RARE CAUSE OF REACTIVE ARTHRITIS: LEPTOSPIROSIS A CASE REPORT AND REVIEW OF LITERATURE

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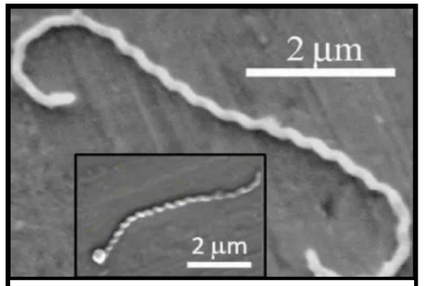
INTRODUCTION

Leptospirosis is considered to be the most widespread zoonosis in the world caused by spirochetes belonging to the order *Spirochaetales* and the family *Leptospiraceae*. Leptospires are coiled microorganisms with hooked ends. They are motile by two periplasmic flagella. Recent phylogenetic and virulence analyses have classified the genus *Leptospira* into 22 species[1].

The incubation period of the disease is 1 to 2 weeks, but ranges from 1day to 30 days[1]. Leptospirosis classically manifests as a biphasic illness[2]. The first phase of the disease (septicemic phase) lasts for about 3 to 10 days duration[1] and coincides with leptospiremia. Symptoms include fever, headache, body ache, mild cough, rash, nausea and vomiting. Signs include conjunctival suffusion, lymphadenopathy, and anorexia[2]. If present, the skin rash is often transient, lasting < 24 hours[3]. This phase is followed by a brief afebrile period of variable duration that, in turn, is followed by the immune phase of illness. Fever returns heralding the second phase of illness (immune phase) that may be accompanied by jaundice and renal failure. During this period, leptospires are excreted in urine[2]. Unfortunately, the distinction between first and second phase is not always clear; milder cases do not always include the second phase, and severe cases may be monophasic and fulminant[1].

Immunological manifestation is rare; and includes antiphospholipid syndrome and reactive arthritis. Such manifestations are likely to be the result of an immunological cross reactivity. Antibodies generated in response to leptospiral infection may cross react with host antigens and could lead to an inflammatory response[2]. Reactive arthritis refers to an infection-induced systemic illness and is characterized by an aseptic inflammatory joint involvement occurring in a genetically predisposed patient with a bacterial infection localized in a distant organ/system[4] involving the musculoskeletal, ophthalmologic, dermatologic, cardiovascular and genitourinary systems[5]. The definition of reactive arthritis must be based on the major and minor criteria that are shown[6 7]:



Microscopic picture of Leptospira
Reference: Internet

Major criteria:

1. Arthritis, with 2 of 3 of the following findings:
   - Asymmetric
   - Mono- or oligoarthritis
   - Affection predominantly in lower limbs
2. Preceding symptomatic infection, with 1 or 2 of the following findings
   - Enteritis (diarrhea for at least 1 day, 3 days to 6 weeks before the onset of arthritis)
   - Urethritis (dysuria or discharge for at least 1 day, 3 days to 6 weeks before the onset of arthritis)

Minor criteria, at least 1 of the following:

1. Evidence of triggering infection
   - Positive nucleic acid amplification test in the morning urine or urethral/cervical swab for Chlamydia trachomatis

- Positive stool culture for enteric pathogens associated with reactive arthritis

2. Evidence of persistent synovial infection (positive immunohistology or Polymerase Chain Reaction for Chlamydia).

A "definite" diagnosis of reactive arthritis is based on the fulfillment of both major criteria and a relevant minor criterion, while a "probable" diagnosis is characterized by both major criteria but no relevant minor criterion or one major criterion and one or more of the minor criteria. The identification of the trigger infection is also required[7].

The term "reactive arthritis" was introduced in the year 1969[8]. It was defined as arthritis, which develops during or soon after an infection elsewhere in the body, but in which the microorganism does not enter the joint cavity. Since then, it has been shown that antigens of the triggering microbe can be detected in the synovial fluid or synovial tissue of affected joints[9] [10] [11]. The triad of arthritis, urethritis and conjunctivitis represents a small part of the spectrum of the clinical manifestations of reactive arthritis and only a minority of patients present with this "classical triad" of symptoms. Human Leukocyte Antigen B27 (HLAB27) seems to be associated with more severe and chronic forms of the 'classical triad' of reactive arthritis. About 30 to 50% patients of reactive arthritis are HLAB27 positive[1].

Arthritis is usually asymmetric and additive, with involvement of new joints occurring over a few days to 1 to 2 weeks. Arthritis typically persists for 3 to 5 months, but more chronic courses do occur. Chronic joint symptoms persist in about 15% patients and in up to 60% patients in hospital-based series, but these tend to be less severe than in the acute stage. Recurrences of the acute syndrome are also common. Low back pain, sacroiliitis, and frank ankylosing spondylitis are also common sequelae. In most studies, HLAB27 positive patients have shown a worse outcome than HLAB27 negative patients[1].

CASE REPORT

A twelve years old female child was admitted to our hospital with complaints of fever, headache, and pain in the right hip joint since past 5 days from admission. Subsequent elaboration revealed a past history of fever, headache and myalgia for around 5 to 7 days around a week before the present complaints, which subsided on taking oral medications. She was of rural origin and there was rat infestation near her house and her father was working as sewage cleaner. On clinical examination, the patient was febrile with 101° Fahrenheit, tachycardia was noted and inguinal lymph nodes were palpable and tender. Local examination of right hip revealed warmth, fullness, tenderness and global restriction of movements. Left hip examination was normal. Patient was started on intravenous antibiotic ceftriaxone on an empirical basis along with Non steroidal anti-inflammatory drugs (NSAIDs) and skin traction. Figure 1 shows the preoperative clinical presentation (from front and side) of right hip of the patient on day of admission.

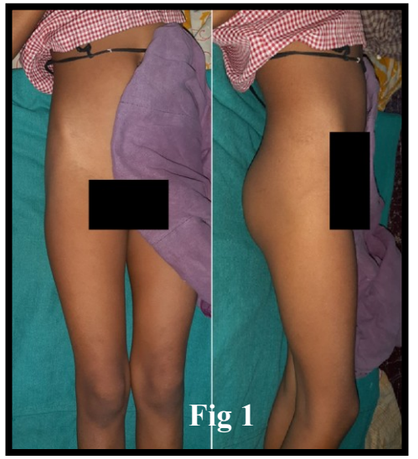
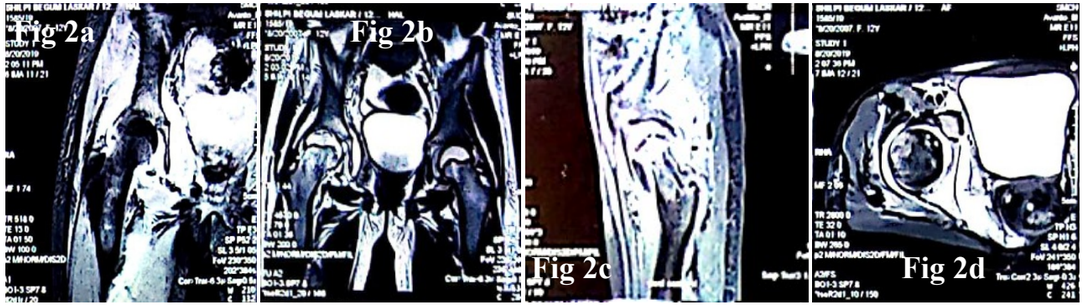


Fig 1

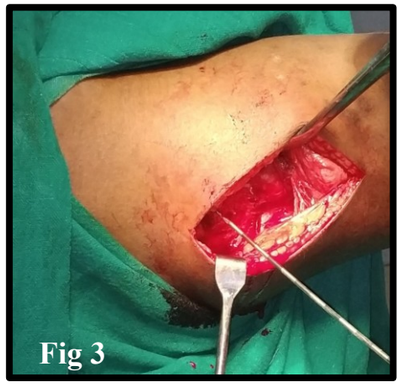
The initial laboratory work-up showed anemia with hemoglobin of 6.4 mg/dL, leukocyte count of 9.04×10^3 cells/µL, and neutrophilia of 74.9%. C-reactive protein was markedly elevated with 93.7 mg/dL, and other biochemical parameters were normal. Chest X-ray and electrocardiogram were normal.

USG of abdomen was normal; blood culture was negative for any growth. Urine examination was normal. USG of the right hip showed synovial proliferation suggestive of synovitis. MRI of both hips revealed hip joint synovitis with arthritis of infective or inflammatory origin (Figure 2a, Figure 2b, Figure 2c, Figure 2d).

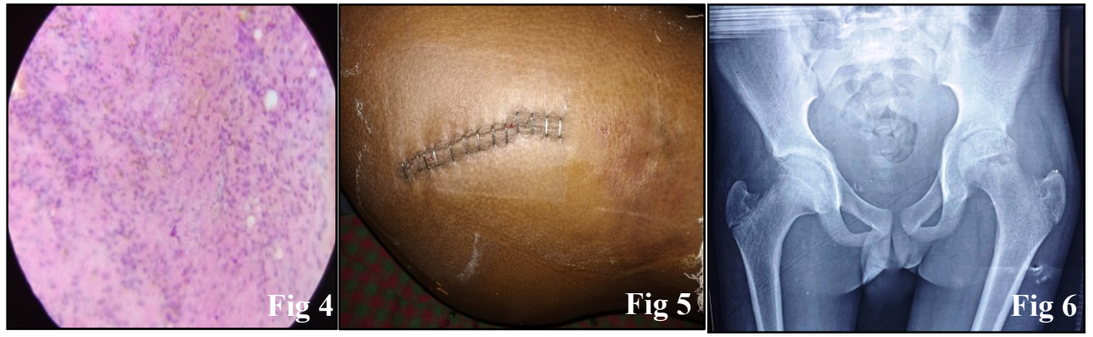
Diagnostic hip aspiration showed clear straw color synovial fluid with 30-50 polymorphonuclear leukocytes per high power field with no other abnormality. Fluid was negative for any infectious organism.



On 10th day, patient started developing icterus with yellowish discolouration of urine. Total bilirubin was 6.16 mg/dL, conjugated bilirubin 5.14 mg/dL, unconjugated bilirubin 1.02 mg/dL, aspartate transaminase 93.5 U/L, alanine transaminase 149.4 U/L, alkaline phosphatase 186.1 U/L, and gamma-glutamyl transferase 77.4 U/L. Serum total protein was 8.22 g/dL, serum albumin was low with 2.83 g/dL. PT-INR was slightly deranged with Prothombin time-International Normalized Ratio (PT-INR) of 1.35. Patient was shifted from intravenous ceftriaxone to cefotaxime, NSAIDs were stopped and symptomatic and nutritional management was done.



Screening for bacterial and viral causes of hepatitis was negative. Screening for *Leptospira* was positive. Patient was continued on intravenous cefotaxime and synovial biopsy was performed for confirming the diagnosis and ruling out any infective pathology. Figure 3 shows the intraoperative view (probe pointing to synovium) during hip biopsy of the patient. There was no evidence of any pus or infected tissue. The synovium or articular cartilage did not show pannus or any evidence of gross destruction, thus ruling out infective arthritis. Synovial biopsy analysis showed no growth of any microorganism and histopathological examination showed fibrocollagenous band infiltrated with mixed inflammatory cells, neutrophils and lymphocytes with no other specific pathology (Figure 4).



In addition, *Leptospira* IgM MAC ELISA test was done which was positive. Patient was thus diagnosed to be having leptospirosis and reactive arthritis secondary to it. She was discharged with oral doxycyline for 10 days. Subsequent follow-up of the patient showed complete healing of the operated site (Figure 5) and follow-up at 6 months showed disappearance of symptoms and near normal restoration of normal hip range of movements. The follow-up roentgenogram of the patient at 6 months shows sclerosis of the acetabular margin (Figure 6) suggestive of post inflammatory sequelae.

DISCUSSION

Reactive arthritis is found to be a rare immune mediated complication of leptospirosis[3]. A detailed search through medical literature showed two such case

reports[12] [13]. Although most textbooks demand the presence of various extra-articular presentations for diagnosis, the disease most often presents solely as arthritis[12]. Although the causes of reactive arthritis are well known, random reports attributed to other causative agents are advisable. The term could be hypothetically attributed to an antigenic activation of the immune system of the patient. *Leptospira* species are acknowledged immunomodulators[12]. The surface lipopolysaccharides (LPS) of *Leptospira* species are highly immunogenic[3], whereas the role of autoantibodies in the second stage of acute leptospirosis is undeniable. Anticardiolipin antibodies and antineutrophil cytoplasmic antibodies have been reported in course of acute leptospirosis[12]. Doxycycline therapy, by eradicating the leptospires and thereby removing the source of antigens, could prevent the formation of immune complexes leading to a decrease in the inflammatory response[2].

CONCLUSION

Reactive arthritis is thus a rare manifestation of leptospirosis. The possibility of leptospirosis should be borne in mind when evaluating patients with reactive arthritis and the propensity of various organisms to produce such a syndrome must be speculated further. A high degree of clinical suspicion is necessary, particularly in endemic areas. Physicians should be aware of the possibility of reactive arthritis due to leptospirosis, as the disease presents with unusual features.

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