Primary Sjögren's Syndrome Complicated by Sarcoidosis

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Sjögren's syndrome and sarcoidosis share several common features, such as keratoconjunctivitis sicca, swelling of parotid glands, lung involvement, cutaneous anergy, T cell-mediated immunodeficiency, an increased CD4⁺/CD8⁺ lymphocyte ratio, and association with the human leucocyte antigen (HLA)-B 8 and DR 3 haplotypes. However, only five patients with primary Sjögren's syndrome and sarcoidosis have been previously reported in the English language literature. The rare case of a 49-year-old Japanese woman with primary Sjögren's syndrome complicated by sarcoidosis is described. The serum angiotensin-converting enzyme level was increased, and histological examination of lung and skin biopsies revealed noncaseating granulomas, indicating that her primary Sjögren's syndrome was complicated by sarcoidosis. (Internal Medicine 37: 174-178, 1998)

Key words: human leucocyte antigen (HLA), dry eye, dry mouth

Introduction

Both Sjögren's syndrome and sarcoidosis are diseases of unknown etiology. Sjögren's syndrome is characterized by symptoms of dry eyes and a dry mouth, and is sometimes accompanied by bilateral enlargement of the salivary and lacrimal glands. Subclinical involvement of the parotid glands and lacrimal glands is relatively common in sarcoidosis patients, although the swelling of these glands is not frequently evident. However, individuals with sarcoidosis can exhibit clinical features similar to those of Sjögren's syndrome (1). Here, we now describe a patient with well-documented primary Sjögren's syndrome complicated by sarcoidosis.

As far as we are aware, only five cases of primary Sjögren's syndrome with sarcoidosis have been described in the English language literature. We discuss the common and discriminating features of Sjögren's syndrome and sarcoidosis.

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Case Report

A 49-year-old Japanese woman, with a history of pulmonary tuberculosis from the age of 15, complained of having a dry mouth in July 1990 and was referred to the Department of

Otolaryngology in Saiseikai Fukushima Hospital. No collectable saliva was produced during a 15-min period without stimulation. Histological analysis of a minor salivary gland in an oral mucosa biopsy revealed focal lymphocytic sialadenitis with degeneration of the ductular epithelium (Fig. 1). A Schirmer test resulted in 3 mm wetting in 5 minutes. Blood tests revealed anemia (red blood cell (RBC), $413 \times 10^4/\text{cmm}$; hemoglobin (Hb), 9.6 g/dl), leukocytopenia (3,000/cmm) and polyclonal hypergamma globulinemia: immunoglobulin G (IgG), 3,206 mg/dl (normal, 800 to 1,950 mg/dl); immunoglobulin A (IgA), 480 mg/dl (normal, 80 to 410 mg/dl) and immunoglobulin M (IgM), 510 mg/dl (normal, 68 to 290 mg/dl). The rheumatoid factor was 2+ and complement (CH_{50}) was 34 U (normal, 30-40 U). The titer of the antinuclear antibody was 1:2,560 (homogeneous and nucleolar pattern), but LE test was negative. The titers of antibodies to SS-A and SS-B antigens were higher than 1:256 and 1:8, respectively, in a double immunodiffusion test. The patient was referred to the Department of Internal Medicine in the same hospital in order to eliminate the possibility of other collagen diseases. She did not exhibit any symptoms such as fever, erythema, skin sclerosis, Raynaud's phenomenon, myalgia or arthritis when she was referred to an internist. On the basis of these observations, primary Sjögren's syndrome was diagnosed, and treatment with prednisolone (10 mg/day) was started.

She suddenly stopped taking prednisolone without permis-

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sion from her doctor in April 1996, and subsequently developed polyarthralgia and papulae on both knees and elbows (Fig. 2). Thereafter, she complained of a dry cough. A chest X-ray revealed fine nodular shadows in the whole lung (Fig. 3A), and computed tomography of the whole lung revealed fine nodular lesions distributed around the alveoli and along the small

vessels and bronchioles (Fig. 3B). Swelling of the subaortic lymph nodes (#5) was also evident (Fig. 3C).

The patient was referred to our department at Fukushima Medical College for further analysis of her lung lesion. A transbronchial lung biopsy and bronchoalveolar lavage performed in June 1996 revealed noncaseating granulomas not

Figure 1. Histological examination of a minor salivary gland in the oral mucosa. Focal lymphocytic sialadenitis with degeneration of the ductular epithelium which is compatible with the histology of Sjögren's syndrome (HE stain, $\times 100$).

Figure 2. Linearly arranged, infiltrating, dark-red papulae around the patellar region.

A

B

C

Figure 3. (A) Fine nodular lesions visible in the whole lung of the chest X-ray. (B and C) Chest computed tomography. Fine nodular shadows around the alveoli and along vessels and bronchioles (A and B) as well as swelling of the subaortic lymph nodes (#5) as indicated by arrows (C) are evident.

Figure 4. Histology of a transbronchial lung biopsy specimen. Noncaseating granulomas with many epithelioid cells and a few Langhans-like giant cells, without any necrotic lesions, are evident. The granuloma lesion shown is partially surrounded by a moderate number of monocytes and lymphocytes (HE stain, $\times 200$).

Figure 5. Histology of a papulae biopsy from the knee region. An irregularly shaped epithelioid cell granuloma is evident in the dermis. A few Langhans-like giant cells are evident in the granuloma, without any necrotic lesions. The granuloma is partially intermingled with a moderate number of monocytes and lymphocytes (HE stain, $\times 300$).

exhibiting necrosis in the alveolar region (Fig. 4) and an increased ratio of CD4⁺/CD8⁺ lymphocytes at 4.21 in the lavage fluid. Histological examination of a biopsy of her skin lesions on the knees also revealed noncaseating granulomas (Fig. 5). Both cultures and polymerase chain reaction analysis of sputum and bronchoalveolar lavage fluid were negative for *Mycobacterium tuberculosis*. The level of angiotensin-converting enzyme in serum was 32.7 U/l (normal, 7 to 25 U/l).

Based on these findings, sarcoidosis was diagnosed (2, 3). The administration of salazosulfapyridine resolved the polyarthralgia as well as the skin lesions and cough. The fine nodular shadows disappeared as revealed by a chest X-ray and the size of the swollen hilar lymph nodes as revealed by chest computed tomography was also decreased (not shown).

Discussion

We described a Japanese woman with primary Sjögren's syndrome complicated by sarcoidosis. The arthralgia and papulae related to sarcoidosis appeared soon after she voluntarily stopped taking prednisolone, suggesting that her susceptibility to sarcoidosis had been suppressed by this drug. Her doctor prescribed prednisolone to prevent the development of hyperviscosity syndrome due to her hypergamma globulinemia, and the treatment decreased these values from IgG, 3,206 mg/dl, IgA, 480 mg/dl and IgM, 510 mg/dl on July 1990 to IgG, 2,283 mg/dl, IgA, 419 mg/dl and IgM, 228 mg/dl on May 13, 1996.

Serological typing studies have revealed associations between the HLA-DR 52 allele (4), the DR 52-associated antigens [DR 3, DR 5 (5) and -DR 6] and DR-8 (6) and sarcoidosis in Japanese patients. Among these sarcoidosis-predisposing HLA-DR alleles, the present patient exhibited HLA-DR 6 and -DR 8. Although HLA-B 8 (7–9) and HLA-DR 3 (10–12) are often associated with Sjögren's syn-

drome and sarcoidosis, our patient exhibited neither of these alleles.

The reported prevalence of abnormal pulmonary lesions varies widely; 9% occurrence in primary and secondary Sjögren's syndrome (13), a 37.5% occurrence of diffuse interstitial lung disease in primary Sjögren's syndrome and an 11.8% occurrence in secondary Sjögren's syndrome (14) and an 8% occurrence of lung fibrosis in primary Sjögren's syndrome (15), although the lesions are usually subclinical and rarely progressive. An abundance of mucosal glands renders the lung a primary target organ in this syndrome, resulting in conditions which include lymphoid interstitial pneumonia, lymphocytic alveolitis, xerotrachea, fibrosis, pseudolymphoma and malignant lymphoma (13). The first two of these pulmonary conditions were considered as candidates for diagnosis of the present case's lung lesions. Lymphoid interstitial pneumonia is classified as interstitial pneumonitis, with reticular shadows localized at the base of the lung in chest X-ray (16), and exhibits a clinical course that is basically chronic. Thus, this patient was not diagnosed with this condition. Alveolitis is a common lung lesion in both Sjögren's syndrome and sarcoidosis, necessitating histological analysis of the lung for its detection.

Almost all sarcoidosis patients exhibit swelling of the mediastinal and hilar lymph nodes as determined by computed tomography (17), as was evident in our patient. Approximately 90% of patients with sarcoidosis have granulomas in the lung or intrathoracic lymphoid tissue, or both (18). Granuloma formation along the alveolar septum and small vessels is a characteristic feature of lung lesions in sarcoidosis, resulting in fine nodular shadows in the lung field on both chest X-ray and computed tomography examination.

Tuberculosis has been proposed as one of the pathogenic factors for sarcoidosis and 4% of sarcoidosis have had tuberculosis (19). The present patient had a history of lung tuberculosis

Primary Sjögren's Syndrome with Sarcoidosis

Table 1. Clinical Features and Laboratory Data of Patients with both Primary Sjögren's Syndrome and Sarcoidosis

Patient/Reference	Patient 1/(23)	Patient 2/(28)	Patient 3/(29)	Patient 4/(30)	Patient 5/(31)
Age (years)/gender	34/F	57/F	42/M	60/F	45/M
Duration of preceding disease (years)	6	10	1	25	1
Symptoms	None	Dry eyes and mouth, dry cough exertional dyspnea	Obstructive jaundice NR	Swelling of parotid glands, generalized arthralgia, dry eyes, mouth, and vagina	Dry mouth, dysphagia, tiredness, Raynaud's phenomenon
Rheumatoid factor	Negative	1 : 256	NR	1 : 40	(++)
Antinuclear antibodies	NR	1 : 400	NR	1 : 320	(++)
Antibodies to SS-A antigen	NR	(+)	NR	NR	Negative
Antibodies to SS-B antigen	NR	(+)	NR	NR	Negative
Chest X-ray	Normal	Normal	NR	Bilateral hilar lymph node enlargement	Bilateral hilar lymph node enlargement
Angiotensin converting enzyme	NR	NR	NR	Normal	(+)
Histology of biopsied tissue	Lung – sarcoidosis Salivary gland – SS	Lung – sarcoidosis Salivary gland – SS	NR	Lung – sarcoidosis Salivary gland – SS	Lung – sarcoidosis Salivary gland – SS
Pattern of onset	SS preceded sarcoidosis	SS preceded sarcoidosis	SS preceded sarcoidosis	SS preceded sarcoidosis	Sarcoidosis preceded SS

NR: not recorded, SS: Sjögren's syndrome.

at the age of 15. Therefore, the occurrence of miliary tuberculosis in the lung field should also be considered in the differential diagnosis of her lung lesions. The erythrocyte sedimentation rate was 68 mm/h, but the CRP value was less than 0.1 mg/ml. Sputum and bronchoalveolar lavage fluid were negative for *Mycobacterium tuberculosis*. The level of angiotensin-converting enzyme in serum and the CD4⁺/CD8⁺ lymphocyte ratio in bronchoalveolar lavage fluid were also high, both of which indicate that the patient no longer had tuberculosis.

Sjögren's syndrome and sarcoidosis share several immunological features, including cutaneous anergy, T cell-mediated immunodeficiency and B cell activation resulting in polyclonal hypergamma globulinemia. Accordingly, various clinical features are common to both Sjögren's syndrome and sarcoidosis. Clinically manifest parotid involvement occurs in 4 to 6% of sarcoidosis patients (20, 21), whereas subclinical involvement of minor salivary glands is apparent in about 50% of such patients (22). The frequency of eye involvement in sarcoidosis varies from 10% (23) to 70% (20), depending on the diagnostic criteria used.

Infectious agents, allergy, autoimmunity, genetic factors, and endocrine factors have been speculated to be involved in the development of Sjögren's syndrome. Interest in the relationship between viruses and Sjögren's syndrome began because some Sjögren's syndrome patients develop lymphoid malignancies (24). Viruses most likely to induce Sjögren's syndrome are either sialotropic or lymphotropic. Such viruses include the Epstein-Barr virus (25), HHV-6 (26) and retroviruses (27).

Infectious agents, chemicals and drugs, allergy, autoimmunity, and genetic factors have all been explored as possible causes of sarcoidosis. It has been postulated that T cell defects may be a result of virus infection.

Even though Sjögren's syndrome and sarcoidosis share immunological and genetic characteristics, we are aware of

only five individuals with both primary Sjögren's syndrome and sarcoidosis who have been described in the English language literature (23, 28–31) (Table 1). However, the number of such patients may be underestimated, because clinical symptoms of both diseases are frequently subclinical. The possibility of the simultaneous occurrence of these two conditions should therefore be considered in patients with a dry mouth and dry eyes. The possibility of misdiagnosing individuals who present with bilateral enlargement of the parotid and lacrimal glands, xerostomia, and keratoconjunctivitis sicca as having Sjögren's syndrome rather than sarcoidosis should also be kept in mind (1). Histological examination of a mucosal minor salivary gland specimen from this patient revealed acinar atrophy, mild fibrosis, and marked periductal focal lymphocyte infiltration. These observations were subsequently interpreted as indicating the early involvement of labial salivary glands in sarcoidosis (1).

Due to the many common features with respect to etiology, genetics, immunology and clinical findings between Sjögren's syndrome and sarcoidosis, a diagnosis of Sjögren's syndrome or sarcoidosis should be based on several criteria, including the presence of antinuclear antibodies, such as antibodies to SS-A and SS-B antigens, a change in angiotensin-converting enzyme levels, and clinical and histological observations.

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