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## Medley of infections-a diagnostic challenge

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## PEER REVIEW

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## Comments

This case report is of extremely importance, since: 1) it's the first case in literature of a 4 co-existing acute infections, two of them mosquito borne diseases and all very common in endemic areas; 2) it shows how a rapid diagnosis is lifesaving in this context; 3) it demonstrates that is essential not to neglect any symptom in a patient to reach the right diagnosis.

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## ABSTRACT

We present a rare case of multiple infections coexisting together. This is one of the rarest cases of four infections which coexisted together in our patient. It is an alarming for the physicians to be aware of such infections as early prompt diagnosis can be lifesaving.

## KEYWORDS

Co-infections, Dengue, Malaria, Hepatitis A, Hepatitis E

## 1. Introduction

Presence of multiple co-infections can pose a diagnostic and therapeutic dilemma for the diagnosis and treatment of the patient. Literature search shows only a handful of case reports with multiple existing concurrent infections[1]. We present a rare case with four infections which is the first of its kind to be reported. We share our experience of the diagnostic and therapeutic challenges encountered with multiple co-infections.

Rarity of the case, unusual associations, good recovery of the patient and possibility of similar or other co-infections which can be lifesaving if timely diagnosed prompted us to report the case.

## 2. Case report

A 22-year-old male resident of Mangalore, a coastal city in India

presented with fever for one week, progressively increasing yellowish discoloration of skin, eyes and urine for 4 d and loose stools for 1 d. He was conscious and oriented with stable vitals. Icterus was present. He had no rash or bleeding from any site. On per abdomen examination he had hepatomegaly and mild splenomegaly with no evidence of ascites. Other systemic examination was unremarkable. Initial investigations revealed low platelet counts (12000/ $\mu$ L), deranged liver functions (total bilirubin: 3076.32  $\mu$ mol/L, direct bilirubin of 2192.32  $\mu$ mol/L and mildly elevated liver enzymes) and deranged renal function test (creatinine 3.1, urea 125, Na 129, K 4.7). Chest X-ray and electrocardiogram was within normal limits. An ultrasonography of the abdomen showed mild splenomegaly and mild hepatomegaly with normal kidney echo texture. A differential diagnosis of malaria was considered. On evaluation peripheral smear was suggestive of mixed malaria. The patient was transferred to the Intensive Care Unit and treated

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with artesunate, intravenous infusion fluids in view of acute kidney injury and symptomatic treatment. Patient's fever did not subside despite treatment, he developed petechiae in the lower limbs and had decrease urine output. Renal functions worsened and patient required hemodialysis in view of oliguria and worsening renal parameters. His platelet counts dropped further and fever was continuous which made us think of additional co-infection, and also disproportionately altered liver function tests prompted us to investigate further for any concurrent infections. The patient was found to be positive for dengue, (dengue IgM capture ELISA), hepatitis E virus infection (EIAgen HEV IgM kit) and hepatitis A (HAV IgM kit). He was negative for HIV, enteric fever, leptospirosis, rickettsia infection, HbsAg and anti-HCV antibodies. Blood culture had no growth. He was managed with *i.v.* antibiotics, hemodialysis, antimalarial, blood and platelet transfusion. Patient improved clinically however blood pressure recordings were persistently on higher side despite no history of hypertension, initial normal cardiac evaluation and normal electrocardiogram. He was started on antihypertensive (Tab amlodipine 5 mg OD) On the 7th day, he was discharged afebrile, hemodynamically stable with normal laboratory parameters. On follow up after 2 weeks, patient was asymptomatic and continued on only antihypertensive medication.

### 3. Discussion

Overlapping clinical presentations, simultaneous transmission of multiple infections can pose diagnostic dilemma to the clinician's. A timely diagnosis and optimal laboratory evaluation remains the mainstay in making correct diagnosis which may be lifesaving in patients with concurrent infections[1].

Dengue and malaria are both mosquito borne diseases and there concurrent infection tends to be more severe than either single infection notably for hematological abnormalities like thrombocytopenia[2]. Prompt diagnosis of acute dual infection can be lifesaving for the patient. Ever since the first case of dual infection reported in 2005[3], possibly because of the growing population, frequent travels, better laboratory services and growing awareness we are witnessing an era of emerging co-infections as a major concern in tropical areas especially. The growing number of case reports reporting the concurrent dual infection should alert the physicians in endemic areas where both infections are rampant, to systemically examine for both diagnosis even if one or other is positive[3-6].

However, what was more alarming in our case was not just the presence of the two deadly mosquito borne co-infection but a shocking presence of four acute infections at the same time. Our experience with such co-infections is scarce. Chaudhary *et al.* reported first case report of a mixed infection due to leptospirosis, dengue, malaria and hepatitis E virus[1]. A similar case of triple

co-infections with leptospira, dengue and hepatitis E by Behera *et al.* was a similar knocking evidence for the medical fraternity to be aware of existence of concurrent infection which causes higher morbidity and mortality if not timely detected and treated[7].

Case reports of dengue and typhoid coinfections have also been reported where in both the cases were timely managed and recovered completely on out-patient basis. In another rare case of triple infection with falciparum, vivax and dengue in a pregnant female timely diagnosis proved lifesaving and patient recovered and was discharged within a week with fetal well being, underscoring the importance of timely management[8]. Our case to the best of our knowledge is the first reported case of four co-infections with malaria, dengue, hepatitis A and hepatitis E and its timely diagnosis with laboratory evidence and treatment with good recovery of the patient further emphasizing the fact that timely management can yield good results and early recovery.

Although unexplained development of hypertension which may be unassociated still remains enigmatic as our experience with such infections is not reported or unknown. Although patient may be having preexisting hypertension but is unlikely in the light of regular medical checkups which patient routinely underwent. The possibility of any of the infection presenting as nephritic syndrome or due to autoimmune reaction can be possible hypothesis for such a presentation. Limited studies show evidences that renin-angiotensin-aldosterone system, and more specifically angiotensin II influence severity of malaria[9]. Although more evidence to consider this association and explore the role of coinfections and immunological pathway is required. No convincing evidence or firm hypothesis can be established at present for this association, but it is a fact that a lot more needs to be researched about multiple coinfections to broaden our insight about it.

The presence of coinfections have shown unusual presentations such as in a recent case reported in a toddler, Epstein Barr virus and Leishmania coinfection presented as rare hemophagocytic lymphohistiocytosis syndrome[10]. Another case of coinfection of malaria and dengue has been reported with unusual presence of rhabdomyolysis with normal creatinine kinase level and non oligouric acute kidney injury[11]. A review article exploring the mystifying relation of coinfections with malaria conclude that presence of multiple infections can have significant challenges in diagnosis as well as treatment and such synergistic infections although often associated with deleterious effects may also have positive effect in few cases due to unique interactions between host and multiple microbes[12]. A lot more needs to be explored about such interactions and a more keen attempt to promptly look and search for multiple infections will not only improve clinical outcome but will also unveil a lot more about immunology, pathology, microbiology and realms of other facts about such multiple infections.

## 4. Conclusion

The above case aims to underscore the importance of awareness of possibility of concurrent infections and appropriate laboratory evidence to search for co-infections which can be crucial in appropriate diagnosis and treatment. More awareness and reporting of such co-infections may open more doors about unknown clinical spectrums and associations when multiple pathogens act together!

## Conflict of interest statement

We declare that we have no conflict of interest.

## Comments

### Background

The authors stated that this is the first reported case of four co-infections in a patient. Simultaneous transmission of multiple infections can pose diagnostic dilemma and problems on the choice of the effective treatment for clinicians. Prompt diagnosis and optimal laboratory exams can be lifesaving for patients.

### Research frontiers

The current research presents a rare case of four acute co-existing infections in 22-years-old male: he was affected by malaria, dengue, hepatitis B and A with altered liver and renal functions, promptly diagnosed with rapid laboratory analysis and cured.

### Related reports

The authors state that this is the first reported case of a multiple (more than 2) infections spreaded in a patient. There is a growing number of case reports on the concurrent dual infection that should keep the attention of the clinicians in endemic areas and move for a rapid diagnosis with effective laboratory exams.

### Innovations and breakthroughs

In this case report the authors highlight the possibility of multiple acute infections at the same time in a single patient living in endemic areas and how their prompted diagnosis was the only chance to save the patient. They demonstrated as well that taking into account all the symptoms detected in the patient, let them investigate on all possible concurrent infections, performing all useful laboratory exams to identify the right cause of disease and finally the right treatment.

### Applications

This article support the importance of a rapid diagnosis in a multiple acute infections scenario, such as that presented in this article. To achieve this aim it is extremely important to consider all the symptoms in a patient and make all the useful analysis to investigate

on them. Focusing on the simultaneous infections presented in this case report, the article shows what kind of laboratory analysis must be performed in the presence of the symptoms described in the article and suggest a possible treatment against malaria, dengue, hepatitis A and B infections at the same time.

### Peer review

This case report is of extremely importance, since: 1) it's the first case in literature of a 4 co-existing acute infections, two of them mosquito borne diseases and all very common in endemic areas; 2) it shows how a rapid diagnosis is lifesaving in this context; 3) it demonstrates that is essential not to neglect any symptom in a patient to reach the right diagnosis

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