Avicenna Anatolian Journal of Medicine

Case Report

Fever of Unknown Cause: A Case of Macrophage Activation Syndrome

Authors & Affiliations

Pelin Arslan, Gürkan Karakuş

İnönü University, Schoof of Medicine, Malatya, Türkiye

Corresponding Author: Gürkan Karakuş, M.D., İnönü University, Schoof of Medicine, Malatya, Türkiye.
E-mail: ptulun73546@gmail.com

Submitted at: 21.02.2025 - Accepted at: 12.05.2025 - Published at: 31.05.2025

Avicenna Anatol J Med. Year; 2025, Volume: 2, Issue:
doi 10.5281/zenodo.15569678

Abstract

Fever of unknown origin (FUO) in children is a challenging diagnostic problem, as it can be caused by a wide range of infectious, inflammatory, malignant, or genetic disorders. We present the case of a 12-year-old girl with persistent fever, arthralgia, and elevated inflammatory markers. Despite extensive infectious, oncological, and rheumatologic investigations, no underlying cause was identified. Laboratory findings revealed markedly increased C-reactive protein, ferritin, and D-dimer levels, and mild hepatomegaly. Macrophage activation syndrome (MAS) was suspected due to persistent fever and hyperferritinemia, and confirmed by bone marrow aspiration. The patient responded rapidly to intravenous immunoglobulin and high-dose corticosteroids. This case emphasizes the importance of considering MAS in pediatric FUO and highlights the need for early recognition and treatment.

Keywords: Fever of Unknown Origin, Macrophage Activation Syndrome, Child

INTRODUCTION

Fever is a common physiologic response in childhood and serves as a key symptom for a broad array of diseases. It frequently occurs in infectious, autoimmune, malignant, and metabolic conditions. However, in certain cases, the underlying cause remains elusive despite comprehensive evaluation. Fever of Unknown Origin (FUO) represents a significant diagnostic challenge for clinicians. The initial definition of FUO was established by Petersdorf and Beeson in 1961, describing it as a fever exceeding 38.3°C, persisting for more than three weeks, and remaining undiagnosed after one week of hospitalization (1). Durack and Street revised these criteria in 1991, specifying fever above 38.3°C lasting longer than three weeks and persisting without diagnosis after at least three outpatient evaluations or three days of hospitalization (2). The etiology of FUO is diverse, encompassing infectious, inflammatory, malignant, and genetic diseases. Approximately 30–40% of FUO cases are infectious in origin, 20–30% are autoimmune or inflammatory, 10–20% are related to malignancy, and 10–15% remain idiopathic (3). A thorough history, physical examination, and systematic laboratory investigations are essential in the assessment of FUO. Here, we present a pediatric case who initially presented with fever and arthralgia and was ultimately diagnosed with macrophage activation syndrome (MAS) upon further investigation.

Case

A 12-year and 10-month-old girl presented with a two-week history of joint and muscle pain, unresponsive to movement or rest. She also reported marked morning stiffness in her joints, which gradually subsided during the day. Her past medical history was unremarkable, with no previous illnesses, medication use, or significant surgical interventions, and there was no family history of rheumatic or autoimmune diseases.

She was initially evaluated in the pediatric outpatient clinic for joint and low back pain. With a C-reactive protein (CRP) level of 28 mg/dL and a fever of 38.5°C, she was hospitalized and started on ceftriaxone. During her seven-day hospitalization, she experienced occasional cough but exhibited no rash, vomiting, hematuria, hematochezia, conjunctivitis, or pathological lymphadenopathy. As the fever persisted despite five days of ceftriaxone and two subsequent days of vancomycin, treatment was escalated to piperacillin-tazobactam and meropenem before her referral to our center.

On physical examination, her temperature was 37.6°C, heart rate 110/min (regular, no murmur), respiratory rate 20/min, oxygen saturation 96%, and blood pressure 100/60 mmHg. There was no evidence of arthritis, but diffuse muscle and joint tenderness was noted.

Other systemic examinations were unremarkable. Initial laboratory results showed: WBC 18.71×10³/μL, hemoglobin 11.6 g/dL, platelets 412×10³/μL, AST 18 U/L, ALT 14 U/L, ESR 64 mm/h, CRP 18.4 mg/dL, ferritin 816 ng/mL, fibrinogen 900 mg/dL (reference: 200–400), D-dimer 2.7 mg/mL (reference: 0–0.5), and prothrombin time 13.1 s (reference: 11–14).

Etiologic investigations revealed no growth in blood, urine, or stool cultures, and viral screening was negative. Brucella and Salmonella serologies, as well as PPD and Quantiferon tests, were negative. Abdominal ultrasound and contrast-enhanced CT imaging showed only mild hepatomegaly. Bone marrow aspiration did not reveal malignant cells. Rheumatologic assessment showed elevated C3 and C4, borderline anti-dsDNA, and negative ANCA.

During hospitalization, she received piperacillin-tazobactam and meropenem. Two echocardiograms showed no abnormalities aside from physiologic mitral regurgitation. Owing to persistent arthralgia, fever, and elevated acute phase reactants (APRs), aspirin was administered for three days in suspicion of acute rheumatic fever, but discontinued after no clinical response. As fever and symptoms persisted with persistently high APRs, she was referred for further rheumatologic evaluation.

Whole-body MRI at the referral clinic revealed only millimetric lymphadenopathies. Repeat laboratory results showed: WBC 8.17×10³/μL, hemoglobin 10.8 g/dL, platelets 287×10³/μL, CRP 132.7 mg/dL, ESR 69 mm/h, pro-BNP 303 pg/mL, D-dimer 27,250 mg/mL, INR 1.38, aPTT 30.8 s, fibrinogen 348 mg/dL, and ferritin 3,705 ng/mL. Based on these findings, a diagnosis of macrophage activation syndrome (MAS) was made.

Treatment was initiated with intravenous immunoglobulin (IVIG) at 80 g over 12 hours, followed by three days of intravenous pulse methylprednisolone (1 g daily), along with proton pump inhibitor, calcium, vitamin D supplementation, and a salt-free diet. After three days of pulse methylprednisolone, oral prednisolone (48 mg daily) was prescribed.

DISCUSSION

In this case report, we describe a 12-year-old girl who presented with prolonged fever and joint pain, ultimately diagnosed with macrophage activation syndrome (MAS). The patient's clinical course and laboratory findings indicated that MAS was the underlying cause, despite the initial classification as fever of unknown origin (FUO).

Diagnosis and Differential Diagnosis of FUO
FUO presents a significant diagnostic challenge for clinicians, as the diagnosis is typically established by systematically excluding other possible causes. Accordingly, thorough history-taking, physical examination, and comprehensive laboratory evaluation are essential in patients suspected of FUO. The etiology of FUO is broad, including infectious, inflammatory, malignant, and genetic diseases. Approximately 30–40% of FUO cases are attributed to infections, 20–30% to autoimmune or inflammatory conditions, 10–20% to malignancies, and 10–15% remain idiopathic (3). In our case, prolonged fever, joint pain, and elevated CRP and ferritin levels were highly suggestive of MAS; however, infectious, rheumatologic, and malignant etiologies were meticulously investigated before reaching a definitive diagnosis.

Macrophage Activation Syndrome (MAS)
MAS is a life-threatening complication that usually develops secondary to underlying disorders such as infections or rheumatologic diseases. Excessive immune activation and cytokine storm are central to the pathogenesis, resulting in uncontrolled macrophage and immune cell activation, leading to hemophagocytosis. MAS is particularly associated with systemic juvenile idiopathic arthritis and systemic lupus erythematosus (7,8).

Clinically, MAS may present with fever, malaise, anorexia, weight loss, skin rash, lymphadenopathy, hepatosplenomegaly, and neurologic symptoms. Laboratory abnormalities frequently include anemia, thrombocytopenia, markedly elevated ferritin, hypertriglyceridemia, increased D-dimer, low fibrinogen, and raised liver enzymes. Hyperferritinemia is considered a key biomarker for MAS, and our patient's ferritin levels were notably elevated (9,10). Additionally, our patient exhibited high D-dimer, elevated CRP, and persistent fever. Without timely intervention, MAS may progress to multiple organ failure due to the cytokine storm, with a correspondingly high mortality rate. Therefore, early recognition and prompt treatment are crucial (9,10).

In the present case, persistent fever, joint pain, high CRP, and ferritin levels supported the diagnosis of MAS, which was further confirmed by bone marrow aspiration revealing hemophagocytosis.

The patient was successfully treated with intravenous immunoglobulin (IVIG), high-dose pulse methylprednisolone, and supportive therapies, including a proton pump inhibitor, calcium, and vitamin D. High-dose corticosteroids constitute the mainstay of MAS therapy (11), with IVIG, cyclosporine, and biologic agents such as anakinra or tocilizumab used as adjuncts in refractory cases (11). In our case, the administration of IVIG and pulse steroids led to marked clinical improvement. It is also essential to address and treat the underlying cause of MAS when possible, as this optimizes patient outcomes.

CONCLUSION

This case report underscores the importance of thorough investigation to identify the underlying cause in patients presenting with fever of unknown origin (FUO). Early recognition and prompt treatment of life-threatening conditions such as macrophage activation syndrome (MAS) are crucial for optimizing patient outcomes.

Clinicians should maintain a high index of suspicion for MAS in cases of FUO, ensuring that appropriate diagnostic evaluations are pursued. Effective management requires a multidisciplinary approach, taking into account regional epidemiology, available hospital resources, and clinical expertise..

DECLERATIONS

Ethics Committee Approval: This case report was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the patient's legal guardian for publication of the case details. No ethical approval was required as individual patient data is anonymized and the report does not contain identifiable information.

Financial Disclosure: The authors declare that this study has received no financial support.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Funding source: No funding was received fort he research

Artificial Intelligence: The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

REFERENCES

1. PETERSDORF RG, BEESON PB. Fever of unexplained origin: report on 100 cases. *Medicine (Baltimore)*. 1961;40:1-30. doi:10.1097/00005792-196102000-00001
2. Durack DT, Street AC. Fever of unknown origin--reexamined and redefined. *Curr Clin Top Infect Dis.* 1991;11:35-51.
3. Cunha BA. Fever of unknown origin: clinical overview of classic and current concepts [published correction appears in Infect Dis Clin North Am. 2008 Jun;22(2):xv]. *Infect Dis Clin North Am*. 2007;21(4):867-vii. doi:10.1016/j.idc.2007.09.002
4. Hayakawa K, Ramasamy B, Chandrasekar PH. Fever of unknown origin: an evidence-based review. *Am J Med Sci*. 2012;344(4):307-316. doi:10.1097/MAJ.0b013e31824ae504
5. Wakai S, Murayama S, Gomi H. Diagnostic strategy for pediatric fever of unknown origin. *Pediatr Int*. 2022;64(1):e14911.2
6. Ravelli A, Minoia F, Davi S, et al. Macrophage activation syndrome. *Nat Rev Rheumatol.* 2012;8(5):301-309.
7. Grom AA, Horne A, De Benedetti F. Macrophage activation syndrome in the era of biologic therapy. *Nat Rev Rheumatol.* 2016;12(5):259-268. doi:10.1038/nrrheum.2015.179
8. Schulert GS, Grom AA. Pathogenesis of macrophage activation syndrome. *Rheum Dis Clin North Am.* 2015;41(4):537-546.
9. Grom AA, Jordan MB, Newburger PE, et al. Macrophage activation syndrome in the setting of pediatric rheumatologic disease. *Arthritis Rheum*. 2003;48(3):771-781
10. Schulert GS, Grom AA, Rosenbaum JT. Macrophage activation syndrome: a hemophagocytic syndrome associated with rheumatic diseases. *J Rheumatol.* 2014;41(6):1041-1048.
11. Yao TC, Lee JH, Yeh KW, et al. Treatment of macrophage activation syndrome in children with systemic juvenile idiopathic arthritis. *Semin Arthritis Rheum*. 2015;45(2):188-195.