

**Persistent Fever, Progressive Cytopenias, and Multisystem Involvement
Mimicking Severe Sepsis in An Adolescent: a Case Report**

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Abstract

Introduction: Persistent fever with progressive cytopenias and multisystem involvement may mimic severe infection and create diagnostic challenges in adolescents. **Objective:** To describe the clinical presentation and diagnostic challenges of an adolescent with persistent fever and progressive multisystem involvement. **Case Report:** A 15-year-old girl presented with persistent fever following bilateral leg pain and swelling, followed by progressive anemia, severe thrombocytopenia, hepatomegaly, ascites, hypoalbuminemia, alopecia, and rash. Laboratory findings showed leukocytosis, elevated inflammatory markers, increased D-dimer, and progressive cytopenias, while blood cultures were negative. Despite broad-spectrum antibiotics, transfusions, and supportive therapy, the patient remained febrile and was referred to a tertiary hospital. **Discussion:** Sepsis and disseminated intravascular coagulation were initially diagnosed, with hemophagocytic lymphohistiocytosis and macrophage activation syndrome considered as differential diagnoses. Further evaluation resulted in a diagnosis of Multisystem Inflammatory Syndrome in Children. **Conclusions:** Persistent fever with progressive cytopenias and multisystem involvement despite antimicrobial therapy should prompt consideration of hyperinflammatory disorders and early referral.

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Introduction

Macrophage activation syndrome (MAS) is a severe and potentially life-threatening hyperinflammatory condition characterized by uncontrolled activation of T lymphocytes and macrophages, resulting in excessive cytokine production and progressive multiorgan dysfunction (Lee et al., 2024; Cron et al., 2023; Dong et al., 2024; Nigrovic, 2025). MAS is considered a form of secondary hemophagocytic lymphohistiocytosis (HLH) and may occur in association with rheumatic diseases, infections, malignancies, and other inflammatory conditions (Lee et al., 2024; Henter et al., 2007; Sztajn bok et al., 2024; Nguyen et al., 2024). The excessive immune activation associated with MAS can lead to widespread inflammation and progressive tissue injury (Hosseinpoor & Salesi, 2024). Common clinical and laboratory manifestations include persistent fever, hepatosplenomegaly, cytopenias, liver dysfunction, coagulopathy, and markedly elevated inflammatory markers (Lee et al., 2024; Henter et al., 2007). These abnormalities may develop simultaneously or progressively during the clinical course, making their temporal evolution relevant to diagnostic assessment. Recognition of this characteristic clinical pattern is therefore essential when evaluating patients with persistent systemic inflammation and evidence of multiorgan dysfunction.

Early recognition of MAS remains challenging because its clinical and laboratory manifestations may overlap substantially with severe infection, sepsis, disseminated intravascular coagulation (DIC), and other systemic inflammatory disorders (Lee et al., 2024; Cron et al., 2023; Bojan et al., 2021). In critically ill children, persistent fever, progressive cytopenias, coagulopathy, and organ involvement may initially be attributed to an infectious process, particularly when the patient presents with signs of systemic inflammation. This overlap can complicate the distinction between uncontrolled infection and an underlying hyperinflammatory syndrome. Hyperinflammation and cytokine dysregulation are central features of MAS and cytokine storm syndromes, in which excessive immune activation may contribute to progressive organ dysfunction (Cron et al., 2023). Delayed recognition of this process may allow the inflammatory response and associated organ injury to progress despite antimicrobial and supportive treatment (Lee et al., 2024; Cron et al., 2023). Accordingly, persistent or worsening clinical and laboratory abnormalities despite appropriate treatment for suspected infection should prompt consideration of MAS, HLH, or another hyperinflammatory condition.

Multisystem inflammatory syndrome in children (MIS-C) represents a hyperinflammatory condition that may present with persistent fever, hematologic abnormalities, and multiorgan involvement, creating substantial clinical overlap with MAS and other cytokine storm syndromes (McGonagle et al., 2021; Patel, 2022). The inflammatory manifestations of MIS-C may include abnormalities involving the hematologic, gastrointestinal, cardiovascular, hepatic, and coagulation systems, further complicating differentiation from severe infection and other inflammatory conditions (McGonagle et al., 2021). Similarities between MAS and other cytokine storm syndromes are partly related to excessive immune activation and dysregulated cytokine production (Ombrello, 2021). MAS and HLH may also share clinical findings such as fever, cytopenias, hepatosplenomegaly, coagulopathy, and progressive organ dysfunction (Lee et al., 2024; Henter et al., 2007). The diagnostic framework for HLH incorporates multiple clinical and laboratory findings because no single manifestation is sufficient to establish the diagnosis in all clinical settings (Henter et al., 2007). Therefore,

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distinguishing sepsis and DIC from HLH, MAS, and MIS-C requires careful evaluation of the clinical course, evolving laboratory abnormalities, and response to initial treatment.

The case report of this study is 15-year-old girl who presented with persistent fever and subsequently developed progressive severe thrombocytopenia, anemia, hypoalbuminemia, hepatomegaly, ascites, and coagulation abnormalities despite broad-spectrum antimicrobial therapy and intensive supportive management. The simultaneous progression of hematologic abnormalities, hepatic involvement, fluid accumulation, and coagulation disturbances raised concern for a systemic inflammatory process beyond an isolated infectious condition. The overlapping features of severe infection, DIC, and hyperinflammation created a diagnostic challenge during the clinical course. The progressive cytopenias were particularly relevant because cytopenia involving multiple blood cell lineages is recognized among the clinical and laboratory manifestations associated with HLH and MAS (Henter et al., 2007; Lee et al., 2024). Persistent fever and multiorgan involvement also represented features that could occur in both severe infection and hyperinflammatory syndromes, requiring consideration of the broader clinical context (Lee et al., 2024; Cron et al., 2023). The aim of this case report is to describe the clinical and laboratory evolution of an adolescent with MIS-C and to highlight the diagnostic overlap among sepsis, DIC, HLH, MAS, and MIS-C in patients presenting with persistent fever, progressive cytopenias, and multiorgan involvement despite antimicrobial and supportive treatment.

Case Report

Case Presentation

A 15-year-old female presented to the emergency room of a regional general hospital with persistent fever. The patient was referred with laboratory test results from an outside facility. Her first complaint was pain and soreness in both lower legs, which arose after participating in a sports competition, approximately 34 days before admission to the regional general hospital. The initial complaint was attributed to physical activity. The patient was brought to a midwife and received a muscle relaxant injection, which temporarily improved the symptoms. Eleven days later, she developed bilateral swelling on both legs, extending from the ankles to the toes, accompanied by fever. The patient went to a local clinic and received paracetamol and oral amoxicillin, but the symptoms did not improve. Two days later, she went to the community health center and received paracetamol, methylprednisolone, and vitamins. The symptoms reportedly improved within the next few days.

The patient started experiencing fluctuating fever, cough, and weakness four days before admission. She was taken to a midwife and received cefadroxil, paracetamol, methylprednisolone, an over-the-counter combination cold preparation (containing paracetamol, chlorpheniramine maleate, phenylephrine, dextromethorphan, and guaifenesin), and an iron tablet. Due to persistent fever, the patient underwent laboratory testing at a private clinic, and the results were taken to the general hospital's emergency department. During the course of her illness, the patient experienced a 3 kg weight loss (from 51 kg to 48 kg) due to reduced oral intake, which began midway through the illness, accompanied by persistent weakness.

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The patient was the elder of two siblings and lived in a household of four. She was delivered spontaneously at full term, with a birth weight of 3.5 kg and a birth length of 48 cm. There was no history of asthma, hospitalization, significant trauma, or developmental delay, and no known contact with a tuberculosis patient. Childhood immunization was reported to be complete, and there was no known allergy to food or drugs. The patient had not been taking any regular medication prior to the current illness. Notably, she had a longstanding history of developing purplish-blue bruises after fatigue or minor trauma. This history is relevant given the severe thrombocytopenia observed during the acute illness, although no prior hematologic evaluation was available to determine its cause.

Clinical Findings

On initial examination, the patient was fully conscious (Glasgow Coma Scale E4V5M6) but appeared weak. Vital signs showed a heart rate of 110 beats/min, good peripheral pulse and a capillary refill time less than 2 seconds, a respiratory rate of 20 breaths/min, blood pressure of 100/60 mmHg (<95th percentile), an axillary temperature of 38.3 °C, and oxygen saturation of 96% on room air. Anthropometric assessment revealed a body weight of 48 kg and a height of 155 cm (body mass index 19.9 kg/m²), consistent with normal nutritional status and normal stature for age. The conjunctivae were pale, with no scleral icterus. There was no epistaxis or gingival bleeding. Chest expansion was symmetrical, with vesicular breath sounds over both lung fields. Heart sounds were normal and regular, with no murmur. Abdominal examination revealed a soft abdomen with present bowel sounds and tenderness in the epigastric region.

Laboratory results brought from a private clinic on the fourth day of illness showed leukocytosis (15,400/ μ L), anemia (hemoglobin 8.2 g/dL, hematocrit 25%), and thrombocytopenia (80,000/ μ L). The Widal test showed antibody titers against Salmonella Paratyphi B O antigen of 1/80, Paratyphi C O antigen of 1/80, and Paratyphi C H antigen of 1/160. Repeat blood counts on admission confirmed persistent anemia and worsening thrombocytopenia (50,000/ μ L). Serial laboratory results across the hospital course at both facilities are shown in Table 2.

Management and Clinical Course

At the emergency department, the patient received initial management consisting of intravenous Ringer's lactate at 20 drops/min, intravenous cefotaxime 1000 mg every 8 hours, intravenous dexamethasone 5 mg twice daily, and oral paracetamol 500 mg every 8 hours. Following this initial treatment, the fever subsided temporarily. The patient was admitted to the regional general hospital and remained hospitalized for approximately two weeks. Throughout the admission she had a fever that recurred on almost every day of illness. No overt bleeding manifestations were observed during the hospital stay. Right upper quadrant abdominal pain appeared during the second week of illness and gradually diminished thereafter. Abdominal distension was noted, with the abdominal circumference reaching 75 cm; this subsequently resolved, with the abdominal circumference decreasing to 70 cm.

During the early phase of the admission, the patient was transferred to the pediatric intensive care unit in the context of tachycardia and was later returned to the regular ward. Owing to progressive anemia and thrombocytopenia, she required repeated blood-product transfusions, comprising packed red cells, platelet concentrates, and 20% albumin;

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intravenous furosemide was given as premedication before each transfusion. From the second week of illness, lower-limb edema developed, initially unilateral and later bilateral, accompanied by hypoalbuminemia (albumin nadir 2.2 g/dL on day 12).

A pruritic erythematous rash appeared on the thirteenth day of illness, initially in the diaper area and later spreading over the body. Around the same period, diffuse hair loss was noted without discrete patches of baldness. Following dermatology consultation, the rash was attributed to diaper dermatitis with miliaria rubra and treated with a topical desoximetasone-gentamicin preparation. Serial complete blood counts (Table 2) demonstrated progressively severe thrombocytopenia, with the platelet count declining from 80,000/ μ L on admission to a nadir of 7,000-9,000/ μ L during the second week of illness, followed by a gradual rise after repeated platelet transfusions. Hemoglobin likewise fell to 5.4 g/dL before improving with red cell transfusion. A peripheral blood smear showed hypochromic microcytic anemia with a leftward shift of the leukocytes and thrombocytopenia, interpreted as suggestive of a bacterial infection, with anemia of chronic inflammatory disease as a differential consideration.

Inflammatory markers were markedly elevated, with a C-reactive protein (CRP) of 174 mg/L on the seventh day of illness and a raised procalcitonin (5.33 ng/mL) on day 10. Liver transaminases were mildly elevated. Coagulation testing on day 10 showed a markedly elevated D-dimer (4977.1 ng/mL FEU), a mildly prolonged prothrombin time (13.8 seconds) with a near-normal activated partial thromboplastin time (30.9 seconds), and a fibrinogen level slightly above the reference range (431.6 mg/dL). Serum albumin was low. Dengue serology showed a non-reactive IgM and a reactive IgG. Urinalysis on the fifth day of illness showed mildly turbid urine with raised urobilinogen and a small number of leukocytes. Electrocardiography showed sinus tachycardia. Abdominal ultrasonography demonstrated hepatomegaly with suspected portal hypertension and ascites, while the gallbladder, pancreas, spleen, both kidneys, urinary bladder, and uterus showed no abnormality as seen in Figure 1. A blood culture isolated coagulase-negative staphylococci from one of two specimen sets; the laboratory interpreted this as a probable contaminant representing normal skin flora rather than a true pathogen, and antibiotic therapy directed at this isolate was not recommended.

Diagnosis and Outcome

The antibiotic regimen was escalated over the course of the admission, from cefotaxime, to the addition of amikacin, and subsequently to meropenem, because of poorly controlled fever. The patient was diagnosed with sepsis and disseminated intravascular coagulation (DIC), with differential diagnoses including hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS). Additional findings included hepatomegaly with suspected portal hypertension, ascites, and miliaria rubra. Despite intensive management, the patient showed no significant clinical improvement and was ultimately referred to a central general hospital for further management. Following referral to the tertiary hospital, the patient underwent further evaluation and was subsequently diagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C). Details of the diagnostic evaluation performed at the tertiary hospital were not available for inclusion in this report. She was later discharged with MIS-C as the final diagnosis. The detailed clinical course and management are shown in Table 1. Written informed consent for publication of this case and the accompanying clinical data was obtained from the patient's parent or legal guardian.

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Table 1
Clinical and Management Timeline

Day of illness	Clinical event	Significant findings	Management & investigations
5	Recurring fever, cough	-	Intravenous dexamethasone discontinued; oral ambroxol started; blood and urine samples obtained for laboratory investigation
6	Recurring fever, cough; improved oral intake	Pale conjunctivae; epigastric tenderness	Intravenous ranitidine; oral paracetamol; blood sample obtained for laboratory investigation
7	Recurring fever, cough; dark brown stools with black portions; no breathing difficulty	Pale conjunctivae; epigastric and right hypochondriac tenderness; lung examination within normal limits	Oxygen via nasal cannula 1 L/min; transfer to PICU; Dengue IgG/IgM serology, CRP, SGOT/SGPT, blood cross-matching
8	Improved fever, cough	Pale conjunctivae	Intravenous fluids; single-dose intravenous dexamethasone 2.5 mg; nebulized ipratropium bromide-salbutamol every 12 hours; packed red cell transfusion 250 mL/24 hours for two days; transfer to regular ward
9	Recurring fever, cough, chest pain on eating, palpitations, right upper quadrant abdominal pain	Pale conjunctivae; distended abdomen (abdominal circumference 75 cm); epigastric and right hypochondriac tenderness; liver and spleen difficult to assess; ECG: sinus tachycardia	Intravenous fluids; platelet concentrate transfusion 50 mL × 4 bags; post-transfusion blood evaluation
10	Improved fever, cough, chest pain, palpitations	Pale conjunctivae; reduced abdominal circumference (73 cm); epigastric and right hypochondriac tenderness	Abdominal ultrasound; evaluation of CRP, urea/creatinine, PT/aPTT, INR, D-dimer, blood culture
11	Recurring fever, cough, chest pain on eating, right upper quadrant abdominal pain aggravated by cough and palpation, left foot swelling	Pale conjunctivae; epigastric and right hypochondriac tenderness; non-pitting edema of the left foot	Intravenous cefotaxime; intravenous amikacin; intravenous dexamethasone 2.5 mg for fever; platelet concentrate transfusion 50 mL × 6 bags; fibrinogen evaluation
12	Recurring fever, cough, chest pain, right upper quadrant abdominal pain, itching, swelling of both feet, weakness	Pale conjunctivae; epigastric and right hypochondriac tenderness; pitting edema of both feet	Intravenous amikacin; intravenous dexamethasone 2.5 mg for fever; albumin 20% 100 mL transfusion; albumin evaluation
13	Recurring fever, cough, itching, diffuse hair loss (without localized bald areas), swelling of both feet, weakness	Pale conjunctivae; epigastric and right hypochondriac tenderness; pitting edema of both feet	Intravenous paracetamol; platelet concentrate transfusion 50 mL × 4 bags; albumin 20% 100 mL transfusion

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14	Recurring fever, cough, itching, diffuse hair loss, red patches over the back and waist, weakness; improved foot swelling	Pale conjunctivae; abdominal circumference 71 cm; papules on the back; edema of both feet resolved	Packed red cell transfusion 250 mL/24 hours for two days; post-transfusion, albumin, and procalcitonin evaluation
15-16	Recurring fever, cough, itching, red patches over the back and waist, weakness	Pale conjunctivae; papules on the back	Intravenous paracetamol; topical hydrocortisone 2.5% every 12 hours
17-18	Recurring fever, cough, itching, red patches over the back, buttocks, arms, and legs	Pale conjunctivae; small scattered erythematous papules on the back, buttocks, arms, and legs; abdominal circumference 70 cm; no abdominal tenderness	Intravenous meropenem started; cefotaxime and amikacin discontinued; topical hydrocortisone discontinued; topical desoximetasone-gentamicin started; repeat blood culture
19	Recurring fever, cough, itching, diffuse hair loss, red patches over the back, chest, and thighs, weakness	Pale conjunctivae; small scattered erythematous macules and papules; abdominal circumference 70 cm; hepatomegaly (liver palpable 2 finger-breadths below the right costal margin)	Referred to central general hospital

Description: Table 1. Clinical and management timeline across regional general hospital. Day of illness is counted from the first day of fever. Intravenous furosemide 20 mg was given as premedication before each transfusion at the regional general hospital. CRP = C-reactive protein; ECG = electrocardiogram; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; PICU = pediatric intensive care unit; PT = prothrombin time; aPTT = activated partial thromboplastin time; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

Table 2
Serial Laboratory Results

Parameter	Private Clinic	Regional general hospital									Unit	Reference
	Day 4	Day 5	Day 6	Day 7	Day 8	Day 10	Day 11	Day 12	Day 14	Day 17		
Complete blood count												
Leukocyte	15.400	10.740	6.030		8.880	11.490		17.460	14.290	13.750	/μL	4.000-10.000
Erythrocyte											/μL	4.0-5.2×10 ⁶
Hemoglobin	8.2	8.2	6.3		5.4	8.8		7.0	6.9	9.4	g/dL	12.0-16.0
Hematocrit	25	25.8	20.1		17.0	26.7		21.4	20.6	28.1	%	37.0-47.0
MCV	74	74.6	74.2		74.2	76.5		78.1	77.7	80.3	fL	81.0-96.0
MCH	24	23.7	23.2		23.6	25.2		25.5	25.3	26.9	pg	27.0-36.0
MCHC	33	31.8	31.3		31.8	33.0		32.7	32.5	33.5	g/dL	31.0-37.0
Thrombocyte	80.000	50.000	18.000		7.000	9.000		29.000	45.000	62.000	/μL	150.000-400.000
Biochemistry												
SGOT				49							U/L	<34
SGPT				42							U/L	<55
Urea				34							mg/dL	8.4-21.0
Creatinine				0.3							mg/dL	0.57-1.11
Albumin								2.2	2.9		g/dL	3.5-5.0
Coagulation												
D-dimer						4977.1					ng/mL FEU	<500
PT						13.8					second	11-13.5
aPTT						30.9					second	25-35
INR						1.30					-	0.80-1.20
Fibrinogen							431.60				mg/dL	200-400
Inflammatory markers												
CRP				174		148					mg/L	<5
Procalcitonin						5.33					ng/mL	<0.05
Ferritin						2002.98					ng/mL	4.63-204.00
Serology												
Dengue IgM				Non-reactive							-	Non-reactive
Dengue IgG				Reactive							-	Non-reactive

Widal: S. Paratyphi B, O	1/80		titer	<1/80
Widal: S. Paratyphi C, O	1/80		titer	<1/80
Widal: S. Paratyphi C, H	1/160		titer	<1/80
Urinalysis				
Colour	Yellow		-	Yellow
Clarity	Cloudy		-	Clear
Specific gravity	1,020		-	1.000-1.030
pH	7.0		-	4.5-8.0
Protein	Negative		mg/dL	Negative
Glucose	Negative		mg/dL	Negative
Ketone	Negative		mg/dL	Negative
Blood	Negative		-	Negative
Leukocyte (microscopy)	5-7		/HPF	0-1
Erythrocyte (microscopy)	0-1		/HPF	0-2
Urobilinogen	+1		mg/dL	Normal
Bilirubin			mg/dL	Negative

Description: Table 2. Serial laboratory results across the two facilities. Values in bold red indicate above the reference range (H); values in bold blue indicate below the reference range (L). Day of illness is counted from the first day of fever. Reference ranges are those used by the regional general hospital laboratory; ranges may differ slightly between facilities. *The Widal titer recorded as 1/160. aPTT = activated partial thromboplastin time; CRP = C-reactive protein; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MPV = mean platelet volume; PT = prothrombin time; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

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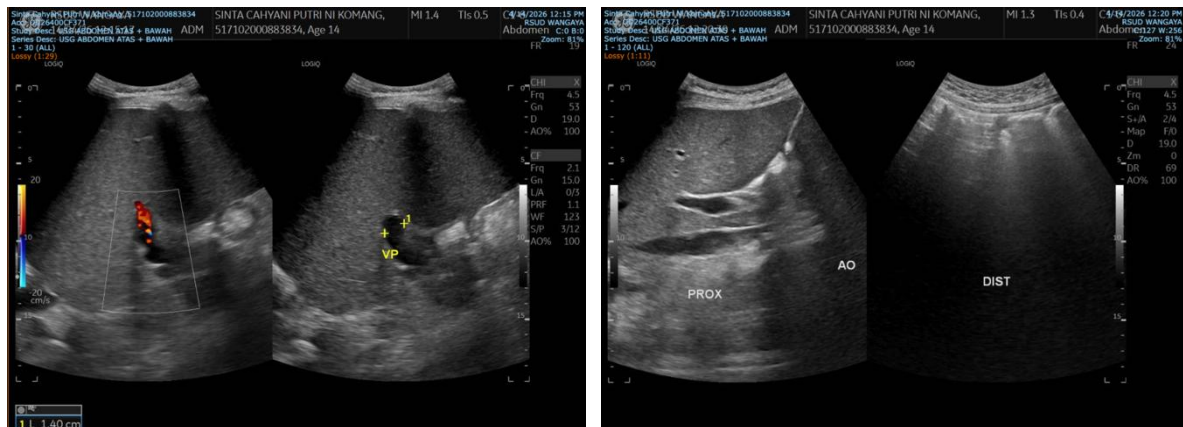


Figure 1. Abdominal Ultrasonography Demonstrated Hepatomegaly with Suspected Portal Hypertension and Ascites

1. Discussion

A 15-year-old adolescent girl presented with persistent fluctuating fever, progressive severe cytopenias, hepatomegaly with ascites, hypoalbuminemia, and widespread mucocutaneous manifestations. The illness evolved over a two-week period before a definitive diagnosis was reached at the tertiary referral hospital. During hospitalization at the regional general hospital, the patient was diagnosed with sepsis and disseminated intravascular coagulation (DIC), while hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) remained important diagnostic considerations. The patient also showed several characteristics commonly associated with MAS, including marked hyperferritinemia, cytopenias affecting multiple cell lines, and coagulation abnormalities (Lee et al., 2024; Cron et al., 2023). Evaluation using the Histiocyte Society HLH-2004 criteria and the 2016 classification criteria for MAS complicating systemic juvenile idiopathic arthritis (Ravelli criteria) showed that only partial criteria were fulfilled, including fever, multilineage cytopenia, and hyperferritinemia (Henter et al., 2007; Ravelli et al., 2016). However, triglycerides, soluble CD25, natural killer-cell activity, and bone marrow examination for hemophagocytosis were not performed, and fibrinogen was elevated rather than reduced as classically expected in MAS (Henter et al., 2007; Ravelli et al., 2016).

DIC, HLH, and MAS are distinct but overlapping hyperinflammatory syndromes that may occur in severe systemic inflammation (Cron et al., 2023; Henter et al., 2007). DIC is characterized by systemic activation of coagulation with consumption of platelets and coagulation factors, typically presenting with thrombocytopenia, prolonged coagulation times, elevated D-dimer, and reduced fibrinogen. HLH results from uncontrolled activation of macrophages and cytotoxic T lymphocytes and is diagnosed using the HLH-2004 criteria, which include fever, splenomegaly, cytopenia, hyperferritinemia, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis, elevated soluble CD25, and reduced natural killer-cell activity (Henter et al., 2007). MAS represents a form of secondary HLH associated with rheumatic diseases and shares similar features, with the Ravelli criteria emphasizing hyperferritinemia, thrombocytopenia, elevated transaminases, hypertriglyceridemia, and hypofibrinogenemia (Lee et al., 2024; Ravelli et al., 2016). Importantly, these syndromes

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may coexist, as cytokine-mediated inflammation in HLH and MAS can produce a consumptive coagulopathy resembling DIC. In the present case, thrombocytopenia, markedly elevated D-dimer, and mildly prolonged prothrombin time initially suggested DIC, whereas multilineage cytopenia and marked hyperferritinemia raised suspicion for HLH or MAS. However, the elevated fibrinogen level (431.6 mg/dL) was inconsistent with overt DIC and classical MAS, and only part of the HLH-2004 and Ravelli criteria were fulfilled.

The final diagnosis of MIS-C was established at the tertiary referral hospital, however, the diagnostic records were unavailable for this report, limiting independent verification of the criteria fulfilled by this patient. Based on the information available, persistent fever and elevated inflammatory markers (CRP 174 mg/L and procalcitonin 5.33 ng/mL), together with hematologic abnormalities, hypoalbuminemia, hepatomegaly, ascites, and mucocutaneous manifestations, indicate systemic inflammation with multisystem involvement. Nevertheless, these findings alone are insufficient to confirm that the patient met the formal diagnostic criteria for MIS-C. Key information, including evidence of recent SARS-CoV-2 infection or exposure, cardiovascular involvement, and the specific organ-system criteria documented at the tertiary hospital, was not available. Accordingly, MIS-C is reported as the final diagnosis assigned by the referral hospital, while the extent to which the available case data satisfy established diagnostic criteria remains uncertain.

The Widal test showed titers of 1:80 for Salmonella Paratyphi B O and S. Paratyphi C O antigens and 1:160 for S. Paratyphi C H antigen. These results were insufficient to establish enteric fever as the cause of the illness, because Widal titers alone have limited diagnostic specificity and must be interpreted in conjunction with clinical findings and, where available, confirmatory testing. Dengue serology was IgM-negative and IgG-positive. This pattern did not provide evidence of an acute dengue infection, although an isolated IgG result cannot definitively exclude dengue in every clinical context. Therefore, neither the Widal results nor the dengue serology independently established an alternative diagnosis, and both should be interpreted as limited findings within the broader differential diagnostic assessment.

The conceptual difficulty in distinguishing MIS-C from MAS reflects a broader understanding that pediatric hyperinflammatory syndromes may represent a continuum of cytokine storm syndromes rather than entirely discrete conditions (Cron et al., 2023; McGonagle et al., 2021). Primary HLH, secondary HLH, severe cytokine release syndrome following chimeric antigen receptor T-cell therapy, and post-infectious hyperinflammatory states such as MIS-C may converge on a common pathway of dysregulated innate and adaptive immune activation despite arising from different triggers (Cron et al., 2023; McGonagle et al., 2021). The coexistence of MIS-C and MAS-like features in this patient may be considered in light of this overlap, but the available evidence does not establish concurrent MAS or confirm a specific shared inflammatory mechanism (Gámez-González et al., 2024; Fujita et al., 2026). Although comparative cytokine data remain limited, current evidence suggests that MIS-C and MAS have overlapping, but not identical, inflammatory profiles, with increased activity of cytokines and chemokines involving interleukin-6, interleukin-1 β , interferon- γ , and interferon- γ -related pathways (McGonagle et al., 2021; Fujita et al., 2026). In this patient, marked hyperferritinemia, progressive multilineage cytopenia, and coagulation abnormalities

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were compatible with a MAS-like hyperinflammatory presentation, however, the incomplete diagnostic workup precluded confirmation of MAS.

Conclusion

This case highlights the diagnostic challenge of distinguishing severe infection from hyperinflammatory syndromes in an adolescent presenting with persistent fever, progressive cytopenias, and multisystem involvement. The combination of severe thrombocytopenia, anemia, marked hyperferritinemia, hepatomegaly, ascites, hypoalbuminemia, coagulation abnormalities, and persistent systemic inflammation despite broad-spectrum antimicrobial therapy raised suspicion for HLH or MAS. However, the patient fulfilled only part of the HLH-2004 and Ravelli criteria, supporting an overlapping hyperinflammatory process rather than a definitive diagnosis of HLH or MAS. The subsequent diagnosis of MIS-C at the tertiary referral hospital further illustrates the clinical overlap among sepsis, DIC, MAS, HLH, and MIS-C. Persistent fever with progressive cytopenias and hyperferritinemia despite appropriate antimicrobial treatment should prompt early evaluation for hyperinflammatory disorders and timely referral for further diagnostic assessment and management.

Reference

- Bojan, A., Parvu, A., Zsoldos, I. A., Torok, T., & Farcas, A. D. (2021). [Macrophage activation syndrome: A diagnostic challenge](https://doi.org/10.3892/etm.2021.10336). *Experimental and therapeutic medicine*, 22(2), 904. <https://doi.org/10.3892/etm.2021.10336>
- Cron, R. Q., Goyal, G., & Chatham, W. W. (2023). [Cytokine storm syndrome](https://doi.org/10.1146/annurev-med-042921-112837). *Annual Review of Medicine*, 74, 321-337. <https://doi.org/10.1146/annurev-med-042921-112837>
- Dong, Y., Wang, T., & Wu, H. (2024). [Heterogeneity of macrophage activation syndrome and treatment progression](https://doi.org/10.3389/fimmu.2024.1389710). *Frontiers in Immunology*, 15, 1389710. <https://doi.org/10.3389/fimmu.2024.1389710>
- Fujita, Y., Shimizu, M., Aihara, S., Nomura, K., Yoshihara, S., Sekine, K., ... & Shiraishi, H. (2026). [Macrophage activation syndrome associated with multi-system inflammatory syndrome in children: a case report and cytokine profile](https://doi.org/10.1080/25785826.2025.2559458). *Immunological Medicine*, 49(1), 115-119. <https://doi.org/10.1080/25785826.2025.2559458>
- Gámez-González, L. B., Murata, C., Garcia-Silva, J., Ulloa-Gutierrez, R., Márquez-Aguirre, M., Rios-Olivares, I., ... & Rekamlatina-3 Mis-C Study Group Investigators. (2024). [Macrophage activation syndrome in MIS-C](https://doi.org/10.1542/peds.2024-066780). *Pediatrics*, 154(6), e2024066780. <https://doi.org/10.1542/peds.2024-066780>
- Henter, J. I., Horne, A., Aricó, M., Egeler, R. M., Filipovich, A. H., Imashuku, S., ... & Janka, G. (2007). HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatric blood & cancer*, 48(2), 124-131.
- Hosseinpour, S., & Salesi, M. (2024). [Macrophage activation syndrome: a review of recent renal findings](https://doi.org/10.34172/jrip.2024.32269). *Journal of Renal Injury Prevention*, 13(1), e32269-e32269. [10.34172/jrip.2024.32269](https://doi.org/10.34172/jrip.2024.32269)
- Lee, J., Bae, K. S., Rhim, J. W., Lee, S. Y., Jeong, D. C., & Kang, J. H. (2024). [Macrophage activation syndrome in children: update on diagnosis and treatment](https://doi.org/10.3390/children11070755). *Children*, 11(7), 755. <https://doi.org/10.3390/children11070755>
- McGonagle, D., Ramanan, A. V., & Bridgewood, C. (2021). [Immune cartography of macrophage activation syndrome in the COVID-19 era](https://doi.org/10.1038/s41584-020-00571-1). *Nature Reviews Rheumatology*, 17(3), 145-157. <https://doi.org/10.1038/s41584-020-00571-1>
- Nguyen, T. T., Kim, Y. T., Jeong, G., & Jin, M. (2024). [Immunopathology of and potential therapeutics for secondary hemophagocytic lymphohistiocytosis/macrophage activation syndrome: a translational perspective](https://doi.org/10.1038/s12276-024-01182-6). *Experimental & Molecular Medicine*, 56(3), 559-569. <https://doi.org/10.1038/s12276-024-01182-6>
- Nigrovic, P. A. (2025). [Macrophage activation syndrome](https://doi.org/10.1002/art.43052). *Arthritis & Rheumatology*, 77(4), 367-379. <https://doi.org/10.1002/art.43052>
- Ombrello, M. M. J. (2021). [COVID-19 and cytokine storm syndrome: are there lessons from macrophage activation syndrome?](https://doi.org/10.1016/j.trsl.2021.03.002). *Translational Research*, 232, 1-12. [10.1016/j.trsl.2021.03.002](https://doi.org/10.1016/j.trsl.2021.03.002)
- Patel, J. M. (2022). [Multisystem inflammatory syndrome in children \(MIS-C\)](https://doi.org/10.1007/s11882-022-01031-4). *Current allergy and asthma reports*, 22(5), 53-60. <https://doi.org/10.1007/s11882-022-01031-4>

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- Ravelli, A., Minoia, F., Davì, S., Horne, A., Bovis, F., Pistorio, A., ... & Cron, R. Q. (2016). 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation collaborative initiative. *Annals of the Rheumatic Diseases*, 75(3), 481-489.
- Sztajn bok, F., Fonseca, A. R., Campos, L. R., Lino, K., Rodrigues, M. C. F., Silva, R. M., ... & Carvalho, M. D. F. F. (2024). Hemophagocytic lymphohistiocytosis and macrophage activation syndrome: two rare sides of the same devastating coin. *Advances in Rheumatology*, 64(1), 28. <https://doi.org/10.1186/s42358-024-00370-2>