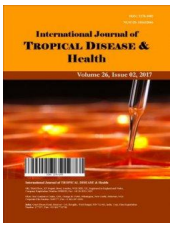

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A Fatal Trio: Concurrent Infection with Malaria Parasite, Dengue and Influenza A (H1N1) Virus Together

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Authors' contributions

This work was carried out in collaboration between all authors. Author AA is the primary consultant internist and contributed to the conception, design, draft, analysis, revision, literature search and final approval of the work to be published. Authors PP and AS were involved with data acquisition, statistical analysis and tabulation of data. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

There have been many case reports in the literature of mixed infection with two or more pathogenic organism including Dengue virus, Malaria parasite, Hepatitis virus, Scrub typhus, and Influenza virus but so far there have been no case reports of Dengue virus, Malaria parasite and influenza A (H1N1) virus concurrent infection together. The vector for all these three infections are different- Female anopheles mosquito for malaria, *Aedes aegypti* mosquito for dengue and direct or indirect contact and inhalation of virus laden aerosols for influenza. This case is unique because here mode of transmission is different yet the patient presented at the same time with this triad of infections and diagnosed on clinical suspicion.

Keywords: Tropical fever, malaria; dengue; influenza A; coinfections.

1. INTRODUCTION

Management of a critically ill patient with more than one microbiological infection concurrently can be challenging, in an intensive care setting. It may be possible for two or more pathogens to infect the same cell causing interaction of their individual pathogenesis. This in turn can lead to

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change in their virulence or host response for better or worse [1].

It is difficult to distinguish influenza, malaria and dengue fever clinically among febrile illnesses in a tropical area known to be endemic for malaria and dengue illnesses. This is more so during the post monsoon period when peak dengue and malaria season coincides with that of other common causes of tropical febrile illnesses. The influenza, malaria, dengue, hepatitis and scrub typhus seasons may overlap, which could lead to diagnostic difficulties. We are reporting the first laboratory- confirmed case of coinfections with Influenza A (H1N1) virus, Dengue virus and *Plasmodium vivax* malaria parasite who had a fatal outcome.

2. CASE REPORT

A 32 years old immunocompetent male resident of Alwar, Rajasthan, India, was working as a laborer in New delhi, India and presented with complaints of fever, chills, nausea, myalgias, headache, pain abdomen and breathlessness of around 2 week's duration. Over the last 2 weeks he took treatment at 4 places and was admitted twice. He also received random donor platelet transfusion for thrombocytopenia. He was brought to triage at Fortis escorts Hospital, Jaipur (FEHJ) on 13.10.2018 with marked breathlessness.

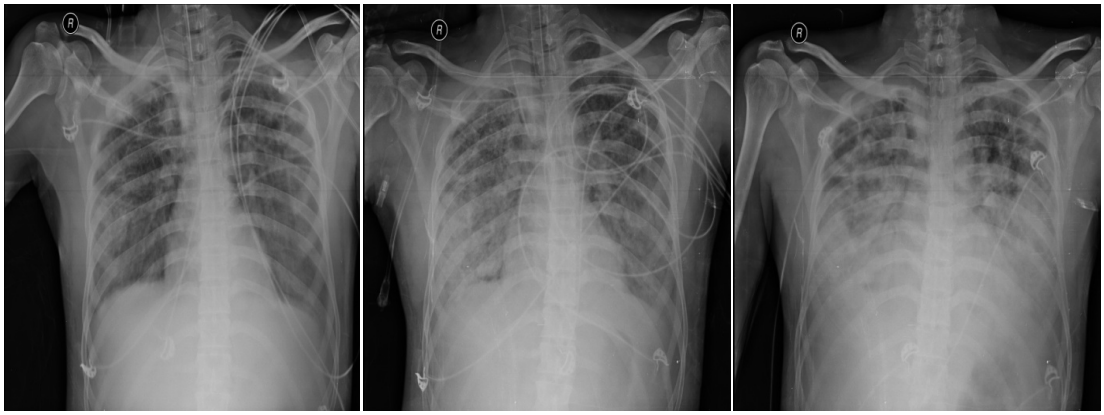
His vital parameters were as follows: Pulse 90 per minute, regular; Blood pressure 139/60 mm Hg, Respiratory rate 35 per minute, SPO2 87% on 10 liter per minute oxygen with mask, and a fever around 100 degree Fahrenheit. He didn't have any clubbing, cyanosis, enlarged lymph nodes or pallor at presentation. He was mildly icteric. On systemic clinical examination his liver was enlarged and tender with a span of 18 cm, spleen was enlarged with a span of 14 cm, and extensive coarse crackles over bilateral lung fields. Other systemic examinations like cardiovascular, and central nervous system was within normal limits. He was detected positive for *Plasmodium vivax* by quantitative Buffy Coat (QBC) test and also for dengue IgM antibodies by rapid immunochromatographic test as well as ELISA. He was admitted in medical isolation ward in view of possible Influenza infection. He was managed with non invasive ventilation initially, meropenem, moxifloxacin, oseltamivir, artesunate, one unit packed red cell transfusion, random donor platelets transfusion (given outside before being admitted at FEHJ) and other supportive drugs along with nebuliization of levolin and ipratropium bromide. Later his nasopharyngeal swab was detected positive for H1N1 RT PCR (real time polymerase chain reaction).

His investigations are in Table 1, and X-ray chest in Fig. 1. Scrub typhus IgM antibodies, Hepatitis B surface antigen, Hepatitis C antibodies, Human Immunodeficiency virus antibodies 1 and 2, P24 antigen were non reactive. His sputum, Endotracheal secretions, blood and urine cultures were sterile. Liver function showed elevated bilirubin with insignificant rise in liver enzymes. Widal test and leptospirosis serology were negative. Ultrasonography abdomen revealed

Table 1. Hematology and biochemistry

Date & parameter	Normal Range	Oct. 11, 2018	Oct. 12, 2018	Oct. 13, 2018	Oct. 14, 2018	Oct. 17, 2018
Hemoglobin	13-17 gm/dl	10.3	9.7	8.5	9.3	9.3
Hematocrit	40-50%	28.8	27.6	25.7	26.7	28.1
TLC	1-10x10^3/cmm	3.92	4.32	8.1	10.7	14.8
DLC	%	N49 L44	N59 L6	N69 L26	N78 15	N60 L33
APC	150-410x10^3/cmm	13	19	50	60	276
Bilirubin Total/Direct	0-1.2/0.1-0.3 mg/dl	11.10/8.50	5.5/2.6	4.58/4.32	5.62/4.67	
AST(SGOT)	4-41 U/L	74	58	50	60	
ALT(SGPT)	17-59 U/L	43	27	23	28	
S. Albumin	3.4-4.8 gm/dl			2.4	2.5	1.9
PT-INR	0.8-1.1/ ratio			0.95		
S. Creatinine	0.7-1.3 mg/dl	0.8	0.9	0.95	0.76	2.04
LDH	135-225 U/L			582	711	
Troponin T HS	0-14 pg/ml					116

TLC: Total leucocyte count; DLC: Differential leucocyte count; APC: Absolute platelet count; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PT-INR: Prothrombin time-International normalised ratio; LDH: Lactic Acid Dehydrogenase.



13.10.2018 15.10.2018 17.10.2018

Fig. 1. X ray chest showing bilateral heterogenous infiltration with pleural effusion

hepatosplenomegaly and bilateral renal concretions. His x ray chest show bilateral heterogenous parenchyma opacities consistent with acute respiratory distress syndrome (ARDS). He had hematuria. Coagulation parameters were within normal limits.

On October 13, 2018 early morning he had to be mechanically ventilated in view of progressive hypoxemia. He later had cardiac arrest and was revived after cardiopulmonary resuscitation as per ACLS protocol. He was managed with vasopressor, fluids, and other supportive treatment. On October 17, 2018, his Electrocardiogram showed ST/T changes with raised high sensitive serum troponin T, suggesting associated myocarditis and cardiogenic shock. He was on high dose vasopressor, developed renal shutdown and succumbed to his illness on October 17, 2018. Family refused for autopsy.

3. DISCUSSION

There have been many case reports in the literature about the mixed infections in a single host but so far there have been no case reports of Dengue, Malaria and Influenza A (H1N1) infection together. This case is unique because of different mode of transmission and vector respectively of these diseases and yet the patient presented at the same time and diagnosed having mixed infections. The possibility of the preceding or concomitant co-infections may have lead to increased severity of his illness.

It may be possible for two viruses (and a parasite) to infect the same cell(s) leading to interaction of the pathologic pathways resulting into change of virulence or altered host response [1]. We could not find any article describing the impact of concomitant infection of dengue, H1N1 and malaria in a single host.

It is known that concurrent infection with different infective agents leads to an overlap of their clinical features and may pose a diagnostic dilemma to the treating internist, especially in endemic areas [1-3]. There have been case reports of coinfections with two or three pathogens in the literature: Dengue with H1N1 virus [1,2], dengue with chikungunya virus [3], dengue with salmonella typhi [4], dengue with leptospira spp. [5], dengue with malaria [6], dengue with hepatitis A and E [7], Leptospira spp., dengue virus and hepatitis E [8], malaria, dengue and hepatitis A [9]. A study has shown that coinfections with different agents may be more severe than a single infection [10].

The H1N1 virus replicates in the epithelial cells of the respiratory system and is known to cause acute respiratory distress syndrome (ARDS). Deregulation of proinflammatory cytokines from macrophages has been shown to be important in the pathogenesis of ARDS by influenza virus [11]. The respiratory epithelium is also a target for dengue virus and ARDS is reported as a rare cause for this condition. Of late there are increasing numbers of cases of ARDS being reported in dengue patients with an incidence of almost 1.8% [12,13,14]. Pulmonary complications, including ARDS, are well described in *P. falciparum* and to a lesser extent in other malaria species. Increased alveolar capillary permeability is the main

pathophysiologic mechanism [15]. Severe disease and ARDS are increasingly reported in *Plasmodium vivax* malaria [13,16]. Our patient had ARDS and which of the three infections contributed to what extent could not be commented.

Influenza myocarditis is also well described in literature and few cases have been reported with Fulminant myocarditis in influenza A [17,18]. Patients with Fulminant myocarditis can present with fatal arrhythmias, atrioventricular blocks and/ or varying degree of cardiogenic shock. Dengue infection is also known to cause cardiac involvement. In one study 37% of dengue patients had myocarditis which had positive correlation with the severity of dengue fever [19]. An atypical and rare presentation of dengue disease marked by a dramatic and fatal cardiogenic shock due to acute myocarditis with histopathology evidence of a possible direct action of dengue virus on myocardium has also been reported [20]. Myocarditis as a complication of *Plasmodium vivax* is extremely rare and has rarely been described in the literature. Mechanism for plasmodium induced myocarditis includes blockage of capillaries by malaria parasite; parasitized red blood cells and pigment laden macrophages can cause myocardial damage [21-23]. The case described also had myocarditis with cardiogenic shock as a terminal event before succumbing to his illness.

Tropical fevers often present as a single infection but are known to occur as multiple coinfections as discussed earlier. They can happen in any combination and still continues to give surprises to all of us. The authors have earlier reported coinfections of dengue virus with *Plasmodium vivax, Plasmodium falciparum* and scrub typhus [24]. Malaria and dengue are difficult to differentiate clinically and yet the treatment of the illnesses is different and delay in appropriate therapy can be devastating, especially in multiple coinfections. Endemic areas of malaria, dengue and influenza A overlap to a large extent in south east Asia and acquisition of both mosquito and airborne infection though uncommon but possible as in this case.

The Patient discussed though sought hospital care early but changed facilities frequently making it difficult for diagnosis. He was admitted with us after the worsening of symptoms, which was perhaps too late. He was diagnosed with Dengue and influenza A H1N1 infection at our facility. He died within 5 days of admission with ARDS, severe myocarditis and cardiogenic shock. It is known that the management of these coinfections requires aggressive early treatment [25].

Therefore, to avoid fatal outcomes, clinicians should consider the diagnosis of coinfections among patients who are critically ill, presents with a prolonged history of fever and have associated multi organ dysfunction syndrome. A high suspicion should be there during the tropical fever season in locations where the epidemic periods for these pathogens coincide. The clinical syndromes produced by influenza and infection with dengue and malaria can be mimicked by each other, making it difficult to diagnose:

4. CONCLUSION

In conclusion, clinicians in endemic and hyper-endemic areas need to be aware of these rare and unusual presentations of mixed infections as an appropriate therapy without delay may results in better outcome.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline family consent and ethical approval has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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