CASE STUDY

Hyperinflammatory syndrome: Two viruses, similar story

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Abstract

Objective: In countries where the co-existence of both dengue fever and COVID-19 infection is predominant, it is often difficult to clinically distinguish between the two entities. The present study highlights the similarities and differences between these viral diseases through two cases.

Results: The first case was of a 38-year-old hypertensive and diabetic female, diagnosed with dengue hemorrhagic fever with leucopenia and thrombocytopenia (26000/mm^3). HRCT chest revealed diffuse mosaic attenuation and small pleural effusion in both lower lobes. Elevation in D-dimer and deranged liver function test were noted. One-month follow-up revealed that she had persistent fever, fatigue, and musculoskeletal and psychological symptoms. Her symptoms improved with hydroxychloroquine 400 mg/day and a tapering course of steroids.

The second case was of a 57-year-old hypertensive male, who presented with resolved mild COVID infection, blanching rash over the dorsal aspect of both hands with active synovitis around left wrist, elbow, and right ankle, and severe painful restriction of the joints. Positive COVID IgG, increased inflammatory parameters, and raised ferritin were noted. The patient showed symptomatic improvement with gradual reduction in inflammatory parameters following tapering dose of steroids and hydroxychloroquine treatment.

Conclusion: Persistence of symptoms and increased inflammatory parameters were noted in both cases post viral clearance, suggesting a non-degenerative immune response, leading to collateral damage. The treating physicians should consider such a possibility and treatment with glucocorticoids in this scenario would be prudent.

Keywords: hyperinflammatory, COVID,dengue

Introduction

The COVID-19 infection was escalated to a pandemic status in March 2020.[1] Over forty-six million patients have been reported to be infected with the virus as of November 1st 2020.[2] Tropical countries also see numerous viral fevers that have a similar presentation as COVID and can be a major cause of misdiagnosis. With the emergence of the dengue season, healthcare workers are faced with the challenge of differentiating these similarly presenting illnesses.[1]

Post-viral inflammatory syndrome, a well-described entity with significant adverse health impacts, has been a matter of debate. The first description of the syndrome dates back more than 50 years.[3] The causes for the development of these sequelae have been attributed to various immune response aberrations. They include cross-reactive antibody response, transient immune suppression, persisting viral antigen, and genome triggering and persisting immune response.[4] These are described in relation to many viral and bacterial infections. Due to the increased incidence of co-existing dengue and COVID infections in India and tropical countries, it is often difficult to distinguish between these two, and the recent discussions related to COVID have brought the syndrome into the limelight.

The present study discusses two separate clinical cases of post-viral inflammatory syndrome that occurred following dengue and COVID-19.

Case 1

A 38-year-old hypertensive and diabetic female, presented with episodes of fever with chills, rigors, myalgia, and fatigue for three months. She was previously admitted to a secondary

care hospital for high-grade fever, nausea, and headache. The patient was evaluated for dengue and tested positive for NS1 antigen, while testing negative for COVID-19 RT-PCR by throat swab. During the course of her hospital stay, she developed dengue hemorrhagic fever with hematemesis and melena, leucopenia, and thrombocytopenia (26000 /mm^3). She received 1 unit of single donor platelet (SDP). HRCT chest revealed diffuse mosaic attenuation and small pleural effusion in both lower lobes. The D-dimer was 5559.96 ng/ml and the liver function test (LFT) showed increased aspartate transaminase (AST-2444 mg/dl), alanine transaminase (ALT- 682 mg/dl), and gamma-glutamyl transferase (GGT-697 U/L). The patient was discharged after 15 days of ICU treatment, with normalized platelets and leucocyte counts.

She was followed up regularly by treating physicians. The fever persisted for five days in a week following discharge and the frequency decreased gradually. There were no symptoms to suggest a focus of infection during this period. She had severe muscular pain and fatigue. She also gave a history of psychological symptoms like feeling low, inability to concentrate, and problems with memory for which a psychiatrist opinion was sought. Clinical investigations repeated after 1 month of discharge, showed a persistent high D-dimer (5697 ng/ml) and increased serum ferritin (329.5 ng/mL) and CRP (76 mg/L). The AST, ALT, and GGT had reduced to 43 mg/dl, 18 mg/dl, and 59 U/L respectively. Doppler of the lower limbs was normal. Transthoracic ECHO showed pulmonary artery systolic pressure (PASP) of 37 mmHg with normal ejection fraction (EF- 60%) and no evidence of infective endocarditis. Evaluation of blood and urine cultures was sterile. CT of neck to pelvis showed splenomegaly (15.5cm), fatty liver, and renal calculi.

The patient was referred to our center upon suspicion of probable rheumatic disease. Her last febrile episode was 10 days prior to the present consultation. Her vitals and systemic examination were normal. Autoimmune workup showed that angiotensin-converting enzyme (ACE) levels were 46.6, and negative for anti-nuclear antibody (ANA), anti-double stranded DNA (dsDNA), ANA profile, and anti-neutrophilic cytoplasmic antibodies (ANCA). Although CRP (34.6) was elevated initially, it showed a dropping trend, and D-dimer also reduced to 2715 ng/ml. Serum ferritin had decreased to a borderline value of 113.5 ng/mL, and lactate dehydrogenase (LDH) was high (338 u/L). Interleukin 6 (IL-6) was 14.48. Test for COVID IgG was negative. Fibrinogen was high with a value of 378.3 mg/dl. The LFT had returned to normal and the dengue profile was negative. In view of persisting raised D-dimer, antiphospholipid antibodies (APLA) profile was carried out and the result was negative. As her autoimmune profile was negative and only inflammatory parameters were high, the diagnosis was concluded as hyperinflammatory syndrome.

The patient was initiated with hydroxychloroquine 400 mg/day and a tapering dose of steroids. She had demonstrated symptomatic improvement in the myalgia and fatigue, with no recurrence of fever at 1-week follow-up. One-month follow-up showed significant improvement in symptoms with mild fatigue and psychological symptoms.

Case 2

A 57-year-old hypertensive male presented with a history of asymmetric polyarthritis of 15 days duration. It started with the involvement of the left elbow and progressed to the knee and ankle in a migratory pattern. He was diagnosed with COVID 1 month prior to the present visit. The episode of COVID infection was mild with the patient having symptoms and signs involving the upper respiratory system. The patient did not require hospitalization or oxygen support during the course of infection.

Due to the initial presentation of single joint involvement (left elbow), the patient was initially evaluated for septic arthritis. Synovial fluid aspiration from the elbow yielded a normal report. Physical examination revealed a blanching rash over dorsal aspect of both hands with active synovitis around left wrist, elbow, and right ankle with severe painful restriction of the joints. The patient had been investigated on day 15 post fever, which showed a normal CBC with increased erythrocyte sedimentation rate (ESR 90 mm/hr) and CRP (22 mg/L) levels.

Investigations repeated at 1-month post fever revealed normal CBC and platelet counts with an elevated ESR (90 mm/hr) and CRP (47.40 mg/L). Workup for chikungunya was also negative. Except for the GGT (121 U/L), the LFT was normal. However, serum ferritin was high (1085 ng/mL) and COVID IgG was positive (7.1 u/ml). He was diagnosed with post-COVID hyper-inflammatory syndrome with synovitis and managed with a tapering dose of steroids and hydroxychloroquine. The patient showed symptomatic improvement with gradual reduction in inflammatory parameters.

Discussion

COVID-19 infection is caused by SARS-CoV-2, which is an

Table 1: Comparison of cases 1 and 2

	Case 1:(Dengue)				Case 2:(COVID)		
	Onset		Post-infection		Onset		Post-infection
Symptoms	High grade fever, Severe headache, nausea and vomiting. Malena		Persistent fever, fatigue, musculoskeletal symptoms, psychological symptoms		High grade fever with upper respiratory tract symptoms, cough		Migratory polyarthritis, skin rash, fatigue
Days post onset of fever	Day 7	Day 60	Day 80	Day 116	Day 15	DAY 30	Day 45
ESR	NA	NA	30	55	90	90	41
CRP	NA	76.4	34.6	19.3	22	47.4	1.6
TC	NA	NA	8400	10720	10800	8190	8550
PLT	26000	NA	3.49	2.44	1.98	2.02	2
D-dimer	NA	5697	2715	414	NA	NA	<25
AST	2444	43	40	21	NA	15	NA
ALT	682	18	23	32	24	30	NA
GGT	697	59	69	95	NA	121	NA

ESR: erythrocyte sedimentation rate; TC: total counts; PLT: platelet counts; CRP: C-reactive protein; AST: aspartate transaminase; ALT: alanine transaminase; GGT: gamma glutamyl transferase

enveloped positive-sense RNA virus belonging to the beta coronavirus genus. The disease can have a varied spectrum of presentations from asymptomatic disease to multi-organ failure. The virus spreads by droplet transmission and enters through the mucous membrane via eyes, nose, and mouth. The dengue virus (DENV), which is a single-stranded RNA virus belonging to the flaviviridae family is responsible for dengue fever. It is a mosquito-borne pathogen.

After mucosal entry of the COVID virus, it infects the pneumocytes and triggers a viral cytopathic effect that incites the innate immune system to release various inflammatory cytokines. These cytokines activate the adaptive immune system, which in turn increases the cytokine concentrations. Leisman et al. proposed that COVID-19 is independent of the classic acute respiratory distress syndrome (ARDS) and cytokine storm syndrome (CSS) is a different entity with much lower IL-6 concentration in comparison to both diseases. The researchers also suggested that COVID-19 is a disease of the blood vessels, separated by three phases, which ultimately ends with endothelial dysfunction.[5]

Endothelial dysfunction is the hallmark of dengue fever. The three principal pathophysiologies responsible for the aberrant immunological response are T-cell immunology, antibody-dependent enhancement (ADE) of the virus, and complement activation in dengue. Even though both dengue fever and COVID infection have different pathophysiology and initial targets, the ultimate damage caused is due to endothelial dysfunction.

Fever is the most common presentation of dengue and COVID. The characteristic pattern of fever in dengue is usually high grade, occasionally with two peaks of temperature also known as saddleback fever. The pattern of COVID-associated fever has not been defined yet, as the presentation can be varied. Both the patients presented initially with high-grade fever. However, the patient diagnosed with dengue had a longer-duration of fever associated with severe headache, nausea, and vomiting. The patient diagnosed with COVID had a short duration of intermittent type of fever lasting for a couple of days.

Garcia et al. have noted the persistence of symptoms post-dengue fever, which is more common in women than men. In concurrence with this finding, the present dengue patient was a female with persistent psychological and physical symptoms post 4 months of infection.[4]

Both dengue and COVID have been shown to be associated with leukopenia and thrombocytopenia. The occurrence of leukopenia and thrombocytopenia with bleeding manifestations is predominantly associated with dengue hemorrhagic fever. It can also be seen in COVID infections.[6] There is evidence to suggest post-viral musculoskeletal sequelae in both COVID and DHF. Studies suggest the occurrence of musculoskeletal symptoms in about 15-44% of post-COVID patients,and in about 12% of the patients with

post-dengue fever.[6,7] The presence of respiratory symptoms is more in favor of COVID infection. Liver injury in dengue fever is mediated by direct injury to the hepatocytes by the virus and can lead to increased liver enzymes. COVID infection also can bring about liver injury, but it is more commonly observed in severe cases.[8]

COVID patients have shown an increased level of D-dimer, especially in severe cases. In the present cases, it has been used as a prognostic tool. In dengue hemorrhagic fever, cytokine release leads to increased vascular permeability, which is concurrently accompanied by a thrombotic state leading to disseminated intravascular coagulation (DIC), which is characterized by increased D-dimer.[8,9]

Multisystem inflammatory syndrome (MIA) is a rare but severe complication seen post-COVID-19 infection, occurring around 2-15 weeks after the infection. It was initially identified in children (MIA-C) in April 2020 and was also later observed in adults (MIA-A). Multisystem inflammatory syndrome is usually characterized by the presence of positive results for current or recent SARS-CoV-2 infection in a patient presenting with fever with laboratory evidence of inflammation and evidence of clinically severe illness requiring hospitalization with multisystem involvement.

The aforementioned cases show the persistent hyperinflammatory state that can follow a viral infection. It has been an entity that existed before, but with the appearance of COVID-19 there has been an increased recording of this syndrome. In both diseases, the persistence of symptoms and increased inflammatory parameters post-viral clearance suggests a non-degenerative immune response, which results in collateral damage and symptoms.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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