A Tale of Two Pathologies: MIS-C in a Patient with Pediatric Systemic Lupus Erythematosus

Abstract

An HIV-negative 9-year-old female was admitted to the pediatric ward at a tertiary hospital in Johannesburg, South Africa for investigation of a suspected rheumatic disorder complicated by proteinuria. She was subsequently diagnosed with pediatric systemic lupus erythematosus complicated by class IV lupus nephritis. Further into her admission, the patient developed hospital-acquired SARS-CoV-2 infection with mild clinical symptoms. Three weeks after her initial COVID-19 diagnosis, the patient developed multisystemic inflammatory syndrome. She was successfully treated with intravenous immunoglobulin therapy, intravenous corticosteroids, and thromboprophylaxis.

Keywords: *COVID-19, MIS-C, nephrology, pediatric, SLE*

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DOI: 10.4103/ijn.ijn_239_22

Received: 16-07-2022
Accepted: 26-09-2022
Online First: 08-03-2023
Published: 30-03-2024

Case Report

A 9-year-old female was admitted to the pediatric renal unit at a Johannesburg hospital, South Africa for an investigation into an underlying rheumatic disorder complicated by proteinuria.

On presentation, she had extensive molluscum contagiosum, finger tapering with dactylitis, large joint arthralgia, and anasarca despite growing well. She was noted to be hypertensive. Her ECG, chest radiograph, echocardiogram, and CT brain were unremarkable. Laboratory investigations were positive for antinuclear antibodies (ANA), anti-double stranded DNA antibodies (dsDNA), and anti-Sjogren's syndrome-related antigen A autoantibody (anti-SS-A). On initial presentation, her renal function and electrolytes were within normal limits. However, she had active urinary sediment with hematuria and a protein-creatinine ratio of 2.286 g/mmol. She tested negative for HIV and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on admission. She was diagnosed with pediatric systemic lupus erythematosus (pSLE) with suspected lupus nephritis. A renal biopsy was performed, which revealed class IV lupus nephritis with 39% cellular crescent formation and an associated necrotizing vasculitis and acute interstitial nephritis. She was pulsed with methylprednisolone, and intravenous cyclophosphamide was administered as induction therapy, following which she showed clinical remission of her disease. She was initiated on mycophenolate mofetil as maintenance therapy and showed clinical and biochemical remission of her disease with no signs suggesting a flare.

The patient developed hospital-acquired SARS-CoV-2 infection with mild respiratory distress and an unremarkable chest radiograph. The patient's clinical course was uneventful, and she showed rapid clinical recovery. Three weeks after her initial COVID-19 diagnosis, the patient developed a persistent fever (>38°C), progressive abdominal distention and tenderness, a desquamating rash on her hands and feet, severe synovitis, a new pericardial friction rub, and respiratory distress complicated by hypoxia requiring supplementary oxygen. Laboratory investigations revealed raised C-reactive protein, D-dimers, and ferritin with associated neutrophilia and lymphopenia. Echocardiogram revealed an active pericarditis with a thickened pericardium and pericardial effusion with fibrin strands. No coronary ectasia, impaired myocardial contractility, and valvular or papillary muscle pathology were seen. Her repeat chest radiograph revealed bilateral diffuse ground glass

How to cite this article: Samson A, Irusen S. A Tale of Two Pathologies: MIS-C in a Patient with Pediatric Systemic Lupus Erythematosus. Indian J Nephrol 2024;34:84-7. doi: 10.4103/ijn.ijn_239_22

infiltrates and a large left-sided pleural effusion [Figure 1]. A diagnosis of multisystemic inflammatory syndrome in children (MIS-C) was made due to the temporal relationship with her COVID-19 diagnosis and development of signs satisfying diagnostic criteria. A lupus flare was considered unlikely as her lupus clinical signs showed resolution following the initiation of therapy for 3 weeks prior to acquiring SARS-CoV-2 infection. Furthermore, her anti-double-stranded DNA antibody remained negative at the time of MIS-C diagnosis [Table 1]. The patient received intravenous immunoglobulin therapy, intravenous methyl prednisone, aspirin, and subcutaneous enoxaparin, to which she responded favorably.

Discussion

Systemic lupus erythematosus (SLE) is an autoimmune condition that affects major organ groups, of which renal involvement, such as lupus nephritis (LN), is a significant cause of morbidity and mortality. Renal involvement is often more severe in children, with 50%–75% of pediatric SLE (pSLE) patients developing renal disease, of which more than 90% occur within the first 2 years of diagnosis. The gold standard to diagnose lupus nephritis in pSLE is renal biopsy with the histological class guiding prognosis and therapy choices.[1]

The histopathological classification of LN is divided into six classes as described by the International Society of Nephrology and the Renal Pathology Society (ISN/RPS) based on the patterns of immune complex deposition within the glomerulus. Class IV (diffuse LN – involving ≥50% of glomeruli) – seen in our patient – is associated with the greatest risk of long-term damage and shows a membranoproliferative pattern of injury with subendothelial immune complex patterns causing a segmental or global endo- or extra-capillary glomerulonephritis (GN) (hypercellularity) with or without a mesangiopathy.[2]

Since the first pediatric case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), children across the globe have been infected with the virus. Although coronavirus disease 2019 (COVID-19) was thought to be less common and less severe in children, some children, following COVID-19, develop a syndrome of hyperinflammatory shock with multiorgan involvement, otherwise termed multisystem inflammatory syndrome in children (MIS-C).

Described as a Kawasaki-type illness with features of toxic shock syndrome, the pathophysiology of MIS-C is poorly understood. During its early emergence, the Royal College of Pediatrics and Child Health (RCPCH), the World Health Organization (WHO), the American College of Rheumatology (ACR), and the United States Centers for Disease Control and Prevention (CDC) rapidly developed case definitions for MIS-C. These case definitions, however, have differing criteria in major distinguishing factors, namely the age of onset, duration of fever, and the requirement for exposure or infection with SARS-CoV-2.[3] As no equivalently accepted definition existed, the Brighton Collaboration Case Definition of MIS-C was published to refine this definition after multiple more cases of MIS-C were reviewed. The definition uses clinical presentation, laboratory results, and other diagnostic findings to define cases as one of five categories, namely a definitive case, a probable case, a possible case, a case with insufficient evidence, and not a case of MIS-C. This case definition also attempts to include features distinctive to MIS-C to distinguish it from mimicking conditions such as Kawasaki disease (KD). Our patient fulfills the criteria for MIS-C as per the case definition of the CDC, WHO, RCPCH, and ACR,[3] as well as a definitive case of MIS-C as per the Brighton Collaboration Case Definition of MIS-C.[4]

Although the definition of MIS-C has been clarified, the association between the risk of developing MIS-C after COVID-19 infection is poorly understood. This poses a challenge in the formation of a clear management strategy for affected patients. While the management of the hyperinflammatory features associated with MIS-C has evolved over the course of the pandemic, the mainstay of treatment has remained intravenous immunoglobulin (IVIG) therapy with the addition of intravenous (IV) corticosteroids, with more refractory cases requiring an escalation to biologic agents such as anakinra, tocilizumab, and infliximab. In addition,

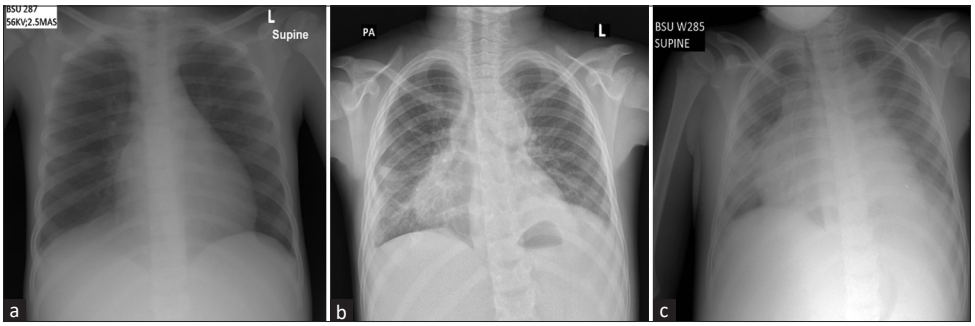

Figure 1: Chest radiographs showing (a) minimal parenchymal involvement at the time of COVID-19 diagnosis and (b) rapid radiological evolution 2 weeks later with increased parenchymal infiltration with (c) further progression of the lung infiltrates and pericardial effusion.

Table 1: Selected blood results for the index patient during the admission

	At Diagnosis		CoViD-19 Diagnosis	MIS-C Diagnosis
	17/07/2020	25/07/2020	01/08/2020	15/08/2020
WCC (x10^9/l)		6.51	1.41	5.63
Hb (g/dL)		11.4	8.9	8.5
Platelets (x10^9/L)		282	190	409
ESR (s)		64		
Sodium (mmol/L)	134	134	134	135
Potassium (mmol/L)	5.5	6.6	4.4	4.3
Bicarbonate (mmol/L)	16	12	18	19
Urea (mmol/L)	13.3	10.3	4.1	15.2
Creatinine (umol/L)	66	40	29	41
Calcium (mmol/L)		1.82	1.73	1.54
Magnesium (mmol/L)		0.99	0.68	0.76
Phosphate (mmol/L)		0.92	0.58	0.88
Albumin		19		12
ALT (U/L)		11		7
AST (U/L)		33		24
GGT (U/L)		17		83
ALP (U/L)		118		10
CRP (mg/L)			<10	215
Ferritin (µg/L)				268
D-Dimer (mg/L)				9.99
SARS-CoV-2 PCR			Pos	
Urine Prot: Creat Ratio (g/mmol)		2.286	0.07	
	Additional/Specialized Investigations			
	17/07/2020	**21/07/2020**		**15/08/2020**
HIV-1/2 Ab/Ag ELISA	Negative			
HIV-1 qualitative PCR				Negative
ANA (tire)	Positive (160)	Positive (320)		
Anti-ds-DNA Ab	Positive (713)	Positive (640)		Negative
Anti-SSA (Ro) Ab	Positive (420)			Negative
Anti-Cardiolipin Ab (IgG/IgM)	Negative			
C3 (0.9–1.8)	1.02			
C4 (0.1–0.4)	0.1			
Blood culture				No growth
				No growth

WCC: White Cell Count, Hb: Hemoglobin, ESR: Erythrocyte Sedimentation Rate, ALT: Alanine Transaminase; AST: Aspartate Aminotransferase, GGT: Gamma-Glutamyl Transferase, ALP: Alkaline Phosphatase, CRP: C Reactive Protein, PCR: Polymerase Chain Reaction, Prot: Creat: Protein: Creatinine, HIV: Human Immunodeficiency Virus, Ab: Antibody, Ag: Antigen, ANA: Antinuclear Antibodies, Anti ds-DNA: Anti-Double Stranded DNA, Anti-SSA (Ro): Anti–Sjögren syndrome-related Antigen A, C3: Complement 3, C4: Complement 4

guidelines recommend antiplatelet and anticoagulation therapy.[4]

To our knowledge, this is the first reported case of MIS-C with concomitant pSLE diagnosis. Although the majority of MIS-C cases were in previously healthy children with no preexisting comorbidities, there have been recorded cases of children with previously diagnosed inflammatory and rheumatological conditions who ultimately developed features characteristic of MIS-C subsequent to COVID-19 diagnosis. A case report from a hospital in New York, USA described a pediatric patient with Crohn's disease with concurrent MIS-C. The patient was successfully treated with infliximab (anti-TNF-α monoclonal antibody) as it was postulated that there was an overlap between his

inflammatory bowel disease and MIS-C to mitigate the morbidity associated with the resultant cytokine storm. Although data is scarce, the immune dysfunction and inflammatory processes associated with these preexisting comorbidities do not seem to predispose these patients to developing MIS-C nor does it confer an adverse outcome. While these patients showed initial clinical deterioration, they were effectively managed with symptomatic and immunomodulatory treatment.[5,6]

Despite our patient's prior pSLE diagnosis and successful treatment with immunosuppressant agents, she ultimately developed the hyperinflammatory response associated with MIS-C and COVID-19 infection which was effectively managed using immunomodulatory strategies and thrombo-prophylaxis.

Conclusion

While data is still evolving in the pediatric population, both the definition and management of MIS-C have advanced dramatically since their initial emergence. The immune-mediated manifestations of MIS-C are still poorly understood; however, the condition has been successfully managed using immunomodulatory strategies and supportive treatment in both previously healthy pediatric patients and patients with preexisting comorbidities, as in our patient with pSLE.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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