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CASE REPORT

Enthesitis-related arthritis in Kikuchi–Fujimoto disease

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Abstract Histiocytic necrotizing lymphadenitis or Kikuchi–Fujimoto disease (KFD) is a rare, benign and self-limiting disorder that characteristically presents with fever and cervical lymphadenopathy. Articular manifestations in the form of arthralgias are common but frank arthritis is distinctly rare and dactylitis has not been reported yet. Herein, we describe a young boy who presented with arthritis and dactylitis as the initial manifestation of KFD. A 14-year-old boy presented with a two-week history of fever, generalized lymphadenopathy and asymmetric polyarthritis, enthesitis and dactylitis of the toes. Two years earlier he presented with arthritis of the knee and ankle joints, which lasted for 12 months. However, he had been asymptomatic for one year. Investigations revealed anemia, leukopenia and raised acute phase reactants. Work-up for infectious etiology, systemic lupus erythematosus and leukemia and lymphoma was negative. Excision biopsy of the cervical lymph node confirmed KFD. Fever, lymphadenopathy and leukopenia dissipated with nonsteroidal anti inflammatory drug therapy, but the arthritis persisted. A trial of methotrexate led to the resolution of the arthritis.

Keywords Enthesitis-related arthritis · Dactylitis · Leukopenia · Necrotizing lymphadenitis · Kikuchi–Fujimoto disease (KFD) · Juvenile idiopathic arthritis (JIA)

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Introduction

Kikuchi–Fujimoto disease (KFD; so-called histiocytic necrotizing lymphadenitis) is an enigmatic, benign, and self-limited syndrome first described in 1972 in Japan [1, 2]. It has subsequently been reported around the world, but more so from the Asian continent. The characteristic clinical presentation includes cervical lymphadenopathy and prolonged fever. The characteristic histopathologic picture of the lymph node clinches diagnosis. It is important to be aware of this rare disease as it can mimic infections (viral, fungal and mycobacterial), hematological malignancies (leukemia and lymphoma) and various connective tissue disorders.

Arthritis in KFD has been described in association with connective tissue diseases like systemic lupus erythematosus (SLE), systemic onset juvenile idiopathic arthritis (JIA), or rheumatoid arthritis [3, 4]. Though arthralgias and myalgias are common, arthritis is very rare and has been only recently described in two case reports consisting of a total of three adult patients from the Indian subcontinent [5, 6]. Both small and large joints were affected. Like other manifestations of KFD, even arthritis is self-limited and not known to persist [5, 6]. Herein, we describe for the first time a young boy presenting with arthritis as the initial manifestation of KFD.

Case

A 14-year-old boy presented with complaints of arthritis and fever of two weeks' duration. The illness started as inflammatory arthritis involving the proximal interphalangeal (PIP) joints of the right hand, left ankle and metatarsophalangeal joints of the left foot. In addition, he had bilateral anterior knee pain localized at the insertion

site of tendon patellae. There was no knee joint tenderness and effusion. He had continuous high-grade fever not associated with any other localizing symptoms. There was no history of skin rash, oral ulcers, photosensitivity, cough, dyspnea, chest pain, oliguria, hematuria, abdominal pain, sore throat, red eye or dysuria. There was no history of preceding diarrhea or dysuria. Two years earlier he presented with arthritis of the bilateral knee and ankles, which lasted one year and recovered completely on applying alternative forms of medical therapy. For the past 12 months, he had been asymptomatic and off all drugs. Family history of seronegative spondyloarthropathies was negative. Examination showed temperature of 38.5 °C, cervical, axillary and inguinal lympadenopathy, and mild splenomegaly. There was no skin rash. Musculoskeletal examination revealed arthritis of the right 3–5th PIP joints (Fig. 1) and left ankle (Fig. 2) and dactylitis of the second and third toes of the left foot. There was severe tenderness over the patellar tendon insertion site on the tibia bilaterally. Cervical spine movements, chest expansion and Schober's test were normal.

Investigations revealed anemia and leukopenia (hemoglobin was 9.2 gm/dl and the total leukocyte count was 2.6×10^9/l). The platelet counts, urinalysis, liver and renal function tests were normal. Erythrocyte sedimentation rate (Westergren) was 90 mm/h and C-reactive protein was 3.2 mg/dl (normal <0.5 mg/dl). Serum ferritin level was normal (21 μg/l). Multiple blood and urine cultures were negative. 2-D echocardiogram did not show any evidence of infective endocarditis. Radiographs of the hands, pelvis, and lumbosacral spine were normal. Magnetic resonance imaging of the knee revealed the presence of a hyperintense signal at the insertion site of tendon patellae on T2-weighted (Fig. 3) and fat-suppressed images, and it was hypointense on T1-weighted images (Fig. 4). Computerized tomograms of the chest and abdomen were normal except for mild splenomegaly. Serology for antinuclear antibodies, antineutrophil cytoplasmic antibodies, antibodies against extractable nuclear antigens, anti Sm, rheumatoid factor, HLA B27, HIV and EBV were negative. Bone marrow examination was normal. Cultures of the bone marrow aspirate for bacteria, mycobacteria, and fungus were negative. Cervical lymph node biopsy showed a partly effaced architecture with marked expansion of the paracortical areas by sheets of histiocytic cells and abundant karyorrhectic debris with interspersed lymphomononuclear cells and focal areas of necrosis, consistent with a diagnosis of KFD (Fig. 5a, b).

The initial treatment consisted of empirical antibiotics and nonsteroidal anti-inflammatory drugs. The antibiotics were discontinued once the culture reports were available; however, nonsteroidal anti-inflammatory drugs were continued. Though the fever and generalized lymphadenopathy remitted and leukopenia recovered by the end of six weeks, the arthritis persisted, requiring the addition of methotrexate. Methotrexate was started and was gradually escalated from 7.5 mg/week to the current dose of 15 mg/week. At the last visit he has been on methotrexate for a

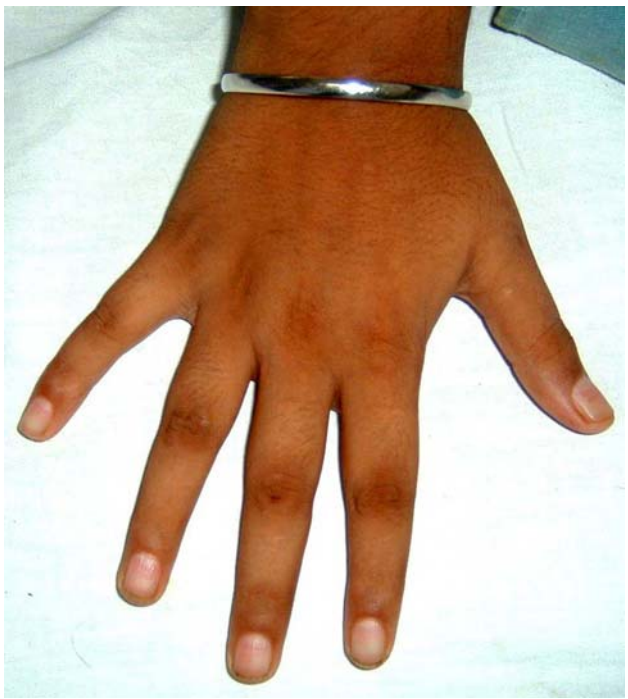

Fig. 1 Photograph of right hand showing erythema over the 3–5 PIP joints

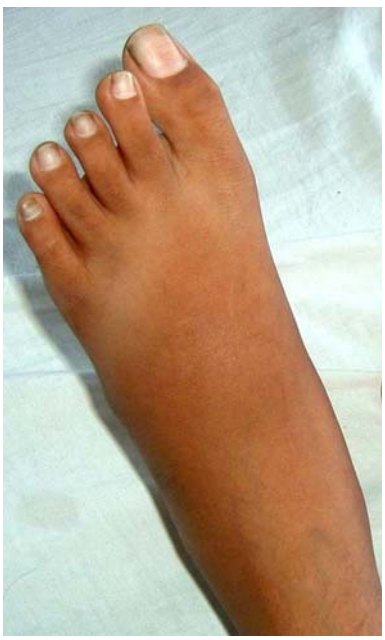

Fig. 2 Photograph of the left foot showing ankle arthritis (taken six weeks after therapy)

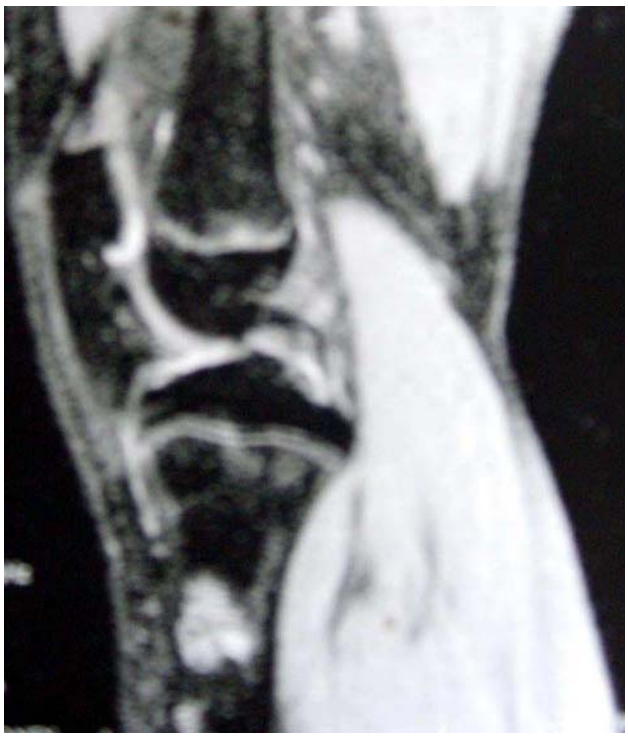

Fig. 3 Magnetic resonance imaging of the knee showing the presence of a hyperintense signal at the insertion site of tendon patellae (T2-weighted)

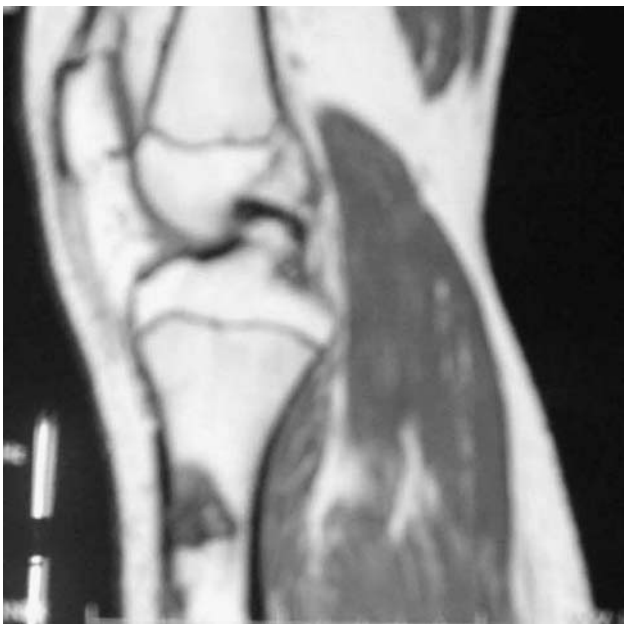

Fig. 4 Magnetic resonance imaging of the knee showing a hypointense signal at the insertion of tendon patellae (fat-suppressed, T1-weighted)

total of 11 months and the arthritis has been in remission for nearly three months; ESR was 12 mm for the first hour and CRP was <0.5 mg/dl.

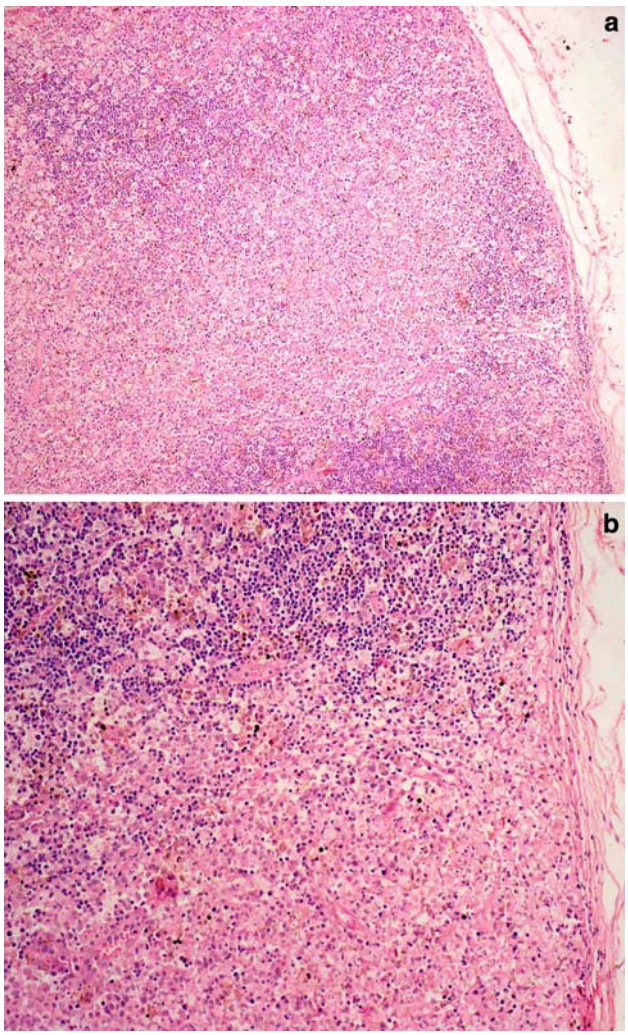

Fig. 5 Cervical lymph node showing focal areas of necrosis with karyorrhectric debris with interspersed lymphomononuclear cells and histiocytes. **a** H&E, ×100; **b** H&E, ×200

Discussion

Our case was unique due to (i) the pattern of arthritis and the presence of dactylitis, which has not been described previously, (ii) the fact that the arthritis persisted (for >6 weeks) in spite of the remission of fever and lymphadenopathy with nonsteroidal anti inflammatory drugs, necessitating the use of methotrexate, and (iii) because the pattern of arthritis mimicked enthesitis-related arthritis (ERA) of JIA. The presence of arthritis and enthesitis fulfilled the updated ILAR classification criteria of ERA [7]. Absence of diarrhea, dysuria, psoriasis skin rash, history of red eye or diminution in vision excluded the possibility of inflammatory bowel disease associated or reactive arthritis (which can present similarly; as asymmetric oligoarthritis, enthesitis or dactylitis).

Pathogenetically, increased expression of tumor necrosis factor (TNF) α and TNF receptors in the synovium in ERA–JIA has been reported [8]. Recently, a resemblance between chronic reactive arthritis and ERA–JIA has been reported based on the increased frequencey of lympho-proliferative responses to enteric pathogens (implicated in causing reactive arthritis) in synovial fluid [9]. However, our patient was negative for HLA B27 and did not have any history of gastrointestinal and genitourinary tract infections to suggest reactive arthritis.

To date there are no reports of arthritis mimicking ERA–JIA in KFD or KFD co-occurring with ERA–JIA. Graham described a case of Nepalese woman presenting with symmetric polyarthritis requiring an eight-week course of prednisolone for her articular symptoms [5]. We chose not to use glucocorticoids in our case because of his growing age, the unacceptable risk of toxicity and the fact that arthritis was persistent and mimicked ERA–JIA.

Our report highlights the fact that in a young boy presenting with a short history of fever, arthritis, dactylitis and generalized lymphadenopathy, one should consider the diagnostic possibility of KFD besides disseminated infections, hematological malignancies and seronegative spondyloarthropathies. Moreover, articular manifestations may not be self-limiting and may require long-term immunosuppressive therapy.

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