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Research Article

Multisystem Inflammatory Syndrome Temporally Related to COVID-19 in Adults

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Abstract

As novel viral pandemic is unfolding and new information about SARS-CoV-2 related illnesses is being released, a new multisystem inflammatory syndrome emerged particularly among children and adolescents temporally related to coronavirus disease 2019 (COVID-19). After several similar cases were reported in the United Kingdom and the United States of America, the World Health Organization recognized this new syndrome on May 15, 2020 and released its case definition. Cases have now emerged in adult patients as well. Physicians need to stay vigilant about this syndrome in adults to promptly diagnose and intervene. This article highlights all cases reported in the literature so far, particularly their common presenting signs, symptoms, and the way these cases are being managed.

Keywords: Multisystem Inflammatory Syndrome; Atypical Kawasaki Disease; COVID-19; SARS-CoV-2; Adults

1. Introduction

Since the beginning of the SARS-CoV-2 pandemic, more than half a million people across the globe have

succumbed their life to it [1]. We are learning more about the acute viral illness associated with respiratory symptoms, yet we have to see the long term effects on health in general. The virus seemed to spare children as they are only 1% of the positive cases [2].

However, recently, new cases of a peculiar inflammatory syndrome associated with this virus have emerged in children [3]. This new syndrome has distinctive features that overlap with Kawasaki disease, another inflammatory disease that is more prevalent among children. Although studies have shown the role of genes linked to the etiology of Kawasaki disease [4], different geographical location, ethnical distribution, disease clusters [5], and seasonal variation in presentation [6] are attributing factors as well.

1.1 Multisystem inflammatory syndrome in children and adolescents temporally related to coronavirus disease-2019

Reports of a new inflammatory syndrome emerged from the United Kingdom (UK) in late April 2020. The United States saw its first case around early May. World Health Organization (WHO) noticed this new entity and a case definition [7] of a multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19 (MIS-C) was released on May 15, 2020. The case definition of MIS-C given by WHO is described in Table 1. A list of differentials diagnoses of MIS-C is long and may include a spectrum of diseases such as Kawasaki disease/shock syndrome [8, 9], haemophagocytic lymphohistiocytosis [8, 9], toxic shock syndrome [8], and macrophage activation syndrome [8, 9].

Children and adolescents from age 0 to 19 years presenting with fever for more than 3 days	AND any two of the following five features:	Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet).
		Hypotension or shock.
		Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP).
		Evidence of coagulopathy (by PT, PTT, and elevated d-Dimers).
		Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain).
	AND	Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin. AND no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.
	AND	Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

Table 1: World Health Organization (WHO) case definition of the multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19.

Characteristics		**Case one [13]**	**Case two [11]**	**Case three [14]**	**Case four [10]**
Clinical data	Age (years)	21 M	45 M	36 M	54 F
	Body mass index (kg/m^2)	-	26.6	-	-
	Presenting symptoms	Fever, abdominal pain, constipation, anorexia, headache	Fever, sore throat, diarrhea, bilateral lower extremity pain, conjunctivitis, diffuse exanthema	Fever, abdominal pain, vomiting, diarrhea, rash, arthralgia	Fever, gastrointestinal symptoms, heart failure symptoms, skin rash
	Physical exam findings	Conjunctivitis, cervical LAD, cracked lips, prominent lingual papilla	Conjunctivitis, cervical LAD, lip cheilitis, periorbital edema with overlying erythema	Conjunctivitis, cervical LAD, cracked lips, hands and feet edema, palmar erythema	-
	Rash character	Maculopapular on palms	Targetoid papules and plaques on the back, palms, neck, thighs, anterior trunk, scalp	Diffuse maculopapular	-
	Blood pressure (mmhg)	-	Hypotensive (Systolic 80-90)	Hypotensive	Hypotensive
	Heart rate	-	Tachycardia, episodic AF with RVR	Tachycardia	-
	Respiration	-	Tachypnea	Tachypnea	-
	ECG	Normal	ST elevation in anterolateral leads (normal coronary arteries on catheterization)	-	-
	Known COVID-19 contact	No	Yes (wife)	No	-
Investigations	Troponin T	Elevated	Elevated (peak=8.05 g/ml)	-	-
	BNP	-	Elevated	-	-
	Inflammatory markers	Elevated	Elevated	Elevated	

	WBC	Lymphopenia with neutrophilia	Lymphopenia, neutrophilia, atypical lymphocytosis, increased band neutrophils	Neutrophilia without lymphopenia	-
	Blood culture	Negative	Negative	-	Negative
	SARS-cov-2 RT-PCR	Negative (nasopharyngeal) Negative (stool)	Positive (sample site unavailable)	Positive (sample site unknown)	Negative (nasopharyngeal)
	SARS-CoV-2 serum serology	Positive	-	Positive IgG Negative IgM	Positive IgG
Imaging	Chest X-ray	Normal	Diffuse interstitial haziness	-	-
	CT scan	Mesenteric LAD, Terminal ileitis	Edema/inflammation in the lower eyelid and pre-septal space, suboccipital LAD	Mild gallbladder wall thickening, small colitis	-
	Echocardiogram	Normal, EF=63%	Global hypokinesia, EF=40%	Moderate tricuspid regurgitation, EF=65%	-
	CT coronary angiogram	Normal coronaries	Catheterization with normal coronaries	Normal coronaries and trace pericardial effusion	-
Mnagement a	IVIG	Yes	Yes	Yes	-
	Vasopressors	-	No	-	Yes
	Corticosteroids	Yes methylprednisolone)	-	Yes (methylprednisolone)	Yes
	Other	Aspirin	Tocilizumab, LMWH	Aspirin	Antibiotics
	Ventilation/oxygen	No	1-2 L/min by nasal cannula	-	-
Outcome	Discharge/death	Discharged on eighth post-admission day on low dose aspirin	Discharged on ninth post-admission day	Discharged on prednisolone taper	Discharged

Abbreviations: LAD, lymphadenopathy; AF, atrial fibrillation; RVR, rapid ventricular response; ECG, electrocardiogram; COVID-19, coronavirus disease 2019; BNP, brain natriuretic peptide; WBC, white blood cells; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcriptase-polymerase chain reaction; CT, computed tomography; EF, ejection fraction; IVIG, intravenous immunoglobulin; LMWH, low molecular weight heparin; L/min, liter per minute; g/ml, gram per milliliters

Table 2: Summary of MIS-C cases reported in adults..

2. Methodology

In this review, we have summarized the presenting signs and symptoms of the multisystem inflammatory syndrome temporally associated with COVID-19 (MIS-C) in adults which was previously seen only in children and adolescents. PubMed, Google Scholar, and bibliographies of relevant articles were searched for required data using search terms like multisystem inflammatory syndrome, atypical Kawasaki disease, in combination with adults, COVID-19, and SARS-CoV-2.

3. Results

We have reviewed and summarized four reports of adult cases having a presentation similar to that of MIS-C (table 2). The median age of these four patients 39 years (range: 21-54). The male to female ratio was 3:1. The initial presentation was consistent in all these cases (n=4) with features including fever, gastrointestinal symptoms, and skin rash. Physical examination findings were also consistent including conjunctivitis, lymphadenopathy, cracked lips, mucositis, and edema (periorbital/limb). The rash was noted as maculopapular and targetoid with diffuse distribution particularly affecting palms. The scalp was involved in one case. Low blood pressure or hypotensive was seen (n=3) in these cases. In 2 cases tachycardia and tachypnea were reported as well Elevation of Troponin T was also reported (n=2). One case had ST elevation on ECG and subsequently underwent catheterization that showed normal coronary arteries. Inflammatory markers were consistently high in all four patients. Like COVID-19, MIS-C also leads to lymphopenia and neutrophilia. CT scans were positive for lymphadenopathy, and inflammation and edema of the bowel wall. Ejection fraction was normal (>60%) in all patients except for one patient (40%) who had ST elevation on ECG. CT coronary angiograms were normal in all patients. Serology for SARS-CoV-2 was positive in all patients. RT-PCR results were positive in only two cases. The typical COVID-19 respiratory disease was not seen in any patient. However, one case had a history of recent exposure to a COVID-19 patient. Management included intravenous immunoglobulins (IVIGs) (n=3), corticosteroids (n=2), aspirin (n=2), and tocilizumab (n=1). Oxygen (2 L/min) was required by one patient. And one patient required vasopressors due to shock and was managed in the intensive care unit [10].

4. Discussion

Disease markers presentation children vs. adults: Inflammatory markers like ferritin, C-reactive protein, erythrocyte sedimentation rate, or procalcitonin, are typically raised in children and adolescents [11]. Lymphopenia with neutrophilia is a common abnormal white blood count finding in these patients. History of prior SARS-CoV-2 infection or exposure may or may not be present. The RT-PCR is positive only in 46% - 62% MIS-C patients hence not reliable while serology is positive in 96% to 100% of these patients and should be ordered in all suspected patients [3]. Vital signs should be monitored closely due to potential progression to shock which is seen in 80% of MIS-C children with severe disease who are admitted in ICU [12]. Although uncommon, shock may ensue anytime in MIS-C patients [8]. The clinical picture and laboratory findings in MIS-C considerably overlap with Kawasaki disease. Whittaker et al. reported that 13 out of 58 children with MIS-C fulfilled the criteria for Kawasaki disease if an additional coronary artery aneurysm criterion was added [13]. The majority of MIS-C in children and adolescents is associated with positive SARS-CoV-2 serology but negative RT-PCR results, hinting towards the possible post-infectious etiology rather than active viral infection [8]. Most children with MIS-C did well on IVIGs and corticosteroids [8]. Although exact pathophysiology remains unknown, the resemblance to Kawasaki disease and prompt resolution with the same treatment approach points towards a similar immune system-mediated

origin. While no treatment options have yet been established separately for adults, based on the case reports we have discussed, management in line similar to that in children is a feasible option. Given the presumed immune-mediated etiology, treatment with intravenous immunoglobulin and corticosteroids has been successful so far in children [8]. Since most of the MIS-C children have positive IgG against SARS-CoV-2, the virus most likely has already cleared and corticosteroids can safely be administered. Tocilizumab, an interleukin (IL) 6 inhibitor, is available as an alternate option for MIS-C in children although physicians are cautioned against the potential coronary artery aneurysm development associated with its use the exact etiology of which remains unknown [11]. Anakinra, an IL-1 inhibitor, has been proposed as a substitute to tocilizumab particularly in patients with coronary artery disease. A child with Kawasaki disease complicated by coronary artery aneurysm was successfully treated when switched to anakinra [14]. The patients who are refractory to IVIGs or whose presentation includes features similar to haemophagocytic lymphohistiocytosis can be treated with anakinra [11]. There is limited data for any direct comparison between any treatment modalities available.

5. Conclusion

Physicians treating adult patients across the globe should remain vigilant to effectively detect the new post-infectious disorder of COVID-19 in adults which was previously regarded as an entity limited only to children and adolescents.

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