Concurrence of sarcoidosis and systemic lupus erythematosus in three patients

S. Begum
C. Li
L.R. Wedderburn
V. Blackwell
D.A. Isenberg

Departments of Rheumatology and
'Dermatology, University College London Hospital, London, UK.

Dr. Begum and Dr Li contributed equally to this work.

Please address correspondence to:
Professor David A Isenberg, Centre for Rheumatology, Department of Medicine, University College London, 40-50 Totten-
ham Street, London, W1P 9PG, UK.

E-mail: d.isenberg@ucl.ac.uk

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ABSTRACT

We present three cases of patients with systemic lupus erythematosus and sarco-
oidosis. Although both of these conditions are thought to involve autoim-
mune mechanisms they occur together only rarely. Our cases suggest that 
their concurrence may be more com-
mon than previously thought, and raise 
issues regarding the management of pa
tients with SLE. We discuss the pos-
sibility that these two diseases are either causally or mechanistically related.

Introduction

The co-existence of systemic lupus ery-
thematosus (SLE) and sarcoidosis in 
the same patient has been reported only rarely over the past 50 years. Here we 
describe three cases of patients with 
both conditions. These cases represent 
3 out of approximately 300 patients 
with SLE cared for over 22 years in 
this unit. As such they might appear to re-
present a prevalence of sarcoidosis in 
our lupus patients of 1%, a figure much 
higher than the prevalence of sarcoido-
sis in most reports.

Case 1

The first patient is a woman of mixed 
Caucasian and Afro-Caribbean de-
scent, who originally presented in 1988 
aged 28 with a rash on the arms and 
legs, breathlessness and hemoptysis. 
She admitted to lethargy and arthralgia.

A ventilation/perfusion scan confirmed 
the presence of small pulmonary em-
boli. The oral contraceptive pill was 
stopped and she was anticoagulated 
with warfarin. At that time she had 
raised antibodies to dsDNA by ELISA 
(400 IU/ml, normal <50, Sheild Dia-
gnostics, Dundee, UK), positive anti 
nuclear antibody (ANA) 1/160 (diffuse pattern), positive antimitochondrial 
antibodies at 1/160 and positive anti-
Ro antibodies. Anti neutrophil cyto-
plasmic antibodies (ANCA) and anti-
cardiolipin antibodies were negative. 
A diagnosis of SLE, fulfilling the revised 
ACR criteria (1), was made. She was ini-
itated on hydroxychloroquine and 
subsequently prednisolone, with good 
response. Her SLE remained inactive over the 
following 5 years, and she was gradu-
ally weaned off steroids. She remained 
well until April 2000, when she pre-

tented with tender raised lumps along 
the border of her left forearm just prox-
imal to the site of a superficial burn. 
There were no symptoms to suggest 
active lupus: her global BILAG (British 
Isle Lupus Assessment Group) index 
score was 4, her dsDNA and ANA titres 
at that time were 34 and 1/160 respect-
ively, and her erythrocyte sedimenta-
tion rate (ESR) was mildly elevated at 
29 mm/hr. There was no history of re-
cent infection, cough, bowel habit dis-
turbance or new drug therapy. Lupus 
profundus was suspected clinically, but 
a biopsy from the site showed a chronic 
inflammatory exudate with non-caseating 
granulomata containing foreign 
body giant cells. Stains and culture for 
acid fast bacilli and fungi were nega-
tive. A chest X-ray further revealed 
biateral hilar lymphadenopathy (BHL), 
and she was found to have a raised angio-
tensin converting enzyme (ACE) 
level of 180 U/L (range 18-50 U/L) and 
a normal serum calcium of 2.57 mmol/ 
L.

A new diagnosis of sarcoidosis present-
ing as cutaneous sarcoid was made, and 
she was started on 30 mg oral pred-
nisolone daily. She developed more 
skin lesions on the other arm and Aza-
thioprine 100 mg daily was added. 
However the lesions remained unre-
ponsive and therapy was switched to 
metothrexate 12.5 mg weekly with 
considerable benefit. To date she has 
remained stable with low dose (7.5 mg 
daily) prednisolone and oral weekly 
metothrexate. HLA typing by serology 
showed her to be: HLA - A2,B7,27, 
DR2.9 and DQ1.

Case 2

A Caucasian female had been investi-
gated age 10 for malaise, fevers and 
alopoeia and was found to have positive 
ANA but a negative ‘LE cell’ test and 
was not given any specific treatment. In 
1989 aged 21 she presented with sec-
ondary amenorrhoea and was found to 
have panhypopituitarism. A magnetic 
resonance scan showed a small lesion 
in the pituitary stalk. She was treated 
with bromocryptine and oestrogen.

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Two years later she developed repeated attacks of pan-uveitis. Further investigations showed interstitial pulmonary disease, though no hilar lymphadenopathy. She had a mildly elevated serum ACE level of 76 (range 18 to 50 U/L), serum IgM of 12 g/L (range 0.6 to 2.8) and IgG of 18.7 g/l (range 8 to 18) with no monoclonal band, and a positive Kviem test. A diagnosis of sarcoidosis was made and she was treated with oral prednisolone and topical steroid eye-drops.

One year later, in 1992, she was referred to our department for a second opinion because of her positive ANA (speckled distribution, titre initially 1/320), when further investigations revealed positive anti-Sm and RNP antibodies, a raised ESR of 67 mm/hr with a normal CRP, and low complement levels (C3 0.55 g/L normal range 0.8 to 1.6). She admitted to Raynaud’s phenomenon but no arthralgia, significant alopecia, oral ulcers, or rash. She subsequently developed raised anti ds-DNA antibodies (titre 78 IU/L) and mild lymphopaenia. The constellation of symptoms and laboratory findings now fulfilled the American College of Rheumatology (ACR) criteria for the diagnosis of SLE. Her lupus symptoms remained relatively mild and treatment with oral prednisolone (average daily dose 10mg) and a short spell of oral cyclosporin (250 mg daily) was dictated by her recurrent uveitis.

In 1997 five years after the diagnosis of SLE was made she developed hypertension and mild proteinuria (0.3 g/24 hr). Renal biopsy showed membranous change with immune deposit consistent with lupus nephritis (WHO grade 5, activity index 0, chronicity index 1). It was thought that, as the biopsy findings were so mild and she was already on oral steroids, no change of therapy was needed. Her renal function has remained stable to date. In addition she developed autoimmune thyroiditis with the presence of high titres of anti-thyroglobulin and anti-microsomal antibodies leading ultimately to hypothyroidism and necessitating daily thyroxine replacement. Her latest clinical review in 2001 showed both her SLE and sarcoidosis to be controlled on oral prednisolone 10 mg daily and no other immunomodulation.

HLA typing by serology showed her to be HLA-A2,3, B7,35,DR1,9 and DQ5,9.

Case 3

The third case, also a Caucasian female, presented in 1985 at the age of 28 years with erythema nodosum and evidence of BHL on chest radiograph. A Mantoux was negative and pulmonary function tests were normal. A diagnosis of sarcoidosis was made. As she was systemically well she was not further investigated and given no specific treatment. A follow up radiograph one year later showed resolution of the BHL. She remained well until 1992, when she developed joint swelling, arthralgia and early morning stiffness. In association with these symptoms she developed Raynaud’s phenomenon and superficial mouth ulcers. Investigations revealed a raised ESR of 70 mm/hr with a normal C reactive protein level, positive anti-dsDNA antibodies (104 IU/L) and positive ANA (titre 1/2560, diffuse pattern). She was also anti-Ro and anti-La and rheumatoid factor positive. This combination fulfilled the revised ACR criteria for SLE, allowing the diagnosis to be made. She was initially treated with anti-malarial with good effect. Five years later in 1997 she had a flare of her lupus characterised by increasing arthralgia, malaise and new malar facial rash. Investigations at that time revealed an ESR of 44, a higher than previous dsDNA titre at 330, and a low complement fraction C3 at 0.58. Prompt recovery followed a short course of oral steroids. At no time has there been any symptoms or sign to suggest a recurrence of her sarcoidosis. Repeat chest radiographs have remained normal.

HLA typing by serology showed her to be HLA-1,2, B7,8, DR2,3, DRB51,52 and DQ 2,6.

Discussion

The co-existence of sarcoidosis and SLE, two conditions which are thought to be at least in part immunologically mediated, in these three patients is interesting. Their co-occurrence has been reported in only a handful of cases over the past 40 years. Among these reports there is no common pattern of which disease presented first or the course of each condition. Pulmonary sarcoidosis has been described in several cases where there was a pre-existing diagnosis of SLE (2, 3). One of these patients, whose sarcoidosis was well controlled by steroids, went on to develop severe and ultimately fatal lupus nephritis. Two other reports described pulmonary sarcoidosis in patients who subsequently developed SLE (4, 5). In one of these cases, lupus was thought to have been present but undiagnosed up to 25 years previously. An early case describes cutaneous sarcoidosis presenting in a patient with discoid lupus (6). Sarcoidosis has been described in a patient with ANA positive nephritis (7). Disseminated sarcoidosis, with granulomata in lungs, skin and bone marrow, has also been reported in SLE (8).

Both diseases may present with similar, though non-specific clinical features, including fevers, arthralgia, lymphadenopathy, sicca symptoms and rash. Sarcoidosis is classically associated with pulmonary involvement, but it is important not to forget that SLE can also present with pneumonitis as well as the more common symptomatic pleural inflammation. Lupus pneumonitis may be acute or chronic, and may result in subsequent fibrosis. Pulmonary hypertension, which is well reported as a complication of pulmonary fibrosis in sarcoidosis, is now recognised as a grave prognostic indicator in SLE.

It is possible that the true incidence of sarcoidosis in patients with SLE may be underestimated. One review of 569 patients with a variety of autoimmune conditions including RA, primary SS and SLE, found the incidence of sarcoidosis in these patients to be 1% (9), similar to our 3 patients within a cohort of 300. This is considerably greater than the incidence (ranging from 2 to 60 per 100,000) of sarcoidosis in the general population (10). These reports and our 3 cases emphasize the need for rheumatologists managing patients with lupus not to assume that the develop-
ment of new skin, neurological or lung manifestations could only be due to an extension of SLE.

SLE and sarcoidosis have similar genetic associations. Both conditions share an increased incidence in the Afro-Caribbean and African-American populations. Risk HLA alleles for lupus include HLA-B8 (15), the HLA-A1-B8-DR3 haplotype as a whole, as well as HLA-DR2 (16). In Caucasian patients the HLA-A1, B8, DR3 haplotype carries a relative risk of 8.3 for the development of lupus (17). Genetic deficiencies of the early components of the classical complement pathway are strongly associated with lupus, thought to be due to defects in the clearance of apoptotic cells (18). Polymorphic differences in the mannose binding protein (16) and the immunoglobulin receptor FcgRIIA (19) are also implicated.

In contrast to these data there are few studies addressing the genetics of sarcoidosis. One family study in Ireland showed a very high prevalence of sarcoidosis in the family members of index cases, although environmental factors cannot be excluded in explaining these data (20). HLA-B8-DR3 has also been reported to be a risk haplotype, in particular for sarcoid arthritis (21, 22). This haplotype also confers an increased risk of a set of other autoimmune conditions including autoimmune thyroiditis, type 1 diabetes, and myasthenia gravis. It is possible that some of the genes which confer an increased risk of SLE are also involved in the pathogenesis of sarcoidosis.

Possible shared immunological features between SLE and sarcoidosis include polyclonal hypergammaglobulinaemia, cryoglobulinemia (11) and the development of a positive ANA (12). However some of these features may be non-specific. A positive ANA has been reported to be as high as 32% in patients with sarcoidosis (13) and can also occur in a wide range of other autoimmune conditions. In a recent study of 34 patients with sarcoidosis, 10 (29%) had ANA as measured by staining Hep2 cells, while 2 (6%) had anti-dsDNA antibodies as measured by the Millipore filter assay (14). However these two patients had normal complement levels and did not go on to develop other features of SLE during 15 years of follow up.

Despite these similarities, recent publications of in vitro and ex vivo immunopathological findings suggest divergent aetiological mechanisms. Sarcoid granulomata contain a large number of activated CD4+ T cells (23), which are oligoclonal in their antigen receptors (24). Early on in the disease these cells are strongly polarised towards a Th1 phenotype, expressing CXCR3, IL-12Rb2 and producing high levels of IFNg and IL-2 (25). In contrast the T cell response in SLE is thought to involve a Th2-like production of high levels of cytokines including IL-10 and IL-4, which may provide T cell help to self-reactive B cells (26). Auto-antibody production, combined with a defect in the clearance of apoptotic cells, is thought to lead to the release of large amounts of nuclear antigens, many of which are themselves the targets of autoantibodies typical of SLE (27).

Patient one was in part of Afro-Caribbean descent, giving her a slightly increased risk of developing both sarcoidosis and SLE. Of note, one of our three patients had the HLA-A1, B8, DR3 haplotype. Case 1 was unusual in that her sarcoidosis presented as cutaneous infiltration. Cutaneous sarcoidosis occurs in 20 - 35% of patients with systemic sarcoidosis and is quite distinct from other cutaneous non-specific manifestations such as erythema nodosum (28) and is more commonly reported in Afro-Caribbean patients (29).

In our second patient, lupus features may in fact have pre-dated the sarcoidosis. Histological evidence of the cause of the pituitary lesion was not obtained, but this was felt likely to be due to sarcoid infiltration, given the subsequent positive Kviem test. In the case of our third patient sarcoidosis was diagnosed and appeared to have resolved completely, several years before the clinical features of SLE were recognised. These cases of patients with sarcoidosis coexisting with SLE represent 3 out of a total of approximately 300 patients with SLE seen in our unit over 22 years, suggesting a prevalence of roughly 1%.

This figure is higher than the prevalence of sarcoidosis in most series from a normal population (10). Although current available data suggest that the two conditions are unlikely to be mechanically related, it remains to be seen whether genetic risk factors may be shared between a subgroup of patients with sarcoidosis and those with lupus. Modern DNA technologies, combined with a fuller understanding of the whole human genome, should allow the precise mapping of such risk-associated loci.

References


