Systemic-onset Juvenile Idiopathic Arthritis in a young child

Ahmed Hamidu,[1] Musa Bello Kofar Na'isa,[1] Daiyabu Alhaji Ibrahim[1,2]

[1]Department of Medicine, Aminu Kano Teaching Hospital, Kano; [2]Department of Medicine, Bayero University, Kano, Nigeria

Abstract

We present a 31-month-old female child who was referred by the pediatricians with 1-year history of recurrent high-grade fever associated with polyarthritis and recurrent skin rash, which disappears within 24 hours of resolution of fever. She had lost the ability to walk unsupported because of persistent arthritis. Her Full Blood Count (FBC) was remarkable for marked leucocytosis, thrombocytosis, and a mild normocytic normochromic anemia; Erythrocyte Sedimentation Rate (ESR) and C-reactive Protein (CRP) were both elevated at 110mm/hour and 200mg/L (<7) respectively while serial blood cultures were negative for septicemia and blood films were negative for acute leukemia; HIV, hepatitis B and C virus, tuberculosis, rheumatic fever, rheumatoid arthritis, and connective tissue disease screenings were all negative. Her hemoglobin genotype is AA. She had repeatedly received treatments for malaria and 'sepsis' with parenteral and oral antimalarials and antibiotics with no permanent relief, hence the reason for referral to the rheumatologist. An assessment of Systemic-onset Juvenile Idiopathic Arthritis (SoJIA) was made when her serum ferritin came back elevated at 670ng/mL (4.63 – 204) and she was commenced on oral ibuprofen with remarkable improvement evidenced by resolution of fever, joint pain and rash and normalization of ESR, CRP and serum ferritin within 8 weeks of treatment. Although SoJIA is rare, it would be worthwhile to include this disease in the differential diagnoses and subsequent evaluation in any child presenting with unexplained recurrent fever associated with body rash and polyarthritis.

Introduction

Systemic-onset Juvenile Idiopathic Arthritis (SoJIA), also called Still's disease, is one of the subtypes of Juvenile Idiopathic Arthritis (JIA) seen in children. SoJIA is an auto-inflammatory condition characterized mainly by systemic symptoms like recurrent high-grade fever, night sweats, and weight loss; affecting both females and males equally and may occur at any time during childhood.[1] It is a rare disease with very few reports from Nigeria[2] and the world at large.[3,4]

The pathogenesis of SoJIA involves dysregulation of the innate immune system with increased production of inflammatory cytokines. Genes that were found to be uniquely upregulated in SoJIA compared with other subtypes included innate immune pathways [interleukin-6, Toll-like receptor/IL-1 receptor, and Peroxisome Proliferator–Activated Receptor-γ (PPARγ) signalling],[5] while genes related to natural killer cells and T- cells are found to be downregulated.[6]

Clinical features of SoJIA are defined by the recent International League of Associations for Rheumatology (ILAR) classification criteria[7] as arthritis of at least 6 weeks in at least one joint with a daily fever of ≥39ºC of at least 2 weeks duration, that is documented to be quotidian for at least 3 days and accompanied by one or more of the following: evanescent, non-fixed erythematosus rash, generalized lymph node enlargement, hepatomegaly and/or splenomegaly, and serositis.[8] It may also be characterized by laboratory evidence of inflammation, including granulocytosis, thrombocytosis, and raised acute phase reactants, including Erythrocyte Sedimentation Rate (ESR), C-reactive Protein (CRP) and hyperferritinemia (usually >500 ng/ml).[9] Diagnosis, however, is possible using these criteria after careful exclusion of more common causes of fever and arthritis in children like bacterial septicemia, viral arthritis, *e.g* HIV-related arthritis, septic arthritis, hemoglobinopathies, rheumatic fever, and acute leukemias.

The goals of treatment in SoJIA are symptomatic relief, controlling underlying inflammatory processes, and achieving and maintaining sustained disease remission.[10] Treatment options include Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), *e.g.* ibuprofen, systemic glucocorticoids, intraarticular glucocorticoids, methotrexate, cyclosporine, and biologics like anakinra, canakinumab, tocilizumab, adalimumab, and etanercept.[5,11]

The pattern and course of the disease may vary. Approximately 40% of children with SoJIA will have a monophasic pattern and undergo remission after a single exacerbation, which may last up to 2 years. About 7% will have a polycyclic pattern in which patients experience recurrent episodes of disease exacerbation followed by remission. Ultimately, up to 50% of patients will have a persistent pattern, which is defined as a persistent disease for at least two years.[5]

Correspondence: Daiyabu Alhaji Ibrahim, Department of Medicine, Bayero University/ Aminu Kano Teaching Hospital, Kano, Nigeria.
E-mail: daigbs@yahoo.com

Key words: Systemic Onset Juvenile Idiopathic Arthritis, fever, rashes, polyarthritis, young child.

Contributions: all the authors made a substantive intellectual contribution. All the authors have read and approved the final version of the manuscript and agreed to be held accountable for all aspects of the work.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate: no ethical committee approval was required for this case report by the Department, because this article does not contain any studies with human participants or animals. Informed consent was obtained from the legal guardians of the patient included in this study.

Informed consent: the patient's legal guardians gave their written consent to use her personal data for the publication of this case report and any accompanying images.

Received: 10 March 2023.
Accepted: 24 May 2023.

Pyramid Journal of Medicine 2023; 6:314
doi:10.4081/pjm.2023.314

Case Report

JAK is a 31-months-old child who was referred to our rheumatology clinic in February 2022 with a history of recurrent daily fever, polyarthritis, and skin rashes for a year. Fever was high grade and intermittent and associated with symmetrical polyarthritis involving the elbows, wrists, knees, ankles, midfoot, and toes. The skin rashes were in the form of pink-to-red-to-brownish macules and patches on the face, palms, arms, legs, and soles of the feet. They appear with daily episodes of fever and disappear within 24 hours following the resolution of fever. She had no history of jaundice, vomiting, diarrhea, or refusal to feed. No cough, difficulty in breathing, or body swelling. No painful micturition, sore throat, ear ache, or ear discharge. No seizures or impairment of consciousness. She had lost the ability to walk around unsupported. She had no family history of sickle cell disease, and no family history of autoimmune diseases. She had repeated treatments with anti-malarials and antibiotics with no permanent relief. On examination, she was pale and febrile with an axillary temperature of 38.8C. She had swollen and tender elbows, wrists, ankles, and mid-tarsal joints. There was an associated inability to walk due to pain, with slight flexion deformities at both elbows (due to pain). The skin showed erythematous macular rashes, mainly on the extremities and trunk (Figure 1). She had no significant peripheral lymphadenopathy, no hepatomegaly, or splenomegaly. Other systemic examinations were unremarkable. Her initial and follow-up FBC, ESR, and serum ferritin are shown in Tables 1 and 2.

Initial laboratory evaluation, while she was with the pediatricians, showed serial blood cultures to be negative for blood infection and blood films negative for acute leukemia. Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and tuberculosis screens (Mantoux test) were all negative. Her rheumatoid factor, anti-CCP, and Anti-Nuclear Antibodies (ANA) were also negative for rheumatoid arthritis and Systemic Lupus Erythematosus (SLE), respectively. Her Anti-Streptolysin O titer (ASO) was normal at 26U/mL (<160), and her hemoglobin genotype is AA hence ruling out rheumatic fever and sickle cell anemia, respectively. An assessment of Systemic-onset Juvenile Idiopathic Arthritis (Still's Disease) was made using the ILAR criteria considering the disease duration and the clinical feature after ruling out some of the most common causes of fever, rash and polyarthritis in our environment. The diagnostic mix in this patient includes the chronic recurrent, daily fever, the erythematous macular rash that accompanies the fever, the recurrent polyarthritis, the raised ESR, hyperferritinemia, marked leucocytosis, thrombocytosis, and normocytic/normochromic anemia. This patient, however, did not present with peripheral lymphadenopathy, hepatomegaly, or splenomegaly. She was commenced on oral ibuprofen at 100 mg three times daily with remarkable improvement within 8 weeks in clinical and laboratory parameters evidenced by the resolution of fever, joint pains and rashes and normalization of WBC count, platelet count, ESR, and serum ferritin (Figure 2, Tables 1 and 2). Oral ibupro-

Table 1. Laboratory investigation results.

Test Done FBC	11/02/22	19/02/22	26/02/22	03/04/22
WBC (x10^9/L)	20.2	14.2	13.1	10.4
Neutrophils (%)	63.5	30.0	56.0	37.0
Eosinophils (%)	4.0	3.9	14.5	8.0
Basophils (%)	0.9	0.3	0.3	0.0
Lympho (%)	19.6	52.0	26.7	50.0
Mono (%)	11.8	13.5	9.4	5.0
Hb (g/dL)	10.1	8.2	8.2	12.0
MCV (fL)	109.0	75.0	75.0	61.5
MCH (pg)	21.3	22.6	22.6	19.3
PLT (x10^9/L)	756.0	689.0	508.0	356.0

FBC, Full Blood Count; WBC, White Blood Cells; Lympho, Lymphocytes; Mono, Monocytes; Hb, Haemoglobin; MVC, Mean Corpuscular Volume; MCH, Mean Corpuscular Haemoglobin; PLT, Platelets.

Table 2. Laboratory investigation results.

Test Done	Date
Serum ferritin (ng/mL)	
670.25 (4.63 – 204)	14/02/22
33.95 (4.63 – 204)	04/03/22
29.20 (4.63 – 204)	03/04/22
ESR	
110mm/Hr	11/02/22
10mm/Hr	03/04/22
CRP	
200mg/L (<7mg/L)	13/02/22

ESR, Erythrocyte Sedimentation Rate; CRP, C-reactive Protein

Figure 1. Erythematous rash on the left thigh and leg of the patient with Systemic-onset Juvenile Idiopathic Arthritis (SoJIA).

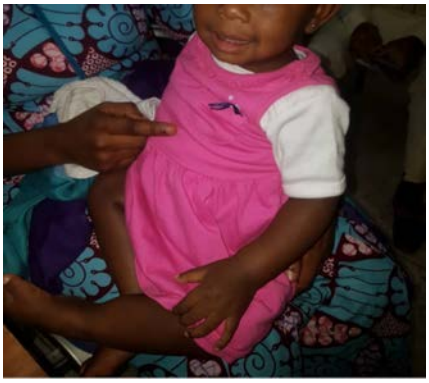

Figure 2. Healed skin lesions in the child with Systemic-onset Juvenile Idiopathic Arthritis (SoJIA).

fen was then reduced to 100 mg twice daily and subsequently to 100mg daily. She is currently on follow-up at our clinic and has gained full developmental milestones appropriate for her age.

Discussion

Juvenile Idiopathic Arthritis (JIA) is defined as inflammatory arthritis of undetermined aetiology beginning in any child before the age of 16 years.[12] It is the most common chronic rheumatic disease in children with several different clinical subtypes, which include Systemic-onset JIA (Still's disease), oligoarticular JIA, extended oligoarticular JIA, polyarticular RF-positive JIA, polyarticular RF-negative JIA, Enthesitis-Related (ERA JIA), juvenile spondyloarthropathy and undifferentiated juvenile arthritis.[13] The subtype is determined by the pattern of illness during the first 6 months of symptom development.[13] There is no definitive laboratory or radiographic finding that is pathognomonic of JIA but laboratory evaluation is necessary to exclude common alternative conditions presenting with arthritis like infectious arthritis, hemoglobinopathies, malignancies, and acute rheumatic fever. Epidemiological studies of JIA have been hampered by a lack of standardized criteria and case ascertainment, resulting in wide-ranging results[14]. Reports from Scandinavian countries show a prevalence of 11-22 per 100,000 per year, while studies from the USA show incidence to range between 4 and 14 cases per 100,000 per year[14].

Ethnicity has been studied and European descent has been associated with a moderately increased risk of JIA.[14]Additionally, JIA subtypes differed significantly between ethnic groups[15].

There have been few developments in terms of environmental risk factors, although infection remains the most favoured hypothesis. No specific pathogens have, however, been consistently identified that trigger the onset of JIA.[15]

JIA had rarely been reported among black Africans in the past,[16] but there has been a recent upsurge in reporting, with most reports coming from Nigeria,[17] Cameroon,[18] and Zambia.[19] The reports show the predominance of the rheumatoid factor-negative polyarticular type.

In the report by Adelowo and Umar,[17] which was an eight and half year audit of JIA cases seen at a private rheumatology practice in Lagos, SoJIA constituted only 13% (n=3) of JIA cases, while 56.5% (n=13) and 30.4% (n=7) were polyarticular and oligo-articular sub-types respectively. Oguntona *et al*.[2] from Sagamu reported a single case of SoJIA in a 14-year-old boy who had been living with the disease for 6 years prior to presentation. His symptoms include a chronic high-grade fever, rash, polyarthritis, and lymphadenopathy but no splenomegaly. He had a markedly elevated ESR and normocytic/normochromic anemia. He responded well to a combination of NSAIDs, glucocorticoids, chloroquine, and methotrexate, although he had stunted growth and joint deformities from the long-standing disease.

To our knowledge, this is the first report of SoJIA from the Northern part of Nigeria, which may be a testimony to the rarity of the disease. The ILAR classification criteria[7] for SoJIA requires the presence of arthritis of at least 6 weeks in at least one joint with a daily fever of ≥39ºC of at least 2 weeks duration, that is documented to be quotidian for at least 3 days and accompanied by one or more of the following: evanescent, non-fixed erythematosus rash, generalized lymph node enlargement, hepatomegaly and/or splenomegaly, and serositis in addition to suggestive laboratory features like hyperferritinemia, raised ESR, marked leucocytosis, thrombocytosis and normocytic/normochromic anemia. Our patient fulfilled the criteria by having chronic fever, arthritis, and rash together with hyperferritinemia, raised ESR, leucocytosis, and thrombocytosis. The patient, however, did not present with lymphadenopathy, hepatomegaly, splenomegaly, or serositis. Common differential diagnoses like septicemia, leukemia, tuberculosis, pediatric HIV infection, rheumatic fever, and sickle cell anemia were also ruled out before arriving at the diagnosis. The documented fever in our patient was not typically ≥39°C stated in the criteria, possibly due to the series of antimalarials and antibiotics that were given to the patient, which might have altered the presentation of the fever. Our patient did not present with lymphadenopathy, splenomegaly, hepatomegaly, or serositis, possibly because these are features seen in the persistent type of the disease as opposed to the monophasic type, which our patient likely had. Her rapid clinical and laboratory response to treatment, without recording a relapse of symptoms despite 8 months' follow-up, is also highly suggestive of a monophasic disease which is known to occur in 40% of patients with SoJIA.[5] The polycyclic and persistent patterns of presentations of SoJIA are known to be more aggressive, and will require more aggressive treatments with glucocorticoids, Disease-Modifying Anti-Rheumatic Drugs (DMARDs) like methotrexate, and biologics.[10] The goals of treatment in SoJIA are symptomatic relief, controlling underlying inflammatory processes, and achieving and maintaining sustained disease remission.[10] Our patient had a good clinical response, as shown by the abatement of the fever, the disappearance of arthritis and rashes, and the normalisation of ESR and serum ferritin. This was achieved with the use of an NSAID (ibuprofen in this case), which is usually the first-line anti-inflammatory agent in children with especially the monophasic type of SoJIA.[10]

Conclusions

Although SoJIA is generally a rare disease in children, it should be considered in the differential diagnoses and subsequent evaluation in any child presenting with unexplained recurrent fever associated with body rash and polyarthritis, especially following the exclusion of more common causes in our environment. A high index of suspicion is therefore needed by practitioners to diagnose the disease early for subsequent referral to a rheumatologist for expert management.

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