INTRODUCTION

Although children and adolescents are at a significantly lower risk of developing serious symptoms following an infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a small percentage may develop a life-threatening Kawasaki-like hyperinflammatory state following the primary infection, a condition...
that was labeled as multisystem inflammatory syndrome in children (MIS-C). More recently, rare occurrences of a similar syndrome have been described in adults (MIS-A) as a complication that manifests a few weeks after recovering from a typically mild coronavirus disease 2019 (COVID-19) infection. The Centers for Disease Control and Prevention (CDC) recently proposed a working case definition of MIS-A as a hyperinflammatory syndrome affecting patients 21 years of age or older who meet clinical criteria of multi-organ involvement and laboratory evidence of systemic inflammation (Table 1).

Here, we describe the case of a young woman who presented with new-onset refractory status epilepticus (NORSE) following a mild COVID-19 infection associated with symptoms, signs, and laboratory findings that satisfied the case definition for MIS-A.

## 2 | CASE PRESENTATION

A 21-year-old previously healthy woman, not yet vaccinated against SARS-CoV-2 and status post a mild COVID-19 infection without pulmonary involvement 5 weeks prior to presentation, started complaining of generalized fatigue associated with continuous low-grade fever resistant to antipyretics for 3 days. On the fourth day, she complained of unremitting nausea and abdominal pain associated with a high-grade fever. That evening, she developed two focal to bilateral tonic-clonic (FBTC) seizures semiologically characterized by oral automatisms and head and eye deviation to the right prior to the onset of the convulsive phase. She was taken to the emergency department of a peripheral hospital where a SARS-CoV-2 polymerase chain reaction (PCR), a lumbar puncture, and basic blood studies were nonrevealing except for an elevated D-dimer of 4500 ng/mL (reference range: <250 ng/mL). She was discharged on levetiracetam 1500 mg twice daily but experienced five FBTC seizures over the subsequent 2 days despite the addition of valproate and lacosamide to her antiseizure medication (ASM) regimen. On day 6, her fever persisted, and she developed convulsive status epilepticus for which she was intubated, transferred to the intensive care unit (ICU), and maintained on a midazolam drip for seizure control. On examination, she was comatose with evidence of bilateral acral peeling of the palms. Her neurologic examination was nonfocal and brain magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and magnetic resonance venography (MRV) were unremarkable. Because continuous electroencephalography (EEG) monitoring was not available at that hospital, the patient was monitored with intermittent 30–60 min EEGs. The EEGs during the acute phase showed generalized slowing of the background as well as intermittent lateralized periodic discharges (LPDs) consisting of sharp and slow waves over the right frontotemporal area that recurred at a frequency of ~1 Hz and that lasted up to 40 s (Figure 1A). In addition, the LPDs evolved intermittently to ictal discharges that started from the same topographic distribution (Figure 1B). Repeat basic cerebrospinal fluid (CSF) studies, including CSF SARS-CoV-2 PCR and a meningitis panel, were negative. An attempt to taper the midazolam drip on day 2 of her ICU admission resulted in breakthrough seizures. Because of the suspicion of an autoimmune encephalitis, she was treated with 1 g of methylprednisolone daily for 3 days (days 2–4 of ICU stay), followed

### Table 1 | CDC case definition for MIS-A (last updated October 7, 2021)

| CDC Case Definition for MIS-A |
|---------------------------------------------------------------|
| A patient aged ≥21 years hospitalized for ≥24 h, or with an illness resulting in death, who meets the following clinical and laboratory criteria. The patient should not have a more likely alternative diagnosis for the illness. |
| I Clinical criteria. Subjective fever or documented fever (≥38.0°C) for ≥24 h prior to hospitalization or within the first three days of hospitalization and at least THREE of the following clinical criteria occurring prior to hospitalization or within the first THREE days of hospitalization. At least ONE must be a primary clinical criterion. |
| a. Primary clinical criteria |
| (i) Severe cardiac illness (includes myocarditis, pericarditis, coronary artery dilatation/aneurysm, or new-onset right or left ventricular dysfunction (LVEF < 50%), 2nd/3rd degree A-V block, or ventricular tachycardia). |
| (ii) Rash AND non-purulent conjunctivitis |
| b. Secondary clinical criteria |
| (i) New onset neurologic signs and symptoms (includes encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs, or peripheral neuropathy (including Guillain-Barre syndrome)). |
| (ii) Shock or hypotension not attributable to medical therapy (e.g., sedation, renal replacement therapy) |
| (iii) Abdominal pain, vomiting, or diarrhea |
| (iv) Thrombocytopenia (platelet count <150 000/μL) |
| II The presence of laboratory evidence of inflammation AND SARS-CoV-2 infection. |
| a. Elevated levels of at least TWO of the following: C-reactive protein, ferritin, IL-6, erythrocyte sedimentation rate, procalcitonin |
| b. A positive SARS-CoV-2 test during the current illness by RT-PCR, serology, or antigen detection |

Abbreviations: CDC, Centers for Disease Control and Prevention; IL-6, interleukin-6; LVEF, left ventricular ejection fraction; MIS-A, multisystem inflammatory syndrome in adults; RT-PCR, reverse transcription-polymerase chain reaction. (source: https://www.cdc.gov/mis/mis-a/hcp.html).

*These criteria must be met by the end of hospital day 3, where the date of hospital admission is hospital day 0.*
by the administration of intravenous immunoglobulin (IVIG) at a total dose of 2 g/kg over 5 days (days 5–9 of ICU stay). While the patient was in the ICU, arrhythmic episodes were noted on telemetry monitoring; she was diagnosed with a probable myocarditis based on the results of a transthoracic echocardiogram (TTE) that revealed mild dilation of the left ventricle associated with severe global hypokinesia and reduced left ventricular ejection fraction (LVEF) of 35%. In addition, she developed episodes of desaturation, and a pulmonary embolism was detected on computed tomography pulmonary angiography (CTPA) for which therapeutic anticoagulation was initiated. On day 6 of her ICU stay, a gradual taper of the midazolam drip was successful, and she was completely weaned from that drug on day 7.

The patient's level of consciousness gradually improved, and she was transferred to the American University of Beirut Medical Center (AUBMC) on day 10 of her ICU stay for further investigation and management. Upon presentation, she was still intubated but off sedation, awake, and obeying simple commands. Her ASMs included a twice daily regimen of phenobarbital, levetiracetam, and lacosamide. Her EEG at AUBMC showed mild generalized slowing of the background with absence of focal slowing or epileptiform discharges (Figure 1C). Laboratory studies revealed a normocytic anemia along with elevated markers of systemic inflammation and a positive quantitative SARS-CoV-2 immunoglobulins G (IgG) test (Table 2). A complete rheumatologic workup, a comprehensive paraneoplastic autoantibody evaluation (PAVAL panel), and antibodies to voltage-gated potassium channel-complex and N-methyl-d-aspartate (NMDA) receptor were all nonrevealing.

An epilepsy protocol brain MRI with and without gadolinium on day 12 of her ICU stay showed a symmetric T2-signal increase involving both orbitofrontal lobes, insulae, and hippocampi, with no restricted diffusion on diffusion-weighted imaging, bleed on susceptibility weighted imaging, or postcontrast enhancement (Figure 2A). An MRI of the spinal cord was normal. A repeat TTE on day 14 revealed a mildly dilated left ventricle with improvement of the LVEF to 55%.

The patient was discharged on a prednisone regimen of 1 mg/kg/day to be slowly tapered over the subsequent few months. At her follow-up visit 3 months later, the patient remained seizure free and was almost back to baseline, except for a mild retrograde amnesia. A repeat brain MRI showed almost complete resolution of the

FIGURE 1 (A) Intermittent lateralized periodic discharges consisting of sharp and slow waves over the right frontotemporal area that recurred at a frequency of ~1 Hz. (B) Electrographic seizure originating from the right frontotemporal area. (C) Repeat electroencephalography (EEG) at our institution revealed a mild generalized slowing of the background with absence of focal slowing or epileptiform discharges.
cortical high T2 signals with some residual increase in the left gyrus rectus (Figure 2B). Written informed consent was obtained from the patient for the publication of this report.

### Table 2: Serum and CSF laboratory findings in our patient

| Laboratory studies | Test                                      | Results         | Reference range |
|--------------------|-------------------------------------------|-----------------|-----------------|
| Serum              | Hematocrit                                | 29%             | 36%—44%         |
|                    | ESR                                       | 79 mm/h         | 0–20 mm/h       |
|                    | CRP                                       | 130 mg/L        | 0.0–2.5 mg/L    |
|                    | Ferritin                                  | 380 ng/mL       | 12–150 ng/mL    |
|                    | IL-6                                      | 25 pg/mL        | <7 pg/mL        |
|                    | D-Dimer                                   | 1900 ng/mL      | <250 ng/mL      |
|                    | SARS-COV-2 PCR                            | Negative        | –               |
|                    | SARS-CoV-2 IgG                            | 1456 AU/mL      | <50 AU/mL       |
|                    | ANA, anti-dsDNA, c-ANCA, p-ANCA           | Negative        | –               |
|                    | Paraneoplastic autoantibody (PAVAL) panel | Negative        | –               |
|                    | Caspr2, LGI-1, NMDA receptor antibodies   | Negative        | –               |
| CSF                | Meningitis panel                          | Negative        | –               |
|                    | NMDA receptor antibodies                  | Negative        | –               |
|                    | SARS-COV-2 PCR                            | Negative        | –               |
|                    | IL-6                                      | 8.6 pg/mL       | <4 pg/mL        |

Abbreviations: ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; anti-dsDNA, anti-double stranded DNA; Caspr2, contactin-associated protein-like 2; CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; LGI-1, leucine-rich glioma inactivated 1; NMDA, N-methyl-D-aspartate.

**Figure 2** (A) Axial fluid-attenuated inversion recovery (FLAIR) on day 12 of hospital admission. Magnetic resonance imaging (MRI) shows symmetrical cortical high FLAIR signal in both frontal lobes, cingulate gyri, and insular cortices. (B) Axial FLAIR at 3 months of follow-up. MRI shows complete resolution of the previously described cortical high FLAIR signals, except for some residual hyperintensity in the left gyrus rectus.

### 3 | DISCUSSION

To our knowledge, this is the first published case of NORSE as an early manifestation of MIS-A. Our patient...
fulfilled the updated CDC case definition of MIS-A. In addition to the documented fever within 3 days of hospital admission, she satisfied at least three of the required clinical criteria (Table 1): Evidence of cardiac involvement with a LVEF <50%, abdominal pain, and an encephalopathy with new-onset seizures. Furthermore, there was laboratory evidence of a systemic inflammation with high levels of C-reactive protein (CRP), ferritin, and erythrocyte sedimentation rate (ESR), and elevated SARS-COV-2 IgG antibodies (Table 1).

The episode of status epilepticus prompted the admission of our patient to the hospital. Her status epilepticus turned out to be super-refractory, since the initial attempts to taper midazolam resulted in seizure recurrence. Our diagnosis of NORSE was based on the new consensus definition proposed by a panel of international experts, as a “clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other preexisting relevant neurological disorder, with new-onset of refractory status epilepticus without a clear acute or active structural, toxic or metabolic cause.” More specifically, our patient was diagnosed with cryptogenic NORSE, since the known etiologies, including viral infections and antibody-mediated autoimmune syndromes, were ruled out. Although quite extensive, our patient exhibited bilateral fluid-attenuated inversion recovery (FLAIR) abnormalities affecting the orbitofrontal lobes, insulae, and hippocampi, which is also in keeping with previously described MRI findings in patients with cryptogenic NORSE.

Although seizures and NORSE were reported to occur in the acute phase of COVID-19 infection, NORSE has not yet been described as a manifestation of MIS-A. A recent systematic review of 221 patients with MIS-A revealed that the hematologic (92%), cardiac (87%), and gastrointestinal (83%) organ systems were the most frequently affected. Although neurologic manifestations were reported in almost 50% of the cases, most of those consisted of headache episodes. A patient who developed a focal motor status epilepticus 2 weeks following recovery from a severe COVID-19 infection was recently reported, with the workup suggesting that it was secondary to a postinfectious inflammation. However, this patient did not fulfill the case definition of MIS-A, since there was no evidence of cardiac, hematologic, gastrointestinal, or dermatologic involvement.

The pathophysiology of MIS is not yet fully understood. The data so far indicate that it represents a delayed postinfectious immune-mediated systemic hyperinflammatory response, given the combination of negative PCR and positive SARS-CoV-2 antibody titers at the time of admission as well as the minimal or lack of pulmonary involvement during the acute COVID-19 infection in most patients. Autoreactive antibodies have been recently identified in MIS-C that may promote an anomalous immune response leading to hyperinflammation. Further immunopathologic studies including testing specimens for a variety of immune markers such as interleukins and tumor necrosis factors may help identify pathognomonic markers. Although there might be an overlap in the underlying mechanisms causing the hyperinflammatory responses in COVID-19 and MIS-A, we believe that the temporal relationship between the occurrence of status epilepticus and the SARS-CoV-2 infection is what differentiates NORSE as part of COVID-19 from that which occurs in MIS-A. Indeed, NORSE that occurs in the setting of a severe SARS-CoV-2 infection is believed to be secondary to an encephalitis, with patients exhibiting a positive PCR and the typical pulmonary manifestations of COVID-19 at the time of the status epilepticus. On the other hand, our patient experienced a mild COVID-19 infection with no pulmonary symptoms and was back to her baseline within a week. A month later she presented with symptoms, signs, and laboratory findings that satisfied the case definition of MIS-A with NORSE as a central nervous system (CNS) manifestation.

One of the notable findings in our patient was the quick response and significant clinical recovery that occurred following the early initiation of treatment with intravenous methylprednisolone and IVIG (started on day 2 of her ICU stay). Within a few days after administration of this therapy, we were able to taper and discontinue the midazolam infusion without seizure recurrence, and that was followed by a gradual recovery of the patient’s baseline mental status. In addition, on the follow-up brain MRI performed 3 months later, there was a near complete resolution of the T2-signal abnormalities. Despite the morbidity associated with MIS-A, the favorable prognosis in our patient is consistent with recent outcome studies shedding light on the efficacy of the combination of IVIG and glucocorticoids in the treatment of this condition.

Our case expands the clinical spectrum of MIS-A and documents the occurrence of NORSE as one of its early clinical manifestations. Although uncommon, MIS-A seems to have a more heterogeneous clinical presentation than previously appreciated and is commonly underdiagnosed. A routine comprehensive clinical and laboratory assessment is needed to screen for this condition, especially in those with post-COVID inflammatory complications. Given the novel findings that we have presented, the case definition of MIS-A needs to be regularly updated based on future prospective studies to avoid misclassification and to provide diagnostic and treatment algorithms tailored to this condition. To note, our observations remain anecdotal as they were based on a single case report. Further studies are needed to corroborate our findings.
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CONFLICT OF INTEREST
None of the other authors have any conflict of interest to disclose. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID
Omar Nawfal https://orcid.org/0000-0002-7066-1811
Ahmad Beydoun https://orcid.org/0000-0002-9047-1185

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