CASE REPORT

Systemic Juvenile Idiopathic Arthritis: A Challenging Diagnosis

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Abstract

Systemic juvenile idiopathic arthritis is a challenging diagnosis. Its onset can be quite nonspecific and suggest other conditions. The authors present the case of a 17-year-old female patient with a clinical picture characterized by oligoarthritis, myalgia, fever, and exanthema. During the clinical investigation, an elevation of the inflammatory markers was found, and infectious, oncologic, and autoimmune diseases were excluded. The patient also met the criteria for macrophage activation syndrome secondary to systemic juvenile idiopathic arthritis. The recognition of this entity involves a high index of suspicion and is crucial because of its implications in terms of morbidity and mortality.

Keywords: Adolescent; Arthritis, Juvenile/diagnosis; Diagnosis, Differential; Fever of Unknown Origin/etiology; Macrophage Activation Syndrome

Introduction

Systemic juvenile idiopathic arthritis is a rheumatologic disease characterized by the dysregulation of the innate immune response, with the elevation of inflammatory cytokines: interleukin (IL) 1, IL-6, IL-8, IL-18, macrophage migration inhibitory factor and tumor necrosis factor, without circulating autoantibodies or autoreactive T-cells. Diagnosis is defined by arthritis in one or more joints, with or preceded by a fever of at least two weeks duration that is documented to be daily (quotidian) for at least three days, accompanied by one or more of the following[1-3]:

- Evanescent (nonfixed) erythematous rash;
- Generalized lymph node enlargement;
- Hepatomegaly and/or splenomegaly;
- Serositis.

Criteria may not be present at the same time, commonly contributing to diagnosis delay. On the other hand, there are no specific laboratory markers, although anemia, leukocytosis (with neutrophilia), thrombocytosis, and elevation of C-reactive protein/erythrocyte sedimentation rate and ferritin are frequent. Minor elevations in aspartate aminotransferase and alanine aminotransferase, hypoalbuminemia, increased globulin levels, and low-grade D-dimer positivity are often present. Antinuclear antibodies (ANA) and rheumatoid factor are almost always negative in systemic juvenile idiopathic arthritis and, therefore, their presence should prompt the consideration of alternative diagnoses. Differential diagnoses include causes of fever of unknown origin like bacterial, parasitic, or viral infection, malignancy, autoimmune diseases, and inflammatory disorders, including autoinflammatory syndromes.[1-4]

Considering the main complications, macrophage activation syndrome is potentially life-threatening if not recognized and treated early on.[5,6]

Case Report

A previously healthy 17-year-old female, born in Angola and resident in Portugal since she was 2 years old, was admitted to the emergency department for joint pain and stiffness of the knees, elbows, wrists, cervical and lumbar region, myalgia of the thighs, odynophagia and chills for the last two weeks. Articular complaints had started five months ago, initially and intermittently affecting the right wrist and knee. On admission, she was febrile (tympanic temperature 37.9ºC) with the painful mobilization of both elbows; swelling, pain, and limited motion of both knees and wrists; pain on cervical and lumbar spine mobilization and erythema of the oropharynx. Cardiac auscultation revealed a mid-systolic murmur (grade II/VI Levine grading scale) without radiation or associated extracardiac sounds. Abdominal and skin examination were unremarkable. Lymphadenopathies were excluded. Laboratory testing revealed hypochromic microcytic anemia (hemoglobin 9.3 g/dL), leukocytosis (17 100 cells/µL) with neutrophilia

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(86%), elevation of acute phase reactants (C-reactive protein 14.9 mg/dL and erythrocyte sedimentation rate 61 mm/h), normal liver enzymes, unchanged renal function and urinalysis, normal creatine phosphokinase, and negative direct antigen detection of *Streptococcus pyogenes* from the throat. Articular radiographs, chest radiography, and electrocardiogram were normal.

After being admitted for clinical observation and investigation, she continued to have intermittent joint pain and lower limb myalgia with partial relief with non-steroidal anti-inflammatory drugs diclofenac 150 mg/day from day (D) 1 to D3, ibuprofen 30 mg/kg/day D4-D10, and indomethacin 2 mg/kg/day D10-D21. Arthritis was confirmed by ultrasound in more than one joint. On the fourth day of hospitalization, fever was also documented, 1-2 daily peaks, maximum 39.4ºC, especially in the afternoon, with good general status between the febrile peaks and lasted for 15 days (D4-D18) despite the fixed analgesia. Between D10-D14 an intermittent urticariform maculopapular exanthema appeared in the region of the thighs and forearm, not related with the fever peaks.

Regarding the investigation, screening for a streptococcal group A infection was negative: anti-streptolysin O antibody, antideoxyribonuclease-B antibody and bacteriological exam of pharyngeal secretions. It is noteworthy that the patient was an inactive carrier for hepatitis B virus (HBV): HBsAg +, Anti-HBc +, HBeAg –, Anti-HBe +, Anti-HBs –. Hepatitis B virus load was 176 copies deoxyribonucleic acid/mL. Other viral and bacterial infections were excluded, namely human immunodeficiency virus (HIV) 1 and 2, hepatitis A, C, D, and E, Epstein Barr virus (EBV), cytomegalovirus (CMV), parvovirus B19, *Borrelia burgdorferi, Rickettsia conorii, Mycoplasma pneumoniae, Chlamydia trachomatis, Chlamydia pneumoniae, Toxoplasma,* and *Brucella*. A complementary laboratory study revealed an elevation of serum amyloid A protein (423 mg/L) and a lupus anticoagulant ratio of 1.6 (reference values: > 1.5-2 moderately positive). The remaining autoimmunity markers were unremarkable: ANA, anti-neutrophil cytoplasm antibodies (ANCA), anti-dsDNA, anticentromere, anti-B2glicoprotein, anticardiolipin and anti-citrulline (CCP2) antibodies, rheumatoid factor, human leukocyte antigen (HLA) B27, C3, C4, CH50, and angiotensin-converting enzyme. Lymphocyte populations and immunoglobulins were also normal. Echocardiogram revealed a small pericardial effusion.

Since admission, a progressive decrease in hemoglobin (minimum 7.2 g/dL), leukocytes (maximum 25,800 cells/µL, minimum 14,300 cells/µL), platelets (maximum 386,000 cells/µL, minimum 288,000 cells/µL), and erythrocyte sedimentation rate (maximum 89 mm, minimum 61 mm) was found. In addition, on D13, there was a significant increase in serum ferritin (maximum 12,207 ng/mL, minimum 3,229 ng/mL), triglycerides (maximum 226 mg/dL), and aspartate aminotransferase (maximum 67 U/L), suggestive of macrophage activation syndrome. Clinically, the patient maintained articular complaints and fever but preserved good general condition and never presented neurological or hemorrhagic manifestations. On D17, bone marrow aspiration and a biopsy were performed, but did not reveal hemophagocytosis, lymphoproliferative disease, or *Leishmania* infection, and so entecavir (0.5 mg/day) was started. On D18, methylprednisolone 30 mg/kg/day (1 g/day) was administered intravenously for three consecutive days followed by oral prednisolone 2 mg/kg/day (60 mg/day), with laboratorial improvement and clinical remission. On the 24th day of hospitalization, she was discharged home and referred to rheumatology and infectiology consultations for a follow-up.

Discussion

This case report demonstrates the challenge that a clinician faces when diagnosing systemic juvenile idiopathic arthritis. In fact, considering the initial clinical picture, other causes had to be considered, namely rheumatic fever.[1,7] Moreover, it was only during hospitalization that fever and exanthema were detected, which was essential to guiding the suspicion toward systemic juvenile idiopathic arthritis.[1-3] Autoinflammatory syndromes, specifically the tumor necrosis factor receptor associated periodic syndrome, was also considered, due to prolonged fever, migratory myalgia, arthritis, and exanthema not related with fever peaks. The increase in serum amyloid A protein and elevated acute reactive agents were in line with this diagnosis.[4] However, against this hypothesis is the fact that the family history was unremarkable for periodic febrile syndromes and the patient had never presented similar previous episodes or other common symptoms such as abdominal pain, ocular inflammation, or periorbital edema. In addition, the immediate and favorable response to corticosteroid therapy was not concordant with this diagnosis.[4] During hospitalization, the patient developed criteria for macrophage activation syndrome secondary to systemic juvenile idiopathic arthritis. Macrophage activation syndrome can occur at any time in the natural history of the disease, although it usually occurs in the first days or weeks of disease presentation. Clinical manifestations are difficulty

in controlling fever with antipyretics, exanthema, lymphadenopathy, and/or hepatosplenomegaly as well as more severe manifestations such as hemorrhagic dyscrasia, hepatic failure, seizures, coma, or shock. Suggestive laboratory abnormalities include pancytopenia (or progressive decreasing in previous hematologic series), increased transaminases, triglycerides, and serum ferritin as well as decreased serum fibrinogen and erythrocyte sedimentation rate values. Paradoxically, C-reactive protein may remain high.[5,6,8] Bone marrow aspiration and biopsy may allow the diagnosis by the demonstration of hemophagocytic macrophages in the bone marrow, although it is not a mandatory condition, and in some cases may not be present.[5,8] In summary, this is a condition that is extremely difficult to diagnose in patients with systemic juvenile idiopathic arthritis, as it may be confused with a flare of the disease itself, demanding a high index of suspicion. As for treatment, after the exclusion of an alternative diagnosis, immunosuppressive therapy was started.[9] Considering HBsAg positivity, the viral load (HBV DNA) was assessed. Because our patient was an inactive HBsAg carrier (HBV DNA < 2000 IU/mL) and susceptible to HBV reactivation with immunosuppressive therapy, entecavir was initiated before immunosuppression.[10]

In conclusion, diagnosing systemic juvenile idiopathic arthritis is complex and requires a judicious etiologic study. Its clinical manifestations may not present typical forms, and the distinction from other diseases is difficult, with an emphasis on the auto-inflammatory syndromes, in which clinical and laboratorial presentation may overlap systemic juvenile idiopathic arthritis.

WHAT THIS CASE REPORT ADDS

- Systemic juvenile idiopathic arthritis is a diagnosis of exclusion and the approach should be addressed on a case-by-case basis.
- Macrophage activation syndrome is the most significant complication and potentially fatal, requiring prompt diagnosis and treatment.
- This case is presented to highlight the fact that systemic juvenile idiopathic arthritis is a diagnosis to be kept in mind while managing a child with fever without an obvious source, after the exclusion of infectious, oncologic, and autoimmune diseases.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

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Artrite Idiopática Juvenil Sistémica: Um Diagnóstico Complexo

Resumo:
A artrite idiopática juvenil sistémica é uma doença de difícil diagnóstico. A apresentação pode ser inespecífica, sugerindo outras etiologias. Os autores apresentam o caso de uma doente de 17 anos com oligoartrite, mialgias, febre e exantema. Da investigação realizada a destacar elevação de marcadores inflamatórios e exclusão de doenças infeciosas, oncológicas e autoimunes. A doente também reuniu critérios compatíveis com síndrome de ativação macrofágica. O reconhecimento desta complicação requer um alto índice de suspeição e é importante pelas suas implicações em termos de morbilidade e mortalidade.

Palavras-Chave: Adolescente; Artrite Juvenil/diagnóstico; Diagnóstico Diferencial; Febre de Causa Desconhecida/etiologia; Síndrome de Ativação Macrofágica