Case Report

Atypical manifestations of dengue infection due to co-infection with either hepatitis A or leptospirosis: two case reports

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Abstract

Febrile illnesses of infective aetiology are common causes of hospital admission in tropical countries. In Sri Lanka, the incidence of dengue infection has markedly increased during the last 15 years whilst infections such as leptospirosis and viral hepatitis A remain endemic. Most of the common infections share a common and non-specific symptomatology, making diagnosis at initial presentation difficult. Similarly co-infections can complicate the clinical course but may remain undetected unless a high index of suspicion is maintained especially during epidemics of one infection. We report two cases of co-infections, highlighting the importance of this possibility. Co-existence of dengue infection with hepatitis A in one patient and with leptospirosis in another patient resulted in an atypical and protracted course of illness with confusing clinical features in either case.

Keywords: co-infection, dengue, leptospirosis, hepatitis A

Introduction

Febrile illnesses of infective aetiology are common in tropical countries leading to hospital admission with a wide range of clinical manifestations. Sri Lanka is one such country where the incidence of dengue has markedly increased during the last 15 years[1] whilst infections such as leptospirosis[1] and viral hepatitis A remain endemic.[2] The clinical diagnosis of the aetiology of an infection is difficult at the outset as presentation with non-specific features is common to all infections. Timely aetiological diagnosis can be an important problem, especially in resource-poor settings with minimal diagnostic facilities[3] as delay in correct diagnosis and institution of timely treatment will complicate the clinical outcome, especially in the case of co-infections. We report two cases of co-infections, highlighting the importance of early consideration of this possibility, especially during epidemics of one infection, where the possibility of the other may be overlooked.

Case 01

A 28-year-old previously healthy male was admitted during a local outbreak of dengue fever, with a history of high grade fever for five days, with associated arthralgia, malaise and loss of

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appetite. There were no other symptoms. All systems examination was normal except for a smooth non-tender hepatomegaly palpable 1cm below the costal margin. Due to the suggestive history and the on-going outbreak, dengue fever was entertained as a likely possibility. On admission, the full blood count revealed a white cell count of 5.39×10^9/µl (neutrophils 67.7%), platelet count of 199×10^9/µl and PCV of 42.1%. Aspartate aminotransferase (AST) was 1000 U/l and alanine aminotransferase (ALT) 1160 U/l. Abdominal ultrasonography revealed an enlarged liver with uniformly increased echogenicity and no intrahepatic duct dilatation. At this time dengue fever complicated with hepatitis was taken as the likely diagnosis which was confirmed by a positive NS1 (Non-structural protein-1) dengue antigen on the fifth day of the illness.

The patient remained clinically stable without features of acute liver failure while the liver enzymes rose further to reach a maximum ALT of 2328 U/l and AST of 1380 U/l by day eight of fever. By this time he was icteric, and serum bilirubin was 64.5µmol/l with a predominant direct fraction. Since cholestasis and very high transaminases are unusual in dengue fever unless the patient has severe hepatic involvement with advanced disease, and the temporal pattern of rising of transaminases was atypical for dengue fever, an alternative diagnosis was entertained. Further investigation revealed a positive hepatitis-A IgM, confirming a diagnosis of co-existing dengue fever and hepatitis A. By day ten, liver enzyme levels were declining and the patient was recovering clinically and he was discharged without further events.

Case 02

A 49-year-old previously healthy male was admitted to Teaching Hospital, Peradeniya during an outbreak of dengue fever, with a history of fever for five days. On admission, his axillary temperature was 101.4 °F. There was associated arthralgia and myalgia but no other symptoms. He was haemodynamically stable and the examination findings were normal. He gave a history of cleaning an abandoned well infested with rodents about one week before the onset of fever, which made leptospirosis highly probable. Due to the on-going outbreak, dengue fever also was considered in the differential diagnosis but on clinical suspicion of leptospirosis he was started on intravenous benzyl penicillin.

Investigations on admission showed a thrombocytopenia (77×10^9/µl) with a neutrophil leucocytosis (11.7×10^9/µl). Alanine aminotransferase (ALT) was 103 U/l and aspartate aminotransferase (AST) 39 U/l. Serum creatinine was 146 µmol/l (normal range: 62-126µmol/l) indicating renal impairment and the urine full report demonstrated 15-20 red cells per high power field. Thus all investigations were in favor of leptospirosis. Further investigation revealed a positive dengue NS1 antigen test on the fifth day of illness. Leptospira IgM antibodies were detected with Enzyme-Linked Immunosorbent Assay (ELISA) after the seventh day of illness, enabling diagnosis as a probable case of leptospirosis. The patient was therefore managed as having a co-infection with dengue virus and leptospirosis. Close monitoring and fluid management were instituted for the management of dengue fever and penicillin was continued as treatment for leptospirosis. He gradually improved and remained haemodynamically stable without developing dengue haemorrhagic fever. Subsequently his renal function recovered completely and he was discharged on day 15 after complete recovery.

Discussion:

Co-infection with different pathogens is a known phenomenon, with several reported cases in the literature.[4, 5] This can pose a challenge to the diagnosis as well as management due to delay in diagnosis, different approaches to management of individual infections and the possible unpredictable outcome in the setting of co-infections.

Dengue fever is an arboviral infection transmitted by mosquitoes of the genus Aedes, which is widely distributed in the tropics including Sri Lanka, affecting up to 50 million people per year.[6] It is a flavivirus with single stranded RNA and has 4 serotypes (DEN 1-4). Since the first outbreak of dengue in Sri Lanka in 1965, the disease ran a quiescent course in the island until the first major epidemic which occurred in 1989 followed by frequent outbreaks.[7] The annual incidence has gradually risen so that 2013 saw 30,063 reported cases from all districts of the country.[1]

Dengue infection could have a presentation varying from a mild viral syndrome to hemorrhagic fever and shock. Better understanding of the disease dynamics has improved the outcome over time but still timely diagnosis and management is a challenge. This is confounded by inconsistency in the availability of suitable diagnostics in the scenario of a non-specific febrile illness, and the clinical presentation of dengue fever being that of a non-specific febrile illness. For example, both leptospirosis and hepatitis A present as similar febrile illnesses in the initial phase[5] and both are also known to occur in outbreaks in Sri Lanka, making early diagnosis a challenge. These two cases draw the attention to an even more complicated matter; co-existence of more than one of these infections in the same patient. Liver involvement is a common occurrence in dengue fever, manifesting as mild to moderate elevations of AST and ALT[8,9] with AST being higher than ALT.[9] However, jaundice is an uncommon finding in dengue illness. In one study, out of 404 patients studied, jaundice and liver failure were seen in only two[9], and in another, jaundice was present in only 4.5% of confirmed dengue cases.[10] In contrast, the elevation in liver enzymes in hepatitis A is more marked. In one study, the mean elevation of AST and ALT was 1442 U/l and 1952 U/l respectively.[11] Jaundice is a common symptom in hepatitis A, the rate of occurrence differing between studies.[12]

In case 1, the atypical observations that a patient without clinical features of severe hepatic involvement of dengue, was icteric, had AST and ALT levels above 1000 U/l, and an ALT level higher than AST, led to the suspicion of co-existing viral hepatitis. Timely diagnosis of both infections allowed appropriate fluid management and necessary monitoring allowing a favourable clinical outcome.

Leptospira sp. are pathogenic spirochetes, and the infection is maintained in nature as a zoonosis. The wide spectrum of disease caused by the organism ranges from subclinical infection to fatal disease.[13] Thus the syndrome may be difficult to distinguish clinically from many acute febrile illnesses including dengue fever.[13]

In case 2, the history of exposure to well-water possibly contaminated with *Leptospira sp.*, raised the suspicion of leptospirosis, even though the case occurred during an epidemic of dengue fever. The abundant water sources around the area in which the patient had been working could also serve as breeding grounds for the vector mosquitoes of dengue virus,

leading to possible exposure to the virus. Aedes being day-biting mosquitoes, and the presence of an on-going dengue epidemic supported this observation. A high degree of suspicion should be maintained in such situations of possible risk of exposure to more than one infection.

Caution is needed when interpreting serological tests in mixed infections. Some infectious agents may cross-react in serological studies giving false positive results; for example, some commercially available IgM assays for dengue may cross-react with antibodies to other flaviviruses.[14] In the two index cases, the possibility of a false positive result for dengue infection was overcome by using non-structural protein-1 (NS-1) specific ELISA assay which has a specificity of 100%.[15] The reported specificity of anti-hepatitis A IgM in the diagnosis of acute hepatitis A is 99%[12] and there are no cases of cross-reactivity between NS-1 antigen assay and hepatitis A or leptospira IgM antibody assay in published literature.

These two cases draw attention to the possibility of mixed infections which may go unnoticed at first but may complicate the clinical course of an illness. Early identification and institution of correct timely treatment cannot be over-emphasized to prevent fatalities, especially during outbreaks of infectious diseases.

Conclusion:

We suggest that mixed infections should be considered as a possibility in a patient presenting with a febrile illness during an infectious disease outbreak, especially when accompanied by atypical features.

Competing interests:
The authors declare that they have no competing interests.

Authors' contributions:
DCL took the history, examined the patient daily, arranged necessary investigations and wrote the manuscript**.** RDMPUK, JWATA and SAMK supervised the management of this case and were major contributors in writing the manuscript. All authors read and approved the final manuscript**.**

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