

# A Confusing Final Diagnosis in the Differential Diagnosis of SARS-Cov-2 Associated Multisystem Inflammatory Syndrome in Children: *Salmonellosis*

Çocuklarda SARS-Cov-2 ile ilişkili Multisistem İnflamatuar Sendrom Ayırıcı Tanısında Kafa Karıştıran Bir Son Tanı: *Salmonelloz*

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## ABSTRACT

Multisystem Inflammatory Syndrome in Children (MIS-C) is a severe clinical condition associated with the SARS-CoV-2 infection characterized by an increased inflammatory response. MIS-C shares common features with other pediatric inflammatory and infectious conditions including bacterial infections. *Salmonella* infections should be kept in mind as a causative agent of bacterial gastroenteritis in the differential diagnosis of patients with suspected MIS-C to avoid misdiagnosis. In this report, a case series of pediatric patients with a final diagnosis of *salmonellosis* were presented, although a primarily diagnosis of MIS-C at admission was considered due to symptoms and findings together with strong laboratory or epidemiological evidence for SARS-CoV-2 infection.

**Key Words:** Children, Misdiagnosis, Multisystem Inflammatory Syndrome, SARS-CoV-2, *Salmonellosis*

## ÖZ

Çocuklarda Multisistem İnflamatuar Sendrom (MIS-C), artmış inflammatuar yanıtla karakterize, SARS-CoV-2 enfeksiyonu ile ilişkili ciddi bir klinik durumdur. MIS-C, bakteriyel enfeksiyonlar dahil olmak üzere diğer pediatrik inflammatuar ve enfeksiyöz durumlarla ortak özellikler taşır. Yanlış tanıdan kaçınmak için MIS-C şüphesi olan hastalarda ayırıcı tanıda bakteriyel gastroenterit etkeni olarak *Salmonella* enfeksiyonları akılda tutulmalıdır. Bu raporda, SARS-CoV-2 enfeksiyonu için güçlü laboratuvar veya epidemiyolojik kanıtlarla birlikte semptomları ve bulguları nedeniyle başvuru sırasında öncelikle MIS-C tanısı düşünülmesine rağmen, kesin *salmonelloz* teşhisi konan pediatrik hastalardan oluşan bir vaka serisi sunulmuştur.

**Anahtar Kelimeler:** Çocuklar, Yanlış Teşhis, Multisistem İnflamatuar Sendrom, SARS-CoV-2, *Salmonelloz*

## INTRODUCTION

Multisystem Inflammatory Syndrome in Children (MIS-C) is a newly reported phenomenon as a complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (1). This Syndrome is a more severe clinical condition than the infection itself, named as “coronavirus disease 2019 (COVID-19)”, and characterized by an increased inflammatory response (1, 2). The pathogenesis of MIS-C is unclear, but has features overlapping with a possible autoimmune etiology and suggestive of vasculitis (1). The patients typically presents 4–6

weeks after infection with fever, multi-organ dysfunction and strongly elevated markers of inflammation, and have molecular or serological laboratory evidence of SARS-CoV-2 infection, or have a strong evidence of contact with an infected person (3). Varied clinical signs and symptoms at initial evaluation were described in MIS-C patients. Most of them have fever and gastrointestinal symptoms alone or accompanied by changes, suggestive of Kawasaki-like disease (4). The situation that makes the disease so important is cardiac dysfunction that occurs in almost half of the patients and results with shock or death (5). However, knowledge about the clinical spectrum of MIS-C remains limited, and the lack of a diagnostic test or universally

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accepted definition makes the differential diagnosis difficult and causes it to be confused with many clinical situations (4, 5). Identification of MIS-C is important because timely initiation of treatment may help to correct the hyperinflammatory state, prevent end-organ damage and death (2). As MIS-C shares common features with other pediatric inflammatory and infectious conditions including bacterial infections and sepsis, the importance of differential diagnosis increases even more (1, 4). In addition, most of the MIS-C patients have gastrointestinal symptoms such as diarrhea together with fever, and of course infectious gastroenteritis with the same symptoms are frequently encountered in pediatric practice (6).

In this report, a case series of pediatric patients was presented diagnosed with *salmonellosis*, although a primarily diagnosis of MIS-C at admission was considered due to symptoms and findings together with strong laboratory or epidemiological evidence for SARS-CoV-2 infection.

## CASES REPORT

Five children (three females, two males) aged 2.5-11.5 years who were admitted to a tertiary care hospital in the last three months of 2020 were presented in this report. All of the patients had a pre-diagnosis of MIS-C and a final diagnosis of confirmed salmonellosis. The suspicion of MIS-C was based on the case definitions established by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) (7,8). For all patients, symptoms and physical examination findings on admission, comorbidities, laboratory tests including blood cell counts, C-reactive protein (CRP), procalcitonin,

interleukin-6, liver function tests, serum creatinine level, coagulation tests, D-dimer, ferritin, blood culture, microscopic examination and culture of stool, viral testing including reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 from nasopharyngeal sample, antibody testing detected IgM/IgG antibodies against SARS-CoV-2, imaging records, supportive treatments, treatments for MIS-C, antibiotherapies, and clinical outcome records were summarized separately in Table I-III.

Serovar determination was not performed on isolates obtained from any patient, since sub-species determination for *Salmonella* strains could not be performed in our center. Therefore, it could not be understood whether the patients had typhoid fever or invasive disease with non-typhoidal *Salmonella* species. Patient 4 and 5 were bacteremic supported by blood cultures. While all *Salmonella* strains were susceptible to ceftriaxone, ciprofloxacin and trimethoprim-sulfamethoxazole, ampicillin resistance was variable. However, clinical or laboratory response to the treatment were not obtained in patients 4 and 5, and antibiotherapy was switched to other agents although resistance to ceftriaxone was not detected. Fever resolved in these patients after 24 hours of the treatment change. Their clinical conditions improved, and no additional treatment was applied for MIS-C.

Patient 4 was a previously healthy child with no cardiac problem. Cardiac findings detected in echocardiography returned to normal on follow-up, but 1st degree Atrioventricular (AV) block was detected before discharge in serial electrocardiograms (ECG) (shown in Table I). Arrhythmia improved without specific treatment, and 24-hour ECG monitoring was reported as normal during hospitalization. At the beginning of the process,

**Table I: Demographic characteristics, symptoms / findings on admission, symptom duration, and molecular / serological laboratory or epidemiological evidence of SARS-CoV-2 infection, for all patients.**

Patients	Gender	Age (year)	Comorbidity	Presenting symptoms	Symptom duration (day)	Physical examination findings	RT-PCR for COVID-19	Antibodies against SARS-CoV-2	Contact with a person infected with COVID-19
1	Female	11.5	Canavan disease	Fever, diarrhea, vomiting, and abdominal pain	1	Toxicity, respiratory distress, and abdominal tenderness	positive	non-reactive	+ (mother)
2	Female	2.5	-	Fever, vomiting, diarrhea, and abdominal pain	3	Dehydration, toxicity, and abdominal tenderness	negative	reactive	-
3	Male	7.5	-	Fever, vomiting, diarrhea, and weakness	7	Dehydration and abdominal tenderness	negative	non-reactive	+ (father)
4	Female	4	-	Fever, abdominal pain, and diarrhea	1	Dehydration and toxicity	negative	non-reactive	+ (father)
5	Male	2.5	Hypogammaglobulinemia	Fever, vomiting, diarrhea, and headache	2	Dehydration, toxicity, and abdominal tenderness	negative	non-reactive	+ (grandmother)

**Table II: Laboratory tests and culture results of the patients.**

Laboratory tests	Patients				
	1	2	3	4	5
WBC (x10 <sup>9</sup> /L)	12.94	4.92	12.96	3.71	2.99
Neu (x10 <sup>9</sup> /L)	10.61	4.46	8.31	2.37	1.95
Lym (x10 <sup>9</sup> /L)	0.6	1.19	2.6	1.02	0.63
Hg (g/dL)	13.5	11.5	12.6	11.5	11
Plt (x10 <sup>9</sup> /L)	248	265	392	217	214
CRP (g/dL)	26	71	58	180	210
Procalcitonin (µg/L)	0.3	0.22	0.16	11.5	226.8
IL-6 (pg/mL)	4.14	3.14	28.5	77.7	232
ESR (mm/h)	9	15	83	32	86
Liver function tests	Elevated	Elevated	Elevated	Elevated	Elevated
Kidney function tests	Normal	Affected	Normal	Normal	Affected
Cardiac enzymes	Normal	Normal	Normal	Elevated	Elevated
Coagulation tests	Normal	Normal	Normal	Prolonged	Prolonged
D-dimer (mg/L)	1.1	1.8	0.9	19.2	3
Ferritin (µg/L)	25	29	226	511	239
Microscopic examination of stool	Rare leukocytes and 8-10 erythrocyte/hpf	Abundant leukocytes/hpf	2-3 leukocytes and 5-6 erythrocytes/hpf	Abundant leukocytes and 8-10 erythrocytes /hpf	Abundant leukocytes/hpf
Stool culture	<i>Salmonella enterica ssp enterica</i>	<i>Salmonella enterica ssp enterica</i>	<i>Salmonella enterica ssp enterica</i>	<i>Salmonella enterica ssp enterica</i>	<i>Salmonella enterica ssp enterica</i>
Blood culture	Negative	Negative	Negative	<i>Salmonella enterica ssp enterica</i>	<i>Salmonella enterica ssp enterica</i>

**CRP:** C-reactive protein (N: 0-5 g/dL), **D-dimer** (N: 0-0.55 mg/L), **ESR:** Erythrocyte sedimentation rate (N: 0-20 mm/h), **Ferritin** (N: 7-140 µg/L), **Hg:** Hemoglobin (N: 11.2-14.6 g/dL), **IL-6:** Interleukin 6 (N: 0-3.4 pg/mL), **Lym:** Lymphocyte (N: 1.5-6 x10<sup>9</sup>/L), **Neu:** Neutrophil (N: 1.5-8 x10<sup>9</sup>/L), **Procalcitonin** (N: <0.16 µg/L), **WBC:** White blood cell (N: 4.8-12 x10<sup>9</sup>/L).

a clear distinction could not be made for the patient's severe cardiac findings as to whether it was due to MIS-C or salmonellosis. However, the fact that the findings returned to normal in a short time with antibiotherapy was considered as salmonellosis-related cardiac involvement, and MIS-C diagnosis was excluded. Abdominal findings of patient 4 and 5 returned normal before discharge. While the source of transmission for *Salmonella enterica ssp enterica* was consumption of raw chicken and raw quail eggs in patient 4 and 5, a clear source for bacterial contamination was not found in other patients. There were no symptoms suggestive of salmonellosis in any of the patients' family members.

## DISCUSSION

Salmonellosis is a disease of global public health importance, and is directly related to water treatment, sewage disposal, animal exposures, and food-handling practices (9). *Salmonella* infections most often cause self-limiting gastroenteritis, but can also cause invasive infections with severe organ involvement that can result in morbidity or mortality (9, 10). Sepsis or

sepsis-like conditions associated with invasive disease may not be attributed to *Salmonella* in the early period and may be confused with other conditions (10). Especially, enteric fever can mimic other infections of the reticuloendothelial system, or non-infectious illnesses such as collagen vascular diseases including juvenile rheumatoid arthritis and Kawasaki disease, and lymphomas (11). Similarly, Kawasaki syndrome and other vasculitis can be misdiagnosed as many infectious diseases (12). On this background of differential diagnosis challenge, MIS-C has emerged as an important cause of morbidity and mortality with the COVID-19 pandemic, and entered the world of pediatricians as a factor that causes serious confusion in diagnosis and treatment of many diseases.

MIS-C is a post-infectious event that occurs in individuals aged 0-21 years and causes symptoms a few weeks after infection with COVID-19 (1,2). Fever is a constant sign for MIS-C; cutaneous manifestations, abdominal symptoms and cardiovascular collapse are also common findings in most patients (13). Gastrointestinal manifestations including abdominal pain, diarrhea and vomiting are observed in 92% of patients; may be severe enough to require surgery, and also

**Table III: Imaging records, supportive treatments, antibiotherapies and clinical outcomes, of the patients.**

Patients	Chest X-ray	Abdominal ultrasonography	Echocardiography	Supportive treatments	Antibiotherapy/duration	Clinical outcome
1	Normal	Normal	Normal	Oxygen and HFNC (High flow nasal cannula) for respiratory distress, intravenous (iv) hydration	Ceftriaxone / 10 days	Cured
2	Undrawn	Normal	Normal	IV hydration	Ceftriaxone / 10 days	Cured
3	Normal	Normal	Normal	IV hydration	Ceftriaxone / 10 days	Cured
4	Normal	Diffuse wall thickening (6 mm) in ileal loops, mesenteric contamination, and intraabdominal fluid (34 mm)	Dilatation in the left ventricle, mild mitral insufficiency, pericardial effusion in the posterior wall (2-3 mm), and bilateral pleural effusion (3 mm)	IV hydration Intravenous immunoglobulin (2 gr/kg) Acetyl salicylic acid (started at anti-inflammatory dose and decreased to antiaggregant dose)	Ceftriaxone / 4 days and Ciprofloxacin / 10 days	Intermittent outpatient controls are ongoing due to cardiac involvement
5	Undrawn	Oval-shaped hypoechoic lymph node with a size of 10x19 mm in the right lower quadrant, diffuse thickening of the intestinal walls (4 mm) and a small amount of fluid between the bowel loops	Secundum atrial septal defekt	IV hydration Intravenous immunoglobulin (2 gr/kg)	Ceftriaxone / 3 days and Trimethoprim-sulfamethoxazole / 7 days	Cured

may be the only additional system findings accompanying fever (13, 14). Cardiac findings are detected in almost 80% of the patients, and half of the patients may progress to a severe shock-like condition requiring intensive care follow-up (4, 13). Due to increased cytokine responses and high inflammatory markers together with other system involvements, and high risk of morbidity and mortality, immediate intervention is essential without delay (5). The necessity of immediate intervention in this disease has revealed a new pediatric emergency, and prompted clinicians to rapidly initiate MIS-C treatment to prevent secondary complications in patients who have direct or indirect contact with COVID-19 and present with non-specific signs and symptoms suggestive of the syndrome. However, with this rapid intervention, possible infectious and non-infectious causes included in the differential diagnosis of MIS-C may be overlooked or delayed in diagnosis. There will even be cases that receive unnecessary treatment since there is no specific marker to make definitive diagnosis of MIS-C. For this reason, a careful analysis and careful examination of differential diagnosis is very important both during the patient's admission and during the follow-up. All of the patients in this case series presented with fever and significant gastrointestinal symptoms. In all of them, the significant elevations in inflammatory markers and strong evidence for infection or indirect contact with COVID-19 forced us to consider the diagnosis of MIS-C firstly. Some of

the patients were even applied MIS-C initial treatments due to the deterioration of the general condition and toxic appearance on admission. Finally, stool and blood cultures obtained for possible infectious causes led us to a definitive diagnosis. To our knowledge, there is only one case report and one case series in the literature, that were considered a pre-diagnosis of MIS-C and were diagnosed with salmonellosis on follow-up (15, 16). There are also rare case reports of pediatric patients presented with findings indicative of MIS-C and were diagnosed with different infectious disease except for salmonellosis (17, 18).

*Salmonella* serotypes are designated based on the immunoreactivity of two cell surface structures, the O and H antigens, and serovars are identified beyond differentiating *Salmonella* isolates by subspecies level (18, 19). Clinically important *Salmonella* consist principally of a single species, *Salmonella enterica*, and *S. enterica* is further subdivided into six subspecies that are designated by taxonomic names: *enterica*, *salamae*, *arizonae*, *diarizonae*, *houtenae* and *indica* (17). The *S. enterica* subspecies covering more than 2500 serovars commonly encountered in clinical practice are grouped as typhoidal and non-typhoidal (11). Infection caused by *Salmonella* bacteria in the non-typhoidal group predominantly cause local intestinal inflammation, while those in the typhoidal group lead to systemic disease named as enteric (typhoid) fever (11, 13).

These differences in the manifestations of infection by the 2 groups of pathogens brings about changes in the approach to infection and treatment plan (9-11). Among *Salmonella* infections, early diagnosis and treatment of typhoid fever with appropriate antimicrobials are essential (11). In *Salmonella* gastroenteritis other than typhoid fever, antimicrobial treatment do not have a clear indication (20). Because antibiotics do not shorten the course of illness and may prolong shedding of the organism in the stool (20, 21). There are also exceptions to the generalization that *Salmonella* gastroenteritis should not be treated; and also non-typhoidal *Salmonella* strains could cause disease mimicking enteric fever (11, 21). After all that mentioned, subtyping and serovar determination of *Salmonella* spp obtained in any culture is important. Unfortunately, serovar determination was not performed on isolates obtained from our patients, and we could not understand whether the patients had typhoid fever or invasive disease with non-typhoidal *salmonella* species. However, the use of raw animal products in patients 4 and 5 made us think that non-typhoidal serovars may be causative agents. The severity of clinical conditions and significantly elevations in inflammatory markers of the patients suggested invasive disease associated with *Salmonella* spp and antibiotherapy treatments were arranged accordingly. *Salmonella enterica ssp enterica* was observed in cultures of all patients, but since serotyping could not be performed, the antimicrobial treatments initiated were completed to the appropriate time for enteric fever or invasive non-typhoidal salmonellosis.

Varying degrees of AV blocks can occur for many reasons including infections and infection-associated myocarditis (22, 23). COVID-19-related cases and MIS-C patients with myocarditis have also been described (24, 25). Peri-myocarditis and arrhythmias are well known complications of *Salmonella* infections and have also been reported in children (26). Abnormal echocardiographic findings detected in patient 4 were interpreted as heart failure due to myopericarditis and secondary pleural effusion. Cardiac complications in this patient may have occurred due to both MIS-C and salmonellosis. However, the cardiac involvement was interpreted as related to the infection more than MIS-C, since the findings did not gradually get worse and resolved spontaneously without additional treatment for MIS-C.

MIS-C overlaps with many other infectious and inflammatory diseases or syndromes that pediatricians often encounter in daily practice. Maintaining a proper clinical suspicion for other possibilities in the differential diagnosis is important in children presenting with clinical signs / symptoms suggestive of MIS-C and laboratory findings consistent with this syndrome. Appropriate index of suspicion is essential to not to miss the diagnosis of other possible infectious or non-infectious diseases and avoid over-treatment due to the possibility of MIS-C. This case series demonstrated the necessity of a careful treatment

plan and a thorough review of other possible diagnoses in each step in children admitted with features suggestive of MIS-C along with severe elevations in inflammatory markers and strong evidences for COVID-19. *Salmonella* infections should be kept in mind as a causative agent of bacterial gastroenteritis in the differential diagnosis of patients with suspected MIS-C who present with increased cytokine levels accompanying fever and gastrointestinal system findings.

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