune/auto-inflammatory diseases, immune compromised states, solid organ transplantation and some metabolic disease [19]. It has a high mortality rate of >50%. The case presented also developed sHLH features and fulfils proposed HLH diagnostic criteria, 2009 [20]. To the best of our knowledge, this is the first case report of sHLH in a patient with severe ZIKV infection.

4. Conclusion

This is an individual case report of fatal ZIKV infection that evolved into a severe form of disease with sHLH syndrome and death. However, the severe outcomes of ZIKV infection are rare. Considering the severity of our case, we would like to highlight the need for increased clinical awareness and watchfulness for such atypical presentations of ZIKV infection. Additionally, Clinicians should be aware that ZIKV infection can present with a clinical picture similar to that of infection with dengue and other arboviruses, including thrombocytopenia, liver dysfunction, hemorrhagic potential and shock. Further research is needed to define the factors that may mediate the pathogenesis of severe, atypical, and fatal ZIKV disease.

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Consent

The authors have written and signed consent from the patient's family for the publication of the case. This was a case report and institutional ethics committee approval was not required.

Conflict of Interest

The authors report no conflict of interest.

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