

# Löfgren's Syndrome: A Clinical Variant of Sarcoidosis

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**L**öfgren's syndrome is an acute variant of sarcoidosis characterized by the triad of erythema nodosum, bilateral hilar adenopathy, and arthritis or arthralgias. Unlike sarcoidosis, which is usually a chronic disease requiring long-term corticosteroid treatment, Löfgren's syndrome has an excellent prognosis. This article describes the clinical course of a patient with Löfgren's syndrome who presented with erythema and fever and was initially diagnosed with cellulitis. The epidemiology and clinical features of sarcoidosis and Löfgren's syndrome are compared, and the diagnosis and treatment of Löfgren's syndrome are reviewed.

## CASE PRESENTATION

A 48-year-old white man with no significant medical history presented to an urgent care clinic in California with leg swelling and fevers. He stated that he had received multiple mosquito bites 3 days before while working in Florida; the next day, he had noticed the swelling and fever.

On physical examination, he was noted to have erythema on his legs below the knees, without edema. Laboratory studies included a complete blood count; plasma levels of urea nitrogen, electrolytes, creatinine, and glucose; and urinalysis. Results were normal with the exception of the leukocyte count, which was  $13.5 \times 10^3/\text{mm}^3$ . He was diagnosed with mosquito bites and secondary cellulitis and sent home with a prescription for cephalexin (500 mg 3 times daily for 10 days).

Three days later, the patient was again seen for the same complaints. The diagnosis of possible osteomyelitis or gout was considered, with the diagnosis of cellulitis being made. A radiograph of his ankles showed soft-tissue swelling, with no other significant findings. A urate level was found to be 4.6 mg/dL. The patient was given a prescription for metronidazole (500 mg twice daily for 10 days) and given ceftriaxone (1 g intramuscularly), in addition to the cephalexin.

Five days later, the patient returned again to the clinic. The leg pain had now worsened and he had tenderness and swelling of his hands, along with fever,

fatigue, nausea, and mild diarrhea. He denied any other symptoms. His temperature was  $39^\circ\text{C}$  ( $102^\circ\text{F}$ ), with other vital signs within normal limits. He appeared in no acute distress. Results of examination of the head, eyes, ears, nose, and throat were normal with the exception of minimal conjunctival injection, and examination of his neck revealed no adenopathy. Results of the cardiopulmonary examination also were normal. Abdominal examination revealed no tenderness and no organomegaly or masses. No peripheral adenopathy was noted. Examination of the feet and ankles revealed erythema with nodules, and edema with warmth was noted on palpation. His wrists and several bilateral metacarpophalangeal joints were erythematous and swollen. Additionally, a chest radiograph showed bilateral hilar adenopathy (**Figure 1**). His leukocyte count was now  $15.4 \times 10^3/\text{mm}^3$ , and the erythrocyte sedimentation rate was 94 mm/h. Liver function tests, electrolyte levels and measures of renal function all were normal.

The diagnosis at this time was polyarthritis, and the patient was admitted to the holding ward of the hospital for further work-up and treatment. He was placed on empiric antibiotic coverage with ceftriaxone, doxycycline, and indomethacin (50 mg 3 times daily). Additional laboratory studies performed at this time included angiotensin-converting enzyme (ACE) level, antistreptolysin-O (ASO) titer, antinuclear antibody titer, and rheumatoid factor level. The ACE level was within normal limits, as were the results of the other studies.

The following day, the patient was seen by the infectious disease specialist and the rheumatology specialist. The patient's erythema with nodules on his shins was determined to be erythema nodosum. A computed tomographic scan of the thorax was performed, demonstrating lymph node enlargement involving the right paratracheal region, the pretracheal/retrocaval

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region, the aortopulmonary window, the subcarinal region, and both hila. An 8-mm nodule was noted in the right middle lobe, and the radiologist raised the possibility of a diagnosis of lymphoma. Because of the radiographic findings and presence of erythema nodosum, the diagnosis of Löfgren's syndrome was made. Because of the severity of his arthritis, the patient was started on corticosteroids (1 dose of solumedrol 125 mg IV).

The patient was discharged home on a corticosteroid taper (prednisone 60 mg daily for 2 weeks, then 40 mg daily for 1 week, then 40 mg every other day for 1 month, followed by tapering of 5 mg every 2 weeks until off), with outpatient follow-up with the pulmonology service for bronchoscopy with trans-bronchial lung biopsy. The biopsy specimen showed small noncaseating granulomas, and bronchial washings showed no malignant cells. Results of acid-fast bacilli cultures and stains, as well as fungal stains, were all negative.

A follow-up chest radiograph performed 1 month later showed no significant abnormalities, and the patient was feeling much better. Nineteen months later, the patient continues to do well, without evidence of active disease or any sequelae.

## DISCUSSION

The constellation of symptoms that make up Löfgren's syndrome were initially described by Sven Löfgren in 1953 in a series of 113 patients.<sup>1,2</sup> It is defined as the association of erythema nodosum with bilateral hilar lymphadenopathy, usually with arthralgias or arthritis. It was first recognized as an acute presentation of sarcoidosis. Some authors recognize a variation of Löfgren's syndrome that presents with periarticular ankle inflammation with bilateral hilar adenopathy.<sup>3</sup> This variant may or may not present with erythema nodosum.

### Features of Sarcoidosis

Sarcoidosis is a multisystemic disease of unknown etiology that may affect any organ or system in the body and is characterized by noncaseating granulomas on biopsy.<sup>4,5</sup> Sarcoidosis has an estimated prevalence of between 1 to 40 cases per 100,000 population, with an annual incidence rate in the United States of 10.9 per 100,000 for whites and 35.5 per 100,000 for African Americans.<sup>4</sup> Females are affected slightly more than males, with the highest incidence in the third and fourth decades of life. Some studies also report a predominance of disease in the southeastern United States, as well as an increased incidence of disease in the late



**Figure 1.** Chest radiograph of the case patient demonstrating bilateral hilar adenopathy.

winter and early spring (our patient presented in July).<sup>6</sup>

Sarcoidosis can present with manifestations in almost any organ system, with the lungs being most common (88%).<sup>4</sup> Other common manifestations include uveitis, splenomegaly, hepatomegaly, and lymphadenopathy. The diagnosis of sarcoidosis requires a compatible clinical picture, the exclusion of other granulomatous disease, and the identification of noncaseating granulomas on biopsy.<sup>3,7</sup>

The prognosis of patients with sarcoidosis is dependent upon the stage of disease at presentation. Stage I disease, defined as hilar adenopathy without pulmonary infiltrates, remits in 60% to 80% of patients. Stage II disease (hilar adenopathy with infiltrates) remits in 50% to 60%, and stage III (infiltrates without adenopathy) remits in fewer than 30%.<sup>4</sup> A significant proportion of patients suffer relapse, however. One study showed that 74% of patients experienced relapse following cessation of corticosteroid treatment for longer than 1 month.<sup>8</sup> Other authors report a relapse rate of 25% to 40% within 2 to 3 months of stopping corticosteroids.<sup>4</sup>

### Features of Löfgren's Syndrome

Up to 35% of cases of sarcoidosis are Löfgren's syndrome.<sup>9</sup> Löfgren's syndrome differs from other types of sarcoidosis, however, in important ways. It is more common in certain geographical areas and races, particularly young white women from Scandinavia and Ireland, and is more uncommon in blacks.<sup>10</sup> Patients with Löfgren's syndrome typically present with erythema nodosum, bilateral hilar adenopathy, and arthritis or arthralgias; other manifestations occur frequently, as well. In a series of 186 patients with Löfgren's syndrome, the following signs and symptoms occurred

**Table 1.** Differential Diagnosis of Erythema Nodosum

Etiology	Cases, %
Idiopathic	34
Sarcoidosis/Löfgren's syndrome	22
Upper respiratory tract infection (viral)	20
Group A $\beta$ -hemolytic streptococcal pharyngitis	7
Tuberculosis	5
Drugs (penicillins, sulfa drugs, oral contraceptives)	3
Other (inflammatory bowel disease, Behçet's syndrome, Sweet's syndrome, malignancy)	9

Data from Garcia-Porrua et al.<sup>16</sup>

(prevalence in parentheses): arthralgia (68%), fever (38%), cough or dyspnea (13%), granulomatous skin lesions (13%), arthritis (13%), hepatomegaly (6%), ocular symptoms (5%), peripheral adenopathy (4%), splenomegaly (2%), hypercalcemia (2%), salivary gland hypertrophy (1%), and central nervous system involvement (1%).<sup>10</sup> In this series, 50% of patients also had an increased ACE level.

### Diagnostic Testing for Sarcoidosis and Löfgren's Syndrome

The ACE level is elevated in 50% to 80% of cases of sarcoidosis.<sup>4</sup> ACE is secreted by epithelial cells in granulomas and is present in pulmonary capillary endothelium. ACE levels can be elevated in granulomatous diseases other than sarcoidosis and can also be elevated in hepatitis, lymphoma, and many other conditions, making it nonspecific for sarcoidosis or Löfgren's syndrome. However, if the ACE level is elevated, it is suggestive of sarcoidosis and can be followed as a marker for treatment success.

Another test initially touted to aid in the diagnosis of sarcoidosis was the gallium citrate Ga 67 scan. Because of its lack of specificity, however, like the ACE level, this test contributes little to the diagnosis.<sup>5</sup> In one study aimed at determining which tests are helpful in evaluating the prognosis of sarcoidosis, serial pulmonary function tests and ACE levels, but not gallium scans, were helpful in predicting persistence of activity in sarcoidosis.<sup>11</sup>

The diagnosis of Löfgren's syndrome requires the presence of 2 of the 3 clinical features that define the syndrome: erythema nodosum and bilateral hilar adenopa-

thy. Arthritis or arthralgias may or may not be present. The need for biopsy to obtain histologic proof of non-caseating granulomas in the presence of either classic Löfgren's syndrome or sarcoidosis is under debate. Some authors believe that biopsy is a reliable means of diagnosing sarcoidosis and advise that it be performed to confirm the diagnosis.<sup>12</sup> Others note that the presence of bilateral hilar adenopathy accompanied by other characteristic findings of sarcoidosis has a positive predictive value of 99.95% for the diagnosis of sarcoidosis; these authors believe that biopsy therefore poses unnecessary risks to the patient and is not advised.<sup>13,14</sup>

Sarcoidosis is not the only disease that causes hilar adenopathy. The differential diagnosis of hilar adenopathy also includes fungal infections (histoplasmosis, coccidioidomycosis), lymphoma, bronchogenic carcinoma, and tuberculosis.<sup>15</sup>

The diagnosis of Löfgren's syndrome should be considered in any patient who presents with erythema nodosum (Table 1). In a series of 106 patients with biopsy-proven erythema nodosum in Spain, approximately 20% (21/106) of them had Löfgren's syndrome (n = 17) or sarcoidosis (n = 4).<sup>16</sup> Interestingly, in this series, only 5 of the 21 patients with either sarcoidosis or Löfgren's syndrome had an elevated ACE level, but all 4 of those with parenchymal lung involvement due to sarcoidosis had an elevated ACE level. The authors concluded that to evaluate for secondary (nonidiopathic) causes of erythema nodosum, the work-up should include serial ASO titers, chest radiography, and checking for a history of an upper respiratory infection.

### Treatment of Löfgren's syndrome

Treatment of most patients with Löfgren's syndrome can be accomplished with short-term bed rest and nonsteroidal anti-inflammatory drugs. Some patients are treated with corticosteroids for more severe symptoms, such as parenchymal pulmonary involvement, noncaseating granulomatous skin lesions, hypercalcemia, and severe arthritis.<sup>9,10,14,17</sup>

The prognosis of patients with Löfgren's syndrome is excellent. In the series of 186 patients discussed previously, only 8% of patients (n = 11) had active disease within 2 years of diagnosis.<sup>10</sup> By 3 years after diagnosis, 6 of these 11 patients had inactive disease, 3 had only minimal symptoms, and only 2 (1.5%) still had significant chronic disease. Only 6% of the patients experienced a relapse (a much lower rate than in patients with sarcoidosis). Most patients were treated conservatively and had remission of disease within 3 to 12 months. In this series, an elevated ACE level at baseline predicted a

higher likelihood of persistent disease or recurrence (14% vs 4% in patients without an elevated ACE level); this result appears to echo findings in the study of 106 patients discussed previously.<sup>16</sup> Overall, the prognosis of patients with Löfgren's syndrome is quite good.

## CONCLUSION

Löfgren's syndrome is recognized as the combination of erythema nodosum, bilateral hilar adenopathy, and usually arthritis or arthralgias, although a host of other signs and symptoms may coexist. It is considered to be a variant of sarcoidosis; however the distinction between the two entities is important, because it has significant bearing on the treatment and prognosis for the patient. One key to the diagnosis of Löfgren's syndrome is the recognition of erythema nodosum, as a significant percentage of all patients with erythema nodosum are diagnosed with Löfgren's syndrome.

The treatment of most patients with Löfgren's syndrome is conservative, with the use of nonsteroidal anti-inflammatory drugs and sometimes bed rest. Corticosteroids are sometimes needed. The prognosis of patients with Löfgren's syndrome is excellent, with a higher remittance rate and a lower relapse rate than in those with sarcoidosis.

**HP**

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