Journal of
Rheumatology and Arthritis

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Case Report Open Access

Macrophage Activation Syndrome in a Girl with Juvenile Dermatomyositis

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Received Date: March 08, 2021 **Accepted Date:** April 08, 2021 **Published Date:** April 10, 2021

Citation: Margarita Ganeva (2021) Macrophage Activation Syndrome in a Girl with Juvenile Dermatomyositis. J Rheumatol Arthritis 1: 1-9.

Abstract

Background: Macrophage activations syndrome (MAS), a hemophagocytic syndrome, is a complication of rheumatic diseases, seen most frequently in children with systemic juvenile idiopathic arthritis. MAS is rarely reported in juvenile dermatomyositis (JDM). MAS can be triggered by various factors including infection or malignancy.

Case Presentation: We report a clinical case of a 9-year-old girl who presented, after sunlight exposure, with proximal muscle weakness, characteristic cutaneous changes including heliotrope discoloration of the eyelids with periorbital edema and Gottron's papules. Based on the clinical signs, a diagnosis of JDM was suspected. Creatine kinase level was not elevated, though characteristic pattern of muscle involvement was seen on thigh muscles magnetic resonance imaging. The patient also had alopecia, aphtous stomatitis, and subtle arthritis with flexion contractures at the elbows and knees. Furthermore, a fall in the complete blood count was observed (with platelet count of 116×10^9/L). A positive test for herpes simplex virus was detected. In addition, jaundice and hepatosplenomegaly were observed. The laboratory studies revealed hepatitis and hyperferritinemia (ferritin 1502 ng/ml). As a result, a diagnosis of JDM, complicated by MAS was established. Pulse therapy with intravenous methylprednisolone and immunoglobulin was started.

Conclusion: MAS is a life-threatening condition and may progress to multiple organ failure. MAS is a rare complication of JDM. Therefore, early recognition and immediate therapeutic intervention are critical for the effective management of MAS.

Keywords: Macrophage Activation Syndrome; Juvenile Dermatomyositis; Triggers; Case Report

List of abbreviations: ACR: American College of Rheumatology; ALC: Absolute Lymphocyte Count; ALP: Alkaline Phosphatase; ALT: Alanine Transaminase; ANA: Antinuclear Antibodies; anti-dsDNA: Anti-Double Stranded DNA; anti-gp210: Anti-Glycoprotein-210; anti-LC-1: Anti- Liver Cytosolic Antigen Type 1; anti-LKM1: Anti–Liver-Kidney Microsomal Type 1; anti-PML: Anti-Promyelocytic Leukemia Protein; anti-RNP: Anti-Ribonucleoprotein; anti- Scl-70: Anti-Scleroderma-70; anti-SLA/LP: Anti-Soluble Liver Antigen/Liver-Pancreas; anti-Sm: Anti-Smith; anti-SS-A: Anti-Sjogren's Syndrome A; an-

ti-SS-B: Anti-Sjogren's Syndrome B; AST: Aspartate Transaminase; CARRA: Children's Arthritis And Rheumatology Research Alliance; CMV: Cytomegalovirus; CRP: C-reactive protein; EBV: Epstein-Barr Virus; EMG: Electromyography; ESR: Erythrocyte Sedimentation Rate; EULAR: European League Against Rheumatism; GGT: Gamma-Glutamyl Transferase; HAV: Hepatitis A Virus; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HSV: Herpes Simplex Virus; Hb: Hemoglobin; Ig: Immunoglobulin; IL: Interleukin; JDM: Juvenile Dermatomyositis; MAS: Macrophage Activations Syndrome; MRI: Magnetic Resonance Imaging; PRINTO: Paediatric Rheumatology INternational Trials Organisation; sJIA: Systemic Juvenile Idiopathic Arthritis; SLE: Systemic Lupus Erythematosus; UVR: Ultraviolet Radiation; WBC: White Blood Cells

Background

Juvenile dermatomyositis (JDM) is a multisystem disease with characteristic changes involving mainly striated muscles and skin. Macrophage activation syndrome (MAS), a form of secondary hemophagocytic lymphohistiocytosis, is a life-threatening complication of rheumatic diseases in children, most commonly of systemic juvenile idiopathic arthritis [1,13]. MAS has been rarely reported in JDM [2-15]. We report a clinical case of a 9-year-old girl with JDM complicated with MAS.

Case Report

The girl presented in July 2014 with abnormal gait and foot pain which appeared mainly in the evening and after physical activities. At that time the parents associated the symptoms with uncomfortable shoes. Six months later the girl was admitted to a Pediatric Department. On examination she had polyarthritis, maculopapular rash over the cheeks and erythema over the nasal tip. The lab studies revealed leucopenia with lymphopenia (white blood cells (WBC) 3.7x10^9/L; absolute lymphocyte count (ALC) 0.78x10^9/L), mild anemia (hemoglobin (Hb) 109 g/l), slightly elevated erythrocyte sedimentation rate (ESR 18 mm/h) with normal C-reactive protein (CRP 0.9 mg/l), slightly positive antinuclear antibodies (ANA) titer (ANA 1:160) and negative anti-double-stranded DNA and antiphospholipid antibodies. At this time point the parents were advised for a follow-up of the child by a pediatric rheumatologist. On discharge treatment with nonsteroidal anti-inflammatory drug was initiated. Methotrexate was prescribed as well, but the parents refused the treatment and decided to try alternative therapy (homeopathy).

In the following months the child deteriorated with persistent arthralgia, progressive muscle weakness, difficult walking, persistent fever, progressive weight loss, and alopecia.

In August 2015 the girl experienced a prolonged ultraviolet radiation exposure due to a summer holiday at the seaside. The child was out in direct sun at the beach. Despite difficulty walking, the parents were bringing the child with the help of a chair, closer to the sea every day. Yellow discoloration of the skin and abdominal pain appeared afterwards. The child was admitted to the Pediatric rheumatology department of Medical University of Sofia in September 2015, more than one year after the disease onset. On admission the patient was febrile (38.8 C^o) and appeared ill, cachectic and jaundiced. On examination marked symmetrical proximal muscle weakness with pain on palpation upon squeezing of the proximal muscles was observed. The girl was unable to perform the usual daily activities on her own (getting in and out of bed, getting dressed, showering, brushing her teeth, combing her hair). Characteristic cutaneous changes were observed with heliotrope discoloration of the eyelids with periorbital edema and a malar rash (Figure 1).

Furthermore, Gottron's papules over the metacarpophalangeal and interphalangeal joints were noticed (Figure 2).

Skin ulcerations over the heel and the elbow were observed, as well (Figure 3).

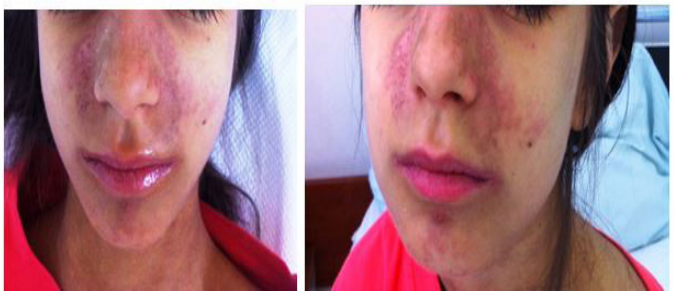

Figure 1: Heliotrope rash

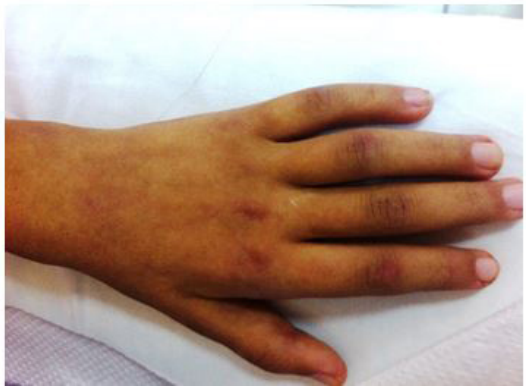

Figure 2: Gottron's papules

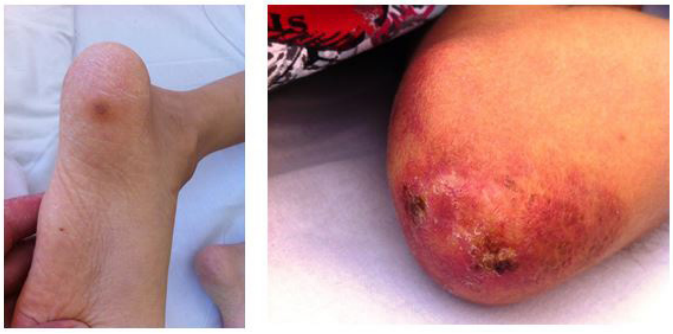

Figure 3: Skin ulcerations

Clinical features were consistent with a diagnosis of JDM. Of note, the creatine kinase was within normal limits (CPK 137 U/l (<142 U/l)). Levels of the other muscle enzymes were elevated with AST (aspartate transaminase) of 925 U/l (<50 U/l), ALT (alanine transaminase) of 162 U/L (< 36 U/l), and LDH (lactate dehydrogenase) of 1058 U/l (260-690 U/l). The inflammatory (ESR 34 mm/h and CRP 4.0 mg/l) and immunology (immunoglobulin (Ig)A, IgM, complement components C3 and C4, anti-dsDNA (anti-double stranded DNA), anti-RNP (anti-ribonucleoprotein), anti-Sm (anti-Smith), anti-SS-A (anti-Sjogren's Syndrome A), anti-SS-B (anti-Sjogren's Syndrome B), anti-Scl-70 (anti-Scleroderma-70), and anti-Jo-1 (anti-histidyl-tRNA synthetase) antibodies) markers were in reference ranges, apart from slightly elevated ANA - 1:160 and elevated IgG - 23.1 g/l.

This patient was also noted to have subtle arthritis with flexion contractures at the elbows and knees, alopecia, butterfly-like rash and aphthous stomatitis, which are features less specific to JDM but have been described previously [16,17].

The diagnosis of JDM was supported by characteristic changes on MRI (Magnetic Resonance Imaging) of her thigh muscles. On the fat-suppressed T_2-weighted MRI images diffusely hyperintensed signal from all the muscles of the thigh was seen. Areas of subcutaneous edema were noted as well (Figure 4).

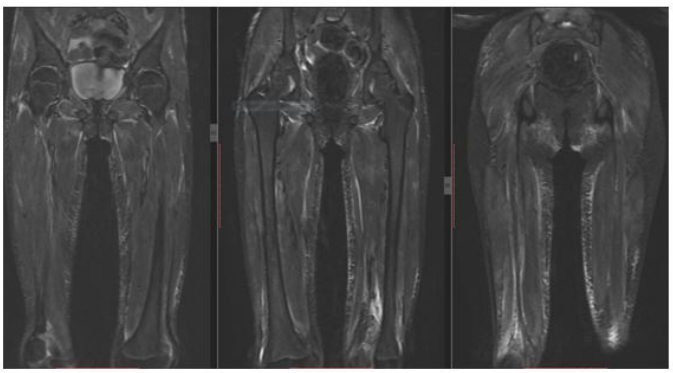

Figure 4: Diffusely hyperintensed signal of the thighs and subcutabeous edema

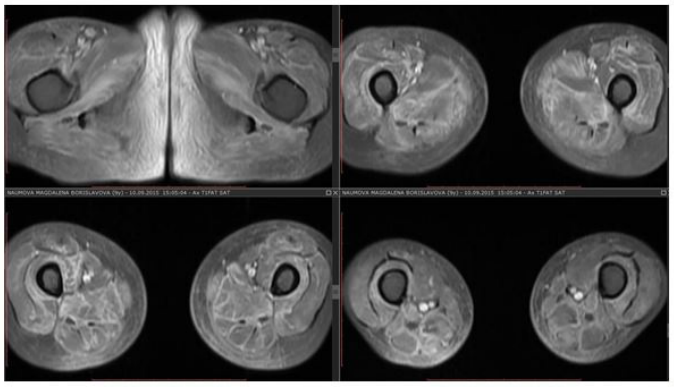

Figure 5: Enhancement of subcutaneous tissue after contrast administration

On the image after contrast administration a contrast enhancement of the subcutaneous tissue, muscle fascia and the muscles was noticed (Figure 5).

Moreover, the diagnosis was complicated by additional clinical and laboratory findings. Jaundice of the sclera and diffusely over the skin was noticed. On abdominal physical exam enlarged liver (3 cm below the costal margin) and spleen (2 cm below the costal margin) were observed. The hepatosplenomegaly was confirmed by abdominal ultrasound. The laboratory studies revealed signs of hepatitis and cholestasis (AST 925 U/l, ALT 162 U/l, GGT (gamma-glutamyl transferase) 282 U/l, ALP (alkaline phosphatase) 253 U/l, total bilirubin 155 μmol/l, direct bilirubin 102/142 μmol/l). Infectious causes of hepatitis were ruled out with no serological evidence of HAV (hepatitis A virus; negative IgM HAV antibodies), HBV (hepatitis B virus; negative HBsAg), HCV (hepatitis C virus; negative anti HCV), CMV (cytomegalovirus; negative IgM and IgG CMV antibodies), EBV (Epstein-Barr virus; negative VCA IgM and IgG antibodies), parvovirus B19 (negative IgM and IgG antibodies). The panel of antibodies for autoimmune hepatitis (anti-Mi2, anti-M2-3E BPO (BPO - branched-chain 2-oxoacid dehydrogenase, pyruvate dehydrogenase and 2-oxoglutarate dehydrogenase), anti-Sp100, anti-PML (anti-promyelocytic leukemia protein), anti-gp210 (anti-glycoprotein-210), anti-LKM1 (anti–liver-kidney microsomal type 1), anti-LC-1 (anti- liver cytosolic antigen type 1), anti-SLA/LP (anti-soluble liver antigen/liver-pancreas), and anti-SS-A antibodies) was also negative. Furthermore, other specific metabolic reasons for development of hepatitis were excluded with levels of α1-antitrypsin in reference ranges. Since the mother of the girl reported fine motor skill impairment in the patient, ceruloplasmin level, with the aim of excluding Wilson disease, was determined and it was in reference range, as well. Upon further evaluation of aphtous stomatitis, IgM testing for herpes simplex virus (HSV) infection was found positive.

Moreover, the differential diagnosis was further complicated by the presence of leucopenia (WBC 3.1x10^9/L) with lymphopenia (ALC 0.68x10^9/L), mild anemia (Hb 110 g/l). Although lymphopenia and anemia have previously been reported with dermatomyositis[18], leucopenia is not common. With the butterfly rash and positive ANA, suspicion for systemic lupus erythematosus was raised but no other notable criteria were present. With weakness and arthritis, mixed connective tissue disease was considered but these features were not specific and the anti-RNP antibodies were negative. Although the association of JDM with malignancies in children is rare, cancer-associated myositis was excluded as well – the manual differential of WBCs was normal; tumor markers (neuron specific enolase; beta2-microglobulin) were negative; abdominal MRI showed normal finding (besides hepatosplenomegaly).

Besides the classical clinical signs of JDM and the characteristic MRI image, persistent fever (up to 39 ^{0}C) and hepatosplenomegaly were observed in the patient. The aforementioned clinical symptoms were associated with pancytopenia with a fall in the platelet count (148→116 x10^9/L) and the ESR (34→8 mm/h). Elevated liver enzymes and bilirubin levels, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia, and additional hypoalbuminemia were also observed. (Table 1) Summing up all of these findings, the final diagnosis of JDM, complicated with macrophage activation syndrome was made. Initial treatment included intravenous methylprednisolone pulse therapy - 30 mg/kg for four consecutive days, followed by 3 mg/kg/d for 10 days with subsequent tapering to 1 mg/kg/d at the end of 2nd month when the girl was discharged. Intravenous infusion of immunoglobulin 2g/kg was also initiated at the time of detection of HSV serology. The girl was discharged with improvement in the range of motions and improved laboratory markers (AST 241 U/L, ALT 417 U/L, LDH 673 U/L, CPK 25 U/L; ferritin 679 ng/ml; CRP 0.43 mg/l; WBC 12.8x10^9/L; Hb 113 g/l; PLT 349x10^9/L; triglycerides 40 mg/dL). During the subsequent follow up period, the laboratory parameters went back to normal, as well as the girl recovered her full motion capacity.

Discussions and Conclusions

MAS, a hemophagocytic syndrome, is seen most frequently in children with systemic juvenile idiopathic arthritis (sJIA). Traditionally, it was thought that about 10% of children with sJIA developed MAS; however, relatively high incidence (30–40%) of sJIA patients with subclinical features of the disease has been reported [19]. MAS is also reported in systemic lupus erythematosus (SLE) and Kawasaki disease [20,21]. Analysis of Li J and colleagues investigated 103 adult patients with MAS and found out that 14 had underlying autoimmune disease and in only 2 of them it was JDM [22]. Nevertheless, MAS is increasingly described in JDM [2-15]. A systematic review describes 12 patients who develop both MAS and JDM [15]. Of note, 2 out of 12 patients were with the amyopathic form of JDM. In three of the described MAS episodes, EULAR/ACR/PRINTO diagnostic criteria for MAS[34] were not fulfilled because of ferritin values lower than the established cutoff (684 ng/ml), although other diagnostic features were present. MAS usually developed at the onset of the disease with 10 out of 12 patients being diagnosed concomitantly with MAS and JDM. With regards to patients' outcome, 10 patients out of 12 completely recovered with only two patients who resulted in fatal outcome.

MAS is caused by excessive activation and expansion of T lymphocytes and macrophages that exhibit hemophagocytic activity. It is characterized by a cytokine storm, with the elaboration of numerous pro-inflammatory cytokines (interleukin (IL)-1β, IL-6, IL-18, tumor necrosis factor-alpha, and interferon gamma) [23]. The cytokine storm and subsequent hyperinflammation lead to extreme hyperferritinemia, cytopenias, liver dysfunction and coagulopathy. There is increasing number of data regarding the cytokine profiles of MAS associated with sJIA or SLE.[24] Still, there is sparse data concerning the immune mediators in JDM-associated MAS.

MAS is most commonly triggered by infections (most commonly EBV or CMV infection) [19,25,26]. In the presented clinical case the triggering factor might be the HSV infection - an underlying condition which may also contribute to the observed laboratory abnormalities (cytopenias, elevated liver enzymes) and thus making the diagnosis of MAS more difficult. Hemophagocytic lymphohistiocytosis triggered by HSV is uncommon [27-31].

Moreover, contributing factor to the development of MAS might be the sunlight - prior to admission to the Department the patient experienced a prolonged ultraviolet radiation (UVR) exposure. The UVR exposure may play a role in the clinical and serologic expression of juvenile myositis as stated by the Childhood Myositis Heterogeneity Collaborative Study Group.[32] We hypothesize that it may play a role also in the developing of MAS in our case.

Malignancies are another concern and a putative triggering factor in patients with MAS, since leukemia and lymphoma are common non-rheumatologic causes of MAS in children.[33] Concurrently, JDM on its own might be also rarely associated with malignancies. With this in mind, malignancy should be excluded in such patients.

Currently, there are no validated diagnostic criteria for MAS in JDM. Therefore, we apply the recently developed EULAR (European League Against Rheumatism)/ACR (American College of Rheumatology)/PRINTO (Paediatric Rheumatology INternational Trials Organisation) classification criteria for MAS in sJIA (Table 1) [34].

According to the criteria of Bohan and Peter for a definite diagnosis of JDM the characteristic cutaneous changes (heliotrope rash and/or Gottron papules) and three of the four others criteria (proximal muscle weakness, elevated serum levels of muscle enzymes, electomyographic changes or muscle biopsy changes) are required [35,36]. In the reported clinical case we observed the classic cutaneous signs, accompanied by profound proximal muscle weakness with normal creatine kinase levels, though AST and ALT were elevated which were likely due to MAS, but possibly also due to myositis. Normal creatine kinase may be at least partially due to decreased muscle mass with long standing history of disease, though not all JDM patients with myositis have elevated creatine kinase at diagnosis [37].

Table 1: EULAR/ACR/PRINTO classification criteria for MAS in sJIA and the findings in our patient

A patient with (suspected) sJIA with:	Our patient:
Fever and serum ferritin > 684 ng/ml and any 2 of the following:	Fever serum ferritin 1502 ng/ml
Platelet count ≤181 × 10^9/L	Platelet count 116 × 10^9/L
Aspartate aminotransferase >48 U/L	Aspartate aminotransferase 925 U/L
Triglycerides > 156 mg/dl	Triglycerides 628 mg/dl
Fibrinogen ≤360 mg/dl	Fibrinogen 166 mg/dl

The diagnosis of JDM requires characteristic electromyographic and/or histopathological changes, however there was technical inability to perform EMG (electromyography) and muscle biopsy. Nevertheless, MRI of the thigh muscles, showing the specific myositis changes supported the diagnosis of JDM.

It is known that liver function tests in MAS typically reveal high serum transaminases activity but only mildly elevated levels of serum bilirubin. Jaundice, as observed in our case, has been reported by Lin and colleagues in 27% of the 104 children with rheumatic diseases who developed MAS [38]. Another report of three cases of cholestasis in JDM has been published by an Argentinian group [39]. The liver biopsies showed evidence of cytoplasmic and ductal cholestasis, with no signs of inflammation, necrosis, or disruption of the lobar and ductal architecture. Since the observed liver damage was reversible, the authors suggest that it was due to immune mediated mechanism - inflammation-induced cholestasis. In a review of MAS in pediatric rheumatic diseases jaundice was described as a symptom at MAS onset in 22% of the patients included in Sawhney S et al study and in 75% of the patients included in Li X et al study [40].

High dose glucocorticosteroids as initial treatment are used to treat MAS. It has been shown that intravenous immunoglobulin therapy is satisfactory in virus-associated MAS [41]. Since, HSV infection was detected in our patient, immunoglobulin treatment was added to the glucocorticosteroids.

MAS is a life-threatening condition and may progress to multiple organ failure. It is associated with high mortality rates reaching 20–30% [1,42]. MAS is a rare complication of JDM. Rigorous investigation for infection is needed especially when potentially infectious features are present. Key clinical and laboratory features to assess for early recognition and immediate therapeutic intervention are critical for the effective management of MAS.

Declarations

Ethics approval and consent to participate

The clinical case description was approved by the ethics committees of the Children's University Hospital of Sofia. The parents and the patient gave their informed consent for publication according to the Declaration of Helsinki.

Consent for publication

The parents and the patient gave their written informed consent for publication.

Availability of Data and Materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

M.G. analyzed and interpreted the patient data, described the clinical case and together with St.St. and K.L were major contributors in writing the manuscript. All authors read and approved the final manuscript.

Acknowledgement

The authors are especially grateful to the patient and her parents for their consent to publish the clinical case. The authors also thank all physicians engaged in the diagnosis and treatment, especially Marin Penkov (Radiology Department, St Ivan Rilski Hospital, Sofia).

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