Acute inflammatory Ankle Arthritis in Northern India – Löfgren’s Syndrome or Poncet’s Disease?

Shriram Garg¹, Anand N Malaviya¹,², Sanjiv Kapoor¹, Roopa Rawat³, Divya Agarwal¹, Amit Sharma⁴

Abstract

Objectives: To analyse patients presenting with acute inflammatory ankle arthritis from an aetiological standpoint; whether they had Löfgren’s syndrome (acute presentation of sarcoidosis), or Poncet’s disease (reactive arthritis due to tuberculosis infection). An additional objective was to establish a simple, practical yet optimal algorithm for diagnostic approach and management of such patients.

Methods: The study included 18 patients from northern India presenting with isolated acute inflammatory ankle arthritis. A combination of complete clinical evaluation, Mantoux test and contrast-enhanced computerised tomography (CE-CT) of the chest was carried out and results analysed.

Results: Among 18 patients presenting as inflammatory ankle arthritis it was possible to classify 10 of them as Löfgren’s syndrome all of whom had negative Mantoux test and bilateral hilar lymphadenopathy without central necrosis. The other 8 patients could be classified as Poncet’s disease as all of them had positive Mantoux test and showed mediastinal lymphadenopathy with or without unilateral hilar lymph nodes, with central necrosis. Finally, appropriate drug treatment (glucocorticoids with glucocorticoid-sparing drugs methotrexate and hydroxychloroquine in patients with Löfgren’s syndrome; standard anti-tuberculosis drugs in Poncet’s disease) gave excellent clinical response and patients remained well over a period of 1 year of follow-up.

Conclusion: Investigated on standard lines without any invasive procedure, patients with isolated inflammatory ankle arthritis could be classified in 2 distinct categories namely: (1) Löfgren’s syndrome in its complete (with EN) or incomplete (without EN) form; (2) Poncet’s disease. Appropriate treatment gave satisfactory response and patients remained well over a period of 1 year of follow-up.

Introduction

Most authorities on pulmonary diseases in India have remarked that sarcoidosis is an under diagnosed disease in this country.¹ Main reason seems to be that it is overshadowed by tuberculosis (TB) and uncommonly, even by leprosy.² Although the extrapulmonary manifestations of the disease are well known they are usually not given adequate importance. Thus, Jindal et al³⁴ have not mentioned musculoskeletal manifestations at all while Sharma & Mohan⁵ have mentioned them only as numbers in a table without any clinical details. From these standpoint musculoskeletal manifestations of sarcoidosis, although well described in the literature,⁶ write-ups on sarcoidosis from India have hardly mentioned much about musculoskeletal aspect of the disease.³⁵ There is only 1 authoritative series of 29 cases of arthritis in sarcoidosis that has described 2 cases (7%) with Löfgren’s syndrome an acute form of sarcoidosis-related arthritis.⁶ There is, however, a report from India that has described Löfgren’s syndrome in 43 patients.⁷

The acute form of arthritis, popularly called Löfgren’s syndrome, is said to be the most common rheumatic manifestation of sarcoidosis, often being the presenting manifestation of the disease and generally having a favourable outcome.⁸ Löfgren first described its presentation as a triad with bilateral hilar adenopathy (Fig. 1) and erythema nodosum.⁹,¹⁰ In their study from The Netherlands, Visser et al have suggested diagnostic characteristics for this disease that consist of inflammatory ankle arthritis in a person < 40 years of age and the duration of ≤ 2 months, with a sensitivity and specificity of 93 and 99%, respectively.⁸

Young adult patients presenting with isolated inflammatory ankle arthritis has been a common problem at this centre as well as reported by others from northern India.¹¹ Quite often these

Fig. 1: Standard radiograph of a patient showing prominent bilateral enlargement of hilar lymph nodes, classified as having Löfgren’s syndrome.
Patients and Methods

This study included 18 consecutive adult patients presenting at this centre with acute ankle inflammatory arthritis of less than 2 months duration in patients younger than 40 years, criteria for Löfgren's syndrome recommended by Visser et al. Patients with ankle arthritis as part of an already established local or systemic musculoskeletal problem (e.g. rheumatoid arthritis, proven tuberculous synovitis etc.) were excluded. The clinical work-up included demographic details, clinical details including family history, past history, social and personal history, constitutional symptoms, musculoskeletal symptoms including joints, soft tissue and bone problems, review of system and drug and medication history. Investigations included routine blood counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), routine biochemistry, liver and renal parameters, plain x-ray and contrast enhanced computerised tomography (CE-CT) of the chest. Mantoux test was performed and interpreted according to the standard methodology. Microbiological studies were carried out as and when a specimen was available or if considered necessary. Response to the treatment and condition on follow-up were recorded and analysed.

Results

Details of clinical manifestations and investigation results are summarised in table 1. A total of 18 patients with isolated inflammatory acute ankle arthritis seen over a period of ~12 months were included in this study. There were 10 males with a male to female ratio of 1:0.8. The age ranged from 22 to 50 yrs with a median of 33 yrs. Age range among males and females were 31-50 yrs (median 35.5 yrs) and 22-32 yrs (median 23.5 yrs) respectively. However, it appeared asymmetrical in severity in the majority with one or the other side being more severely inflamed. The infection had a characteristic brawny violaceous indurated inflammatory oedematous swelling. Healing on treatment was slow with peeling of the skin over inflamed area. Additional musculoskeletal findings included knee involvement 5/18 (3 bilateral, 2 unilateral), 5/8 of those with knee involvement also had wrist, elbow, and metacarpophalangeal (MCP) joint(s) with some degree of enthesitis, and 1 patient had metatarsophalangeal + MCP joint involvement. Extra-articular features included erythema nodosum lesions in 7 of the 18 patients (biopsy-proven in 3/7), posterior uveitis in 1 and breathlessness in 1. On contrast-enhanced computerised tomography (CE-CT) of chest, 10 of the 18 (55.5%) patients showed poorly enhancing bilateral hilar lymphadenopathy without any central necrosis (Fig. 2). Two of these patients showed ground-glass appearance at lung bases suggestive of possible early interstitial lung disease (ILD). All the 10 of these patients were Mantoux negative (table 1). CE-CT chest among the remaining 8 patients (87.5%) showed the following findings: no abnormality detected in 1 patient; among the remaining 7 patients, poorly enhancing mediastinal or paratracheal lymph nodes, or unilateral hilar lymph nodes, in any combination were observed, often with central necrosis and parenchymal lesions (Fig. 3). All of these 8 patients showed a positive Mantoux test (table 1). Subanalysis of these 8 patients who did not have bilateral hilar lymphadenopathy showed bilateral paratracheal lymph nodes in 2, unilateral paratracheal or unilateral hilar lymph nodes in 5, central necrosis in the lymph nodes in 3, associated lung parenchyma lesions suggestive of TB in 1, and no abnormality detected in 1 patient.

When the patients were classified on the basis of Mantoux test results (table 1) all the 10 patients who were Mantoux negative had the following characteristics: absence of involvement of any additional musculoskeletal region other than the ankles, extra-articular involvement in some that included monocular posterior uveitis in one, erythema nodosum in 4 patients (one biopsy proven). This group was diagnosed as having Löfgren's syndrome, an acute presentation of sarcoidosis. The other group of 8 patients who were Mantoux positive had the following characteristics: Additional musculoskeletal involvements (joints...
Table 1: Characteristics of 18 patients who presented with acute ankle inflammatory arthritis.

<table>
<thead>
<tr>
<th>Additional MSK involvement i.e. joints other than ankles, additional tenosynovitis, enthesitis etc.</th>
<th>Absent</th>
<th>Present</th>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra-articular manifestations:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema nodosum (EN)</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monocular posterior uveitis*</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral hilar lymphadenopathy**</td>
<td>10</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral/bilateral paratracheal lymph nodes</td>
<td>0</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with/without unilateral hilar lymphadenopathy, necrosis, lung parenchymal lesions***</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mantoux test</td>
<td>10</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patient had ankle involvement, bilateral hilar lymphadenopathy and was Mantoux negative.

**None of them had any additional MSK involvements but some of them did have extra-articular manifestations (e.g., EN, uveitis).

***All of them were Mantoux positive

other than ankles, enthesitis, tenosynovitis, and extra-articular involvement by way of erythema nodosum in 3 patients. This group was, therefore, diagnosed as having a form of reactive arthritis due to TB, also known as Poncelet's disease.9

Patients diagnosed as Löfgren’s syndrome were treated with glucorticoids (GC) along with GC-sparing drugs namely hydroxychloroquine (HCQ) and methotrexate (MTX).1,10,18 The ankle joint disease, other additional clinical features if any, responded rapidly with most patients becoming totally asymptomatic over a period ~ 8-12 weeks. Although radiological features improved in all the patients over 6 months complete clearing of the lymphadenopathy did not occur in some of the patients. The patients were advised long-term follow-up. In contrast to this group, the group with the diagnosis of Poncelet’s disease was treated with standard line of anti-tuberculosis drugs (ATT) without any nonsteroidal anti-inflammatory drugs. They were however, permitted paracetamol with or without tramadol for pain control, if needed. All the 8 patients responded satisfactorily with complete clinical as well as radiological response.

Discussion

As mentioned earlier, sarcoidosis is an under-diagnosed disease in this country, with gross under-recognition of extrapulmonary manifestations of the disease including musculoskeletal manifestations that has been reported in 15-40% of the cases in the literature.4,11,13 However, rheumatologists in India have been interested in arthritis in sarcoidosis and have described a series of 29 cases among which there were 2 patients with Löfgren’s syndrome.8 Similarly Indian rheumatologists have been regularly seeing acute presentation of sarcoidosis in the form of Löfgren’s syndrome although there is a paucity of publications in this field except a major write-up recently.9

This study of 18 patients from India, a high-burden TB region of the world, presenting with acute inflammatory ankle arthritis clearly demonstrated that there were two distinct categories within this group. A group of 10 of these patients showed bilateral hilar lymphadenopathy without central necrosis and a negative Mantoux test. Some of them also showed erythema nodosum and one of them showed monocular posterior uveitis as well. Interestingly, none of them showed involvement of any other additional musculoskeletal regions. This clinical picture was considered rather typical of Löfgren’s syndrome, a form of acute sarcoidosis, in its complete form (i.e. those with EN) or incomplete form (without EN).11,14 The second group was that of 8 patients who were Mantoux positive and, on CE-CT chest imaging, did not show bilateral hilar lymphadenopathy but showed only mediastinal and/or paratracheal and/or unilateral hilar lymphadenopathy often with central necrosis and associated lung parenchyma lesions suggestive of TB. These patients often had additional musculoskeletal involvements by way of arthritis of joints other than ankles, enthesitis and tenosynovitis. Some of them also showed extra-articular manifestations by way of EN. Thus, it was possible to classify patients presenting with acute-subacute inflammatory ankle arthritis-periartritis in 2 distinct categories on the basis of clinical pattern of joint involvement, a Mantoux test and chest imaging without any invasive procedures. These categories included: (1) acute presentation of sarcoidosis called Löfgren’s syndrome in its complete (with EN) or incomplete (without EN) form.11,14 (2) TB-related reactive arthritis that could be classified as Poncelet’s disease.16 Although there are several reports on Poncelet’s disease from India,6,18,20 its presentation with ankle arthritis has been emphasised only by Duggal and Khosla.9

This approach to classification of the patients with inflammatory ankle arthritis proved to be extremely useful in their treatment. All the patients categorised as Löfgren’s syndrome showed highly satisfactory clinical response to the treatment (see ‘Results’ above). The ankle joint disease, other additional clinical features if any, responded rapidly to GC along with GC-sparing MTX and HCQ with most patients becoming totally asymptomatic over a period ~ 8-12 weeks. Similarly, the group with the diagnosis of Poncelet’s disease showed satisfactory clinical as well as radiological response to standard line of anti-tuberculosis drugs (ATT) that was given without any nonsteroidal anti-inflammatory drugs. Many authorities consider Löfgren’s syndrome as a benign self-limiting condition not requiring conservative treatment e.g., rest and nonsteroidal anti-inflammatory drugs. However, in patients with severe arthritis or additional pulmonary/extra-pulmonary manifestations GC are recommended.1,13,17 Considering that the disease in our cases was severe enough to seek a specialist opinion and, on clinical evaluation also they were considered ‘severe’ enough to require additional treatment. The use of GC for any length of time among Indian is fraught with the danger of unmasking metabolic syndrome. Therefore, as a rule we have been using GC-sparing drugs namely methotrexate and hydroxychloroquine.17,18

Based upon this experience it could be stated that in the Indian context, a high- TB burden region of the world, patients presenting with inflammatory ankle arthritis should be thoroughly evaluated clinically with special emphasis on joints other than ankle if any, any other musculoskeletal manifestations like tenosynovitis, enthesitis etc., and extra-articular manifestations. Careful history of TB in the past or in the family would be important. This should then be followed by a standard Mantoux test and chest imaging that should include CE-CT of the chest specifically looking for poorly enhancing hilar, mediastinal (including paratracheal) lymphadenopathy, with or without central necrosis; and any parenchymal lesions. On the basis of these parameters the patients would then be classified as either having Löfgren’s syndrome or Poncelet’s disease. In this series of patients there was no need for any invasive investigations for reaching a diagnosis. This is in variance with the approach followed by Duggal and Khosla who used invasive procedures in several patients to reach a diagnosis.9 Once the patients were categorised accordingly,
specific treatment directed to sarcoidosis or TB respectively, give satisfactory results.

The main weakness of the present study is the lack of microbiological or histopathological diagnostic confirmation. However, this weakness is partially offset by the follow-up observation of > 1 year.

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References