CASE REPORT OPEN ACCESS

Juvenile Idiopathic Arthritis Complicated by Macrophage Activation Syndrome: A Case Report

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Abstract

Juvenile Idiopathic Arthritis (JIA) is an autoimmune disorder affecting children under 16, causing joint inflammation, fever, rash, and iridocyclitis. In some cases, JIA can lead to Macrophage Activation Syndrome (MAS), a secondary hemophagocytic lymphohistiocytosis often triggered by systemic juvenile idiopathic arthritis (s-JIA). An 18-year-old male with a past medical history of JIA presented with persistent high-grade fever, abdominal distension, and systemic symptoms non-responsive to antibiotics. MAS was confirmed after bone marrow aspiration and high-dose intravenous methylprednisolone were used. The report emphasizes the importance of early recognition and treatment of MAS to prevent severe complications and improve outcomes in patients with JIA. This case report details the diagnostic process, including specific disease activity scoring, imaging findings, and key immunological markers, to strengthen the clinical presentation. It emphasizes the importance of early recognition and treatment of MAS to prevent severe complications and improve outcomes in patients with JIA, aligning with current registry data and systematic reviews on MAS in JIA.

Keywords: Juvenile Idiopathic Arthritis (JIA), Macrophage Activation Syndrome (MAS), Systemic Juvenile Idiopathic Arthritis (s-JIA), Hemophagocytic Lymphohistiocytosis (HLH), autoimmune disorders in children, cytokine storm, NK cell dysfunction.

1. INTRODUCTION

Juvenile Idiopathic Arthritis (JIA), also known as Juvenile Rheumatoid Arthritis (JRA), is an autoimmune joint disorder that affects children under the age of 16. While JIA is considered uncommon, the specific reasons and genetic tendencies are still unclear. It often presents as joint inflammation, along with symptoms such as fever, rash, swollen lymph nodes, enlarged spleen, and iridocyclitis [1, 2]. Certain children have a type of Juvenile Idiopathic Arthritis (JIA) that resolves on its own within a few months, while others have a long-lasting form of the illness. Diagnosis relies mainly on clinical signs, involving tender, inflamed, and painful joints that may impede normal growth and development. JIA is divided into three different clinical categories, the first one is known as Still's disease, seen in 20% of cases with symptoms like fever, rash, splenomegaly, lymphadenopathy, pericarditis, or pleuritis; the second subtype is Monoarticular or Pauciarticular form of disease, affecting up to four joints; and the third one is Polyarticular JIA, impacting five or more joints, mainly in girls and frequently linked to high rheumatoid factor (RF) levels [1]. Symptoms such as joint inflammation, lymphadenopathy, splenomegaly, iridocyclitis, rash, and fever are the initial indication of Juvenile Rheumatoid Arthritis (JRA) in pediatric patients. Iridocyclitis can happen with or without symptoms like conjunctivitis and eye pain, and may result in complications such as scarring and glaucoma [3]. Clinical observations are the main method of diagnosing JRA, with additional tests for ANA

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and RF used to confirm and distinguish between subtypes of the disease. ANA and RF are usually absent in Still's disease, the first subtype of JRA, while iridocyclitis is more frequently linked with the monoarticular subtype [4].

Macrophage Activation Syndrome (MAS) is a severe and potentially deadly manifestation of rheumatic disorders, recognized as a secondary form of hemophagocytic lymphohistiocytosis (HLH) [5]. It mainly impacts individuals diagnosed with systemic juvenile idiopathic arthritis (s-JIA) [6]. Between 7 and 14% of children with systemic juvenile idiopathic arthritis (s-JIA) are impacted by MAS, while approximately 30 to 40% of these patients may have subclinical or hidden MAS [7]. More than 20% of individuals with the initial stages of s-JIA develop MAS, which can occur suddenly or be sparked by infections or changes in medication [6]. In a clinical setting, MAS is recognized by continuous high fever, enlargement of the liver and spleen, reduced levels of all types of blood cells, liver problems, blood clotting disorders, central nervous system complications, elevated ferritin levels, and NK cells dysfunction. A key feature of MAS is the identification of hemophagocytic macrophages in the bone marrow [8].

The development of Macrophage Activation Syndrome (MAS) in systemic juvenile idiopathic arthritis (s-JIA) is mainly caused by the overactivation of T lymphocytes and macrophages, resulting in a notable rise in cytokines like IL-1, IL-6, IL-18, IFN-γ, and TNF-α. Adding to the difficulty is the insufficient production of IL-10, a substance that usually controls the immune response. Genetic mutations that impact the cytolytic function of NK cells and CTLs are also important, as they interfere with the typical immune response and add to the cytokine storm. In addition, constant production of certain cytokines such as IL-6 and IL-18 causes dysfunction in NK cells, worsening the situation. In summary, the interaction between cytokine imbalance and genetic factors is what causes the intense inflammatory response seen in MAS [8-13]. This case emphasizes the challenges and significance of addressing MAS in individuals with autoimmune histories who display systemic inflammatory symptoms. This report aims to present a detailed account of a rare presentation of MAS in an adult with a history of JIA, incorporating detailed clinical, laboratory, and imaging findings to enhance diagnostic and therapeutic insights. We also aim to contextualize this case within existing literature and registry data to highlight similarities and differences with larger patient cohorts, particularly regarding disease activity, diagnostic markers, and treatment outcomes.

2. CASE REPORT

An 18-year-old male who previously had juvenile idiopathic arthritis presented in emergency department with symptoms of high fever, decreased appetite, and abdomen fullness that have been ongoing for a month. He described experiencing sporadic headaches and stomach pain. Three years ago, he had a fever and polyarthritis, which led to a diagnosis of juvenile idiopathic arthritis, and he was treated with steroids and methotrexate. His symptoms improved with the treatment but unfortunately, he lost his follow up. He again developed similar symptoms, he tried different over the counter pain killers and NSAIDs but his symptoms persisted. The patient had a normal developmental history and received vaccinations according to national recommendations. There is no familial background in autoimmune diseases. On examination, his vitals were: heart rate 106/bpm, oxygen saturation 92% on room air, body temperature 103 F, breathing rate 18/bpm, and blood pressure 110/70 mmHg. He had a pale complexion and appeared anxious, lymph nodes were palpable in the anterior cervical chain bilaterally that was non-tender, not adherent to superficial and underlying skin and no oozing of any discharge. His liver was palpable 10cm below the right sub costal margins with a firm texture, and his splenic notch was palpable 2cm below left costal margins. Rest of the systemic examination was unremarkable. Disease activity scoring using the Juvenile Arthritis Disease Activity Score (JADAS-27) was performed, indicating severe disease activity prior to treatment (JADAS-27 score: 28, indicating high disease activity). Lab results revealed low red blood cell indices, such as hematocrit at 28.4% (Normal: 37 to 52%) and hemoglobin at 7.3 g/dL (Normal: 12 to 18 g/dL). 2.64 x 103/uL was his white blood cell count (normal: 4–10 x 103/L). CRP rose to 33 mg/dL (normal: < 0.5 mg/dL), the platelet count increased to 430 x 109/L (normal: 150-400 x 109/L), and the ESR increased to 25 (normal: 0-15 mm/h). Liver function tests revealed elevated ALT, 62 (normal: 10–40 U/L), and AST, 55 U/L (normal: 10–40 U/L). Hepatitis C and B screenings were reported negative. Coagulation studies showed low fibrinogen levels at 97 mg/dl (Normal: 150-350 mg/dL). Ferritin levels were raised, 710 ng/L (Normal: 12 to 300 ng/mL) Tests for infectious and rheumatological diseases, including rheumatoid factor, were negative. Urinalysis revealed no abnormalities, but serum triglycerides were elevated, 170mg/dL (Normal: <150 mg/dL). Immunological markers showed markedly elevated IL-6 levels (45 pg/mL, normal <7 pg/mL) and a decreased NK cell activity (2% cytotoxicity, normal >10%). Abdominal ultrasound showed significant hepatosplenomegaly without focal lesions, consistent with the clinical examination. No other specific imaging findings suggestive of malignancy or primary infection were noted. His general physician advised him antibiotics. Despite the use of various antibiotics, the patient's fever persisted. Due to his medical history and low blood cell counts, he was evaluated for Macrophage Activation Syndrome (MAS). The bone marrow biopsy results show increased hematopoietic activity with hyperplastic alterations and significant hemophagocytic activity, confirming a diagnosis of Macrophage Activation

Syndrome in a patient with Idiopathic Juvenile Arthritis. The lack of iron deposits and presence of invasive cells indicates a reactive process rather than a cancerous condition. Hemophagocytosis in bone marrow aspiration supported the diagnosis of MAS (Fig. **1**).

King Edward Medical University Lahore
Department of Pathology
Hematology Section
Bone Marrow Examination Report

Patient's Name: [redacted]
Age: 18y/M
Sample Date: 06-12-21
Report Date: 13-12-21
Lab No: [redacted]
Trephine: 21BM604

BONE MARROW ASPIRATION:
Site: Right posterior superior iliac spine
Cellularity: Good cellularity smears and fragments
Erythropoiesis: Hyperplastic with megaloblastic change M:E ratio is 1.5:1
Leucopoiesis: Active.Giant myelocytes and metamyelocytes are seen
Megakaryocytes: Present.
Macrophage: Marked hemophagocytic activity is seen.
Perls iron stain: Absent.

TREPHINE BIOPSY:
Good length trephine biopsy. Histological examination reveals normal bony trabeculae with preserved fat spaces. Cellularity is 80%.Trilineage hematopoiesis is active .No area of infiltration by lymphoma,carcinoma or metastatic tumour is seen at the site tested.

Opinion: **Patient has Idiopathic juvenile arthritis and marked hemophagocytic activity in bone marrow aspirate favouring MACROPHAGE ACTIVATION SYNDROM.**
NOTE: Absent iron stores and megaloblastic change in marrow refers to double deficiency anemia.
Advised: VitaminB12 and folate supplementation with hematological follow up is advised.

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Figure 1: Bone marrow aspiration biopsy report of the patient.

For a patient with a background of juvenile idiopathic arthritis (JIA) and displaying signs of ongoing high-grade fever, hepatosplenomegaly, and hematologic issues, potential diagnoses include a JIA flare-up, regional infections such as malaria and dengue, sepsis, leukemia, and Macrophage Activation Syndrome (MAS). The identification of MAS was given higher importance once infections, sepsis, and leukemia were ruled out, as indicated by the patient's symptoms and bone marrow biopsy revealing marked hemophagocytosis. Initial treatment with broad-spectrum antibiotics was unsuccessful, so high-dose intravenous methylprednisolone was administered, effectively relieving symptoms. The patient was later prescribed oral steroids and has continued to improve during follow-up visits, confirming the treatment regimen's effectiveness for MAS. The effectiveness of treatment for the patient with Macrophage Activation Syndrome was measured by assessing clinical symptoms (such as fever and abdominal pain), laboratory values (like hemoglobin, CRP, and ferritin), vital signs, follow-up assessments, and response to treatment. These parameters indicate a successful improvement following high-dose intravenous methylprednisolone and oral steroids. Post-treatment, the JADAS-27 score decreased to 4, indicating low disease activity, further confirming treatment efficacy.

3. DISCUSSION

MAS is a hyperinflammatory state characterized by the proliferation and activation of T cells and macrophages, creating an excessive inflammatory response and hypersecretion of cytokines such as IFNγ, TNF, IL-1, IL-6, IL-10, IL-12, IL-18, and macrophage colony-stimulating factor [14]. Macrophage Activation Syndrome (MAS) is characterized by persistent fever, liver failure, splenomegaly, lymphadenopathy, and neurological symptoms. It is often severe and resistant to anti-infection medications. Key laboratory results include leukocytopenia, thrombocytopenia, coagulation issues, elevated liver enzymes, hypertriglyceridemia, hyperferritinemia, and NK-cell dysfunction. A systematic review by Briciu *et al.* (2021) in Pediatric Research analyzed 40 studies and confirmed these characteristics, emphasizing MAS as a hyperinflammatory condition. The review highlights the importance of laboratory findings for diagnosis and underscores the necessity for prompt recognition and treatment [15].

The presented case of Macrophage Activation Syndrome (MAS) aggravating systemic juvenile idiopathic arthritis (s-JIA) demonstrates the intricacies of immunological dysregulation as well as the diagnostic and therapy problems. This debate examines new literature to contextualize the findings and improve our knowledge of this serious illness. MAS is recognized as a life-threatening consequence of rheumatic disorders such as SJIA. Schulert and Grom's review underlines how MAS can be induced by a variety of events, including infections and medication changes, which corresponds to the beginning and development observed in our case [16]. This case report discusses the differential diagnosis of Macrophage Activation Syndrome (MAS) in a patient with Juvenile Idiopathic Arthritis (JIA). Several potential diagnoses were considered, including flare of JIA, infections (Malaria, Dengue), sepsis, leukemia, and MAS. The patient's severe systemic symptoms, pronounced hepatosplenomegaly, persistent high-grade fever, and the presence of infections were considered, but specific diagnostic tests (Key diagnostic tests included Complete Blood Count (CBC), Liver Function Tests (LFTs), ferritin level, blood cultures, bone marrow biopsy, and serological tests for infections (malaria and dengue) to Rule them out. MAS emerged as a strong contender due to its association with JIA and the overlap of clinical features. The case highlights the importance of early diagnosis and treatment, as MAS can manifest severe systemic symptoms and be potentially life-threatening. Comparing this case to the larger MAS patient cohorts documented in registries like the

multinational MAS/sJIA registry and the Eurofever registry, our patient's presentation aligns with typical features of MAS, including high fever, cytopenias, hepatosplenomegaly, hyperferritinemia, and an excellent response to corticosteroids. However, the patient's age (18 years) at MAS presentation, despite a JIA history, places him at the older end of the pediatric spectrum, which is less commonly reported in some JIA-focused MAS series. The specific immunological markers such as elevated IL-6 and decreased NK cell activity observed in our patient are consistent with the known cytokine storm pathology in MAS, as widely reported in systematic reviews and research studies [16].

Recent research investigate the pathophysiological role of cytokines, with a specific emphasis on IL-1, IL-6, IL-18, and IFN-γ, in MAS. This case is consistent with the findings of Minoia *et al*., who discovered that MAS is characterized by a 'cytokine storm', which causes significant tissue damage and organ dysfunction. This excessive inflammation condition requires specific treatments that target the inhibition of cytokines [6]. Current treatment methods include the utilization of immunomodulators such as corticosteroids, as demonstrated in the patient's case, as well as more specific interventions such as IL-1 and IL-6 inhibitors. Ravelli *et al*. (2015) stated that therapies focusing on IL-6, like tocilizumab, have exhibited potential in managing inflammation in s-JIA and decreasing the occurrence of MAS [17]. Patients with MAS encounter treatment challenges, with high-dose intravenous corticosteroids being the primary initial treatment, followed by oral prednisolone. If corticosteroids don't improve, drugs like cyclosporine-A, etoposide, and cyclophosphamide are used, with cyclosporine-A being effective in HLH-2004 protocol treatment and etoposide preserved for refractory cases [14]. This is consistent with our strategy of starting off with high-dose intravenous methylprednisolone, then transitioning to oral steroids, leading to significant enhancement in our patient. While this case report lacks a control group, the established efficacy of high-dose corticosteroids in MAS, as supported by numerous clinical trials and consensus guidelines (e.g., the 2016 EULAR/ACR recommendations for MAS in sJIA), provides a strong framework for understanding the therapeutic success observed here. This case serves as a valuable example of prompt diagnosis and management based on current best practices, even without direct comparison to an untreated cohort.

4. CONCLUSION

In conclusion, MAS (Macrophage Activation Syndrome), a potentially fatal syndrome, should be considered in young patients with unexplained fever, cytopenias, hepatosplenomegaly, and autoimmune disorders. Early recognition and treatment are crucial for managing this potentially fatal syndrome. A thorough medical history and persistent investigative approach are essential in complex clinical scenarios. Early diagnosis of JIA (Juvenile Idiopathic Arthritis), especially in children, can initiate proper treatment and prevent mortality.

PATIENT'S CONSENT

Written informed consent was obtained from the patient prior to participation.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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AUTHOR CONTRIBUTIONS

AI: Study concept and design

FK: Drafting of work and manuscript writing

FZ: Data collection

MYI: Final review

REFERENCES

[1] An Q, Jin MW, An XJ, Xu SM, Wang L. Macrophage activation syndrome as a complication of juvenile rheumatoid arthritis. Eur Rev Med Pharmacol Sci. 2017; 21(19): 4322-6.

[2] Kwon HJ, Kim YL, Lee HS, Lee SM. A study on the physical fitness of children with juvenile rheumatoid arthritis. J Phys Ther Sci. 2017; 29(3): 378-83. https://doi.org/10.1589/jpts.29.378

[3] Muro Y, Iwata N, Tanaka Y, Kodera M, Kono M, Akiyama M. Anti-dense fine speckled 70 autoantibodies in Japanese children with dermatomyositis, localized scleroderma, and idiopathic arthritis with iridocyclitis. J Rheumatol. 2017; 44(5): 711-2. https://doi.org/10.3899/jrheum.161409

[4] Sun YH, Wei ST, Zong SH. Correlation between IL-4 gene polymorphism as well as its mRNA expression and rheumatoid arthritis. Eur Rev Med Pharmacol Sci. 2017; 21(17): 3879-85.

[5] Shimizu M. Macrophage activation syndrome in systemic juvenile idiopathic arthritis. Immunol Med. 2021; 44(4): 237-45. https://doi.org/10.1080/25785826.2021.1912893

[6] Minoia F, Davì S, Horne A, Demirkaya E, Bovis F, Li C, *et al.* Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a multinational, multicenter study of 362 patients. Arthritis Rheumatol. 2014; 66(11): 3160-9. https://doi.org/10.1002/art.38802

[7] Sağ E, Uzunoğlu B, Bal F, Sönmez HE, Demir S, Bilginer Y, Özen S. Systemic onset juvenile idiopathic arthritis: a single center experience. Turk J Pediatr. 2019; 61(6): 852-8.

[8] Gabr JB, Liu E, Mian S, Pillittere J, Bonilla E, Banki K, Perl A. Successful treatment of secondary macrophage activation syndrome with emapalumab in a patient with newly diagnosed adult-onset Still's disease: case report and review of the literature. Ann Transl Med. 2020; 8(14): 887. https://doi.org/10.21037/atm-20-3127

[9] Locatelli F, Jordan MB, Allen C, Cesaro S, Rizzari C, Rao A, *et al.* Emapalumab in children with primary hemophagocytic lymphohistiocytosis. N Engl J Med. 2020; 382(19): 1811-22. https://doi.org/10.1056/NEJMoa1911326

[10] Mizuta M, Shimizu M, Inoue N, Nakagishi Y, Yachie A. Clinical significance of serum CXCL9 levels as a biomarker for systemic juvenile idiopathic arthritis associated macrophage activation syndrome. Cytokine. 2019; 119: 182-7. https://doi.org/10.1016/j.cyto.2019.03.018

[11] Bracaglia C, de Graaf K, Marafon DP, Guilhot F, Ferlin W, Prencipe G, *et al.* Elevated circulating levels of interferon-γ and interferon-γ-induced chemokines characterise patients with macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. Ann Rheum Dis. 2017; 76(1): 166-72. https://doi.org/10.1136/ annrheumdis -2015-209020

[12] Shimizu M, Kizawa T, Kato R, Suzuki T, Yachie A. Macrophage activation syndrome in neonates born to mothers with adult-onset Still's disease: perinatal effect of maternal IL-18. Clin Immunol. 2019; 207: 36-9. https://doi.org/10.1016/j.clim.2019.07.005

[13] Shimizu M, Mizuta M, Okamoto N, Yasumi T, Iwata N, Umebayashi H, *et al.* Tocilizumab modifies clinical and laboratory features of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. Pediatr Rheumatol. 2020; 18: 1-7. https://doi.org/10.1186/s12969-020-0399-1

[14] Alkoht A, Hanafi I, Khalil B. Macrophage activation syndrome: a report of two cases and a literature review. Case Rep Rheumatol. 2017; 2017: Article ID 5304180. https://doi.org/10.1155/2017/5304180

[15] Bojan A, Parvu A, Zsoldos IA, Torok T, Farcas AD. Macrophage activation syndrome: A diagnostic challenge. Exp Ther Med. 2021; 22(2): 904. https://doi.org/10.3892/etm.2021.10336

[16] Schulert GS, Pickering AV, Do T, Dhakal S, Fall N, Schnell D, *et al*. Monocyte and bone marrow macrophage transcriptional phenotypes in systemic juvenile idiopathic arthritis reveal TRIM8 as a mediator of IFN-γ hyper-responsiveness and risk for macrophage activation syndrome. Ann Rheum Dis. 2021; 80(5): 617-25. https://doi.org/10.1136/annrheumdis-2020-217470

[17] Ravelli A, Davì S, Minoia F, Martini A, Cron RQ. Macrophage activation syndrome. Hematol Oncol Clin North Am. 2015; 29(5): 927-41. https://doi.org/10.1016/j.hoc.2015.06.010