Sex-Specific Manifestations of Löfgren's Syndrome

Johan Grunewald and Anders Eklund

Division of Respiratory Medicine, Department of Medicine, Karolinska Institutet; and Karolinska University Hospital Solna, Stockholm, Sweden

Motivation: **It has been debated whether patients need to have erythema nodosum to be classified as having Löfgren's syndrome. In this study, we have therefore in detail evaluated and compared a large number of patients with an acute onset of sarcoidosis and bilateral hilar lymphadenopathy (BHL), with or without erythema nodosum (EN). This study is important because it may lead to a more accurate definition of Löfgren's syndrome, and an exact phenotype of patients is crucial in modern medical research.**

Background: **Löfgren's syndrome is commonly regarded as a distinct clinical entity.**

Methods: **We have in detail evaluated a large group of patients (n = 150) with an acute onset of sarcoidosis with BHL, in most cases with fever, EN, and/or bilateral ankle arthritis or periarticular inflammation. Within this group, 87 patients had EN (EN positive), whereas 63 were without EN (EN negative), though with distinct symmetric ankle inflammation.**

Results: **EN-positive and EN-negative patients were identical in every aspect except that there were significantly more women in the EN-positive group: 58 women (67%) in the EN-positive group compared with only 17 (27%) women in the EN-negative group ($p < 0.0001$). In all other aspects, such as age, smoking habits, seasonal clustering of disease onset, rate of positive biopsies, chest radiography, pulmonary function, bronchoalveolar lavage cell distributions including the typically increased CD4/CD8 ratio, and clinical development of the disease, the EN-positive and EN-negative groups were close to identical. The two groups were also identically strongly associated with HLA-DRB1*0301/DQB1*0201, with 60 (69.0%) and 44 (69.8%) patients having this particular HLA type in the EN-positive and EN-negative groups, respectively. Such patients recovered to the same degree—that is, at almost 100%.**

Conclusions: **We conclude that manifestations of Löfgren's syndrome differ between men and women, with EN found predominantly in women, whereas a marked periarticular inflammation of the ankles or ankle arthritis without EN is seen preferentially in men.**

Keywords: HLA; Löfgren's syndrome; sarcoidosis; sex

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

It has been debated whether patients need to have erythema nodosum to be classified as having Löfgren's syndrome.

What This Study Adds to the Field

The manifestations of Löfgren's syndrome differ between men and women, with erythema nodosum being found predominantly in women.

Sarcoidosis is a granulomatous disorder characterized by distinct immunopathologic features, typically with lung-accumulated and activated $CD4^+$ Th1 cells (1, 2). A genetic predisposition to sarcoidosis is suggested by different clinical appearances in distinct ethnic groups and by familial clustering (3, 4). One distinct clinical phenotype in a subgroup of patients was originally described in 1952 by the Swedish pulmonologist Sven Löfgren. Until then, erythema nodosum (EN) was usually seen as a sign of infection with *Mycobacterium tuberculosis* or with β-hemolytic streptococci, but Dr. Löfgren was the first to describe that the combination of EN and bilateral hilar lymphadenopathy (BHL) was a manifestation of acute sarcoidosis (5, 6). Moreover, Dr. Löfgren in subsequent reports pointed out the favorable prognosis for these patients (7). The syndrome was later named "Löfgren's syndrome" and has come to include patients with an acute onset of the disease with BHL, fever, and EN in some reports, and with the addition of patients with BHL, fever, and ankle arthritis or periarticular inflammation in other reports (8, 9). Löfgren's syndrome is regarded as a distinct clinical entity with a characteristic beneficial disease outcome, often with complete spontaneous resolution.

A large number of HLA class I and II alleles have been reported to be overrepresented in sarcoidosis, and especially HLA-DR3 was early recognized to associate with sarcoidosis in general and in particular with acute manifestations of the disease, such as EN and ankle arthritis or periarticular inflammation (i.e., features linked to a good prognosis) (10–13). Subsequent studies have corroborated a strong association with specific HLA alleles (14) (i.e., HLA-DRB1*0301), and in such patients identified a typical lung accumulation of $CD4^+$ T cells expressing a particular T-cell receptor (TCR) for antigen, AV2S3, suggesting the presence of a specific antigen (15).

However, despite the distinct clinical, genetic (HLA), and immune characteristics of this patient group, there is still a controversy whether EN is strictly required for classification as Löfgren's syndrome. Our own clinical impression, from a large number of patients with sarcoidosis attending our outpatient clinic, which specializes in interstitial pulmonary diseases, is that patients with acute sarcoidosis with BHL and ankle arthritis or distinct periarticular inflammation but without EN are similar to those with EN regarding other clinical manifestations and disease outcome. We thus hypothesized that both of these patient groups should be included in the definition of Löfgren's syndrome. We therefore evaluated 150 Scandinavian patients attending the Division of Respiratory Medicine at Karolinska University Hospital, Solna, between 1979 and 2005, with an acute onset of sarcoidosis with BHL. Among these patients, 87 cases had EN (EN positive), whereas 63 cases were without EN (EN negative) but had marked periarticular inflammation or arthritis of the ankles.

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Correspondence and requests for reprints should be addressed to Johan Grunewald, M.D., Ph.D., Department of Medicine, Division of Respiratory Medicine, Karolinska Institutet Lung Research Laboratory L4:01, Karolinska University Hospital Solna, S-171 76 Stockholm, Sweden. E-mail: johan.grunewald@ki.se

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METHODS

Study Subjects

All patients (n = 150) attended the outpatient clinic at the Karolinska University Hospital, Solna, Sweden, and were monitored for at least 2 yr. Although the vast majority of patients (n = 121) were consecutively seen and monitored by one of the authors, data on a few patients were obtained retrospectively from patient records only. All patients had an acute onset of the disease typical for Löfgren's syndrome, in most cases referring to a specific date, with symptoms including BHL, fever, bilateral ankle arthritis or distinct periarticular inflammation, and/or EN. Patients were carefully examined to exclude other causes of pulmonary inflammation, such as hypersensitivity pneumonitis or manifestations of systemic diseases, and diagnosed through their typical clinical manifestations, positive biopsies, or elevated CD4/CD8 ratios in bronchoalveolar lavage fluid (BALF).

All patients were further characterized by conventional chest radiographic staging (stage I, BHL, or stage II, BHL with parenchymal infiltrates) at disease onset, and by bronchoscopy, which was performed in 118 patients. BALF cell differential counts were obtained from 104 and BALF CD4/CD8 ratios evaluated in 98 patients. Pulmonary function tests (PFTs; VC, $FEV_{1.0}$, and diffusing capacity of carbon monoxide [D_{LCO}]) were performed within 6 mo after disease onset in 134 patients. Thirteen (14.9%) EN-positive patients and 12 (19.0%) EN-negative patients were treated with oral steroids at the time of diagnosis.

All patients were categorized as either having a nonresolving disease, defined through signs of ongoing disease 2 yr after disease onset and including those with a chronic stable as well as those with a chronic progressive disease, or as having a resolving disease, with no signs of sarcoidosis after 2 yr of disease.

All included subjects gave their informed consent for participation in the study, which was approved by the local ethics committee at the Karolinska University Hospital.

BAL, BALF Cell Preparation, and Flow Cytometry

BAL was performed as described previously (16), and BALF cells were separated and analyzed (CD4/CD8; AV2S3 staining) in a flow cytometer as described (17).

PFTs

FEV_1 and VC were performed using a SensorMedics 2400 spirometer (SensorMedics Ltd., BV Bitthoven, The Netherlands). D_{LCO} was analyzed by single-breath technique. The results of VC, FEV_1, and D_{LCO} are presented as % predicted (18) (Table 1).

Preparation of DNA from Whole Blood Cells and HLA Typing

Whole blood was used for genomic DNA extraction. HLA-DRB1 and HLA-DQB1 alleles were analyzed with the polymerase chain reaction–sequence-specific primer technique (19, 20).

Statistical Analyses

An unpaired *t* test was used to analyze and compare data on age, pulmonary function, and BAL parameters between subjects. Differences between groups regarding sex and HLA-DRB1 alleles were tested using a χ^2 analysis. Spearman's ranking test was used for analyzing seasonal clustering. A p value of less than 0.05 was considered significant. The statistical analyses were done using the GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, CA).

RESULTS

Patient Characterization

All 150 patients had an acute onset of the disease, with BHL, marked periarticular inflammation or arthritis of the ankles, and/or EN, and in most cases fever, and they were accordingly classified as having Löfgren's syndrome. Eighty-seven patients had EN (EN positive), and in 67 (79.8%) of these patients, bilateral ankle arthritis appeared concomitantly. In 63 patients, there was no history of EN, but all had distinct signs of periarticular inflammation or arthritis of the ankles. The median age was 37 (range, 24–71) yr in the entire group, with no difference in the EN-positive group (38 [24–61] yr) or the EN-negative group (37 [25–71] yr). There were significantly more women in the EN-positive group, with 58 women (67%) in this group compared with only 17 (27%) in the EN-negative group ($p < 0.0001$) (Figure 1). The female dominance among EN-positive patients was also pronounced in patients older than 45 yr, with 84% women, in contrast to only 29% women in the EN-negative group ($p < 0.001$). Most patients were never-smokers, 109 (72.7%), whereas 14 (9.3%) were ex-smokers (since > 2 yr) and 27 (18%) patients were current smokers, with a similar distribution in EN-positive and EN-negative patients. In support of the diagnosis, biopsies were positive in 44 of 129 samples (34.1%): 25 (33.3%) in the EN-positive group and 19 (35.2%) in the EN-negative group.

Chest radiographic staging showed that all patients had BHL. Thirty-four patients (22.7%) had BHL together with pulmonary infiltrates (stage II), which was close to identical in EN-positive and EN-negative patients (Table 1). PFTs showed normal volumes, and slightly reduced D_{LCO}, with similar values in the two groups (Table 1). In the entire patient group, 27.9% of the patients had a D_{LCO} value less than 80% of predicted, which was similar in the two subgroups, with 29.3% in the EN-positive group and 25.9% in the EN-negative group.

Bronchoscopy with BAL was performed in 118 patients, showing, as expected, signs of T-cell alveolitis with increased relative numbers of BALF lymphocytes (20.2 [median]; range,

TABLE 1. PATIENT CHARACTERIZATION AT DISEASE ONSET

	All Patients	EN Positive	EN Negative
Chest X-ray stage			
Stage I	116 (77.3%)	67 (77.0%)	49 (77.8%)
Stage II	34 (22.7%)	20 (23.0%)	14 (22.2%)
Lung function tests*			
VC, % predicted (n = 130)	98.5 (60.0–135)	99.0 (69.0–135)	97.5 (60.0–134)
$FEV_{1.0}$, % predicted (n = 134)	98.0 (62.0–131)	98.0 (70.0–125)	98.0 (62.0–131)
D_{LCO}, % predicted (n = 127)	87.0 (52.0–126)	84.5 (52.0–126)	89.0 (63.0–123)
BAL cell data			
Relative numbers of lymphocytes in BAL (n = 104), %*	20.2 (3.0–66.0)	19.3 (3.0–61.0)	21.8 (3.0–66.0)
Relative numbers of $CD4^+$ BAL T cells expressing AV2S3, %*	29.8 (11.4–44.0)	30.0 (14.0–40.2)	29.0 (11.4–44.0)
BAL CD4/CD8 ratio (n = 98)*	6.8 (0.8–32)	7.0 (0.8–32)	6.6 (1.0–20)
Number of patients with BAL CD4/CD8 ratio > 4.0	72 (73.5%)	42 (75.0%)	30 (71.4%)

Definition of abbreviations: BAL = bronchoalveolar lavage; D_{LCO} = carbon monoxide diffusing capacity; EN = erythema nodosum.
* Values listed for these categories are shown as median values with range (minimum to maximum).

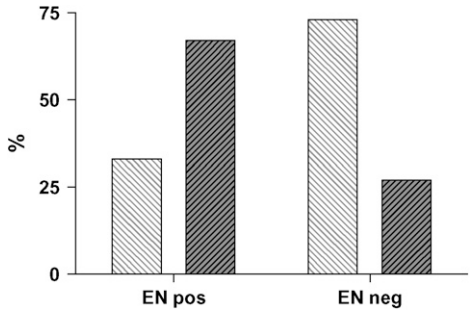

Figure 1. Sex difference. Relative numbers of women and men in acute sarcoidosis patients with EN (EN pos) and in patients without EN (EN neg). *Light-gray hatched bars*, males; *dark-gray hatched bars*, females.

3.0–66%), with similar values in EN-positive and EN-negative patients (Table 1). An elevated BALF CD4/CD8 ratio (≥ 4.0) was found in 72 of 98 samples (73.5%), again with similar results in EN-positive and EN-negative patients (Table 1). Median values of the CD4/CD8 ratios were also close to identical in EN-positive and EN-negative patients (Table 1). It is known that, among DRB1*0301/DQB1*0201-positive patients with sarcoidosis, $CD4^+$ BALF T cells expressing TCR AV2S3 accumulate in the lungs (15). In this population (n = 45), 29.8% (median value) of the $CD4^+$ BALF T cells expressed AV2S3, with close to identical values in the EN-positive and EN-negative groups (Table 1).

There was a preference for disease onset in the first months of the year, with a significant negative correlation between numbers of patients with disease onset and time over the calendar year for both EN-positive (Spearman's rho = -0.777, $p < 0.01$) and EN-negative patients (Spearman's rho = -0.686, $p = 0.01$). In particular, disease onset was common in January (16.7% of all patients), April (13.3%), and May (13.3%) (Figure 2).

Disease Outcome and HLA-DRB1*0301/DQB1*0201 Alleles

Disease outcome was evaluated in 128 of the patients, categorizing them into resolving or nonresolving patients depending on signs of disease activity 2 yr after disease onset. Four of these 128 patients (3.1%) had recurrent episodes of the disease, and were not categorized. One hundred and eight (84.4%) patients in the entire patient group had a resolving disease. In EN-positive patients, 66 (85.7%) had a resolving disease, similar to the number in the EN-negative group (42 [82.4%]).

The DRB1*0301/DQB1*0201 alleles, which are in strong linkage disequilibrium and cannot be separated in this population, have previously been shown to associate with Löfgren's syndrome and a beneficial disease outcome in Scandinavian patients with sarcoidosis (12–14). One hundred and four (69.3%) patients were positive for DRB1*0301/DQB1*0201, with close to identical distribution frequencies in EN-positive and EN-negative patients (60 [69.0%] and 44 [69.8%], respectively). Almost every DRB1*0301/DQB1*0201-positive patient had a resolving disease, 51 of 52 (98.1%) in the EN-positive and 35 of 35 (100%) in the EN-negative group. For comparison, only 22 (55.0%) of the DRB1*0301/DQB1*0201-negative patients (n = 40) had a resolving disease.

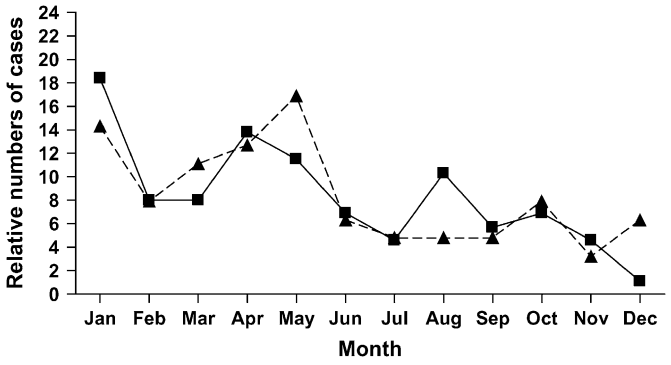

Figure 2. Seasonal distribution. Relative numbers of patients (EN pos and EN neg are shown separately) in relation to the month of disease onset. *Squares* on *solid line*, EN pos; *triangles* on *dashed line*, EN neg.

DISCUSSION

A thorough clinical phenotyping has become increasingly important in modern medical translational research, and it is therefore necessary to exactly define clinical syndromes. One example is Löfgren's syndrome, originally described by the Swedish doctor Sven Löfgren, who noticed that the association of EN and BHL was a distinct sign of acute sarcoidosis (5, 6). It was later questioned whether other patients with acute sarcoidosis, but without EN, also should be included in the same syndrome (21). In the present study, we thoroughly evaluated and compared two subgroups of patients fulfilling the criteria for acute sarcoidosis. Although all patients had an acute onset of the disease with BHL, only some had EN (EN positive), and the remaining EN-negative patients were distinguished by marked periarticular inflammation or arthritis of the ankles.

The two patient subgroups were of similar age and had similar smoking habits, and in both groups, approximately one-third of the mucosal lung biopsies showed granulomas, which may reflect a similar degree of granuloma formation in the lungs. The disease onset, which most often was specified to one particular day, was similarly clustered to the first months of the year, with a significantly reduced incidence for both groups along the calendar year. A seasonal clustering indicates the influence of environmental factors—for example, viral infections—which might trigger the disease. The high incidence in January, April, and May might allow speculations on an increased exposure for microorganisms after Christmas and Eastern holidays, respectively, as a result of social gatherings. The hypothesis of antigen exposure goes well with the lung-accumulated T cells expressing a particular TCR (AV2S3). The similar clustering for the two patient subgroups is also in line with the suggestion that EN-positive and EN-negative patients have different manifestations of the same disease, with the same etiology. Several previous studies on acute sarcoidosis with EN, as well as on acute sarcoid arthritis, reported a seasonal clustering to the spring months (22–25).

All patients presented, per definition, with BHL, but, in addition, 22.7% had pulmonary infiltrates (stage II), a finding similar to previous reports (8, 25), and with no difference between the two subgroups. PFTs at onset revealed normal volumes and a tendency to a reduced D_{LCO}, in congruence with other reports on patients with Löfgren's syndrome (8). The EN-pos and EN-negative patients also had close to identical lung inflammatory responses, as reflected by the same numbers of lung-accumulated T cells (i.e., T-cell alveolitis), as well as similar numbers of $CD4^+$ T cells in the BALF. The equal numbers of lung-accumulated TCR AV2S3 expressing $CD4^+$ T cells indicate an identical immune response toward the same antigen. The outcome of the disease was similarly good in the two groups, with around 85%

of the patients having a resolving disease, comparable to previous studies (8, 25).

Close to 70% of the patients in both groups were DRB1*0301/DQB1*0201 positive, which was dramatically more than in normal, healthy Scandinavian control subjects, where 17% have these alleles (14). A recent Dutch study on patients with sarcoid arthritis, corresponding to our EN-negative subgroup of patients, also found a strong association with this particular HLA type, 78% in the patients versus 19% in healthy control subjects (25). In our study, the disease outcome in DRB1*0301/DQB1*0201-positive patients was identically remarkably good in both groups, with close to 100% patient recovery. On the contrary only about half of DRB1*0301/DQB1*0201-negative patients with Löfgren's syndrome recovered within 2 yr, and such patients should therefore be monitored more closely and possibly be treated at an early stage.

Patients with an acute onset of the disease, BHL, ankle arthritis or marked periarticular inflammation of the ankles, but without EN have been regarded as having a disease of uncertain relationship to sarcoidosis. In Dr. Löfgren's own early studies on acute sarcoidosis, he discussed "the bilateral hilar lymphoma syndrome," in which he included both EN and joint pains/swollen joints (5, 6). Subsequently, based on clinical observations, the EN-negative patients were suggested to have a variant of Löfgren's syndrome (26, 27). These important clinical observations have been substantiated more recently by Mana and colleagues (21).

With our present study, adding inflammatory, immune, and genetic (HLA) parameters to these clinical studies, we can now definitively establish that manifestations of Löfgren's syndrome differ among women, who preferentially have EN often together with ankle arthritis or periarticular inflammation, and men, who do not have EN but have marked periarticular inflammation or arthritis of the ankles, sometimes referred to as acute sarcoid arthritis. EN is considered to be a hypersensitivity response to a wide range of inciting factors, resulting from the deposition of immune complexes (28, 29). EN may be associated with, besides sarcoidosis, a broad variety of diseases, such as infections, rheumatologic systemic disorders, inflammatory bowel diseases, medications, and autoimmune disorders. Dr. Löfgren and, more recently, the ACCESS study (A Case-Control Etiologic Study of Sarcoidosis) (30) pointed out a predominance of women among patients with EN; EN has been estimated to be three to six times more frequent in women (i.e., also when associated with diseases other than sarcoidosis) (31). Before puberty, the incidence is roughly equal, indicating that sex hormones are important for developing EN (32, 33). However, in our patients, the dominance of women in the EN-positive group remained in patients older than 45 yr.

We conclude that women are significantly overrepresented among patients with acute sarcoidosis with EN, whereas men with the same acute sarcoidosis syndrome instead generally present without EN but with signs of bilateral ankle arthritis. The two groups are identical with respect to clinical aspects such as pulmonary function, seasonal clustering, a strong tendency to a spontaneous recovery, inflammatory parameters, specific immune reactions, and the strong association with HLA-DRB1*0301/DQB1*0201. Both subgroups should therefore be included in the entity Löfgren's syndrome and monitored in an equal way, and be expected to have the same favorable outcome. Thus, patients with an acute onset of the disease, most commonly with fever, and with BHL, EN, and/or ankle arthritis or marked periarticular inflammation of the ankles have, by this definition, Löfgren's syndrome.

Conflict of Interest Statement: Neither author has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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References

1. Newman LS, Rose CS, Maier LA. Sarcoidosis. *N Engl J Med* 1997;336: 1224–1234.
2. Muller-Quernheim J. Sarcoidosis: immunopathogenetic concepts and their clinical application. *Eur Respir J* 1998;12:716–738.
3. Luisetti M, Beretta A, Casali L. Genetic aspects in sarcoidosis. *Eur Respir J* 2000;16:768–780.
4. Rybicki BA, Iannuzzi MC, Frederick MM, Thompson BW, Rossman MD, Bresnitz EA, Terrin ML, Moller DR, Barnard J, Baughman RP, *et al*. Familial aggregation of sarcoidosis: A Case-Control Etiologic Study of Sarcoidosis (ACCESS). *Am J Respir Crit Care Med* 2001; 164:2085–2091.
5. Löfgren S, Lundback H. The bilateral hilar lymphoma syndrome; a study of the relation to age and sex in 212 cases. *Acta Med Scand* 1952;142: 259–264.
6. Löfgren S, Lundback H. The bilateral hilar lymphoma syndrome: a study of the relation to tuberculosis and sarcoidosis in 212 cases. *Acta Med Scand* 1952;142:265–273.
7. Löfgren S. Primary pulmonary sarcoidosis. *Acta Med Scand* 1953;145: 425–474.
8. Mana J, Gomez-Vaquero C, Montero A, Salazar A, Marcoval J, Valverde J, Manresa F, Pujol R. Lofgren's syndrome revisited: a study of 186 patients. *Am J Med* 1999;107:240–245.
9. Grunewald J, Eklund A, Olerup O. Human leukocyte antigen class I alleles and the disease course in sarcoidosis patients. *Am J Respir Crit Care Med* 2004;169:696–702.
10. Brewerton DA, Cockburn C, James DC, James DG, Neville E. HLA antigens in sarcoidosis. *Clin Exp Immunol* 1977;27:227–229.
11. Smith MJ, Turton CW, Mitchell DN, Turner-Warwick M, Morris LM, Lawler SD. Association of HLA B8 with spontaneous resolution in sarcoidosis. *Thorax* 1981;36:296–298.
12. Hedfors E, Lindstrom F. HLA-B8/DR3 in sarcoidosis: correlation to acute onset disease with arthritis. *Tissue Antigens* 1983;22:200–203.
13. Gardner J, Kennedy HG, Hamblin A, Jones E. HLA associations in sarcoidosis: a study of two ethnic groups. *Thorax* 1984;39:19–22.
14. Berlin M, Fogdell-Hahn A, Olerup O, Eklund A, Grunewald J. HLA-DR predicts the prognosis in Scandinavian patients with pulmonary sarcoidosis. *Am J Respir Crit Care Med* 1997;156:1601–1605.
15. Grunewald J, Janson CH, Eklund A, Ohrn M, Olerup O, Persson U, Wigzell H. Restricted V alpha 2.3 gene usage by CD4+ T lymphocytes in bronchoalveolar lavage fluid from sarcoidosis patients correlates with HLA-DR3. *Eur J Immunol* 1992;22:129–135.
16. Eklund A, Blaschke E. Relationship between changed alveolar-capillary permeability and angiotensin converting enzyme activity in serum in sarcoidosis. *Thorax* 1986;41:629–634.
17. Planck A, Eklund A, Grunewald J. Markers of activity in clinically recovered human leukocyte antigen-DR17-positive sarcoidosis patients. *Eur Respir J* 2003;21:52–57.
18. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:5–40.
19. Olerup O, Zetterquist H. HLA-DR typing by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours: an alternative to serological DR typing in clinical practice including donor-recipient matching in cadaveric transplantation. *Tissue Antigens* 1992;39:225–235.
20. Olerup O, Aldener A, Fogdell A. HLA-DQB1 and -DQA1 typing by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours. *Tissue Antigens* 1993;41:119–134.
21. Mana J, Gomez-Vaquero C, Salazar A, Valverde J, Juanola X, Pujol R. Periarticular ankle sarcoidosis: a variant of Lofgren's syndrome. *J Rheumatol* 1996;23:874–877.
22. James DG. Erythema nodosum. *BMJ* 1961;5229:853–857.
23. Badrinas F, Morera J, Fité E, Plasencia A. Seasonal clustering of sarcoidosis [letter]. *Lancet* 1989;2:455–456.
24. Glennas A, Kvien TK, Melby K, Refvem OK, Andrup O, Karstensen B, Thoen JE. Acute sarcoid arthritis: occurrence, seasonal onset, clinical features and outcome. *Br J Rheumatol* 1995;34:45–50.

25. Visser H, Vos K, Zanelli E, Verduyn W, Schreuder GM, Speyer I, Breedveld FC, Hazes JM. Sarcoid arthritis: clinical characteristics, diagnostic aspects, and risk factors. *Ann Rheum Dis* 2002;61:499–504.
26. Scadding JG. Sarcoidosis. London: Eyre & Spottiswoode Ltd; 1967.
27. Caplan HI, Katz WA, Rubenstein M. Periarticular inflammation, bilateral hilar adenopathy and a sarcoid reaction. *Arthritis Rheum* 1970;13:101–111.
28. Hedfors E, Norberg R. Evidence for circulating immune complexes in sarcoidosis. *Clin Exp Dermatol* 1974;16:493–496.
29. Jones JV, Cumming RH, Asplin CM. Evidence for circulating immune complexes in erythema nodosum and early sarcoidosis. *Ann N Y Acad Sci* 1976;278:212–219.
30. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H Jr, Bresnitz EA, DePalo L, Hunninghake G, Iannuzzi MC, Johns CJ, *et al.* Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med* 2001;164:1885–1889.
31. Orchard TR, Chua CN, Ahmad T, Cheng H, Welsh KI, Jewell DP. Uveitis and erythema nodosum in inflammatory bowel disease: clinical features and the role of HLA genes. *Gastroenterology* 2002;123:714–718.
32. Söderstrom RM, Krull EA. Erythema nodosum: a review. *Cutis* 1978;21:806–810.
33. Gordon H. Erythema nodosum: a review of one hundred and fifteen cases. *Br J Dermatol* 1961;73:393–409.