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Case Report

Dengue Fever and Acute Hepatitis A Infection, Coexistence Versus Cross Reactivity: First Case Report in a Three Siblings

Badria Al Jahdhami[1], Laila Al-Shaqsi[1], Aasma Rasul[1], Zuwaina Al-Yarubi[1], Kawther Medani[1], Waleed Al-Ruzaiqi[1], Hilal Al Hashami[2]* and Nada Al Siyabi[3]

[1]*Pediatric Department, Al Nahdha Hospital, Muscat, Oman*

[2]*Pediatrics Department, Pediatrics Infectious Diseases, Royal Hospital, Muscat, Oman*

[3]*Microbiology Department, Al Nahdha Hospital, Muscat, Oman*

***Corresponding Author:** Hilal Al Hashami, Pediatrics Department, Pediatrics Infectious Diseases, Royal Hospital, Muscat, Oman.

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Abstract

Dengue fever virus (DFV) and hepatitis A virus (HAV) infections are endemic in developing countries and they can coexist in endemic areas. Both viruses cause hepatitis picture. However, HAV causes more transaminitis compared to DFV and in rare cases can lead to hepatic failure. On the other hand, DFV can cause plasma leak syndrome, thrombocytopenia and bleeding tendency. Both Hepatitis A and dengue fever can be diagnosed serologically by detecting their specific antibodies in the serum; IgM in the acute stage and IgG in the convalescent stage. Other diagnostic methods like PCR and viral culture are not routinely available and needs specialized laboratories. This paper reports three siblings who presented with acute hepatitis picture. The first case, the index case, has history of recent travel to Pakistan while the others have not. Two of them (the index case and one sibling) subsequently developed pleural effusion and ascites which raised our suspicion of Dengue fever, although there was no thrombocytopenia. All the siblings' IgM serologies were positive for both HAV and DFV. However; since DFV cannot be transmitted locally due to absence of the vector (*Aedes aegypti*); repeated serology for DFV was done at the convalescent stage and showed no IgG response. This brings us to the conclusion that IgM for DFV can cross react with HAV antibodies. In addition, plasma leak can be a common clinical feature of Hepatitis A infection although it is rarely reported and it can be explained by the reduced oncotic pressure due to hypoalbuminemia.

Keywords: *Dengue Fever; Acute Hepatitis A; Coexistence; Cross Reactivity*

Introduction

Hepatitis A virus (HAV) infection is endemic in developing countries and it can be easily transmitted faeco-orally. It is not a common problem in Oman except in some parts of the country and most of diagnosed cases either have -or contacted somebody with- history of travel to endemic areas. Clinical features include fever, vomiting, diarrhea and jaundice with tender hepatomegaly. The illness can be very mild and may pass unnoticeable, however, in some cases it can cause severe hepatitis with hepatic dysfunction (deranged coagulation and hypoalbuminemia) [1]. Diagnosis is usually made by the detection of HAV-specific Immunoglobulin M (IgM) antibodies in the blood. Additional tests are there, including reverse transcriptase polymerase chain reaction (RT-PCR) to detect the hepatitis A virus RNA, but requires specialized laboratory facilities [1]. Treatment is supportive by avoidance of unnecessary hepatotoxic medications and maintaining comfort and adequate nutritional balance [1].

On the other hand; Dengue virus is a mosquito-borne viral infection, caused by one of four dengue viruses and transmitted by female mosquitoes mainly of the species *Aedes aegypti* and to a lesser extent, *Aedes albopictus*. This mosquito also transmits chikungunya, yellow fever and Zika infection. Dengue is found in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas [2]. Symptoms of infection usually begin 4 - 7 days after the mosquito bite and typically last 3 - 10 days [3]. Usually It causes flu-like illness, headache and myalgia with thrombocytopenia and transaminitis, and occasionally develops into a potentially lethal complication called dengue shock syndrome due to vascular damage leading to plasma leak and fluid accumulation in peritoneal and pleural spaces causing respiratory distress, severe bleeding, shock or organ impairment [3].

Similar to hepatitis A, Dengue fever is commonly diagnosed serologically by detecting specific IgM antibodies in the serum. IgG starts rising by the second week of the illness. In addition, (ELISA) directed against Non-Structural glycoproteins (NS1 Antigen) have demonstrated very high concentrations during the early clinical phase of the disease [4]. Additional diagnostic methods like viral culture and molecular methods (RT-PCR) are present but it is time consuming and very costly [5]. So, the best way to confirm the infection is by detecting IgM in the acute phase and IgG in the convalescent phase.

There is no specific treatment for dengue fever, but early detection and access to proper medical care lowers fatality rates from 20% to below 1% [3]. Treatment is mainly supportive by maintenance of body fluid volume.

Case Report

A three-year old Omani girl, presented on 26th February 2017 with one-month history of fever, five days history of non-bloody diarrhea and yellowish discoloration of sclera along with passing dark urine. Fever initially was intermittent and became continuous, high grade with chills for one-week before admission and associated with abdominal pain, loss of appetite and decreased activity. No history of vomiting. The patient received symptomatic treatment from primary health care with no improvement.

There was a history of travel to Pakistan one month prior to presentation for a period of six weeks visiting family relatives. She developed fever and diarrhea two days prior to coming back to the country for which she received symptomatic treatment and improved. However, fever recurred soon after arrival to Oman.

Her past medical history and family history were both unremarkable.

On Physical examination, she looked alert but ecteric, with mild periorbital puffiness. No pallor, nor palpable lymph nodes. She was afebrile, HR 120 beat/min, BP 113/56mmHg, respiratory rate 32 per minute, oxygen saturation was maintained 100% in room air.

Chest examination showed equal bilateral good air entry, cardiovascular auscultation revealed normal heart sounds with no murmur. Abdomen was distended with tender palpable liver 4 cm below costal margin, no splenomegaly.

The initial laboratory investigations were sent that included: Full blood count, liver function test, blood culture, malaria parasite and hepatitis screen (Table 1).

Initial impression of Acute Hepatitis A infection was made based on the clinical presentation with the travel history to endemic country. She received initial supportive management.

On fourth day of hospitalization, she started to be tachypneic, respiratory rate 60 per minute, with increase in her abdominal distention and positive shifting dullness. There was reduced air entry in her right lung. Chest x-ray revealed right sided pleural effusion. Ultrasound (US) abdomen showed minimal ascites with hepatomegaly. blood investigations were repeated and showed improvement in liver enzymes, mild hypoalbuminemia of 27 and normal coagulation profile. At this point a differential diagnosis, like Dengue fever, Brucellosis

Investigation	26 Feb 2017	28 Feb	1st March	5th March Discharge	12th March	20th March
CBC	Hb 11.5 g/dl Plt 255 10 3/ul WBC 17.6 10 9/L	Hb 9.68 g/dl Plt 255 10 3/ul WBC12.6 10 9/L	Hb 10.4 g/dl Plt 270 10 3/ul WBC 18 10 9/L	Hb 9.6 g/dl Plt 198 10 3/ul WBC 11 10 9/L	Hb 10.1 g/dl Plt 455 10 3/ul WBC 14 10 9/L	
LFT	Total Bilirubin 170 umol/L ALT 1111 U/L ALP 168 U/L Albumin 29 g/l AST365 U/L	Total Bilirubin 116 umol/L ALT 533U/L Albumin 29 g/l	Total Bilirubin 110 umol/L ALT 426 U/L Albumin 27 g/l		Total Bilirubin 39 umol/L ALT 79 U/L Albumin 42 g/l	
Viral Hepatitis screening*	HAV Ab positive HBsAg negative HBC Ab negative					
Dengue Serology**			IgM positive IgG negative NS1 negative			IgM positive IgG negative NS1 negative
Brucella			Negative			
MP Screening	Negative					
ANA/ RF			Negative			
Blood C/s	Negative		Negative			

Table 1

*CBC: Complete Blood Count; LFT: Liver Function Test; MP: Malaria Parasite; ANA: Antinuclear Antibodies; RF: Rheumatoid Factor. *Done by Architect i1000 immunoassay, **Done in the public health lab by Panbio ELISA.*

or possible autoimmune diseases were thought of. So additional Investigations were done as in table 1. she was treated with intravenous (IV) ceftriaxone for the possibility of parapneumonic effusion and she received one dose of albumin infusion as she had symptomatic hypoalbuminemia although serum albumin was not very low. One day after albumin infusion, her general condition showed improvement with regression of hepatomegaly, edema, and resolution of ascites and pleural effusion. Dengue virus serology panel was done in the public health lab by Panbio ELISA and it showed positive IgM antibodies and negative IgG and NS1 Ag which indicate acute recent Dengue virus infection. Two days later the results of hepatitis A virus IgM (done by Architect i1000 immunoassay) released as positive also. So a final diagnosis of coexistence of hepatitis A and Dengue fever was made and she was discharged after eight days of admission in a stable condition, with improvement in her Liver functions. On follow up, her clinical condition and liver function showed further improvement (Table 1).

Few days after her discharge her two sisters (who never travelled to Pakistan) a 4 and 9 years old, presented with similar picture of fever, vomiting and jaundice with elevated liver enzymes. They were admitted with impression of acute hepatitis A. However; one of them (the 9 years old) developed ascites and pleural effusion also. Dengue fever serology was sent for both sisters and IgM came as positive for

both. However; since Dengue fever cannot be transmitted locally due to absence of the vector (*Aedes aegypti)* (at the time of writing this case report); it was decided to repeat Dengue Fever serology at convalescent stage for all the three siblings. It was resulted as persistently negative IgG despite positive IgM.

This led to the conclusion that Dengue virus infection is unlikely and the IgM was positive due to cross reactivity with hepatitis A virus antibody as there was no epidemiological risk documented for the two sisters who never travelled to Pakistan and there was no local transmission of Dengue fever in the area of residency because of the absence of *Aedes aegypti* mosquitoes in the region *(*at the time of writing this case report). In addition, NS1 antigen was negative for all the siblings which make diagnosis of Dengue fevers unlikely.

Discussion

Cross-reacting antibodies have been described for many infections causing false positive results. Therefore, a positive IgM assay results require cautious interpretation, with consideration of clinical course and epidemiological correlation. In doubtful or unusual cases confirmation by other serological or molecular testing methods is required [6].

On reviewing the literatures, a few articles reported cases of coexistence of Dengue fever and hepatitis A infection in endemic areas. Most reported cases are from India [7-9]. However, we couldn't find any article reporting the cross reactivity of hepatitis A and Dengue viruses, all the reported cross reactivity was between hepatitis A and other flaviviruses, and between Dengue virus and other haemorrhagic viruses like yellow fever virus. According to our knowledge this case report is the first reported case of cross reactivity of hepatitis A and Dengue fever.

Syed Ahmed Zaki and Vijay Lad [7] reported a 4 years old girl with fever and jaundice, PCR for dengue virus was positive, but later due to Highly elevated liver enzymes, deranged prothrombin time, and prolonged fever the possibility of coexistent viral hepatitis was suspected and hepatitis A IgM was positive. This reported case theoretically could also represent cross reactivity of DFV and HAV infection similar to our reported case and that HAV IgM could be a false positive result representing DFV antibodies.

In addition; plasma leak syndrome is reported very well in dengue fever due to increased vascular permeability leading to fluid accumulation in peritoneal and pleural spaces. In the other hand; acute hepatitis A infection theoretically can also cause plasma leak due to hepatic dysfunction and low serum albumin level leading to reduced intravascular oncotic pressure. However we found very few reports of ascites and pleural effusion as a complications of acute HAV infection [9,10]. While it happened in two out of three siblings in our cases. But what is more interestingly in our cases is that this complication happened after the first week of the illness when the liver enzymes were improving and with serum albumin level of more than 25 g/L and it responded very well to a single dose of albumin infusion.

Conclusion

According to our knowledge this is a first reported case of Hepatitis A that had a cross reactivity with Dengue Fever in a child with a history of travel to endemic country of both diseases. A rare case that was initially has positive IgM for hepatitis A and Dengue fever with subsequent convalescence follow up serology showed negative Dengue IgG. This case highlights the need to be vigilant when we encounter a positive serological test for an infection in a non-endemic area and the need to consider the possibility of cross reactivity with other infections. In addition, plasma leak syndrome is not an uncommon clinical feature of Hepatitis A infection which responded dramatically to albumin infusion.

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