CASE REPORT

Concurrent COVID-19 and dengue with hyperferritinaemia: A case report

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SUMMARY

The current pandemic of coronavirus disease 2019 (COVID-19) poses a bigger challenge to the population in tropical countries where dengue fever is also endemic as both diseases share similar clinical and laboratory features. In COVID-19, hyperferritinaemia is associated with severe disease and clinical outcome while in dengue fever, hyperferritinaemia is a key feature of haemophagocytic lymphohistiocytosis (HLH), which is a complication with high mortality. In this case report, we present a case of co-infection of COVID-19 and dengue with hyperferritinaemia in Queen Elizabeth Hospital, Sabah, Malaysia.

INTRODUCTION

The ongoing COVID-19 global pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA betacoronavirus. Clinical features of COVID-19 such as fever, myalgia, fatigue and skin rash, and laboratory abnormalities such as lymphopaenia, thrombocytopaenia, increased liver enzymes and raised inflammatory markers are also seen in dengue fever, caused by the dengue virus (DENV). This poses a diagnostic challenge especially during the current pandemic when the healthcare system is strained by the large numbers of ill patients requiring treatment for COVID-19. Here, we report a case of a patient afflicted with both polymerase chain reaction (PCR) proven COVID-19 and dengue with hyperferritinaemia.

CASE REPORT

A 41-year-old man, non-smoker with underlying hypertension, was admitted to the Queen Elizabeth Hospital, Sabah, Malaysia for asymptomatic COVID-19 which was detected as part of contact screening. Nasopharyngeal swab for SARS-CoV-2 PCR was positive eight days prior to admission. PCR detection was done with BGI real-time fluorescent rt-PCR assay (SLAN-96S, China) with a cycle threshold value of 27.71 (RdRp gene) and 28.86 (N gene). There was no history of recent travel. On the 3rd day of admission, he started having fever (henceforth referred to as day-1 of fever). On day-3 of fever, he required nasal cannula oxygen supplementation due to desaturation. Oxygen saturation was 94% on ambient air. Lungs were clear on auscultation. Blood investigations revealed lymphopaenia (0.59 x10^3/uL) and raised C-reactive protein (CRP) (45.3mg/L) and ferritin (6381ng/mL). Procalcitonin was 0.58ng/mL. Chest radiography showed ground glass opacities over bilateral lung fields (Figure 1). In view of diagnosis of COVID-19 with pneumonia requiring oxygen therapy, he was started on dexamethasone 6mg once daily. He was also started on piperacillin-tazobactam for empirical treatment of hospital-acquired infection.

He was weaned off oxygen supplementation within 24 hours. However, he remained febrile with multiple spikes of temperature in the ward. He also had an episode of unprovoked gum bleeding. Clinically he was normotensive with good peripheral perfusion with no signs of plasma leakage. Serial blood investigations showed decreasing platelet and white blood cell counts and increasing liver enzymes (aspartate aminotransaminases more than alanine aminotransaminases) (Table I). He was thence screened for dengue fever. Dengue screening taken on day-4 of febrile phase revealed a positive dengue NS1 and negative dengue IgM and IgG, and multiplex real-time reverse transcriptase PCR (rt-PCR) for dengue revealed the detection of DENV serotype 3 (Bio-Rad CFX96, USA). Human immunodeficiency virus and hepatitis screening was negative. Blood smears for malarial parasites were also negative.

Serum ferritin showed an increasing trend to >40000ng/ml, serum triglyceride was 3.65mmol/L and fibrinogen was 225.2mg/dL. He was also noted to have splenomegaly of two fingerbreadths below the costal margin. In view of marked hyperferritinaemia, a diagnosis of dengue-related haemophagocytic lymphohistiocytosis was considered. HScore for reactive haemophagocytic syndrome was 199, which translated to an 80-88% probability of haemophagocytic syndrome, while HLH-2004 score was 4 (fever, splenomegaly, hypertriglyceridaemia and hyperferritinaemia).

Dexamethasone therapy was increased to 8mg 12-hourly (10mg/m^2 per day) on day-7 of illness. Subsequently his blood parameters improved, and dexamethasone was then tapered off over a total of 14 days. He remained stable throughout his hospitalisation, and he was discharged home on the 19th day of admission. A follow-up review at a health clinic after 1 week revealed a recovered liver function with normalising serum ferritin.

DISCUSSION

The hyperinflammatory phase of COVID-19 manifests as systemic inflammation resulting in multiorgan and respiratory failure, and elevation of inflammatory cytokines

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Table I: Serial blood investigation of patient during admission. The last temperature rise was on day-5 from fever onset. The last column refers to blood parameters during post-discharge review at the health clinic. TWBC denotes total white blood count, ALT alanine aminotransferase, AST aspartate aminotransferase, CRP C-reactive protein, and LDH lactate dehydrogenase.

Day from fever onset	2	3	4	5	6	7	8	9	10	13	15	24	Normal range
Haemoglobin (g/dL)	15.1	16.3	15.6	14.2	14.3	14.6	15.5	13.6	13.0	14.3	13.1	12.7	13.0-17.0
TWBC (x10^3/µL)	4.66	5.57	3.36	3.53	4.41	8.15	11.87	12.46	11.93	10.48	10.65	6.8	4.0-10.0
Neutrophil (x10^3/µL)	3.46	4.27	2.16	2.25	2.11	4.47	7.22	8.96	9.00	6.82	7.27	4.5	2-7
Lymphocyte (x10^3/µL)	0.59	0.71	0.83	0.81	1.80	3.01	2.74	1.85	1.35	2.24	2.08	1.9	1-3
Platelet (x10^3/µL)	165	147	66	20	13	35	75	133	197	263	241	261	150-410
Haematocrit (%)	43.2	44.9	44.9	39.8	41.4	41.0	43.4	38.7	36.7	41.8	39.4	35.9	40-50
Urea (mmol/L)	5.3	5.6	6.0	5.0	5.3	5.6	6.2	6.3	6.5	7.1	5.6	3.9	3.2-7.4
Creatinine (µmol/L)	93.7	104.2	105	77.9	68.5	65.5	72.3	66.4	70.9	68.7	66.3	82	63.6-110.5
ALT (U/L)	95	102	110	130	167	214	196	172	156	190	128	46	0-55
AST (U/L)	90	116	171	256	355	270	171	124	90	73	43	-	5-34
CRP (mg/L)	45.3	34.2	18.5	11.1	8.1	6.2	6.2	4.2	3.2	2.3	5.7	11.1	<5
LDH (U/L)	404	482	585	831	810	551	487	411	382	335	231	-	125-220
Ferritin (ng/mL)	6381	-	23118	>40000	>40000	31543	16073	11300	7584	5043	4078	959	21.8-274.7
Fibrinogen (mg/dL)	286.0	-	280.9	-	228.4	225.2	-	202.1	-	-	-	-	200.1-442.6
Triglyceride (mmol/L)	-	-	2.70	-	-	3.65	-	-	2.37	-	-	-	<1.7

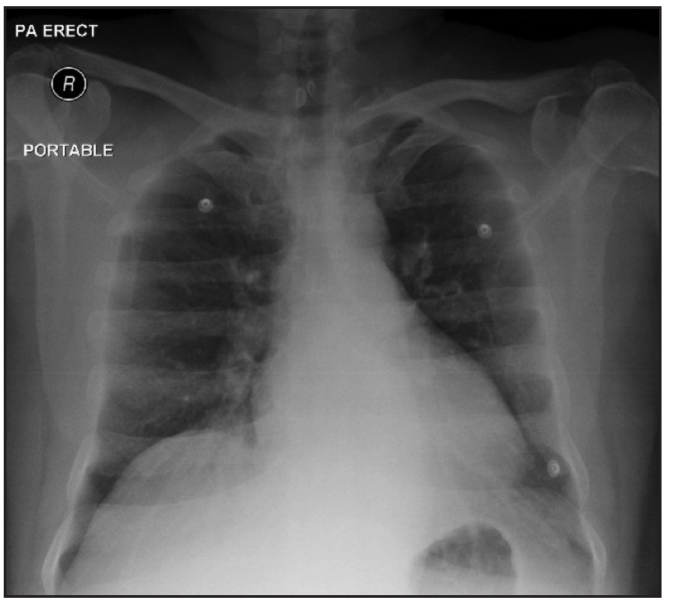

Fig. 1: Chest X-ray showing ground glass opacities with interstitial infiltrates over bilateral lung fields.

and markers such as interleukin-6, CRP, LDH, ferritin and D-dimer. Current data suggest that this phase is caused by a dysregulated host innate immune response. The hyperinflammatory response in COVID-19 shares similar clinical characteristics with dengue-associated HLH, which is a state of uncontrolled hyperinflammation caused by persistent stimulation of lymphocytes and histiocytes resulting in hypercytokinaemia. Ferritin levels have been used as a prognostic tool for COVID-19 as they have been shown to be significantly higher in patients with severe disease, though concentrations rarely exceed the HScore threshold of 2000ng/mL within 16 days after the symptom onset.[1]

There are many case reports of co-infection of dengue and COVID-19 worldwide,[2,5] however, as of writing, none had reported hyperferritinaemia or suspected HLH. It is unknown if a concurrent infection of both diseases results in a more severe clinical course, or if it increases the risk of hyperinflammation. In this case, we hypothesised that the patient may be progressing to HLH in view of clinical findings of fever, splenomegaly, hypertriglyceridaemia and hyperferritinaemia. A diagnosis of HLH should be considered if the patient fulfils ≥4 of the 8 HLH-2004 diagnostic criteria, or if HScore probability of HLH is 70% or greater. However, bone marrow examination was not performed. Case reports have described findings of dyserythropoiesis and haemophagocytosis on bone marrow aspirates in patients with clinically diagnosed HLH, though it is not commonly performed in dengue fever due to risk of bleeding.

Dengue-associated HLH is also more commonly seen in severe dengue,[3] defined as the presence of severe plasma leakage leading to shock, haemorrhage, and organ involvement. DENV serotype 2 has also been associated with a higher prevalence of severe dengue by a study by Suppiah et al. Interestingly, our patient does not fulfil the criteria for severe dengue and serotyping had revealed infection with DENV serotype 3.

There is a marked heterogenicity of literature regarding management of acquired HLH. Various case reports of dengue associated HLH have shown clinical improvement in patients after a brief course of corticosteroids,[4] as opposed to a more prolonged corticosteroid therapy used for other forms of acquired HLH with a protracted course of disease trigger. Likewise, a meta-analysis by the World Health Organisation (WHO) Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group published in September 2020 have shown a reduction in mortality in COVID-19 patients with hypoxia with the use of systemic corticosteroids for 7-14 days. In our case, the patient responded well to treatment with just a short course of dexamethasone, and blood parameters had normalised at a reassessment 2 weeks after corticosteroids were stopped.

Concerns regarding serological cross-reaction of SARS-CoV-2 and DENV have been highlighted by case reports of false-positive results from serological testing for dengue IgM in patients with COVID-19. This was first reported in a case report from Singapore[5] in March 2020, which described two patients who initially tested positive for dengue IgM but later confirmed to have SARS-CoV-2 infection. In dengue-endemic areas, this carries serious consequences for the public health as a presumed diagnosis of dengue based on positive serological testing may result in a missed or delayed diagnosis of COVID-19. It is thus imperative that patients presenting with fever and a positive dengue serological test to be screened for COVID-19 especially during an active outbreak. Likewise, a co-infection of dengue fever should be considered in a patient with confirmed COVID-19 presenting with a constellation of persistent fever, leucopaenia and thrombocytopaenia, especially in tropical countries where dengue fever is prevalent.

CONCLUSION

A diagnosis of COVID-19 and dengue coinfection should always be considered in the setting of a dengue-endemic area. A high index of suspicion for dengue-related haemophagocytic lymphohistiocytosis is crucial in patients with hyperferritinaemia as mortality is greatly reduced by prompt initiation of corticosteroids. Further research is warranted to study the outcome of COVID-19 and dengue coinfection, and serological cross-reactivity between both conditions should be considered in the management of the ongoing pandemic.

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