MEASLES-ASSOCIATED CYTOKINE STORM IN A CHILD: A CASE REPORT

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Abstract

Objectives: Cytokine storm (CS) represents a dysregulated hyperinflammatory state that can lead to multiorgan dysfunction. Prompt recognition is crucial in reducing morbidity and mortality. A 13-year-old previously healthy, unvaccinated boy presented with 8 days of high-grade fever, conjunctivitis, maculopapular rash, hoarseness, epigastric pain, and arthralgia. On admission, the patient had tachypnea, hypotension, hepatomegaly, and oliguria. Laboratory results showed thrombocytopenia, hypoalbuminemia, and markedly elevated CRP, procalcitonin, ferritin (> 5,000 ng/mL), AST (640 U/L), ALT (843 U/L), and D-dimer (> 20,000 ng/mL). Cytokine profiling revealed elevated IL-6 (622 pg/mL), IL-18 (122.4 pg/mL), and TNF-α (347 pg/mL). Flow cytometry demonstrated reduced $CD3^+$ and $CD4^+$ T-cell counts and a low CD4/CD8 ratio. RT-PCR confirmed the presence of the measles virus (MeV) with a cycle threshold of 22, while all other microbiological tests and cultures returned negative. The patient was diagnosed with a measles-associated CS and treated with supportive care, broad-spectrum antibiotics, and intravenous immunoglobulin (IVIG) of 0.4 g/kg/day for 3 days. His fever subsided within 48 hours, and he was discharged in stable condition on day 7. Early identification of CS through cytokine and immunologic profiling is crucial for initiating timely immunomodulatory therapy.

Keywords: Children; Cytokine storm; Measles; Intravenous immunoglobulin.

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INTRODUCTION

Measles is an acute, highly contagious viral disease caused by the MeV, predominantly affecting children. In recent years, the global resurgence of measles has been linked to declining vaccination coverage, leading to increased incidence and complex disease patterns [1, 2]. While the majority of measles cases are self-limiting, a subset of patients, especially those with underlying risk factors, may develop complications such as acute laryngotracheitis, pneumonia, encephalitis, or, more rarely, CS [1, 2]. CS is a severe systemic inflammatory response resulting from immune dysregulation. It is characterized by excessive activation of immune cells and uncontrolled release of proinflammatory cytokines such as IL-6 and TNF-α, which can lead to widespread tissue damage, multiorgan dysfunction, and potentially death if not recognized and managed promptly [3, 4]. The clinical manifestations of CS are often nonspecific and highly variable, particularly in pediatric patients, making early diagnosis challenging. Moreover, it can be easily misdiagnosed as severe sepsis or multisystem inflammatory syndrome in children (MIS-C), delaying targeted treatment and increasing the risk of morbidity and mortality [4, 5]. Timely recognition and prompt initiation of immunomodulatory therapy are critical in improving outcomes in patients with CS [6]. The following case aims to: *Highlight a rare but life-threatening complication of measles-associated CS in an unvaccinated child and emphasize the pivotal role of early diagnosis and IVIG therapy in managing this condition.*

CASE PRESENTATION

A 13-year-old previously healthy male with no notable perinatal history and normal nutritional status (height-for-age: -0.38SD, weight-for-age: +0.19SD, BMI-for-age: +0.6SD) presented with an 8-day history of persistent high-grade fever with increasing intensity. He developed bilateral conjunctivitis, hoarseness, respiratory difficulty, epigastric pain, diarrhea, rash, and arthralgia. On admission, he was tachypneic (RR: 35 breaths/min), hypotensive (BP: 98/62mmHg), tachycardic (HR: 142 beats/min), oliguric, and had hepatomegaly. Initial laboratory investigations revealed thrombocytopenia, hypoalbuminemia, and markedly elevated levels of IL-6, IL-18, TNF-α, LDH, ferritin, and D-dimer *(Table 1).* Flow cytometry revealed a reduction in CD3+ and CD4+ T cells, as well as a decreased CD4/CD8 ratio *(Table 2).* Extensive microbiological evaluation, including PCR and cultures from nasotracheal

aspirates (NTA) and blood, was negative for 13 common respiratory pathogens, Adenovirus, CMV, EBV, influenza A/B, SARS-CoV-2, and 65 additional pathogens *(Table 3)*. Only the MeV PCR was positive with a low cycle threshold of 22. The patient was diagnosed with CS syndrome secondary to severe measles pneumonia. He received respiratory support, hemodynamic stabilization, fluid balance management, high-dose vitamin A, and empirical antibiotics (Meropenem 20 mg/kg IV every 8 hours, Vancomycin 20 mg/kg IV every 8 hours). Immunomodulatory therapy with IVIG at a dose of 0.4 g/kg/day was initiated for 3 consecutive days (T1 - T3) *(Figure 1)*. His condition improved rapidly, with defervescence within 48 hours of IVIG initiation, enabling de-escalation of antibiotics. The patient was discharged after 7 days of treatment in stable condition.

Table 1. Peripheral blood cell counts, biochemical, and immunologic parameters at serial time points.

Parameters	Reference range	T1	T2	T3	T4
WBC (10^3/µL)	5.5 - 15.5	1.2	2.0	4.3	7.5
Hb (g/dL)	11 - 14	108	120	127	134
PLT (10^3/µL)	150 - 450	52	97	227	422
CRP (mg/L)	0 - 5	165	84	19.55	1.84
PCT (ng/mL)	< 0.05	98	63	17	0.2
Albumin (g/L)	30 - 50	28	30	34.4	36
AST (U/L)	2 - 48	640	123	77.6	31.2
ALT (U/L)	2 - 29	843	300	210	86.2
ALP (U/L)	130 - 560	320	122.8	99.4	94
Ferritin (µg/L)	4 - 67	5,262	1,500	550	262
LDH (U/L)	120 - 300	1,580	592	400	283
IL-6 (pg/mL)	< 7	622	123	8.64	4.5
IL-18 (pg/mL)	5 - 10	122.4	NA	85.95	NA

Parameters	Reference range	T1	T2	T3	T4
TNF-α (pg/mL)	5 - 10	347	NA	76.9	NA
Troponin I (ng/mL)	< 0.04	4	4.3	3.2	3.5
D-Dimer (µg/mL)	< 500	20,000	5,200	945	471
Fibrinogen (mg/dL)	160 - 390	4.52	4.41	4	3.2
INR	0.84 - 1.2	1.22	1.2	1.1	1.2

(T1: At hospital admission (before treatment); T2: After first dose of IVIG; T3: After second dose of IVIG; T4: After third dose of IVIG; WBC: White blood cell; CRP: C-reactive protein; IL: Interleukin; TNF: Tumor necrosis factor; LDH: Lactate dehydrogenase; INR: International normalised ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase)

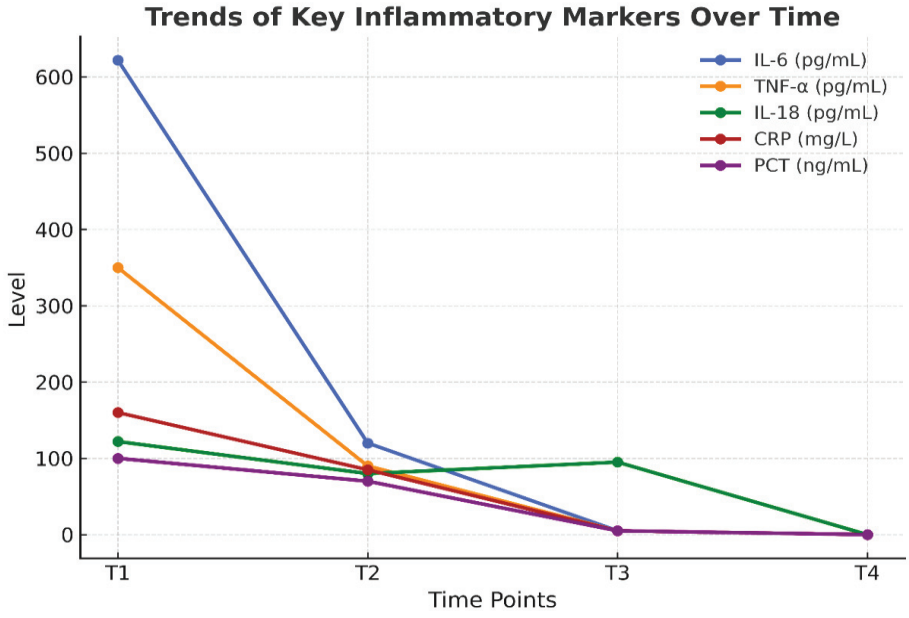

Figure 1. Trends of key inflammatory markers following IVIG therapy.

Serial changes in IL-6, TNF-α, IL-18, CRP, and PCT levels over four time points (T1 - T4). T1: At hospital admission; T2 - T4: After first, second, and third IVIG doses, respectively. A marked decline in cytokine and inflammatory markers was observed following IVIG treatment, consistent with clinical improvement.

Table 2. Biochemical and immunologic parameters at key time points.

Parameters	Reference range	T1	T2
CD3 (cells/µL)	1,000 - 2,200	778	1,483.2
CD4 (cells/µL)	530 - 1,300	261.8	540
CD8 (cells/µL)	330 - 920	464.45	792.6
CD4/CD8	1.0 - 2.0	0.56	0.68
CD19 (cells/µL)	110 - 570	220	370
CD16 + CD56 (cells/µL)	70 - 480	191.7	324
IgA (mg/dL)	63 - 484	95.25	72.8
IgG (mg/dL)	540 - 1,822	1,657	1520
IgM (mg/dL)	41 - 183	77.74	59.61
IgE (mg/dL)	0 - 200	237	32.6
Vitamin D (ng/mL)	30 - 40	14.5	17.52
Vitamin B12 (pg/mL)	197 - 771	862	1,206
Vitamin A (µmol/L)	1.05 - 4.9	0.85	2.42
Magie (mmol/L)	0.7 - 0.86	0.72	0.81
Kẽm (µmol/L)	12 - 15	12.2	14.34
Iron (µmol/L)	2.9 - 22.9	16.2	18.15
Phosphat (mmol/L)	1.05 - 1.85	1.23	1.37

(T1: At admission; T2: After 7 days of treatment; Ig: Immunoglobulin)

Table 3. Etiological investigations at the time of diagnosis.

Pathogen/Test	Result
MeV PCR	Positive with a low cycle threshold of 22
Epstein-Barr virus PCR	Negative
Cytomegalovirus PCR	Negative
NTA culture	Negative
Panel 13 bacterial NTA	Negative
Adenovirus PCR	Negative
Mycoplasma pneumoniae PCR	Negative
Influenza A/B rapid test	Negative
SAR-CoV-2 rapid test	Negative
Blood culture	Negative
PCR 65 pathogen in blood	Negative

DISCUSSION

Measles is typically a self-limited viral illness in children, but complications can arise in certain populations. Children with comorbidities such as immunodeficiency or malnutrition are at increased risk for severe disease and complications, including laryngotracheitis, pneumonia, sepsis, and rarely CS. Late complications such as subacute sclerosing panencephalitis also highlight the long-term risks of measles. However, even previously healthy, unvaccinated children can develop severe immune-mediated responses, as demonstrated in this case [2, 7]. CS is a life-threatening hyperinflammatory condition marked by excessive and dysregulated cytokine release, resulting in systemic inflammation and multiorgan dysfunction [3]. While classically associated with viral infections such as influenza, EBV, or SARS-CoV-2, CS has also been described in rare cases of measles infection, particularly in unvaccinated children [8]. The patient presented here was a previously healthy 13-year-old unvaccinated boy who developed rapid-onset multisystem involvement with high fever, conjunctivitis, respiratory distress,

hepatomegaly, and shock. Laboratory findings showed hallmarks of CS, including elevated IL-6, IL-18, TNF-α, ferritin, LDH, and D-dimer, together with lymphopenia and hypoalbuminemia (*Table 1*). Immunophenotyping further revealed decreased $CD3^+$ and $CD4^+$ T cells, with a reduced CD4/CD8 ratio (*Table 2*), consistent with profound immune dysregulation as previously observed in measles-induced immunopathology. The immunophenotypic findings in our patient, with significant depletion of $CD3^+$ and $CD4^+$ T cells, further support the profound immunosuppressive effects of measles, which likely contributed to the development of CS and risk of opportunistic infections in this case. Importantly, comprehensive microbiological investigations were negative for co-infections. PCR confirmed MeV with a low cycle threshold value (22), and all other bacterial and viral pathogens tested negative (*Table 3*). The diagnosis of measles-associated CS was supported by clinical findings, immunological parameters, and exclusion of alternative etiologies. These findings support the diagnosis of measles-associated CS, a clinical entity that is rarely recognized but carries a high risk of deterioration if untreated. The case highlights the necessity of early recognition of CS in children with severe measles, especially in unvaccinated individuals. In our patient, early warning signs, such as persistent fever, progressive respiratory compromise, elevated IL-6, IL-18, TNF-α, CRP/PCT, D-Dimer, and ferritin levels exceeding 5000 μg/L, enabled the clinical doctors to suspect CS and initiate immunomodulatory therapy promptly. This aligns with recent recommendations emphasizing ferritin, IL-6, IL-18, TNF-α, and D-dimer as accessible biomarkers for early detection of CS [4]. According to Griffin (2021), the MeV causes a unique state of immunosuppression by infecting and depleting memory T and B lymphocytes, effectively erasing prior immune memory and increasing susceptibility to opportunistic infections. This post-measles immune suppression may last for weeks to months, even after clinical recovery. In our patient, reduced $CD3^+$ and $CD4^+$ T cells, along with hypoalbuminemia and lymphopenia, support this pathophysiology and may have contributed to the uncontrolled inflammatory cascade observed in CS [9].

There is no standardized therapy for CS in the context of measles. However, IVIG has been reported as a potential immunomodulatory option due to its anti-inflammatory and anti-cytokine properties. In our case, high-dose IVIG (0.4 g/kg/day for 3 days) was administered early (T1 - T3), resulting in rapid defervescence within 48 hours and parallel reduction in inflammatory markers, allowing early de-escalation of antibiotics and discharge after only 7 days of hospitalization (*Figure 1*). The clinical response observed in our patient supports the immunomodulatory potential of IVIG in virus-induced CS, as described in other contexts. This case report and literature review highlighted the effectiveness of IVIG in attenuating hyperinflammatory responses in COVID-19-related CS, demonstrating rapid improvement in fever, inflammatory markers, and organ dysfunction following IVIG administration. While evidence remains limited, these findings, along with our case, suggest that early IVIG therapy may play a critical role in dampening the cytokine cascade and improving outcomes, particularly in severe viral infections where corticosteroids have not yet been clearly indicated [10]. This is consistent with prior reports showing favourable outcomes with IVIG in viral-associated CS, including measles and influenza [6].

CONCLUSION

This case underscores the importance of high clinical suspicion for CS in children with severe measles and systemic hyperinflammation. In resource-limited or rapidly deteriorating scenarios, early administration of IVIG may provide a life-saving immune-modulating effect.

Ethics: This study was conducted in accordance with the institutional regulations of the Department of Pediatrics, Military Hospital 103. The Department of Pediatrics, Military Hospital 103 granted permission for the use and publication of the research data. The authors declare to have no conflicts of interest in this research.

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