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Macrophage activation syndrome in a patient with systemic onset of the juvenile idiopathic arthritis

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Abstract

Systemic onset juvenile idiopathic arthritis (sJIA) is defined as arthritis affecting one or more joint usually in the juvenile age group (< 16 years of age) with or preceded by fever of at least 2 weeks duration that is documented to be daily ("quotidian") for at least 3 days which may be associated with evanescent (non-fixed) erythematous rash or generalized lymph node enlargement or hepatomegaly/splenomegaly/both or serositis. Macrophage activation syndrome (MAS) is a life-threatening complication of sJIA marked by sudden onset of non-remitting high fever, profound depression in all three blood cell lines (i.e. leukopenia, anemia, and thrombocytopenia), hepatosplenomegaly, lymphadenopathy, and elevated serum liver enzyme levels. In children with systemic juvenile idiopathic arthritis, the clinical picture may mimic sepsis or an exacerbation of the underlying disease. We report a case of a 16-year-old female patient presenting with high grade fever with joint pains and generalized weakness which proved to be systemic onset juvenile idiopathic arthritis with macrophage activation syndrome after ruling out all other differential diagnoses and responded well to intravenous steroids.

Key words: juvenile idiopathic arthritis, macrophage activation syndrome, fever.

Introduction

Systemic onset juvenile idiopathic arthritis (sJIA) is one of the most common pediatric chronic illnesses. The prevalence rate of the disease varies widely in different series (3.5–5 cases/100,000) and the yearly incidence varies in the range 0.4–0.9 cases for 100,000 children [1]. sJIA as a subtype includes about 10–15% of all juvenile idiopathic arthritis (JIA) patients [2, 3]. At onset, it is clinically well distinguished from other forms of JIA by the prominence of extra-articular features such as spiking fevers, a salmon-colored skin rash, lymphadenopathy and serositis [4]. However, diagnosis is often challenging, since the disease can mimic infections and malignancies. Unlike the other forms of JIA, the affected child looks very ill, especially during fever spikes, and may present with a life-threatening complication known as macrophage activation syndrome (MAS).

Macrophage activation syndrome associated with JIA was first described by Hadchouel et al. in 1985 [5]. This syndrome occurs primarily with the systemic form of JIA, and the average period of JIA prior to MAS onset is from 4.2 to 4.8 years [5, 6]. The clinical findings of MAS are acute and dramatic. Typically, patients become acutely ill at presentation with non-remitting high fever, hepatosplenomegaly, lymphadenopathy, severe cytopenia, liver disease, and intravascular coagulation.

Case report

A 16-year-old female patient presented with a history of fever, joint pains, amenorrhea and generalized body swelling since 6 months. Fever was of high grade, intermittent in nature, associated with erythematous rashes which were localized to the upper trunk and back. Joint pains mainly involved the elbow and knee joints, and were associated with redness and swelling

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restricting movement. There was a history of recurrent oral ulcers, decreased appetite and significant weight loss. There was no history of urinary disturbances, bleeding tendencies, abdominal distension, altered bowel habits, altered mentation, photosensitivity or bluish discoloration of skin/mucous membranes. There was no past history of delayed developmental milestones, blood transfusions, diabetes, or thy. There was no family thyroid disease or any other chronic illness. No family member suffered from a similar disease.

On general examination, the patient was febrile with an oral temperature of 39.6°C. Vitals were within normal limits. Pallor, pedal edema and facial puffiness were evident. There were enlarged, non-tender, mobile lymph nodes present in the cervical region. Erythematous, non-tender, non-blanchable rashes were present over the chest and upper back (Fig. 1). Per abdomen examination revealed hepatosplenomegaly. Cardiovascular, respiratory and central nervous system examination was essentially normal. On musculoskeletal examination, the patient had tenderness over bilateral hip joints, knee joints and small joints of hands (proximal interphalangeal joints and metacarpophalangeal joints) associated with swelling and redness.

On the day of patient admission the laboratory investigations revealed some abnormalities including anemia with hemoglobin of 7.9 g/dl, leukopenia with a leukocyte count of 3000/mm^3, and platelet count of 150 × 10^3/µl. Renal function parameters were normal with blood urea of 18 mg/dl (10–50), serum creatinine 0.6 mg/dl (0.7–1.3), serum uric acid 5.1 mg/dl (4–7), serum calcium 7.9 mg/dl (8.5–10.5) and serum phosphate 3.4 mg/dl (2.5–4.5). Random blood sugar of the patient was 93 mg/dl. Liver function tests were slightly deranged, with serum alanine aminotransferase (ALT) of 60 U/l (up to 40), serum aspartate aminotransferase (AST) 79 U/l (up to 40), serum alkaline phosphatase (AP) 243 U/l (30–117), total serum bilirubin 0.8 mg/dl (0.2–0.8) and serum total protein 6 g/dl. The lipid profile was within the normal range. Anemia work-up showed MCV (mean corpuscular volume) of 125.4 fl/cell, MCH (mean corpuscular hemoglobin) 37.3 pg/cell, and MCHC (mean corpuscular hemoglobin concentration) 30.1 g/dl, revealing a macrocytic picture. The corrected reticulocyte count was 0.16% and the serum ferritin level was 1144.6 µg/l.

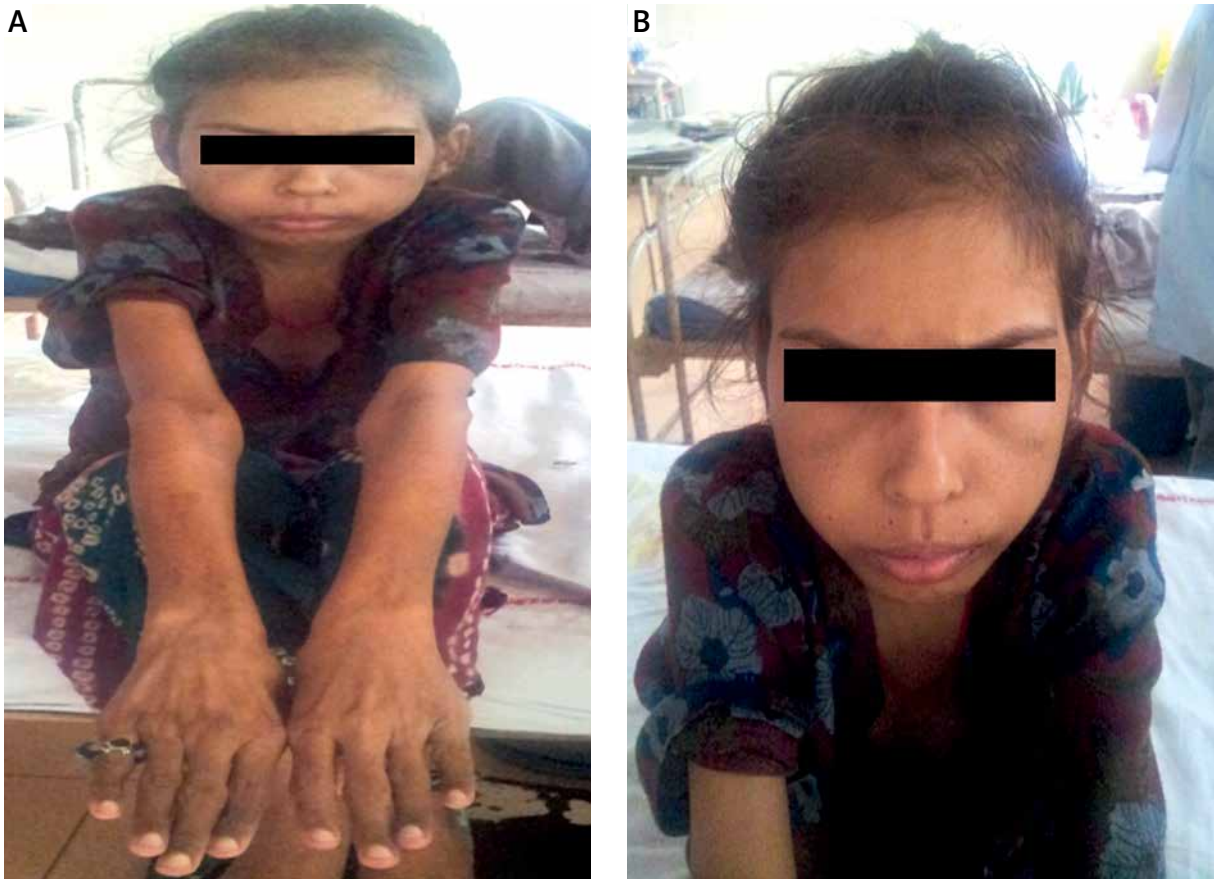

Fig. 1. File picture of the patient at the time of presentation.

Direct and indirect Coombs' tests were negative, and hemoglobin electrophoresis was normal. Erythrocyte sedimentation rate (ESR) was raised with a value of 140 mm/1st hour. The serum fibrinogen level was 280 mg/dl. Additional investigations included raised C-reactive protein (CRP; 100 mg/dl), negative antinuclear antibodies (ANA), negative rheumatoid factor (RF) and negative anti-dsDNA. Anti-SS-A/Ro antibodies, anti-SS-B/La antibodies and HLA-B27 were negative. To rule out infectious causes of fever a series of tests was performed: the malaria card test, Widal test, serology for *Leptospira*, *Leishmania* and scrub typhus, blood and urine cultures, Mantoux test, HIV antibodies, Hbs-antigen and anti-HCV antibodies. We also performed a heterophile test for Epstein-Barr virus infection and excluded presence of antibodies in IgM/IgG class to parvovirus B19 and autoantibodies for cytomegalovirus. None of the performed tests confirmed viral or bacterial infection.

Eye examination was normal. Ultrasonography of the abdomen showed hepatosplenomegaly and presence of free fluid. Echocardiography was normal. Lymph node biopsy showed diffuse follicular hyperplasia which suggested a chronic inflammatory state. Bone marrow aspiration revealed megaloblastic erythropoiesis. Minor salivary gland biopsy was undertaken to exclude Sjögren's syndrome, but there were no typical inflammatory infiltrates. Radiological investigations included X-ray of chest, hands and knees and magnetic resonance imaging (MRI) of the sacroiliac spine, which were normal (Fig. 2, 3).

In view of the patient being a 16-year-old female with a history of fever, polyarthritis and rash, examination revealing hepatosplenomegaly and lymphadenopathy, and investigations showing high ESR and ferritin values, with absence of ANA and RF, a possible diagnosis of systemic onset juvenile idiopathic arthritis was established.

As the patient had moderate to high grade fever, generalized edema, swollen and tender joints, and poor general condition, a possible association of JIA with MAS was suspected. The presence of ferritin > 684 ng/ml, platelet count of ≤ 181 × 10^9/l, AST level 79 U/l and serum fibrinogen level of 280 mg/dl satisfied the 2016 criteria for classification of MAS in sJIA, and hence the diagnosis was made.

During the course of hospital stay, the patient received anti-inflammatory therapy, blood transfusions, glucocorticoids and methotrexate. The patient recovered dramatically within a span of two weeks.

Discussion

The diagnosis of sJIA should be considered in children or adolescents with typical spiking fevers associated with arthritis or polyarthralgia. This is often a challenging diagnosis since many other causes for the fever need to be excluded. sJIA may present at any age, and there is no clear gender predominance. Any joint may

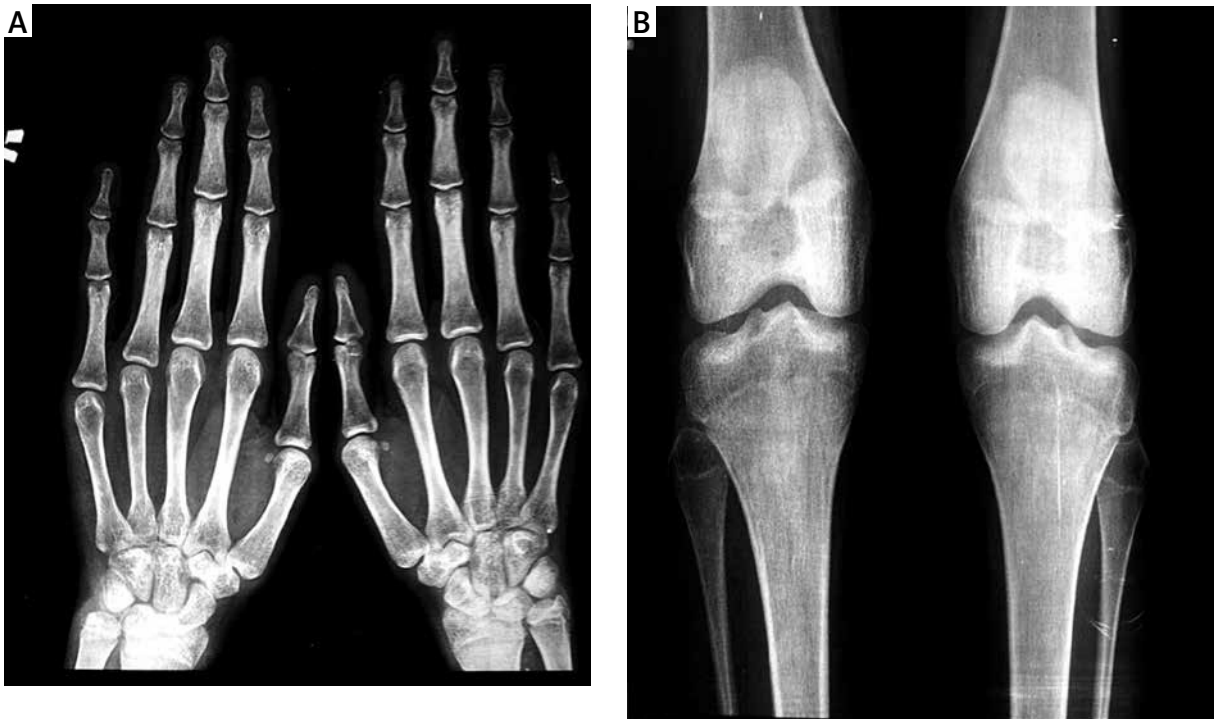

Fig. 2. X-rays of bilateral hands and knees, which were normal.

be affected at disease onset, and involvement may be oligo- or polyarticular, but arthritis tends to increase in severity over time. The typical spiking fever goes up to 39°C or 40°C once or twice daily and returns rapidly to 37°C or below [4].

The diagnosis of sJIA is based on internationally recognized classification criteria. Since the presence of arthritis is mandatory, the diagnosis can only be suspected at disease onset in patients without arthritis. JIA is defined by the presence of arthritis for at least 6 weeks with an onset before 16 years of age, after exclusion of all other causes.

Classification criteria for sJIA [7]. Arthritis with or preceding daily fever with a duration of at least 2 weeks accompanied by at least 1 of the following symptoms during the first 6 months:

- erythematous rash,
- lymphadenopathy,
- hepatomegaly and/or splenomegaly,
- serositis.

Exclusion criteria:

- psoriasis or history of psoriasis in the patient or first degree relative,
- arthritis in a boy (6 years old or more) positive for HLA-B27,
- ankylosing spondylitis, enthesitis with arthritis, sacroiliitis and inflammatory bowel disease, Reiter

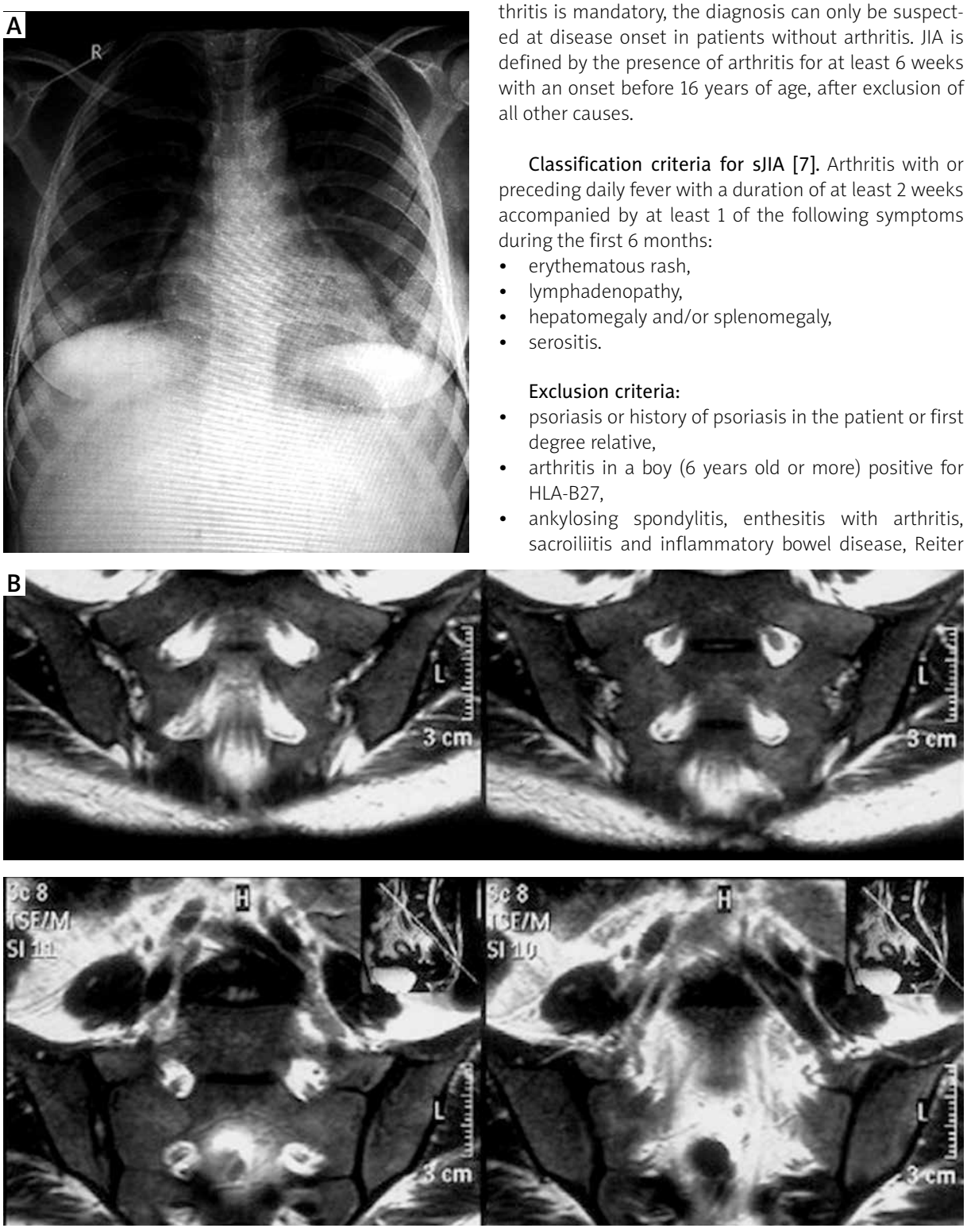

Fig. 3. Chest X-ray of the patient, which was normal (A). MRI of sacro-iliac spine, which was normal (B).

syndrome or acute anterior uveitis in a first degree relative,
- presence of rheumatoid factor type IgM confirmed in an interval of at least 3 months apart.

Laboratory tests show a decrease of the inflammatory parameters and relative hypofibrinogenemia (often normal, rather than elevated levels due to systemic inflammation), elevated liver enzymes, hemocytopenia, high ferritin levels and increased serum triglycerides. This complication, resembling reactive hemophagocytic lymphohistiocytosis, can be life-threatening and needs to be quickly detected and treated to avoid a fatal outcome. The diagnosis of MAS associated with active sJIA may be difficult: specific diagnostic guidelines have been developed to help the physician.

Macrophage activation syndrome belongs to a group of hemophagocytic syndromes: histiocytic disorders associated with an underlying systemic disease. Although MAS is most common in JRA, it can occur in patients with other rheumatic disorders such as adult-onset Still's disease, Behçet's disease and systemic lupus erythematosus. Trigger factors are drugs (aspirin, nonsteroidal anti-inflammatory drugs, gold preparations, methotrexate, tumor necrosis factor blocking agents) and viral infections, particularly Epstein-Barr virus and the herpes virus family [8].

The diagnosis of macrophage activation syndrome requires the presence of any 2 or more of the following laboratory criteria or 2 or more of the following clinical criteria [9]:
- Laboratory criteria:
  – decreased platelet count (< 262 × 10^9/l),
  – elevated aspartate aminotransferase levels (> 59 U/l),
  – decreased WBC count (< 4 × 10^9/l),
  – hypofibrinogenemia (≤ 2.5 g/l).
- Clinical criteria:
  – central nervous system (CNS) dysfunction (e.g., irritability, disorientation, lethargy, headache, seizures, coma),
  – hemorrhages (e.g., purpura, easy bruising, mucosal bleeding),
  – hepatomegaly (≥ 3 cm below the costal margin).
- Histopathologic criterion: Evidence of macrophage hemophagocytosis is found in the bone marrow aspirate sample. The demonstration of hemophagocytosis in bone marrow samples may be required in doubtful cases.

The above criteria are of value only in patients with active sJIA. The thresholds of laboratory criteria are provided only as an example. The clinical criteria are probably more useful as classification criteria rather than as diagnostic criteria because they often occur late in the course of macrophage activation syndrome and therefore may be of limited value in the early diagnosis of the syndrome.

Very recently, in the year 2016, European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) approved classification criteria for MAS complicating sJIA, after quantitatively validating the criteria in patient data sets. As per the criteria, a febrile patient with known or suspected systemic juvenile idiopathic arthritis is classified as having MAS if the following criteria are met [10]:
- ferritin > 684 ng/ml and any 2 of the following:
- platelet count ≤ 181 × 10^9/l,
- aspartate aminotransferase > 48 U/l,
- triglycerides > 156 mg/dl,
- fibrinogen ≤ 360 mg/dl.

Laboratory abnormalities should not otherwise be explained by the patient's condition, such as concomitant immune-mediated thrombocytopenia, infectious hepatitis, visceral leishmaniasis, or familial hyperlipidemia.

The pathogenesis of MAS is still unclear. It has been explained that the over-activated T lymphocytes and macrophages are found in various organs, and perforin deficiency and some cytokines such as tumor necrosis factor-α (TNF-α), interleukin 1 (IL-1), IL-6, and interferon gamma (IFN-γ) play roles in the pathogenesis of MAS. High ferritin levels observed in MAS are not just the product of inflammation but rather may contribute to the development of the cytokine storm. Perforin is a cytotoxic protein that lymphocytes secrete to kill virus-infected cells and has the function of control of lymphocyte proliferation. Therefore, perforin deficiency may lead to persistent lymphocyte activation [11–13].

In order to treat the hemophagocytic syndrome, initially all NSAIDs, disease-modifying antirheumatic drugs and/or immunosuppressants should be withdrawn. There is no role of antibiotics. Corticosteroids are the drugs of choice, particularly pulse therapy with methylprednisolone [14]. The second drug currently indicated in the literature is cyclosporine A, particularly for patients who are not responsive to corticosteroids. Other therapeutic modalities that can be employed are intravenous gamma globulins, cyclophosphamide, plasmapheresis and etanercept – an inhibitor of tumor necrosis factor.

The importance of reporting this case was to highlight the association of the macrophage activation syndrome with sJIA and its clinical implications. The abnormal clinical and laboratory indices should direct the treating physician to the presence of this complication even though its association is rare. Timely diagnosis and appropriate initiation of treatment of the condition could be life-saving in these patients.

Summary

We conclude that MAS is a complication of the systemic form of JIA with elevated morbidity and mortality. The presence of acute liver failure and pancytopenia in patients with JIA should alert health professionals to a diagnosis of MAS. Early recognition, differentiation from systemic activity of the systemic JIA itself and the rapid introduction of aggressive treatment contribute to better prognosis.

The authors declare no conflict of interest.

References

1. Gurion R, Lehman TJ, Moorthy LN. Systemic arthritis in children: A review of clinical presentation and treatment. Int J Inflam 2012; 2012: 271569.
2. Schneider R, Laxer RM. Systemic onset juvenile rheumatoid arthritis. Baillieres Clin Rheumatol 1998; 12: 245-271.
3. Woo P. Systemic juvenile idiopathic arthritis: Diagnosis, management and outcome. Nat Clin Pract Rheumatol 2006; 2: 28-34.
4. Behrens EM, Beukelman T, Gallo L, et al. Evaluation of the presentation of systemic onset juvenile rheumatoid arthritis: Data from the Pennsylvania systemic onset juvenile arthritis registry (Pasojar). J Rheumatol 2008; 35: 343-348.
5. Hadchouel M, Prieur AM, Griscelli C. Acute hemorrhagic, hepatic, and neurologic manifestations in juvenile rheumatoid arthritis: possible relationship to drugs or infection. J Pediatr 1985; 106: 561-566.
6. Sawhney S, Woo P, Murray KJ. Macrophage activation syndrome: a potentially fatal complication of rheumatic disorders. Arch Dis Child 2001; 85: 421-426.
7. Petty RE, Southwood TR, Manners P, et al. International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004; 31: 390-392.
8. Ravelli A. Macrophage activation syndrome. Curr Opin Rheumatol 2002; 14: 548-552.
9. Ravelli A, Magni-Manzoni S, Pistorio A, et al. Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. J Pediatr 2005; 146: 598-604.
10. Ravelli A, Minoia F, Davì S, et al. 2016 classification criteria for Macrophage Activation Syndrome complicating systemic juvenile idiopathic arthritis. Ann Rheum Dis 2016; 75: 481-489.
11. Henter JI. Biology and treatment of familial hemophagocytic lymphohistiocytosis: importance of perforin in lymphocyte-mediated cytotoxicity and triggering of apoptosis. Med Pediatr Oncol 2002; 38: 305-309.
12. Henter JI, Elinder G, Söder O, et al. Hypercytokinemia in familial hemophagocytic lymphohistiocytosis. Blood 1991; 78: 2918-2922.
13. Stepp SE, Dufourcq-Lagelouse R, Le Deist F, et al. Perforin gene defects in familial hemophagocytic lymphohistiocytosis. Science 1999; 286: 1957-1959.
14. Mouy R, Stephan JL, Pillet P, et al. Efficacy of cyclosporine A in the treatment of macrophage activation syndrome in juvenile arthritis: report of five cases. J Pediatr 1996; 129: 750-754.