SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2012; 29; 128-131

Are clinical features in Löfgren's syndrome-related erythema nodosum different from idiopathic erythema nodosum?

S. Dönmez[1], B. Kısacık[2], Ö.N. Pamuk[1], Y. Pehlivan[2], E. Aydoğdu[1], Ö.A. Yürekli[3], A.M.Onat[2]

[1] Department of Rheumatology, Trakya University Medical Faculty, Edirne-Turkey; [2] Department of Rheumatology, Gaziantep University Medical Faculty, Edirne-Turkey; [3] Department of Internal Medicine, Sema Hospital, Edirne-Turkey

Abstract. *Background and Objectives:* We retrospectively evaluated acute sarcoidosis (Löfgren's syndrome) patients diagnosed at 2 centers and compared the clinical features of Löfgren's syndrome (LS) related erythema nodosum (EN) to patients with idiopathic IEN who were diagnosed within the same time frame. *Methods:* Thirty patients (10 males, 20 females) who were diagnosed with LS and were being followed up for the last 8 years at 2 centers were included. Thirty patients (4 males, 26 females) who were admitted to the rheumatology outpatient clinics for IEN during that time period were taken as controls. The clinical and laboratory features at the initial admission, treatment modalities and response were recorded. *Results:* Twentyfour (80%) patients with LS related EN had arthritis and/or arthralgia. Fifteen of them had only findings of periarticular ankle inflammation and 4 had polyarthritis. When LS related EN patients were compared to IEN patients, the former group had more arthritis and/or arthralgia ($p<0.001$), leucocytosis ($p=0.02$), lymphopenia ($p=0.005$) and thrombocytosis ($p=0.05$), and higher ESR ($p=0.02$). Twentyfive (83.3%) patients with LS related EN were administered oral corticosteroids. In 21 patients, hilar lymphadenopathy disappeared on control chest x-ray and CT; in 3 patients, minimal residual lymph node enlargement was persistent. During a median follow-up of 54 months (range: 10-84 months), none of the LS related EN patients had clinical relapse. *Conclusions:* Apart from BHL, arthritis and/or arthralgia especially periarticular ankle inflammation is the feature which could be used to differentiate LS related EN from IEN. There is more need for steroids in LS patients and the symptoms quickly resolve with steroids. *(Sarcoidosis Vasc Diffuse Lung Dis 2012; 29: 128-131)*

Key words: Löfgren's syndrome, sarcoidosis, erythema nodosum

Introduction

The acute form of sarcoidosis is also known as Löfgren's syndrome (LS) and the characteristic clinical features are bilateral hilar lymphadenopathy (BHL) together with erythema nodosum (EN) (1-3) Other important features are arthritis and arthralgia; and the patients generally go to rheumatology clinics. Arthritis, arthralgia especially around the ankle joint is a very frequent finding (1, 2, 4).

Erythema nodosum is a frequent clinical finding and there are many diseases in its differential diagnosis. Many series about EN have been reported (5,6); however, there is no data in literature about whether there are any distinguishing features between sarcoidosis-related EN and IEN.

In this study, we retrospectively evaluated the clinical features, treatments and outcome in LS re-

Received: 26 December 2011
Accepted after Revision: 12 June 2012
Correspondence: Dr. Ömer Nuri Pamuk
Eski Yildiz Cad. Park Apt. No:22 Daire: 18
34349, Beşiktaş, Istanbul-Turkey
Tel. 0090 284 2369796
Fax 0090 284 2352730
E-mail: omernpamuk@yahoo.com

lated EN and IEN patients diagnosed at 2 centers. In addition, we compared their features to IEN patients who were admitted within the same time period.

Methods

Thirty patients (10 males, 20 females) diagnosed with acute sarcoidosis at 2 centers within the last 8 years were evaluated. The diagnostic criteria for LS included EN, arthritis and/or arthralgia together with unilateral or bilateral or right paratracheal adenopathy –with or without pulmonary parenchymal involvement. The control group included 30 patients (4 males, 26 females) with IEN which was not associated with any other disease or drug intake and who were admitted to rheumatology outpatient clinics.

Erythema nodosum was defined as a cutaneous reaction consisting of inflammatory, tender, erythematous nodular lesions, located primarily over the extensor surfaces of the lower extremities. All patients with IEN were questioned in detail and a thorough physical examination including articular involvement was performed, especially, in search for disorders leading to EN. Involved joints were recorded. Periarticular ankle inflammation was defined as a soft tissue inflammation surrounding the ankle and not a true arthritis. In addition, all patients were questioned about common cold or flu in the preceding week; about drug intake in the preceding month, respiratory symptoms, oral aphthae and chronic diarrhea.

Thorax CT, anti-streptolysin O and tuberculin skin tests, throat and sputum cultures were obtained all of the patients. Patients with Behçet's syndrome, poststreptococcal EN, inflammatory bowel disease, tuberculosis were excluded from the study. Patients with IEN had no significant chest x-ray and thorax CT findings.

For the classification of chest x-rays, the criteria suggested by De Remee was used (7). According to these criteria, stage I consisted of BHL; stage II, BHL plus pulmonary parenchymal involvement; stage III, pulmonary parenchymal involvement without BHL. When there was doubtful hilar lymphadenopathy on chest x-ray, it was confirmed by thorax CT. Twentyfive (83.3%) patients with LS had BHL on chest x-ray, one had right paratracheal enlargement. The chest x-ray of 4 patients (13.3%) revealed doubtful hilar enlargement. The presence of BHL in these patients was confirmed by thorax CT. Thorax CT was available for evaluation in 25 patients. Only 2 patients had findings of pulmonary parenchymal involvement compatible with stage II disease. Transbronchial biopsy was performed in 8 patients, and histopathologic examination showed noncaseating granuloma in only 7 of them.

The clinical features, whole blood count, biochemical tests, chest x-ray or thorax CT, and antibody results of all subjects were obtained from hospital files. The treatment modalities used for acute sarcoidosis patients and their results were recorded down. For those patients who were unable to attend outpatient clinic visits, follow-up data were obtained by phone calls. Steroid therapy was given to patients with stage II or more, extrapulmonary involvement and refractory symptoms like EN or fever to NSAIDs.

Relapse was defined as the reappearance of the disease after suppression of therapy and recurrence was defined as the reappearance of the disease after a spontaneous remission.

For statistical analysis of data, chi-square and unpaired t tests were used.

Results

The general clinical features of patients with LS related EN are seen on table 1. Four patients with LS related EN had uveitis, one had bone cyst, and one had hypercalcemia. Skin lesions other than EN were detected in 4 patients. One of them had a scar lesion and 3 had maculopapular lesions. ANA was positive in 3 patients, anti-dsDNA in one patient, and RF was positive in 2 patients.

When patients with LS related EN were compared to those with IEN, the former group had more frequent arthritis and/or arthralgia ($p<0.001$), leucocytosis ($p=0.02$), lymphopenia ($p=0.005$), thrombocytosis ($p=0.05$), and higher mean ESR ($p=0.02$). In addition, there were more male patients in the acute sarcoidosis group when compared to the IEN group ($p=0.067$) (Table 2).

Twentyfour (80%) subjects had arthritis and/or arthralgia. Fifteen of them had only signs of periarticular ankle inflammation. Periarticular ankle inflammation was significantly more common in LS

Table 1. General clinical features of acute sarcoidosis.

	n (%)
M/F	10/20
Uveitis	4 (13.3)
Other skin lesion	4 (13.3)
Hilar lymphadenopathy in chest x-ray	25 (83.3)
Positive transbronchial biopsy	7 (23.3)
Arthritis and/or arthralgia	24 (80)
Stage I	28 (93.4)
Stage II	2 (6.6)
Steroid usage	25 (83.3)
Azathioprin usage	4 (12.9)
Methotrexate usage	1 (3.3)
Hydroxychloroquine usage	1 (3.3)

related EN group than in IEN patients (p<0.001). There was polyarthritis in 4 LS related EN patients. Three LS related EN patients presented with asymmetric lower extremity oligoarthritis and 2 patients presented with knee monoarthritis. Arthritis and/or arthralgia were more common in female (18/20, 90%) patients than in male (6/10, 60%) patients (p=0.14).

All patients were administered different doses of steroids. As the complaints of 25 (83.3%) Löfgren patients did not regress with NSAIDs, 20-60 mg oral steroids were administered. There were significantly less patients who needed steroids in the IEN group than in the LS group (33.3%, p<0.001). Corticosteroids were tapered to nearly 5 mg within 3-4 months and discontinued mostly within 6 months or rarely in 1 year. For patients who could not tolerate the discontinuation of steroids, azathioprine was given in 4 cases, methotrexate in one case, and hydroxychloroquine in one case. Only one IEN patient used steroid sparing therapy because of requirement of high dose steroid to control symptoms.

One year later, the follow-up for 24 LS patients was available. Control chest x-ray and CT showed the disappearance of hilar lymphadenopathy in 21 cases, and persistence of minimal residual hilar lymph nodes in 3 cases. After a median follow-up of 54 months (range:10-84 months), no clinical relapse or recurrence were observed in any of the patients with LS. Twenty-one patients with IEN were followed regularly for at least a year, and 9 patients were lost to follow-up. All of them are symptom-free without any therapy.

Discussion

In our study, we compared features of our LS related EN patients with IEN patients. We observed that periarticular ankle inflammation, systemic fever, leucocytosis, lymphopenia, and thrombocytosis were more frequently associated with LS related EN. In addition, elevation in ESR was more prominent in patients with LS related EN. There were more male patients in the LS related EN group even if this was not significant. As a result, the chest x-rays of patients who are admitted with EN should be obtained and they should be evaluated for sarcoidosis.

Löfgren's syndrome is an acute and relatively frequent form of sarcoidosis. Series of general sarcoidosis patients reported from different geographic regions reported that the clinical presentation in

Table 2. The comparison of clinical features of acute sarcoidosis and idiopathic erythema nodosum

	LS related EN	IEN	p
n	30	30	-
Male, n (%)	10 (33.3)	4 (13.3)	0.067
Age (year)	41.8±11.9	42.1±13.9	0.76
Arthritis and/or arthralgia, n (%)	24 (80)	9 (30)	<0.001
Periarticular ankle inflammation, n (%)	15 (50)	2 (6.7)	<0.001
Fever (38°C), n (%) 2	1 (70) 1	2 (40) 0	.02
Steroid usage, n (%)	25 (83.3)	10 (33.3)	<0.001
Steroid sparing agent, n (%)	6 (20)	1 (3.3)	0.1
ESR (mm/hr)	69.9±33.2	43.7±28.3	0.002
CRP (mg/dl)	5.5+3.8	4.2+5.3	0.29
WBC >10.000/mm^3	18 (60)	9 (30)	0.02
Hgb (g/dl)	12.1±1.9	12.5±1.7	0.49
Platelet >450.000/mm^3	7 (23.3)	1 (3.3)	0.05
Lymphocyte <1500/mm^3	11 (36.7)	2 (6.7)	0.005

LS: Löfgren's syndrome, IEN: idiopathic erythema nodosum, ESR: erythrocyte sedimentation rate

8.4% to 50% of patients was acute sarcoidosis (1,2,6). One series from our country stated that 19.1% of sarcoidosis patients presented with Löfgren's syndrome (1). It was reported that LS patients were more likely to be young (1). The mean age of our patients was similar to general LS series; but, it was not different from IEN.

The complaint which most frequently made patients refer to rheumatology outpatient clinics was arthritis. Especially, arthralgia and arthritis of the ankle joint was very frequent in our LS related EN patients. Previously published series also reported that inflammation of the ankles was a feature of LS (1, 8, 9). Arthritis and arthralgia were a bit more frequent in our patients than in other series. A contributing factor to this might have been the evaluation of LS patients who were admitted to a rheumatology clinic.

Leucocytosis and lymphopenia were significantly more frequent in LS patients than in patients with IEN. One study evaluated bone marrow involvement in sarcoidosis and reported that lymphopenia was more frequent in sarcoidosis (10). We did not perform bone marrow evaluation in this study. The frequencies of fever and high ESR were also higher in LS related EN group than in IEN patients. The inflammatory response triggered by LS related EN was probably more prominent.

Because of the continuation of symptoms like fever, EN and high ESR with NSAIDs, steroids were administered to most patients with LS, in spite of the reported drawbacks with steroids. In the IEN group, the frequency of steroid usage was less frequent than in LS patients. Symptoms like fever and EN regressed quickly after steroid therapy in most of the patients. In addition, hilar lympadenopathy regressed within one year. A higher rate of relapse which was feared because of steroid administration was not observed within a 54-month median follow-up. The prognosis in LS is quite good when compared to chronic sarcoidosis and spontaneous remission is frequent (9, 11, 12). Therefore, it is not usually necessary to administer long-term therapy. In our patients, steroids were generally tapered minimal dose within 3-4 months and discontinued after 6 months. There were indications to use steroid-sparing drugs in only 6 patients.

The diagnosis of acute sarcoidosis was confirmed histopathologically in only 7 of our patients. There was no need for biopsy in other patients with typical clinical findings and presentation. All our patients had good response to therapy, and there was no serious relapse in any of them. Therefore, we conclude that there might be no need for biopsy if the clinical presentation is typical. One study revealed that broncoscopic biopsy yielded the diagnosis in 60% of cases, and transbronchial fine needle biopsy in 53% of cases in stage I patients; when the two methods were combined the probability of a positive result rose up to 83% (11,13).

We observed that LS related EN patients had more frequent joint involvement especially periarticular inflammation, than IEN patients. In addition, lymphopenia and inflammatory response findings like fever, leucocytosis and high level ESR were more prominent in LS related EN patients.

References

1. Yanardag H, Pamuk ON, Karayel T. Löfgren syndrome in Turkey. Intern Med J 2003; 33: 535-7.
2. Ohta H, Tazawa R, Nakamura A, et al. Acute-onset sarcoidosis with erythema nodosum and polyarthralgia (Löfgren's syndrome) in Japan: a case report and a review of the literature. Intern Med 2006; 45: 659-62.
3. Grunewald J, Eklund A. Löfgren's syndrome. Human leucocyte antigen strongly influences the disease course. Am J Respir Crit Care Med 2009; 179: 307-12.
4. Mañá J, Montero A, Vidal M, Marcoval J, Pujol R. Recurrent sarcoidosis: a study of 17 patients with 24 episodes of recurrence. Sarcoidosis Vasc Diffuse Lung Dis 2003; 20: 212-21.
5. Mert A, Kumbasar H, Ozaras R, et al. Erythema nodosum: an evaluation of 100 cases. Clin Exp Rheumatol 2007; 25: 563-70.
6. Kisacik B, Onat AM, Pehlivan Y. Multiclinical experiences in erythema nodosum: rheumatology clinics versus dermatology and infection diseases clinics. Rheumatol Int 2012 Mar 24. [Epub ahead of print]
7. DeRemee RA. The roentgenographic staging of sarcoidosis. Historic and contemporary perspectives. Chest 1983; 83: 128-33.
8. Mañá J, Gómez-Vaquero C, Salazar A, Valverde J, Juanola X, Pujol R. Periarticular ankle sarcoidosis: a variant of Löfgren's syndrome. J Rheumatol 1996; 23: 874-7.
9. Mañá J, Gómez-Vaquero C, Montero A, et al. Löfgren's syndrome revisited: a study of 186 patients. Am J Med 1999; 107: 240-5.
10. Yanarda H, Pamuk GE, Karayel T, Demirci S. Bone marrow involvement in sarcoidosis: an analysis of 50 bone marrow samples. Haematologia (Budap) 2002; 32: 419-25.
11. Mushlin SB, Drazen JM, Samuels MA, Mark EJ. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 33-2002. A 28-year-old woman with ocular inflammation, fever, and headache. N Engl J Med 2002; 347: 1350-7.
12. Baughman RP, Winget DB, Lower EE. Methotrexate is steroid sparing in acute sarcoidosis: results of a double blind, randomized trial. Sarcoidosis Vasc Diffuse Lung Dis 2000; 17: 60-6.
13. Morales CF, Patefield AJ, Strollo PJ Jr, Schenk DA. Flexible transbronchial needle aspiration in the diagnosis of sarcoidosis. Chest 1994; 106: 709-11.