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Case Study

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POST SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2): MULTISYSTEM INFLAMMATORY SYNDROME IN ADULTS (MIS-A) MIMICKING A FUNGAL INFECTION

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BACKGROUND

Multisystem inflammatory syndrome, a multifaceted condition seen mostly in children after COVID-19 infection (Coronavirus disease -19), was first reported in the UK in April 2020. Since then, it has been fringing into the adult population, with cases being reported since June 2020. The clinical manifestations of the condition are widespread involving multiple systems such as mucocutaneous, cardiac, gastrointestinal, hematological and neurological system. These symptoms are associated with elevated inflammatory markers, the persistence of fever, and signs of shock. In addition, the respiratory system that is typically involved in patients with SARS-CoV-2 is not always seen in the MIS. MIS-A not only differs in the involved age group from MIS-C, but it also tends to be more severe, given the underlying medical conditions and a probable frail immune system.[1,2] Differentiating MIS-A from acute COVID-19 infection is grueling. While evaluating the patients with severe COVID-19 infection, physicians should also have a high degree of suspicion for MIS-A, because of a high proportion of patients may be suffering from MIS-A.[3] We will be describing how a rare case of MIS-A, unraveled by multiple brainstorming differentials ameliorated with the administration of steroids, stressing the importance of a focused diagnosis.

KEYWORDS: Differentiating MIS-A from acute COVID-19 infection is grueling.

CASE PRESENTATION

A 45-year-old female presented with complaints of a frontal headache for 4 days. She also had complaints of low-grade fever and nausea for a day which subsided with medication. The patient tested positive for COVID-19 by Reverse transcriptase Polymerase chain reaction (RT PCR) test a month back, during which she received prophylactic antibiotics and supportive measures. No steroids were used. She also has a history of hypothyroidism for which she is currently taking medication.

At this visit, she tested positive for COVID IgG antibody, but the antigen and IgM were negative. No significant neurological abnormalities were detected. On auscultation of her lungs, bilateral crepitations were observed. However, she did not require O2. Due to desaturation the day after her admission, she was started on O2 at a baseline of 1-2 liters/min. About 5 days after admission, she developed an upper abdominal pain

INVESTIGATIONS

Her blood profile including CBC (Complete blood count), and LFT (Liver function test) were unremarkable on admission. However, inflammatory markers like C-reactive protein, D-dimer, procalcitonin, and ferritin were elevated. Magnetic resonance imaging (MRI) of the brain revealed features of ethmoidal and maxillary sinusitis but was otherwise unremarkable. A chest X-ray was done which revealed multiple inhomogeneous opacities bilaterally in the mid and lower zones (**Figure 1**).

Computed Tomography (CT) of chest revealed a moderate-sized area of consolidation in the right upper lobe, likely having an infective origin of possible fungal etiology (**Figure 2**). The differentials considered at this moment were Mucor mycosis, tuberculosis, and aspergillosis. She was started on the antifungal Micafungin.

A bronchoalveolar lavage was done because of suspicion of Mucor mycosis/fungal infection. The results of the same revealed a total cell count of 150 cells/ mm3, the differential count showed a normal neutrophil to lymphocyte ratio of 50/10, macrophages were about 30%, and epithelial cells were 10%. Bronchoalveolar Lavage (BAL) was negative for atypical cells and granulomas.

She also underwent a gene expert analysis which was negative, cultures were sterile and Potassium hydroxide (KOH) was negative for fungal elements. Also, the sputum sample for Acid-fast bacillus was negative. Since there was a high suspicion of Mucor mycosis, opinions from Ophthalmology and Otorhinolaryngology were taken, but were unremarkable.

The Galactomannan test was negative as well. The blood picture was suggestive of leucocytosis and thrombocytopenia. At this time, an echocardiogram was done, which reported moderate Pulmonary Arterial Hypertension, grade II Tricuspid Regurgitation, Mitral Regurgitation, and trace Pericardial Effusion. A repeat echocardiogram done on day 5 showed mildly dilated right and left atrium, and severe Tricuspid Regurgitation.

Her cell counts were normal on admission but started to derange soon. She developed thrombocytopenia (platelet count of 56-64 K/uL, normal: 150-400K/uL), leucocytosis (WBC count of 22.6-25.2 K/uL, normal:10-15) and anemia (hemoglobin ranging from level of 7.8-9.3 gm/dl). Her hemoglobin fell to 7 g/dl on day 7 after admission. She had a normal MCV (mean corpuscular volume) with low hematocrit.

Patient's inflammatory markers were found to be drastically elevated 3 days after admission, with the value of D-dimer being 1579.2 ng/mL (normal: <500 ng/ml), C-reactive peptide of 374.6 mg/L (normal in disease-free population: <3mg/dL, in SARS CoV-2 it can rise up to 30-50 mg/dL), lactate dehydrogenase (LDH) of 223 U/L (normal: 140-280 U/L), and Ferritin of 840.7 ng/mL (normal: 12-263 ng/ml).

Contrast-enhanced computed tomography (CECT) of abdomen performed because of the complaint of abdominal pain, revealed Acute Edematous Pancreatitis (**Figure 3**). However, her amylase and lipase levels were normal. Thus, a viral or drug-induced pancreatitis was suspected. Her triglyceride was elevated with levels being 409mg/dL. This was followed up by an ultrasound of abdomen and pelvis, which revealed a normal gall bladder and common bile ducts.

Her LFTs were modestly elevated with values of Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) being 41 U/L (normal: 20-65 U/L) and 43 U/L (normal: 15-37 U/L) respectively. Alkaline Phosphatase (ALP) and Gamma Glutamyl Transferase (GGT) of 225 U/L (normal: 50-136 U/L) and 203U/L (up to 30U/L) were seen respectively. Her Amylase and Lipase levels were 35 U/L and 63.8 U/L on the 5th day and 60 U/L and 75.7 U/L on the 8th day after admission.

Her NT pro-BNP (at 12568 pg/mL) levels were markedly elevated at the time when the Echocardiogram was done. Her fibrinogen level was 599 mg/dL. Her Procalcitonin levels on the 2nd day of admission were high at 10.5 ng/mL, pointing towards a secondary bacterial infection. This was followed by a gradual decline subsequently. Further evaluation of the blood urine and sputum cultures were found to be sterile.

Other tests performed to rule out an underlying rheumatological phenomenon including ANA (Anti-nuclear antibody), cardiolipin, serology film array, etc were negative.

After initiation of steroids, serial monitoring of her blood parameters showed a decreasing trend. She was discharged after a clinical and laboratory evaluation and showed significant improvement.

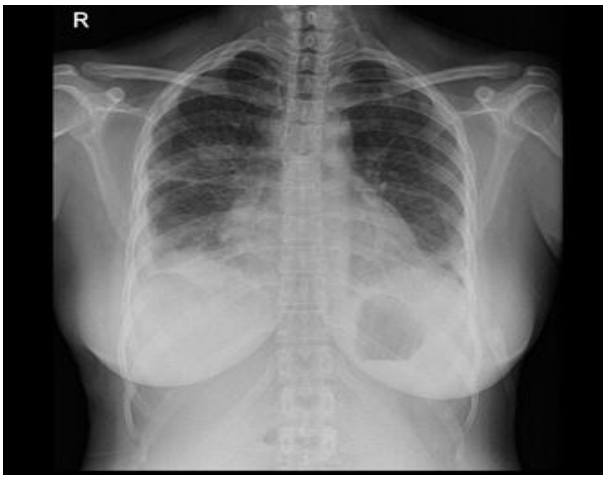

Figure 1: Chest X Ray showing multiple inhomogenous opacities in bilateral mid and lower zones.

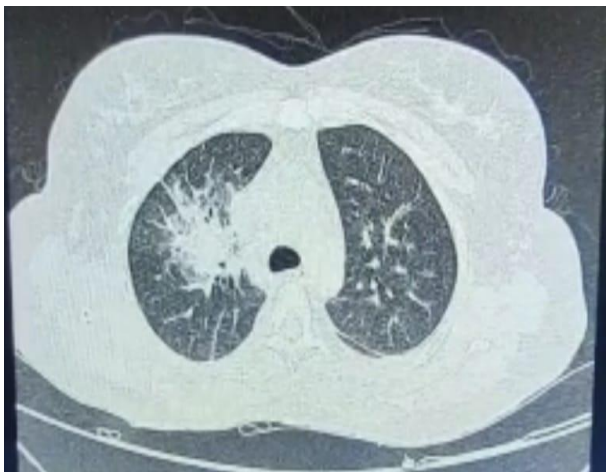

Figure 2: CT thorax showing multiple parenchymal parenchymal fibrotic and atelectatic bands noted

bilaterally. Moderate sized area of consolidation in the right upper lobe.

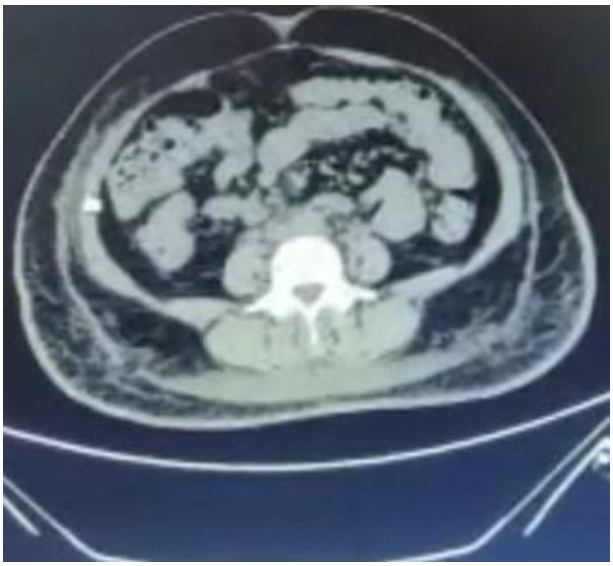

Figure 3: Contrast enhanced CT abdomen showing an acute oedematous pancreas with mild peripancreatic fat stranding.

DIFFERENTIAL DIAGNOSIS

1. Viral or bacterial pneumonia: There was a patch of consolidation on the X-ray in the superior lobe of the lung. Thus, broad-spectrum antibiotics were initiated. Cultures after 3 days turned sterile, and the patient responded to steroids.
2. Pulmonary thromboembolism: Elevated D dimers in the setting of breathlessness and desaturation.
3. Mucor mycosis: Post COVID-19 infection, the presence of a patch on HRCT chest with a possible infectious etiology. Along with the possibility of sinusitis (headache and fever with MRI brain that was done for cavernous vein thrombosis revealing ethmoidal sinusitis) increased the suspicion of this condition which on further analysis was negative for galactomannan, KOH mount, and BAL. However, since these are not diagnostic of Mucor mycosis a certain duration of antifungals was considered as well.
4. Cavernous vein thrombosis: Presentation of headache, fever, and nausea with elevated D dimers increased our suspicion of CVT, for which an MRI brain was done, which did not reveal features of thrombosis of the vessels acutely.

TREATMENT

Iron deficiency was noted, and the patient was started on supplements. She was started on Posaconazole for a suspected fungal infection and in order to cover secondary bacterial infections, she was started on broad-spectrum antibiotics (initially Ceftriaxone then it was titrated to Piperacillin and Tazobactam and further escalated to Etoperidone and Sulbactam).

The patient was shifted to the ICU about 4 days after admission because of tachycardia and hypotension and was on antifungals for possible invasive fungal infections. Since her Blood pressure dropped to 80/50mmHg, she was started on Noradrenaline, Amiodarone, and Labetalol for new onset of atrial fibrillation. A diuretic was also started as she had signs of heart failure.

Because of her lack of improvement with the extensive medications, and the results of her investigations hinted towards the diagnosis of MIS-A, she was started on Dexamethasone injection. Consequently, an improvement in her blood counts was seen, her requirement of O2 subsided and there were no fluctuations in her temperature.

OUTCOME AND FOLLOW-UP

After initiating steroids in the patient, her requirement for oxygen dropped, her laboratory parameters showed a drastic improvement, and X-ray features were reversed.

DISCUSSION

MIS can involve multiple systems and occurs a few weeks after infection with SARS-CoV-2. The proposed mechanisms for the same could be antibody-mediated post-SARS-CoV-2 infection or dysregulated immune response.[3] The features of MIS have features similar to Kawasaki disease, macrophage activating system, or even a cytokine release syndrome.[4]

In a recently published case series, the case definition of MIS-A was described as per the following criteria: 1) severe illness requiring hospitalization in a person aged ≥21 years, 2) a positive test result for current or previous SARS-CoV-2 infection during admission or in the previous 12 weeks, 3) severe dysfunction of one or more extrapulmonary organ systems, 4) laboratory evidence of severe inflammation and 5) absence of severe respiratory illness.[5] Our case met most of the criteria mentioned above which are currently the guidelines for the diagnosis of the condition.

Patients may have had a preceding COVID infection that could have been asymptomatic. As the RT-PCR test can come out to be negative a few weeks after, a positive antibody response should indicate a previous SARS-CoV-2 infection.[6] This was also seen in our case, as our patient was IgG positive for SARS-CoV-2 and was negative for antigen or IgM. Rarely, the RT-PCR can be positive for weeks. Also, the antibody tests are not highly suggestive of MIS-A.

In a case series report of 15 patients with MIS-A, about 60% had acute COVID symptoms, 33.3 % of patients required ICU admission, and 20% were diagnosed with shock. The mean interval of admission for MIS-A after COVID-19 infection and the median number of organ systems affected were 28 days and 4, respectively.[7] In congruence with our patient, who required ICU

admission and developed severe shock requiring vasopressor administration during the infection phase about a month ago, and had the involvement of the Gastrointestinal (CT findings of Acute Edematous Pancreatitis), Hematological (decreased hemoglobin and thrombocytopenia), and Cardiac (abnormal echocardiogram findings and high NT pro-BNP) system.

The clinical presentation of MIS-A is suffused and severe, making its diagnosis even more challenging. As per a case series done in the United Kingdom on MIS-A, fever was the most common symptom. Specific systems that can be involved in MIS-A include mucocutaneous, cardiac, gastrointestinal, and neurological systems.

It has been observed that further evaluation of cardiac manifestations like chest pain can show changes in ECG changes with arrhythmia, elevated troponin levels, or cardiac dysfunction (both right and left ventricle) on echocardiogram.[8] This was seen in our case, as the patient had signs of heart failure including pedal edema, which prompted an echocardiogram which revealed dilated RA and LA associated with Tricuspid Regurgitation and Mitral Regurgitation.

The next common manifestation described in the case series report as was seen in the case was the gastrointestinal manifestation of abdominal pain.[9] Our patient also had this symptom, and the CECT done for it revealed Acute Edematous Pancreatitis.

However, our case revealed no indication of any neurological signs or dermatological manifestations which are other involved systems in MIS-A.

Laboratory parameters that were found to be elevated in these patients were D-dimer (ranging between 271 to 8691), CRP (ranging between 84 to 580 mg/L), and Ferritin (between 196 to >100,000 ng/mL).[9] Our patient's D-dimer was found to be elevated (334-4488) as well indicating a possible underlying coagulopathy. CRP ranged from 39.8 to 308 and Ferritin in the range of 800's. In contrast to the study which showed a reduction in the lymphocyte count, our patient initially had elevated lymphocyte counts.

Chest X-ray findings and hypoxemia are considered rare findings in patients with MIS-A. However, our case had an HRCT report of bibasilar atelectasis moderate-sized right upper lobe consolidation of the lung, reported as an infectious etiology. Her laboratory picture with increased inflammatory markers and clinical picture of hypoxemia in the setting of prior infection with COVID-19 increased the probability of a diagnosis of fungal infection and the possibility of a secondary bacterial infection for which antifungals and broad-spectrum antibiotics were started.[10]

A differential of fungal pneumonia should be considered in patients with severe COVID-19 infection.[11] The complexity of the disease is in the negative biomarkers (such as beta D glucan) and its prevalence in immunocompetent individuals. Although rare in most parts of the world, India has reported a considerable number.[12]

The diagnosis of fungal infection requires serology, antigen testing, and PCR-based assays.[13] As was done in our case, where a Bronchoalveolar lavage sample was tested for fungal elements by doing a KOH mount, and cultures (blood and sputum) were found to be negative as well. Galactomannan being negative and there being evidence of sinusitis on MRI, there was an increased suspicion for Mucor mycosis. The patient was thus started on Micafungin and Posaconazole per the evidence.[11]

Other than the age limit, our patient fits the MIS-C case definition criteria of both CDC and WHO.[14,15] As per the two case reports where the manifestation of the patients was similar to the vasculitis condition, Kawasaki disease in children responded positively to Steroids, Aspirin, and IVIg. However, the use of Tocilizumab and anticoagulant Low Molecular Weight Heparin has in one case shown to be of benefit.[16,17] Our patient had also responded to the initiation of steroids, while she was already on an anticoagulant for her elevated inflammatory markers.

The etiopathogenesis is not clearly understood in the case of patients with MIS. However, in children, the pathogenesis studies were in terms of immune dysregulation and the SARS-CoV-2 virus itself. One such hypothesis is the IgG mediated activation of the immune system (more so of CD8+ T cells) which differentiates this from an acute severe COVID infection.[18] As per a study done by Pang J et al, there was no difference in the viral phenotypes between patients who develop MIS-C and those who do not, thus implying a possible immune mechanism.[19]

Our case throws light on the point that patients presenting with post COVID-19 symptoms need to be evaluated for MIS-A along with secondary infections because the treatment plan should include the usage of steroids along with necessary antibiotics.

LEARNING POINTS

1. In Patients with a recent history of SARS CoV-2 and a presentation of pneumonia, a possibility of Multisystem inflammatory syndrome should be considered.
2. Patients may have an atypical presentation involving the lungs, mimicking various other respiratory conditions including pneumonia or pulmonary thromboembolism. Thus, differentiating a severe COVID infection from the possibility of a multisystem inflammatory syndrome should be considered.

3. The increased prevalence of the 'BLACK FUNGUS' (as is colloquially referred to), Mucor mycosis, although is one of the most important differentials as was seen in our case, MIS-A is something that flanks Mucor mycosis post-SARS CoV-2. Steroids are contraindicated in fungal infections however are the drugs of choice in MIS-A. Underlying the importance of the diagnostic consideration.

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