Dengue vigilance in COVID-19 pandemic

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Case Report

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ABSTRACT

Dengue fever is a significant health burden in Malaysia. Up to 3.6 billion people are living in the tropics and subtropical areas where dengue infection is endemic. COVID-19 is an emerging global pandemic. Dengue and COVID-19 share certain similar clinical symptoms. COVID-19 was reported to cause false positivity in dengue serology. Herein, we report two cases. The first case was a dengue and COVID-19 co-infection. The second case was a false positive dengue serology, echoing previous reported finding of false positive dengue serology by this new virus. Approach in handling dengue-like illness during this COVID-19 pandemic is discussed. Similarities and differences of these two viral diseases are summarized and discussed.

KEY WORDS: dengue, COVID-19, hydroxychloroquine, cytokine release syndrome

INTRODUCTION

Dengue fever is a mosquito-borne viral disease. It was first reported in Malaysia in 1902[1]. Beginning 1960s, dengue began to spread into urban areas of Penang and Kuala Lumpur. By the early 1970s, it had spread to whole Malaysia and till to date it remains as a significant health burden in Malaysia[2]. Up to 3.6 billion people are estimated to now live in the tropics and subtropical areas where dengue viruses are endemic[3]. Globally, it is estimated that approximately 50 million to 200 million dengue infections, 500,000 cases of severe dengue, and over 20,000 dengue related deaths occur annually[3].

In December 2019, an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection occurred in Wuhan, Hubei Province, China and spread across China and beyond[4]. World Health Organisation (WHO) subsequently named the disease as coronavirus disease (COVID-19)[5]. Till to date, more than 2.6 million people have been infected with COVID-19, affecting more than 200 countries and territories and two international conveyances[6].

The first case of COVID-19 in Malaysia was reported on 25th January 2020. Reported new cases remained relatively low[7]. However, the trend changed in March 2020,where an upsurge of positive cases was reported which was linked to a religious gathering held in Kuala Lumpur. Within the duration of two weeks, beginning 12th March 2020, the number of new cases exponentially increased from 149 cases to 5532 cases. At the time when this case report was written, the number of recorded deaths has gone up to 93 [8]. Mortality rate in Malaysia was estimated to be 1.6%[8].

Dengue and COVID-19 may be difficult to distinguish because they share similar clinical features namely fever, muscle ache, headache, diarrhea, nausea and vomiting[9,10]. Adding to this complexity, they may share similar laboratory findings namely thrombocytopenia, leucopenia, transaminitis and acute kidney injury[9,10]. Yan *et al*.[11] reported two cases where their patients were initially presented with symptoms suggestive of dengue fever, demonstrated transient positive serology (IgG and IgM), which subsequently found to be positive for COVID-19. Dengue PCR was found to be negative. The authors highlighted the importance of considering COVID-19 when dengue rapid serology test was positive, as failure in recognition may lead to serious consequences not only to patients but also to general public. In this case report, we

illustrate the first reported case of COVID-19 and dengue co-infection, followed by another case which echoes Yan *et al.*, highlighting the possibility of cross-reactivity of COVID-19 contributing to false positivity in dengue serology. We highlight the approach to dengue-like illness in this COVID-19 pandemic crisis. The clinical characteristic, outcome and potential treatment of these two diseases were also reviewed.

CASE REPORTS

The first case was a 14-year-old female with no relevant medical illness and travelling history. She presented with fever, myalgia, anorexia, vomiting and headache for 4 days. She had leucopenia, thrombocytopenia and a normal chest radiograph. A rapid dengue test was performed, showing nonstructural protein 1 antigen (NS1Ag) and IgG positive. Dengue IgM was negative. A COVID-19 RT-PCR test was performed due to the concern of false positive in dengue serology, which surprisingly turned out to be positive. Further history revealed that she might contract it from her church member. Her fever resolved at day 6 of illness. She denied any worsening of chest symptoms. She was started on hydroxychloroquine for 7 days. Thrombocytopenia resolved at day 10, preceded by resolution of the leucopenia. She experienced slight transaminitis (alanine transferase 179U/L) at recovery phase, which gradually improved when she was discharged home. A repeated dengue serology (by ELISA) at day 9 of illness demonstrated that her IgM had seroconverted to positive. The final diagnosis was dengue fever with no warning signs with COVID-19 co-infection.

The second case was a 62-year-old male with underlying co-morbids of diabetes mellitus, hypertension, dyslipidemia and stable ischemic heart disease. He presented with fever, cough, myalgia and arthralgia for a week. Blood investigation noted thrombocytopenia with reducing trend of lymphocyte count. Dengue rapid test was performed, noted IgG positive, with negative dengue IgM and NS1Ag. In view of his respiratory symptoms and positive encounter with the religious gathering cluster mentioned above, a COVID-19 nasopharyngeal swab was taken for reverse transcription polymerase chain reaction (RT-PCR) test. It was then noted to be positive. He continued to remain febrile till day 10 of illness, which he then fully resolved. Chest radiograph noted a pneumonic patch at the right middle zone; however he did not need any oxygenation. He was treated with hydroxychloroquine (HCQ) and lopinavir-ritonavir (Kaletra®) for 7 days. Thrombocytopenia resolved by day 8 of illness. No other end organ damage noted. His repeated dengue serology at day 11 of illness noted negative for all NS1Ag, IgM and IgG. The first dengue rapid test was deemed to be false positive. He was discharged home well after his repeat oropharyngeal swab was negative.

DISCUSSION

In contrary to what was reported by Yan *et al.*[11], we report a subject with true COVID-19 and dengue fever co-infection by demonstrating the seroconversion of IgM from negative to positive, possibly the first officially reported case worldwide. Case 2 highlights the possibility of false positive dengue rapid combo test, when only IgG was detected. A systematic approach to patients with dengue-like illness at primary care or emergency department will help to safeguard the general public and health care workers in this COVID-19 pandemic. Table 1 summarizes the cases that had been published till to date.

Standard precautions, along with contact precautions should be advocated by wearing personal protective equipment (PPE) such as apron, and gloves, when screening this group of patients. Subjects should be screened for respiratory symptoms, travelling history, contact history, and history of residing at high epidemic area. Those who answer yes to any of the above questions need to be handled with droplet precautions. They should be managed in an isolation room. Appropriate PPE should be used when attending to these subjects [12]. Basic laboratory tests such as complete blood count, kidney function and liver function tests should be carried out. Dengue rapid combo test should be made available and nasopharyngeal swab or sputum should be sent for COVID-19 RT-PCR test. A N95 respirator should be worn while performing a nasopharyngeal swab. A positive dengue serology must be interpreted with care. An attempt to ascertain the diagnosis of dengue with COVID-19 co-infection or false positive serology test should be made. This step is crucial, as it will affect the monitoring, and fluid management of the subject, especially in the event of a more severe disease. Fig 1 summarizes the recommended algorithm to approach patients with dengue-like symptoms.

Dengue serology can be detected using ELISA technique and is more widely used for diagnosis. It is a laboratory test of choice in later stage of disease[13,14]. IgM become detectable by day 3 to day 5 after onset of illness and is increasingly detectable from 50% by days 3-5 after onset of illness to 99% by day 10 of illness. Anti-dengue serum IgG is generally detectable at low titres only at the end of the first week of illness, increasing slowly thereafter. Serum IgG remains detectable after several months, and probably even for life[13,14]. Thus, a repetition of dengue serology by few days later to demonstrate the seroconversion of IgM may help confirming the diagnosis. In the setting where dengue serology titer is presence, the increasing titer of either IgM or IgG may help to give better understanding of the diagnosis[14]. However, the interpretation of dengue serology should be taken into account that false positivity may occur due to cross-reaction with other flaviviruses (e.g. West Nile disease, Yellow Fever Virus and Japanese Encephalitis), non-flaviviruses (e.g. malaria, leptospirosis, toxoplasmosis and syphilis), and connective tissue disease (rheumatoid arthritis)[14]. During this pandemic, COVID-19 infection(as suggested in Case 2) may also cause cross-reactivity, however, more studies is required to confirm this[11].

Dengue at early stage can be confirmed by detection of the virus, viral nucleic acid or NS1 protein antigen. NS1Ag test is easy to perform, but less sensitive than viral isolation and RNA detection. Nuclei acid detection is the most sensitive and specific method to use. Viral detection is highly specific, but may not be as sensitive in detecting the virus. The latter two are highly specialized and expensive that they may not be widely available. Specimen will require special storage temperature and short transportation time between collection and extraction. The sensitivity of all three tests mentioned are affected by the day of illness, whereby the sensitivity is reduced by day 5 of illness[13,14]. Thus, in early stage of the disease, these tests can be considered to confirm the diagnosis of dengue. Fig 2 illustrates the proposed algorithm to approach dengue serology in the midst of COVID-19 pandemic.

Though there may be similarities in the initial clinical characteristics for both dengue and COVID-19, the clinical course, monitoring, and management differ. Dengue is well known for fever of 3-7 days, followed by a critical phase (24 - 48 hours) and finally the recovery phase. During the critical phase, patient may have

increased in capillary permeability that leads to leakage of plasma to the extravascular space[13,14]. This will lead to hypovolemia or shock. A persistent hypoperfusion may eventually lead to organ impairment, metabolic acidosis and intravascular coagulopathy. These may ultimately lead to severe hemorrhage. Dengue warning signs include abdominal pain, persistent vomiting and/or diarrhea, restlessness, altered conscious level, clinical fluid accumulation, mucosal bleed or tender liver[13,14]. In comparison, SARS-CoV-2 virus appears to gain entrance to the lung via the angiotensin converting enzyme 2 receptors[15], thus leading to a predominant respiratory presentation and complications. Those with severe disease have a median time from disease onset to admission of 10 days, and median time to death was 16 days [16]. The presence of one or more of the following: advanced age (>60 years), cancer, more underlying diseases, or major infections, appear to contribute to higher fatality[16]. Complications observed commonly includes acute respiratory distress syndrome and cardiac injury[16]. The cause of more pronounced myocardial injury may need further exploitation. However, similar to severe dengue, cytokine releasing syndrome or "cytokine storm" was observed in severe COVID-19[17–19]. This is due to an abnormal immune response involving the production of cytokines or chemokines, activation of T-lymphocytes and disturbances of haemostatic system. The mediators involved includes C3a, C5a, tumour necrosis factor-α, interleukin 2, 6 and 10, interferon-α and histamine are elevated[13]. It had been reported that the mortality rate of COVID-19 was higher (5%) than dengue (1.14%)[20,21], It is unknown at this stage that how SARS-CoV-2 and dengue viruses interact in the host, though our first case presented appeared to be uncomplicated and the disease course appeared more towards dengue infection. More case reports or prospective cohort studies are required to provide better understanding of this scenario.

The management of dengue includes close monitoring, good supportive care, and judicious use of fluid replacement. Blood transfusion is advocated in approaching more severe disease, when occult hemorrhage is suspected[13,14]. Similar to severe dengue, WHO recommends conservative fluid usage during acute resuscitation in COVID-19. Crystalloid is the fluid of choice. As COVID-19 involves more severe lung disease, early intubation, prone ventilation has been advocated[22].No medication has been listed to be effective in COVID-19. Few drugs had been repurposed and are undergoing testing. These drugs are hydroxychloroquine (HCQ), chloroquine (CQ), remdesivir, lopanivir-ritonavir, intravenous immunoglobulin, convalescent plasma, tocilizumab, favipiravir and traditional Chinese medicine[23]. Gautret *et al*. shows that HCQ is associated with significant viral load reduction and its effect is reinforced by azithromycin[24]. It is believed that HCQ acts on the entry and post-entry stages of SARS-CoV (severe acute respiratory syndrome–associated coronavirus) and SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infections, likely via effects on endosomal pH and the resulting under-glycosylation of angiotensin-converting enzyme 2 receptors that are required for viral entry[24]. The United States Food and Drug Administration (FDA) issued an emergency use authorization for HCQ to be used to treat adults and adolescents who weigh 50kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible[25]. However, certain experts have advised against its use in view of its potential cardiotoxicity concern, namely *torsades de pointe*. This is especially true when its usage is in combination with azithromycin[26]. Wang *et al.* demonstrated that HCQ is able to inhibit dengue in vitro, whereby HCQ triggers

the host defense machinery by inducing reactive oxidative stress (ROS-) and mitochondrial antiviral signal (MAVS-) mediated innate immune activation against dengue virus infection[27].Chloroquine (CQ) has also been reported to demonstrate dengue inhibitory ability, both in vitro [28,29]and in vivo (Aotus Monkey)[30].CQ was found to potentially alleviate dengue related symptoms[31]. However, CQ did not demonstrate effect on duration of disease, intensity, and days of fever[31]. No effect was found on viraemia and NS1 antigenemia [32]. More studies need to be done in the usage of antimalarial for COVID-19 and dengue co-infection with more objective outcome measured to confirm its efficacy for both diseases. Table 2 summarizes the similarities and differences between COVID-19 and Dengue.

CONCLUSION

In conclusion, dengue and COVID-19 share certain clinical and laboratory characteristics. Thus, dengue like-illness needs to be approached with caution in this COVID-19 pandemic, to safeguard health care workers and public. A few medications have been repurposed and under investigation for COVID-19 treatment. Among those that potentially be helpful for both COVID-19 and dengue are HCQ and CQ. However, more evidence are needed to determine its true safety and efficacy. We hope that this case report will stir more research and discussion on dengue and COVID-19 co-infection in the future, focusing on the clinical presentation, progression, laboratory findings, treatment and outcome.

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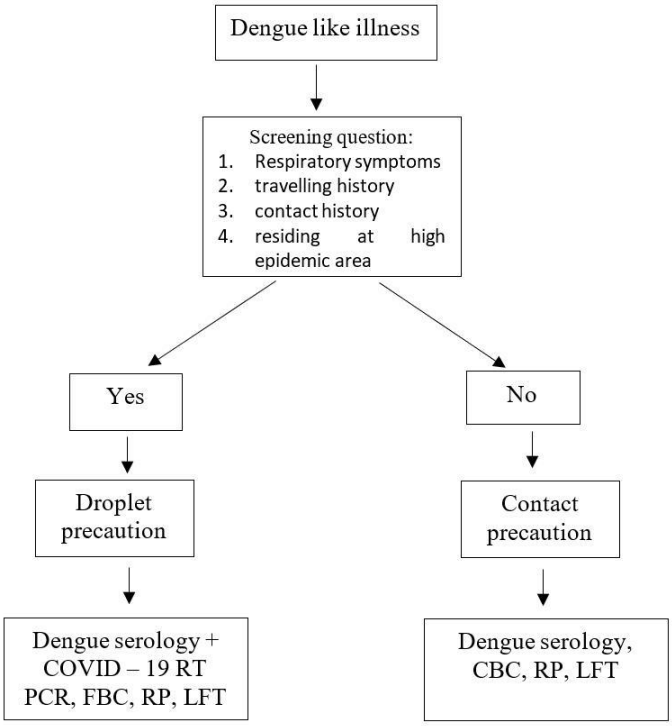

Fig 1: Proposed algorithm for approaching patients with dengue-like illness. Patients with dengue like illness, arriving at primary or emergency care settings should be screened with designated questionnaire. High risk subjects should be approached with droplet precaution, while low risk subjects should approached with contact precaution to minimize unnecessary PPE usage.

Legend: RT-PCR: reversed transcriptase polymerase chain reaction, FBC/CBC: full/ complete blood count; RP: Renal profile; LFT: Liver Function Test

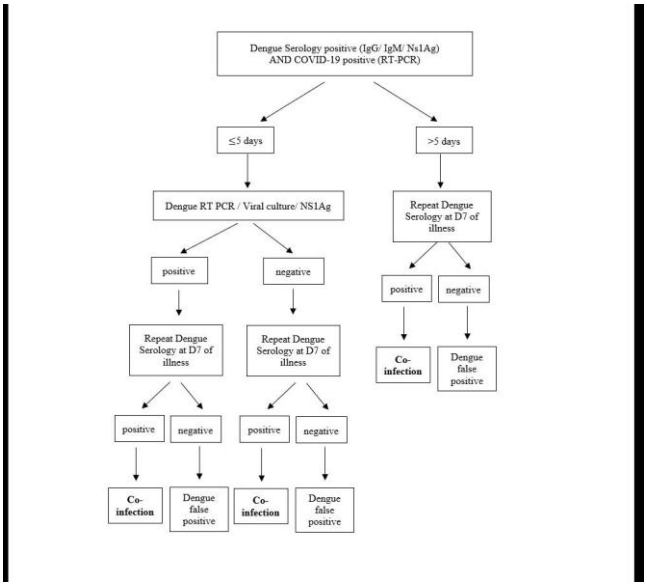

Fig 2: Proposed algorithm to ascertain dengue- COVID-19 co-infection versus dengue serology false positive.

Legend: IgG/ IgM: Immunoglobulin G/ M; NS1Ag: dengue non structural protein 1 antigen; RT-PCR: reversed transcriptase polymerase chain reaction; D7: day 7

Table 1: Summary of current reports on dengue and COVID-19

S. No	Age	Gender	Initial clinical presentation	Laboratory	1st Dengue serology (day of illness/ result)	2nd Dengue serology (day of illness/ result)	3rd Dengue serology	COVID-19 (Day of illness/ result)	Diagnosis	Reference
1	57y.o	Male	Fever, cough for 3 days	↓ Platelet Normal CXR ↓ lymphocyte	D3 NS1A/ IgM/ IgG: negative	N/A IgM/ IgG – positive	N/A Dengue PCR negative NS1Ag/ IgM/ IgG – negative	N/A Positive	False positive dengue	[11]
2	57y.o	Female	Fever, myalgia, mild cough for 4 days Diarrhea for 2 days SOB at D8	↓ Platelet ↓ lymphocyte ↑ALT/ AST/ Bilirubin CXR normal	D4 IgM positive	Dengue PCR – negative	-	D8 Positive	False positive dengue	
3	14y.o	Female	fever, myalgia, anorexia, vomiting and headache for 4 days	↓Platelet ↓ WCC ↓ lymphocyte ↑ALT CXR normal	D4 NS1Ag/ IgG positive IgM negative	D9 IgM positive	-	D4 Positive	Dengue and COVID-19 co-infection	
4	62y.o	Male	Underlying DM/ HPT/ dyslipidemia fever, cough, myalgia and arthralgia for a week	↓ Platelet ↓ lymphocyte CXR: pneumonic patch	D7 IgG positive IgM and NS1Ag negative	D11 NS1Ag, IgM, IgG - negative	-	D7 Positive	False positive dengue	

Summary of clinical presentation, laboratory investigation, dengue laboratory investigation, COVID-19 results and final diagnosis of the cases published till date.

y.o: years old; SOB: shortness of breath; ALT: alanine transferase; AST: aspartate transferase; WCC: white cell count; CXR: chest radiograph; DM: Diabetes mellitus; HPT: hypertension; N/A: not available; NS1Ag: dengue nonstructural protein 1 antigen; IgG: immunoglobulin G, IgM: Immunoglobulin M; D: Day

Table 2: Similarities and differences of dengue and COVID-19

Disease / Clinical	**Dengue**		**COVID-19**	
Clinical characteristic	fever (100%),	100%	fever	88.5%
			cough	68.6%
			myalgia or fatigue,	35.8%
			expectoration	28.2%
	headache (70.89%),	70.89%	dyspnea	21.9%
			headache or dizziness	12.1%
	myalgia/bone soreness	62.03%	diarrhea	4.8%
			nausea and vomiting	3.9%
	skin rash	54.43%		
Laboratory characteristic	leucopenia	(75.32%)	lymphocytopenia	(64.5%)
	thrombocytopenia	(77.85%)	increase of CRP	(44.3%)
	deranged ALT	(57.59%)	increase of LDH	(28.3%)
	deranged AST	(77.85%)	leukocytopenia	(29.4%)
Recommended diagnostic test	**< 5days** NS1Ag RT- PCR Viral culture IgM (50%)	**> 5 days** Dengue Serology	RT-PCR	
Fatality rate	1.14%		5%	
Recommended Management	Conservative fluid management		Conservative fluid management Early intubation Prone ventilation	
Potential Off-label management	hydroxychloroquine chloroquine IVIG steroids		hydroxychloroquine, chloroquine, remdesivir, lopanivir-ritonavir, intravenous immunoglobulin, covalescent plasma, tocilizumab, favipiravir traditional Chinese medicine	
References	[10,20,21]			

Clinical and laboratory characteristics, disease course, fatality rate, and management of dengue and COVID-19 were as shown

ALT: alanine transferase; AST: aspartate transferase; CRP: C- reactive protein; LDH: lactate dehydrogenase; NS1Ag: NS1 protein antigen; RT-PCR: reverse transcriptase- polymerase chain raction; IVIG: intravenous immunoglobulin