

# The First Fatal Post-COVID-19 Adult Patient with Multi-System Inflammatory Syndrome in Israel

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Coronavirus disease-2019 (COVID-19) is recognized as a respiratory illness, which includes pulmonary consolidations, hypoxemic states, and hypercoagulopathic tendencies with a broad clinical severity. Recently, more reports have described post-infection manifestations. These include multi-system inflammatory syndrome in children (MIS-C) with more than 400 cases published since the start of the coronavirus disease pandemic. In October 2020, the U.S. Centers for Disease Control and Prevention (CDC) published 27 cases [1] describing the new multi-system inflammatory syndrome in adults (MIS-A). Nine of the cases were reported directly to the CDC, 7 from published case reports and another 11 patients found in three distinct case series.

The CDC uses five criteria to diagnose patients with MIS-A:

- Severe illness requiring hospitalization in patients < 21 years of age
- Positive test result for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (PCR, antigen, or antibody)
- Severe dysfunction in one or more extra pulmonary systems
- Laboratory evidence of severe inflammation
- Absence of severe respiratory failure

The dataset included patients between the ages of 21 and 50, the majority of

whom were of Hispanic, Asian, or African descent. One patient was Caucasian with presenting symptoms of fever, chest pain, and a rash and was subsequently diagnosed with reduced ejection fraction requiring vasopressor support [2].

We describe the first case in Israel of 59-year-old Caucasian female who fulfilled the CDC criteria with a rapid deterioration resulting in death.

## PATIENT DESCRIPTION

A 59-year-old Caucasian, with a medical history of hyperlipidemia and hypertension presented to the emergency department of Shamir Medical Center (Assaf Harofeh) in November 2020 with fever, severe weakness, odynophagia, and cervical lymphadenopathy of 3 days duration. She was diagnosed with COVID-19 by a PCR test 20 days prior to her arrival with no respiratory symptoms and reportedly normal oxygen saturation throughout her quarantine time.

Her vital signs and oxygen saturation on room air were normal. Her vital signs and oxygen saturation on room air were normal. On examination, swelling of right cervical lymph nodes, with discomfort on palpation was noted with a macular rash found on the neck and chest. The remaining physical examination was normal. Laboratory results displayed normal blood count and kidney function, a very mild increase in liver function tests, primarily hepatocellular, aspartate transaminase (AST) 39  $\mu\text{L}$ , alanine transaminase (ALT) 51  $\mu\text{L}$ , alkaline phosphatase (ALP) 115  $\mu\text{L}$  (normal values AST <

32  $\mu\text{L}$ , ALT < 31  $\mu\text{L}$ , ALP < 117  $\mu\text{L}$ ) and a mild impairment in the coagulation tests. Inflammatory markers C-reactive protein (CRP) and ferritin were markedly increased. SARS-CoV-2 from a nasopharyngeal swab was positive, blood cultures were negative, and chest X-ray was unremarkable. Examination by an ear, nose, and throat specialist revealed right jugulodigastric lymph node swelling. Computed tomography (CT) neck examination showed mild enlarged lymph nodes on the right side with signs of small liquefaction within one of the nodes. Broad-spectrum antibiotic treatment was initiated with ampicillin, and subsequently converted to ceftriaxone and clindamycin due to suspected soft tissue involvement.

During the first 2 days of hospitalization the patient reported an improvement in the swelling and tenderness in the neck, but complained of diarrhea and palmar edema, which was attributed to initiation of a new antibiotic therapy. Procalcitonin level was 0.52  $\mu\text{g/L}$  (normal < 0.5  $\mu\text{g/L}$ , highly suspicious of bacterial infection > 2  $\mu\text{g/L}$ ) and the inflammation markers continued to rise. On the third day of hospitalization the patient started complaining of shortness of breath and oxygen saturation dropped to 94%, corrected by nasal cannula -oxygen.

Blood pressure was 97/51 mmHg. CT angiography ruled out pulmonary embolism and showed wide coronary sinus and inferior vena cava (IVC) with hepatic vein reflux and a normal sized heart. Minimal pleural exudates and small amounts of free fluid were noted around the pancre-

as and the gallbladder with no widening or stones in the common bile ducts or gallbladder. The liver was noted to have mild periportal edema. The patient was transferred to the intensive care unit (ICU) with a mild rise in troponin to 0.06 ng/mol (normal level < 0.013 ng/mol). The electrocardiogram (EKG) demonstrated a normal axis, sinus rhythm, and mild ST elevation in leads 1 and 2.

Liver function tests were increased: AST 235 µg/L, ALT 174 µg/L, and lactate dehydrogenase (LDH) rose to 1293 µg/L (normal 240–480 µg/L). The patient developed severe metabolic acidosis pH 7.28 with lactate 6.8 mmol/L (normal 0.2–2.2 mmol/L) and CRP peaked at 368.7 mg/L. Amylase and lipase were within normal limits and blood cultures returned negative. The patient was intubated. Due to suspected cholecystitis a percutaneous ultrasound guided cholecystostomy was performed draining clear and sterile bile. Hydrocortisone, mucomyst, high dose noradrenaline, glypressin, and adrenaline were administered, as well as meropenem and flucanazole antibiotics.

During the 30 hours in the ICU, the patient rapidly deteriorated and levels of hepatocellular enzymes continued to rise into the thousands, with lactate levels reaching 20 mmol/L and LDH 22159 µg/L. Kidney failure was treated by continuous veno-venous hemofiltration. Heart and respiratory failure as well as severe shock did not respond to treatments and the patient was pronounced dead 5 days after admission. A post-mortem examination was not performed.

**COMMENT**

A soft tissue infection was initially suspected in our patient presenting with local tender lymphadenopathy, which was treated accordingly with appropriate antibiotic. However, as the patient quickly deteriorated, with shock and multi-sys-

tem failure, other diagnoses were sought and ruled out including pulmonary embolism, pancreatitis, and acute myocardial infarction.

Although fulminant bacterial infection causing rapid and deteriorating shock cannot be completely ruled out; the lack of improvement with broad-spectrum antibiotics, the absence of bacterial growth on repeated blood cultures, the borderline procalcitonin, and the sterile bile fluid strongly refutes this diagnosis. Thus, a potential post-COVID-19 complication is most feasible particularly in view of the increasing number of patients with post-COVID-19 complications who are re-admitted. Such a post-infection complication is the MIS-A syndrome, common in children and recently emerging in adults.

Our patient fulfilled all the CDC criteria for MIS-A, presenting with clinical findings similar to those of MIS-A patients, including lymphadenopathy, odynophagia, fever, and a mild rash. There was also an increase of inflammatory blood markers and a mild increase in liver function tests and creatinine, through the first days of admission with a typical fulminant rapid, deterioration in the last 48 hours of hospitalization, resulting in death.

Taken together, the typical findings on admission, the systemic nature of the disease, the very high levels of inflammatory markers and the absence of evidence of an infectious agent together with failure of antibiotic treatment underscore the diagnosis of a multi-system inflammatory disorder, namely MIS-A, in our patient. It is of note that our patient is somewhat different from the reported MIS-A patients thus far, to the best of our knowledge, being the oldest reported case and also not of racial minority.

MIS-A is a rare but potentially fatal illness that needs to be considered in all patients with a positive antigen or PCR SARS-CoV-2 test, inflammatory mark-

ers, and systemic fever. This new disease exhibits unclear pathogenesis, although some findings suggest a thrombotic microangiopathy-like syndrome that may be responsible [3]. It is also unclear whether MIS-A is a severe manifestation and continuation of the COVID-19 infection itself or a post-infection immune response; however, if recognized in its early manifestations, deaths may be avoided. According to the CDC most of the 27 cases reported were successfully treated with intravenous immunoglobulin (IVIG), steroids, and anticoagulation with good outcomes, similar to that of 655 children treated for MIS-C [4]. What is ambiguous is whether this treatment is suitable in the case of rapid deterioration, or if induction of treatment is crucial before the cascade of events. Clinicians need to be acutely aware of mild signs of organ failure in any form after COVID-19 so that suitable therapy can be administered in a timely manner.

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**Too often I would hear men boast of the miles covered that day, rarely of what they had seen.**

Louis L'Amour (1908–1988), American novelist and short-story writer