

Case Series

Serological co-infection of dengue and COVID-19: case series in Bangladesh

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ABSTRACT

Parallel symptoms and laboratory findings between dengue and coronavirus disease 2019 (COVID-19) present a diagnostic contest in some dengue-endemic countries in Asia. In this study, we described ten cases of suspected COVID-19-dengue co-infection in a tertiary care hospital in Bangladesh. Serological data showed that patients with positive results for dengue virus (DENV) NS1 antigen and anti-dengue IgG and IgM were also reactive to COVID-19 rapid antibody tests, suggesting dengue with COVID-19 coinfection. The present study indicated a public health concern regarding COVID-19 and dengue detection in Bangladesh as well as in other dengue-endemic countries and it was important for these nations to manage both pathogens concurrently.

Keywords: Dengue, COVID-19, Co-infection, Bangladesh

INTRODUCTION

COVID-19 is a respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has now extent to most countries around the world, resulting in a global pandemic.¹ SARS-CoV-2 is mainly spread from one person to another through droplets during coughing and sneezing, from symptomatic and probably from asymptomatic individuals as well.² Although there is yet no specific medication for treating COVID-19, multiple medicines are being assessed in clinical trials.³ The pandemic is still ongoing in Asian countries in which dengue, caused by dengue virus (DENV), has been endemic for decades. Some countries in the region are experiencing dengue outbreaks among the COVID-19 pandemic producing an extra-burden on assets and well-being.⁴ Adding to this, with comparable clinical features for both diseases, makes a serious problem of misdiagnosis and the opportunity of double infection happening within the same individual at the same time. Rapid tests are useful for easy, convenient and

fast diagnosis, particularly in areas where diagnostic capabilities are limited. Various rapid tests for the detection of COVID-19 antibodies were commercially available and widely used soon after the COVID-19 pandemic began, while dengue antigen/antibody rapid tests have been accessible for years. Though, the precision of these differ and are predisposed by the day in the disease progression that the test is accomplished.⁴ Confirmatory tests for both COVID-19 and dengue are done through nucleic acid amplification tests using polymerase chain reaction (PCR) tests. However, these often require referral to more advanced facilities, adding time to the yield of results. Altogether, these have consequences for both patient care and public health, particularly in diagnosing the COVID-19 cases in low-resource countries in Asia. In this case series, we outlined and compared 10 cases of suspected COVID-19-dengue mixed infection based on clinical presentation and raised the concern of cross-reactivity of SARS-CoV-2 and DENV based on rapid serology tests in Bangladesh.

CASE SERIES

Ten cases of suspected COVID-19-dengue co-infection were reported in Holy Family Red Crescent Medical College Hospital in Dhaka, Bangladesh. Among them three patients were below 40 years and rest of them belonged to above 40 years.

Table 1: Biomarkers of dengue and COVID-19 of 10 case series.

Biomarkers	Lowest	Highest
COVID-19 related biomarkers		
Ferritin (ng/ml)	69	1331
CRP (mg/dl)	1	88
D-dimer (mg/dl)	<0.10	4.19
Creatinine (mg/dl)	0.75	2.01
ALT (U/l)	17	121
Dengue-related biomarkers		
Platelet count (per ml)	13000	286000
Haematocrit (%)	30.2	49.1
Leukocyte count (per ml)	2300	13100
Albumin (g/dl)	2.8	4

The first case was a 70 year old woman presenting with a 3 day onset of high and continuous fever as well as nausea with HTN. She did not report cough, sore throat or shortness of breath. Dengue rapid tests were positive for NS1 antigen and anti-dengue IgM and anti-dengue IgG were negative. Simultaneous RT-PCR for SARS-CoV-2 of nasopharyngeal swab was positive. Other vitals were normal upon admission and initial blood report showed leukopenia (3000 per ml), thrombocyte count of 70,000 per ml and elevated levels of alanine transaminase (ALT, 121 U/l). Other laboratory parameters and radiology tests including chest X-ray were normal. On the day of admission, the patient was hypotensive and had to undergo fluid resuscitation. Follow up blood count showed decreasing leucocyte (2500 per ml) and platelet counts (41,000 per ml), but there were no signs of plasma leakage, bleeding, shock or other complications and platelet count raised to 180000 per ml on discharge; haematocrit count was 36% and then reduced to 32.6%. Ferritin level 1331 ng/ml, CRP was 17.2 mg/dl and D-dimer was high 2 mg/l, whereas albumin was low 2.8 g/dl. She got human albumin and injection remdisivir. The patient was diagnosed with dengue fever, HTN with COVID-19 and survived.

The second case was a 49 year old woman with a 3 day high and continuous fever, dry cough, anorexia and vomiting, without any shortness of breath with history of stroke. Vital signs were normal upon admission and initial blood count showed thrombocyte count was 178,000 per ml. Dengue rapid tests were positive for NS1 and anti-dengue IgM, while negative for anti-dengue IgG. COVID-19 RAT test was also reactive. On the day of admission, the patient was hypotensive and had to undergo fluid resuscitation and the platelet count dropped

to 184,000 per ml on the second day. The platelet count dropped to 57,000 per ml on 7 day. Then it raised to 196,000 per ml and 230,000 per ml on 11 and 12 day; haematocrit count was 38.4% and then reduced to 32.9%. Ferritin level 69 ng/ml, CRP was 1 mg/dl and D-dimer was high 1.5 mg/l, whereas albumin was low 2.8 g/dl. She got human albumin. The patient was diagnosed with dengue hemorrhagic fever (DHF) with COVID-19 with history of stroke.

The third patient was a 32 year old woman with a fever of 3 days onset, cough, weakness, anorexia, leg pain, retro-orbital pain and headache. She reported no other symptoms. Upon admission, vitals were normal with a body temperature of 37.8 °C. Other physical examinations were normal. On the day of admission, she was tested positive using a dengue NS1 antigen rapid test. Subsequent RT-PCR analysis of the nasopharyngeal swab of the corresponding patient confirmed her as SARS-CoV-2-positive despite the fact that chest X-ray was normal. Serotyping RT-PCR test on serum sample collected on day 7 of admission came with undetected DENV and was positive for NS1 and both anti-dengue IgM and IgG. Platelet counts dropped to 73000 per ml on admission which dropped to 44000 per ml on 5th day. Then gradually raised to 53000 per ml, 76000, 10100, 137000 and 1,98000 on discharge; haematocrit count was 38.4% and then reduced to 32.9%. CRP was 68.8 mg/dl and D-dimer was high 1 mg/l. She was diagnosed with dengue fever with COVID-19.

The fourth patient was 47 years old male with fever for 7 days and cough for 5 days. Dengue rapid tests were positive for NS1 and anti-dengue IgM, while negative for anti-dengue IgG. COVID-19 RT-PCR test was also reactive. Platelet count dropped to 108,000 per ml on the day of admission. Haematocrit count was 42.9% and then reduced to 39.6%. She had leukopenia 3200 per ml. Ferritin level 69 ng/ml, CRP was 1 mg/dl and D-dimer was high 1.5 mg/l, whereas albumin was low 2.8 g/dl. Creatinine and CRP was elevated to 1.38 and 26.6 respectively. He got steroid inhaler with spacer and advised to proning 12 hourly. The platelet count gradually increased to 1,12000 then 168,000 and 22000 on 5th day. His fasting blood sugar raised to 10 mmol/l and insulin was added on 3rd day and was well controlled. He got remdisivir injection. The patient was diagnosed dengue fever (NS 1+ve) with COVID-19.

The fifth patient was 27 years old lady complaining of fever for 3 days, per vaginal bleeding, nausea and pain in the abdomen. On the day of admission, she was tested positive using a dengue NS1 antigen rapid test. Subsequent RT-PCR analysis of the nasopharyngeal swab of the corresponding patient confirmed her as SARS-CoV-2-positive despite the fact that chest X-ray was normal. The platelet count dropped to 132,000 per ml on the day of admission. SpO₂ was 92% got 2.5 l O₂ through high flow nasal cannula. Platelet count dropped to 76,000 then gradually increased to 155000 on discharge. She had

leukopenia 2500 per ml. Haematocrit count was 37.4% and then reduced to 35.6%. CRP was 88 mg/dl and creatinine was 1.8 mg/dl. She was diagnosed COVID-19 with dengue fever (NS 1+ve).

The sixth patient was 65 years old male presented with fever and cough for 5 days. His SpO₂ was 87% and admitted to high dependency unit (HDU), got 10-15 l O₂ with reservoir bag and steroid inhaler with spacer and ipratropium bromide. Nasogastric tube was inserted. Platelet count dropped to 80,000. He had been admitted to HDU then when the critical condition improved shifted to cabin. His anti-dengue IgG was positive. COVID-19 RT-PCR test was also reactive. Platelet count dropped to 44000 on 3rd day then gradually increased to 137,000 and 288000 on discharge. Ferritin, D-dimer, creatinine and CRP raised to 1324 ng/ml, 4.19 mg/ml, 2.1 mg/dl and 68.8 mg/dl. He had leukopenia 2500 per ml. Haematocrit count was 37.4% and reduced to 33.3%. He was diagnosed as a case of COVID-19 pneumonia with dengue fever (IgG +ve) with DM, HTN, IHD, CKD, electrolyte imbalance with pontine infarct.

The seventh case was 60 years female with the complaints of fever and cough for 7 days and body ache. Dengue IgM was positive. COVID-19 RT-PCR test was also reactive. She got remdisivir and pulfibro (anti-fibrotic). The patient was hypovolemic and got fluid resuscitation. Platelet count fall to 70,000 on 4th day then gradually raised to 125000, 178000 on day of discharge. Haematocrit count was 33.8% and reduced to 30.2%. CRP and creatinine level elevated to 5.5 mg/dl and 2.01 mg/dl respectively. She had leukopenia 2300 per ml. She was diagnosed as a case of COVID-19 with DF (IgG+ve) with DM with HTN with bronchial asthma.

The eighth patient was a lady of 42 years with the complaints of fever for 5 days, shortness of breath and productive cough for 2 days. Her SpO₂ was 85% and got O₂ 10-15 l and inhaler with spacer bronchodilator with the advice of proning. Her platelet count fall to 22000 on day of admission. Then gradually raised to 185000, 211000 and 250000 on discharge. Haematocrit count was 37.4% and reduced to 33.3%. CRP and creatinine level elevated to 43.2 mg/dl and 1.52 mg/dl respectively. She had leukopenia 3500 per ml. She was diagnosed with COVID-19 with dengue fever (IgG and IgM+ve) with HTN with BA with depressive disorder.

The ninth patient was 21 years old male presented with the complaints of fever for 5 days, cough for 3 days and nausea and vomiting 2 days. His RT-PCR was reactive. His SpO₂ was 97% and got O₂ 4-6 l. His platelet count fall to 76000 on 6th day and then gradually raised to 170000, 210000, 232000 and 457000 on discharge. Ferritin level raised to 1320 ng/ml. SGPT and CRP was slightly raised to 74.46 and 12 mg/dl respectively. He had leukopenia 3340 per ml. He got remdisivir. He was diagnosed as a case of COVID-pneumonia with DF.

The tenth patient was 40 years old male complaints of fever for 7 days and chest discomfort for few days and admitted in coronary care unit (CCU). Rapid test for dengue NS1 and IgG was positive and RT-PCR was also reactive. His SpO₂ was 97% and got O₂ 4-6 l. When his condition was stable shifted to cabin. Platelet count fall to 151000 on 2nd day of admission and gradually raised to 156000 and 165000 on discharge. Ferritin level raised to 600 ng/ml. While creatinine and SGPT was elevated to 1.07 mg/dl and 58 IU/l. He had leukopenia 3800 per ml. He was diagnosed as a case of COVID-19 with DF (NS1 and IgG +ve) with anxiety neurosis.

DISCUSSION

In dengue-prevalent countries such as in Asia, misdiagnosis between COVID-19 and dengue may be highly challenging and might affect controlling of these diseases. About 80% of COVID-19 cases were mild to moderate with nonspecific symptoms and mimic dengue.⁵ Apart from fever, which was the chief complaint of most cases of dengue and COVID-19, skin manifestations including rash or petechiae, which were commonly found in dengue, have also been commonly reported in COVID-19 and thus, the challenge of discriminating one from another was increased.⁶ The easiest, most appropriate and fastest point-of-care testing to diagnose dengue and COVID-19 was by rapid serology tests. Though, cross-reactivity between COVID-19 and dengue had been reported in Singapore, Thailand and Indonesia, where dengue antibodies were detected in confirmed COVID-19 patients (false-positive dengue serology among COVID-19 patients).⁷⁻⁹ Our data also recommended the probable cross-reactivity between DENV and SARS-CoV-2 which headed to false-positive COVID-19 serology among dengue patients. This was also reported earlier in Italy where 1 out of 44 DENV-positive sera resulted in a false-positive result for COVID-19 antibodies.¹⁰ The present study also accentuated the probability of coinfection of DENV and SARS-CoV-2 in dengue-endemic countries in Asia that might necessitate distinctive controlling approaches in clinical settings. A recent study found that a false-positive result could occur for both COVID-19 serology among dengue patients and reciprocally, dengue serology among COVID-19 patients.¹¹ The cross-reactivity between SARS-CoV-2 and DENVs while using a rapid serology test will be an important obstacle to trust on the laboratory diagnosis of COVID-19 (as well as dengue) on the basis of the use of rapid serology tests, predominantly in the early phase of infection. A systematic review of 15,976 samples revealed the inadequacy of pooled results for IgG, IgM, IgA, total antibodies and IgG/IgM (using a combination of ELISA, chemiluminescence immune-assays and lateral flow assays). Though the sensitivities of all methods were less than 30.1% through the first week of onset of symptoms, the numbers were improved in the second week and reached the highest in the third week; 72.2% (day 8-14), 91.4% (15-20 days) and 96.0% (21-35 days) for IgM/IgG combination.^{12,13} This designated that the antibody tests,

in particular rapid test retaining lateral flow immunoassays, have restricted aids in the point-of-care testing. Mixed infection of dengue and COVID-19 required special attention from all dengue-endemic countries in Asia, especially with the inadequate assets. Two cases of co-infection were stated earlier in Reunion Island and in Mayotte in France.^{14,15} Yet probable co-infection was also detected in Asia.¹⁶ It was reported coinfection occurred among 4 out of 20 patients and coinfection was related to a high mortality rate in a study done in Bangladesh, frightening the dengue-endemic countries in the region.¹⁷ Hence, sustainable dengue-preventive procedures, including strengthening vector control measurers during the COVID-19 pandemic, more laboratory testing facilities that can conduct PCR testing was critical.

CONCLUSION

The present study provided proof of cross-reactivity between DENV and SARS-CoV-2, leading to false-positive COVID-19 serology among dengue patients. It underlines the significance of a simple and reasonable rapid test that is proficient of distinguishing DENV and SARS-CoV-2 with high sensitivity in the early phase of infection and enhance the laboratory system capabilities in the area. Adding to this, healthcare workers in dengue-endemic countries through the Asian continent would be conscious of coinfection of DENV and SARS-CoV-2 and its hazardous influence on patient mortality rate. Filtering the current guidelines to lodge the diversity of both contagious diseases (and their pathogenic causality) is of the supreme importance. Follow up studies are required to assess the consequence of dengue and COVID-19 coinfection in the Asian regions.

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