DENGUE COINFECTION IN A CASE OF ENTERIC FEVER: A DIAGNOSTIC AND THERAPEUTIC DILEMMA

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Abstract:
Presence of coinfection may make the otherwise straightforward presentation, diagnosis and management of the either disease complicated. Dengue and enteric fever coinfection is uncommon, though as a single disease both are common in tropical countries. Here, coinfection by dengue and enteric fever has been described in a 14-year-old boy residing in the tropic. Diagnosis of dengue was suggested by positive serological tests, and Salmonella paratyphi *A was isolated by blood culture. Presence of enteric fever presumably protracted the course of illness by dengue fever. The patient was managed successfully by intravenous ceftriaxone, along with supportive care. So, the physicians practicing in the endemic region should have high degree of suspicion while dealing with the febrile patients in clinical practice.*

Key Words: *Dengue Fever, Enteric Fever, Coinfection, Bangladesh.*

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Introduction:

Coinfection by 2 or more pathogens may alter the clinical presentation of the individual disease, produce diagnostic and therapeutic dilemma, and may worsen the prognosis. The infecting organisms may be viruses, bacteria, protozoa, fungi or helminths. Both dengue and enteric fever are common in tropics, and share some ecological features, it is possible to be simultaneously infected by both the diseases. Actually, a few cases of such dengue-enteric fever coinfection have been reported so far, mostly from India.[1-5] Given that both dengue and enteric fever are endemic in Bangladesh, coinfection involving them is likely here as well, though to the best of our knowledge, none have yet been reported. On the other hand, high degree of suspicion is needed to think of the probability of dengue-enteric fever coinfection in individual patient, though uncommon, otherwise grave consequences may result. That is why, here, a case of dengue and enteric fever coinfection has been described in a 14-year-old boy.

Case Presentation:

A 14-year-old boy presented with high fever, headache and bodyache for 4 days, without cough, throatache, dysuria and abdominal pain. Physical examination revealed a febrile patient with pulse 96/min, blood pressure 120/70 mmHg, respiratory rate 24/min, and temperature 103^0 F. His precordium was normal, chest clear, no organomegaly, lymphadenopathy, or rash. He was already on azithromycin and paracetamol by self-medication. The investigation findings on the 5^{th} day of fever were as follows: total leucocyte count $6600/mm^3$; neutrophil 48%, lymphocyte 44%, monocyte 7%, eosinophil 1%; platelet count 280,000/mm^3; hemoglobin (Hb) 11.7 g/dl, hematocrit 40.5%, erythrocyte sedimentation rate 49 mm in first hour, serum AST 45 u/l, serum creatinine 1.1 mg/dl, and normal serum electrolytes. Urinalysis showed pus cells 10-12/HPF, red cells 10-12/HPF, granular cast 1-2/HPF, and albumin (+++). Dengue non-structural 1 (NS1) antigen test (using the kit Dengue NS1 Detect^{TM} Rapid Test, manufactured by InBios International, Inc., Seattle, WA 98104, USA) on the 4^{th} day of fever was positive, and immuno-chromatographic test (ICT) for dengue antibodies (using the kit Bio Tracer^{TM} Dengue IgG/IgM Rapid Card, manufactured by NanoEnTek Inc., Korea) on the 7^{th} day of fever showed: IgG negative, IgM positive, indicating primary infection. Chest X-ray (CXR) and abdominal ultrasound (USG) were normal. A diagnosis of dengue fever with acute glomerulo-nephritis was made, and the patient was offered standard supportive treatment including paracetamol

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and oral rehydration saline. There was no evidence of clinical improvement in next few days, rather the patient developed vomiting and abdominal pain. Urine culture was negative. Blood culture (by FAN method in BACTEC 9050 Automated Blood Culture Analyzer) on the 4th day of fever yielded growth of *Salmonella paratyphi* A, which was resistant to azithromycin, but sensitive to ceftriaxone, cefixime, ceftazidime, cotrimoxazole, ciprofloxacin, and chloramphenicol. Considering the presence of vomiting and abdominal pain, ceftriaxone 2g IV daily was started and continued for 14 days, along with supportive care. Serial platelet counts and hematocrits on 7th, 8th, 9th, 10th, and 14th day of fever were: 150,000/ mm^3 and 41.0%, 120,000/ mm^3 and 43.0%, 100,000/ mm^3 and 47.0%, 110,000/ mm^3 and 44.0%, 150,000/ mm^3 and 42.0%, respectively. On the 10th day of fever, investigation findings were: AST was 78 u/l, serum creatinine 1.0 mg/dl and pus cells 4-6/HPF, red cells 3-5/HPF, and albumin (++) in urine. On the 14th day, AST was 50 u/l, and there was 1+ albumin in urine. The patient improved gradually, and became afebrile on the 5th day of ceftriaxone therapy. Follow-up blood, urine and stool cultures 1 week after completion of antibiotic therapy were negative.

Discussion:

Coinfection is common in human, and the true prevalence of coinfection likely exceeds 1/6th of the global population.[6] Globally, hepatitis C virus (HCV) and human immunodeficiency virus (HIV) (HCV/HIV) coinfection affects 2.3 million people[7], visceral leishmaniasis and HIV (VL)/HIV) coinfection has been reported from 35 countries[8], whereas, malaria/HIV coinfection claims more than 2 million lives each year.[9] Tuberculosis (TB)/HIV coinfection is well-recognized, and despite overall declining trend of new TB cases and deaths, new TB/HIV coinfections are on the rise.[10] Both dengue and enteric fever are common in tropics, including Bangladesh. In the world, nearly 390 million dengue infections occur per year, of which 96 million manifest clinically.[11] On the other hand, 17.8 million cases of typhoid fever occur each year in Low and Middle Income Countries (LMICs).[12] In Bangladesh, the incidence of typhoid fever was 3.9 and 2.0 episodes/1,000 person-years in an urban slum in 2000-2001[13] and 2003-2004[14], respectively. On the other hand, since 2000, regular outbreaks of dengue occur in Bangladesh.[15]

To date, only several cases of coinfection by dengue and enteric fever are known. Both dengue and enteric fever are tropical diseases, and occur predominantly in monsoon season. The case of coinfection presented here occurred in monsoon season of the region. Dengue is commonly associated with bicytopenia, and like many other viral infections, may create transient immunodeficiency which may provide optimum milieu for Salmonella to infect the host. In the present case, bicytopenia was not evident, presumably due to the simultaneous presence of Salmonella infection and its influence on hemogram. In endemic regions, it is difficult to distinguish between dengue and enteric fever by clinical presentation alone especially in the early stage. Timely diagnosis and proper management of these diseases is of paramount importance, because failure of doing so may lead to significant morbidity, and even mortality. Dengue itself is a self-limiting disease in majority; presence of concurrent enteric fever presumably protracted the course of febrile illness beyond the 1st week. Both NS1 antigen study and ICT for dengue antibodies are commonly used reliable serological tests for the diagnosis of dengue fever, as has been employed here; the former being positive in early febrile phase of illness, and the latter being positive on day 5 or beyond.[16,17] For the single dengue NS1 antigen test which can be done by enzyme-linked immunosorbent assay (ELISA), as well as, by ICT method, the sensitivity and specificity have been found to be 67% and 99% for ELISA and 71% and 99% for ICT in a meta-analysis.[18] And the sensitivity further improves to 83% when combination of NS1 antigen assay and IgM anti-dengue antibody tests were used.[18] The ICT-based NS1 antigen assay used here has got 76.5% sensitivity and 95.3% specificity (manufacturer's information leaflet), whereas the ICT-based anti-dengue antibody assay has 91.3% sensitivity and 92% specificity (manufacturer's information leaflet). Also, chances of false-positivity are virtually nil as there are no known cross-reacting flavivirus diseases like Japanese encephalitis and yellow fever in the region. However, the exact infecting serotype of dengue virus could not be determined as virus isolation and real-time polymerase chain reaction (RT-PCR) are not readily available for clinical use in the country. Regarding the diagnosis of enteric fever, microbiologic culture of blood or bone marrow remains the mainstay of laboratory diagnosis[19,20], whereas the role of Widal test is controversial[20,21] For the case presented here, the diagnosis of enteric fever was confirmed by positive blood culture. *S. paratyphi* A was resistant to azithromycin, though this is a reasonable choice in the current era of multi-drug resistant enteric fever. However, the organism was sensitive to ceftriaxone.

Dengue-enteric fever coinfection has been reported sporadically as a cause of pyrexia especially in the endemic zones, mostly from India. Jagadishkumar et

al. diagnosed dengue by detecting IgM antibody and typhoid fever by positive blood culture in a 3-year-old child.[1] Vigna et al. presented 2 cases of coinfection, 1 diagnosed by serological tests only, and the other by positive NS1 antigen and RT- PCR for dengue and growth of S. typhi in blood culture for typhoid fever.[2] Bansal et al. managed 2 cases of dengue-enteric fever coinfection successfully as outpatients.[4] Srinivasaraghavan et al. in their case utilized NS1 antigen and IgM antibody for dengue fever and Widal test and blood culture for enteric fever.[5] Previously, Sudjana and Jusuf reported similar coinfections from Indonesia.[22] Sharma et al. conducted a study to find out the coinfection rates in North Delhi; of the 141 serologically-diagnosed dengue cases, 11 were coinfected with enteric fever, evidenced by positive Widal test, so, the coinfection rate was 7.8%.[23] In a more recent study involving 100 pyrexia cases, coinfection rate was 9%; dengue-typhoid constituted 22.22% of the coinfections.[24] This is presumably an overestimation, resulting from the fallacy associated with the use of Widal test and IgM anti-dengue antibody for the diagnosis of enteric fever and dengue, respectively; use of blood culture, NS1 antigen, plaque-reduction neutralization test (PRNT) and RT-PCR could cut down the false-positive cases.

In the endemic region, while dealing with a febrile patient especially in the monsoon, it may be a reasonable, and probably cost-effective approach to ask for serological test for dengue (NS1 antigen study or specific anti-dengue antibody detection, or both, according to the time of presentation) and blood culture at first contact to save time, reduce morbidity, and probably mortality as well.

Dengue and enteric fever coinfection is uncommon, though as a single disease both are common in tropical countries. Presence of coinfection may make the otherwise straightforward presentation, diagnosis and management of the either disease complicated. So, the physicians practicing in the endemic region should be aware of the possibility while dealing with the febrile patients in clinical practice.

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