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What is This?
GRAND ROUND

Co-existing sarcoidosis, systemic lupus erythematosus and the antiphospholipid antibody syndrome
Case Reports and Discussion from the Brigham and Women’s Hospital Lupus Center

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Sarcoidosis, systemic lupus erythematosus (SLE) and antiphospholipid antibody syndrome (APS) are chronic conditions of immune dysregulation whose aetiologies remain mysterious. Expression of sarcoidosis and SLE within individuals has been reported in a handful of cases in the last 60 years. In this study, we report two cases of sarcoidosis and SLE occurring together, and each case demonstrated complications associated with the presence of antiphospholipid antibodies. Clinical, serological and pathological findings confirmed the diagnoses in each case and both patients improved with therapy. The association of sarcoidosis, SLE and APS is unique and may present difficult therapeutic options, as well as to shed light on their immunopathogenesis. Lupus (2009) 18, 202–205.

Key words: antiphospholipid antibody; sarcoidosis; systemic lupus erythematosus

Introduction

Sarcoidosis is a systemic disease of unknown cause that affects humans by the development and accumulation of granulomas.1 It commonly involves the lungs, eyes and skin and may also affect the central nervous system, heart, skeletal muscle, visceral organs and joints. The diagnosis is usually established with a typical chest radiograph in patients with compatible clinical features and often noncaseating granulomas on biopsy, with all other causes of granulomas ruled out.1 Patients with systemic lupus erythematosus (SLE) may develop similar clinical findings, and SLE may be accompanied by persistently elevated levels and antibodies to phospholipids and associated vascular thrombotic events.2 We have recently seen two patients with the unusual combination of SLE, sarcoidosis and clinical events associated with antiphospholipid antibodies. One patient had long standing SLE that was complicated by the antiphospholipid antibody syndrome (APS) and years later developed sarcoidosis. The other patient presented with APS but was later found to also have sarcoidosis and SLE. The triplex of SLE, APS and sarcoidosis occurring together is rare and to our knowledge has not yet been previously described.

Case 1 – presentation

A 48-year-old woman was diagnosed with SLE in January 1985. Manifestations have included biopsy-proven class IV glomerulonephritis, malar rash, weakness and arthritis. She was initially treated briefly with cyclophosphamide and continued on corticosteroid therapy for 8 years and was subsequently treated with hydroxychloroquine monotherapy. There were no respiratory complications. In 1991, she began to experience worsening cold temperature-exacerbated
chest pain. An exercise stress test with subsequent nuclear cardiac imaging showed coronary disease, and she was treated with a daily oral nitrate.

In October 1994, at the age of 34, she was admitted after an acute episode of worsening chest pain. An EKG showed T-wave inversions anterolaterally. Cardiac catheterization showed an 80% ulcerated left anterior descending artery stenosis with thrombosis. She underwent balloon angioplasty of the left anterior descending artery resulting in residual 20% stenosis. Laboratory results at this time showed a positive Russell’s viper venom test and lupus anticoagulant screen. Anticardiolipin IgG was also elevated at 53 (0–22 G/L), anti-nuclear antibody (ANA) was positive at 1:2560 in a diffuse pattern and her anti-dsDNA antibodies were 49 (0–15 IU). She was started on warfarin. Repeat testing showed persistent elevation of anticardiolipin IgG and lupus anti-coagulant 4 months later, confirming the diagnosis of APS.

In February 2005, she developed an extensive new rash on her forehead, ears and eyelids. Skin biopsies were taken of this new lesion, as well as of a chronic lesion on the right elbow. Pathologic examination showed superficial and mid-dermal non-necrotizing granulomas on both of the specimens. Special stains for acid fast bacilli and fungi were negative. The patient also continued to have a persistent dry cough. A chest radiograph showed right paratracheal hilar adenopathy (Figure 1). An angiotensin converting enzyme (ACE) level was normal and a purified protein derivative (PPD) skin test for tuberculosis was negative. A positron emission tomography (PET) scan of the chest showed extensive tracer uptake involving bilateral hilar lymph nodes consistent with sarcoidosis. She was started on 1 mg/kg of prednisone. Azathioprine was started because of persistent rash. One year later, her rash and hilar adenopathy had resolved and her prednisone was tapered and discontinued.

Case 2 – presentation

A previously well 46-year-old male presented with an idiopathic pulmonary embolism in April 2006. A hypercoaguability workup showed IgM anticardiolipin antibodies greater than the assay range and a positive Russell viper venom test. There had been no prior history of pulmonary embolism or deep venous thrombosis. There was also no family history of clots. His great aunt had SLE. Warfarin was started and repeat testing of anticardiolipin IgG and IgM 6 months later showed persistent elevations.

During follow-up for his pulmonary emboli, a chest radiograph followed by a chest computed tomogram (CT) scan both showed mediastinal and paratracheal lymphadenopathy. A PET scan was performed in February 2007 showing multiple foci of abnormal fluorodeoxyglucose (FDG) activity bilaterally within the mediastinum, bilateral hilar regions, subcarinal regions and broad areas of abnormal FDG activity in the posterior costophrenic sulci of both lungs.

In March 2007, pathology from mediastinoscopically resected lymph nodes showed noncaseating granulomas. Acid fast bacilli stains and cultures were negative. In April 2007, the patient reported joint pains in his wrists, hands and feet, associated with morning stiffness of many hours. He also noted a history of exertional dyspnoea and a prolonged cough after upper respiratory infections. There were no ocular or skin problems. Physical exam showed some fullness over his skin with intermittent telangiectasias. There was no sclerodactyly. Joint exam showed fullness over the bilateral metacarpophalangeal joints, wrists, elbows and metatarsophalangeal tenderness. Laboratory tests showed an ANA that was greater than 1:1280 in a speckled pattern. Anti-smith antibody was 229 (0–20 IU). The white blood cell count was 3000/mm³ and an erythrocyte sedimentation rate was 32 mm/h. Rheumatoid factor was 155 (1–15 IU/mL); anti-cyclic citrullinated peptide antibodies were negative. Total haemolytic complement (CH50) was 150 (150–250 U/mL). Hepatitis B and C antibodies were

Figure 1  Chest X-ray showing bilateral hilar enlargement.
negative. A standard chemistry profile, liver function test and urinalysis were normal. Pulmonary function tests showed a mild reduction in diffusing capacity. He was diagnosed with concomitant SLE and sarcoidosis. He was treated with prednisone and hydroxychloroquine. Prednisone was tapered as his polyarthritis improved and the patient did well in follow-up.

Discussion

We have recently followed two cases of SLE occurring together with both the APS and sarcoidosis. The first report of co-existent SLE and sarcoidosis was by Teilum in 1945 who described two patients with noncaseating granulomas in the lungs, lymph nodes and blood vessels at autopsy. These cases led to the first suggestion that sarcoidosis and SLE may both be related to the same underlying immunopathological process. Since that time, the coexistence of SLE and sarcoidosis has been described in 20 or more case reports. The true incidence of co-incident sarcoidosis and SLE is unknown. Begum, et al. reported three patients with existing SLE and sarcoidosis in a practice of approximately 300 patients. In an earlier study, 569 patients with inflammatory connective tissue diseases (including rheumatoid arthritis, SLE, Sjogren’s syndrome and scleroderma) were screened annually over a 10-year period for symptoms and signs of sarcoidosis via chest radiograph to assess bilateral hilar adenopathy. Six patients were found to have biopsy-proven sarcoidosis on examination of skin, mediastinal lymph node or transbronchial tissue. All were women with a mean age of 42 years. In the same study, none of 894 randomly selected control patients with non-inflammatory rheumatic conditions (myofascial syndromes, fibromyalgia and osteoarthritis) who were identically screened were found to have sarcoidosis. SLE was the most common connective tissue disease to be associated with sarcoidosis, followed by rheumatoid arthritis, Sjogren’s syndrome and scleroderma. Other autoimmune disease rarely associated with sarcoidosis include ankylosing spondylitis, reactive arthritis, polymyositis, dermatomyositis, autoimmune haemolytic anaemia, thrombocytopenia, thyroiditis, uveitis and primary biliary cirrhosis (see Table 1).

Given the potential increased incidence of sarcoidosis in patients with SLE, several comparisons have been made at the underlying common immunopathological processes. Both diseases show evidence of B cell hyper-reactivity such as hypergammaglobulinaemia, increased response to alloantigens and the presence of blood cell isoantigens. Both diseases are also paradoxically associated with impaired cellular immunity including decreased cutaneous delayed hypersensitivity, decreased lymphocyte response to mitogens in vitro and reduced numbers of circulating T cells. One key difference between the two entities, in addition to antibodies against nuclear antigens in SLE, is that increased complement levels have been reported in sarcoidosis, whereas they are commonly decreased in active SLE (see Table 2).

Although SLE and the APS commonly occur together, the English literature contains five previous reports of co-incident sarcoidosis and APS. Ina, et al. reported an increased incidence of antiphospholipid antibodies in a study of 55 patients. The presence of antiphospholipid antibodies was associated with the increased frequency of extrathoracic

<table>
<thead>
<tr>
<th>Autoimmune disorders associated with sarcoidosis</th>
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<tbody>
<tr>
<td>SLE</td>
<td>Decreased</td>
</tr>
<tr>
<td>RA</td>
<td>Decreased</td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
<td>Increased</td>
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<tr>
<td>Systemic sclerosis</td>
<td>Increased</td>
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<tr>
<td>Haemolytic anaemia</td>
<td>Increased</td>
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<tr>
<td>Thrombocytopenia</td>
<td>Increased</td>
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<tr>
<td>Primary biliary cirrhosis</td>
<td>Increased</td>
</tr>
<tr>
<td>Uveitis</td>
<td>Impaired</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>Normal or Increased</td>
</tr>
<tr>
<td></td>
<td>Present in 5–30%</td>
</tr>
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<td></td>
<td>Present in 38%</td>
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Table 2: Immunological features of SLE and sarcoidosis

<table>
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<tr>
<th>SLE</th>
<th>Sarcoidosis</th>
<th>References</th>
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<tbody>
<tr>
<td>Decreased</td>
<td>Decreased</td>
<td>4,20</td>
</tr>
<tr>
<td>Decreased</td>
<td>Decreased</td>
<td>4,20</td>
</tr>
<tr>
<td>Increased</td>
<td>Increased</td>
<td>4,20</td>
</tr>
<tr>
<td>Increased number of functional B cells</td>
<td>Increased</td>
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</tr>
<tr>
<td>Impaired</td>
<td>Impaired</td>
<td>20</td>
</tr>
<tr>
<td>Decreased</td>
<td>Normal or Increased</td>
<td>4</td>
</tr>
<tr>
<td>Present in 95–100%</td>
<td>Present in 5–30%</td>
<td>4</td>
</tr>
<tr>
<td>Present in 57%</td>
<td>Present in 38%</td>
<td>22,28</td>
</tr>
</tbody>
</table>

Abbreviations: DTH: delayed type hypersensitivity; Ig: immunoglobulin; ADCC: antibody-dependent cell-mediated cytotoxicity; ANA: anti-nuclear antibody.
lesions in sarcoidosis and persistence of abnormal findings on chest radiograph. The authors suggested that the presence antiphospholipid antibodies may be a prognostic factor in sarcoidosis. It was later noted that this report might have underestimated the impact of antiphospholipid antibodies on sarcoidosis because β2-glycoprotein-I-dependent antibody was not tested in this study.\textsuperscript{25}

Both sarcoidosis and SLE may present with similar clinical features such as fevers, arthralgias, lymphadenopathy, sicca symptoms, rash and respiratory complaints. There must be a high index of suspicion to diagnose these as concurrent illnesses because one can imagine that symptoms of one may be ascribed to each disease process. Even though both SLE and sarcoidosis are associated with antiphospholipid antibodies, the co-occurrence of the APS with SLE and sarcoidosis is unique. Continued analysis of the molecular pathways involved in these diseases may shed light on shared immunopathologic mechanisms underlying these conditions.

References