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Coexistence of Sjögren's syndrome and sarcoidosis: a report of five cases

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BACKGROUND: Sjögren's syndrome (SS) and sarcoidosis are diseases that can affect the salivary glands and result in the loss of salivary gland function. Most of the criteria used for the diagnosis of SS exclude sarcoidosis before establishing the diagnosis of SS. However, several reports have suggested the coexistence of both SS and sarcoidosis in the same patient.

OBJECTIVE: The purpose of this study was to present five cases that support a true coexistence of sarcoidosis and SS.

METHODS: Clinical and laboratory findings of patients with evidence of having both SS and sarcoidosis were reviewed. The diagnosis of SS was based on the European community criteria; the diagnosis of sarcoidosis was based on the presence of serological, radiographic and/or histopathologic findings that are consistent with sarcoidosis.

RESULTS: All patients fulfilled the criteria for the diagnosis of both diseases.

CONCLUSION: Our findings appear to support a true coexistence of sarcoidosis with SS. Therefore, it is reasonable to suggest removing the exclusion of sarcoidosis from the diagnostic criteria for SS.

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Keywords: coexistence; diagnosis; multi-system disease; salivary gland; sarcoidosis; Sjögren's syndrome; xerostomia

Introduction

Sjögren's syndrome (SS) is a chronic inflammatory disease that primarily affects the exocrine glands. The etiology is not known; however, genetic, environmental and hormonal factors have been implicated in the pathogenesis of SS (1–3). Although the key manifestations of SS are dry mouth and dry eyes, SS is a multi-system disease. There is no single diagnostic test that is specific for SS and its diagnosis is based on a combination of clinical, serological and histologic findings. Despite the several criteria that have been proposed for the diagnosis of SS, due to its vague onset and course, there is up to 10 years delay in the diagnosis (3), and more than half of the cases may remain undiagnosed (3–6).

Sarcoidosis is another chronic multi-system inflammatory disease of unknown etiology and its pathogenesis is believed to be multifactorial (7). Although the primary characteristic feature of sarcoidosis is hilar lymphoadenopathy and pulmonary granulomas, it is also a multi-system disease and its early manifestation is often vague and difficult to diagnose (7, 8). The diagnosis of sarcoidosis may also require a combination of clinical, and radiographic, histologic, or serological findings (8). Sarcoidosis shares several features with SS in that it can be insidious and may develop over many years. Like SS, the multi-system nature and the vague onset and course of sarcoidosis make it difficult to be diagnosed in the early stages of the disease (9, 10). Sarcoidosis is one of the exclusion entities for the diagnosis of SS (11, 12); however, several clinical observations and literature evidence suggest a true coexistence of the two diseases (13, 14). In this study, we report five new cases of coexisting sarcoidosis and SS.

Methods

With the approval of the Institutional Review Board, the database of patients attending the Salivary Gland Dysfunction clinic was reviewed for cases that were diagnosed with both SS and sarcoidosis.

The diagnosis of SS was based on the 1993 European criteria (11). Patients fulfilled four or more of the criteria used for the diagnosis of SS, which include: ocular symptoms, oral symptoms, objective evidence of ocular involvement, objective evidence of reduced salivary

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output, presence of at least one autoantibody (ANA, RF, SS-A, SS-B), and/or a positive salivary gland biopsy with one or more focus score (grade ≥III).

The diagnosis of sarcoidosis was based on the basis of a positive history of the disease with compatible clinical findings supported by a well-documented finding of one or more of the following: compatible radiological findings, histologic demonstration of non-caseating granuloma (NCG) and/or elevated levels of ACE (8). As a routine, the diagnosis of sarcoidosis was also verified by medical consultation with a rheumatologist and pulmonary specialist.

The histologic patterns of both SS and sarcoidosis are the hallmark of the diseases in the appropriate clinical settings. The coexistence of both diseases was considered when patients presented with the histologic features of both diseases, or where the patient met both diagnostic criteria for both diseases.

Results

We identified five patients who met the diagnostic criteria for both SS and sarcoidosis. All patients were females; four white and one black. The mean age at the time they were diagnosed with SS was 51.8 ± 17.6 years (range, 34–80 years) and the mean age, when they were diagnosed with sarcoidosis was 52.2 ± 16.7 years (range, 35–80 years) (Table 1).

All patients fulfilled four or more of the 1993 European Community criteria for the diagnosis of SS (11). In addition, all patients met the criteria for the diagnosis of sarcoidosis. Tables 1 and 2 show the clinical and laboratory findings of each patient included in this report. Table 3 shows the frequency of other clinical symptoms among the study population.

Table 1 Demographics of the study population

			Age (years) and diagnosis		*Sicca symptoms*	
Patient no.	*Gender*	*Race*	*SS*	*Sarcoidosis*	*Dry mouth*	*Dry eyes*
1	F	W	34	47	Yes	Yes
2	F	W	48	48	Yes	Yes
3	F	W	42	35	Yes	Yes
4	F	B	55	51	Yes	Yes
5	F	W	80	80	Yes	Yes

F, female; W, white; B, black; SS, Sjögren's syndrome.

Table 3 Frequency of other clinical manifestations

Symptoms	*Patients (%)*
Oral (dry/sore mouth, difficulty swallowing, difficulty chewing, burning mouth, salivary gland enlargement)	100
Ocular (dry eyes, sandy feeling, tired eyes, intolerance to light and/or air, foreign body sensation, itching, discharge, excessive tearing)	100
Nasal (sinusitis, dry nose, nasal bleeding, nasal congestion)	100
Skin (dry skin, rash, Raynaud's phenomenon)	80
Vaginal (dry, burning, recurrent yeast infections)	80
Gastrointestinal (constipation, reflux, diarrhea)	80
Respiratory (shortness of breath, recurrent bronchitis, chronic cough, abnormal chest radiographs (compatible with sarcoidosis)	60
Ear (hearing, tinnitus)	60
Joint (pain)	100
Muscle (ache, fibromyalgia, fatigue)	60
Neurologic (numbness and neuropathy)	20

There was no specific pattern concerning age, gender, or presenting symptoms among the patients regardless of whether the initial diagnosis was SS or sarcoidosis. All patients had symptoms of dry mouth, dry eyes, and other parts of the body (generalized exocrinopathy); however, the respiratory symptoms were not present in all the patients, Table 3. None of the patients had significant complications during their clinical follow-up (mean, 2.3 years; range, 0.5–4 years), except for patient 4 who developed serious respiratory infection 4 years after the diagnosis of SS and 8 years after the diagnosis of sarcoidosis. A brief summary of the clinical presentation of each patient is presented.

Patient 1 is a 48-year-old white female who was referred to the Salivary Dysfunction Clinic at Baylor College of Dentistry for evaluation of dry mouth symptoms. Her medical history revealed a diagnosis of SS when she was 34 years old and sarcoidosis at 47 years. She reported dryness of the mouth, eyes, nose, skin, and vagina. She also had recurrent sinusitis, nasal congestion, chronic cough, Raynaud's phenomenon, tinnitus, fatigue, fibromyalgia, and joint pain. Her laboratory findings are summarized in Table 2. A 2-year follow-up did not reveal any significant complication.

Patient 2 is a 48-year-old white female. She was referred by her rheumatologist for evaluation of a possible SS. Her medical history revealed a diagnosis of primary biliary cirrhosis and sarcoidosis, verified by biopsies of the liver and lung, respectively. At

Table 2 Laboratory findings of the study population

Patient no.	*MSG*	*Autoantibodies*	*Radiograph*[a]	*NCG*	*ACE*	*Serum Ca*[2]
1	IV	ANA, SSA, SSB	NA	Lungs, LN	NA	Elevated
2	NA	ANA, SSA, SSB	Positive	Lungs	Normal	Normal
3	IV	Negative	Positive	Lungs, LN, SG	Elevated	Normal
4	IV	ANA	Positive	Lungs, liver	Elevated	Normal
5	III	Negative	NA	NA	Elevated	Normal

MSG, minor salivary gland biopsy; NCG, non-caseating granuloma; ACE, angiotensin-converting enzyme; NA, not available; ANA, antinuclear antibody; SSA, anti-SSA antibody; SSB, anti-SSB antibody; LN, lymph node; SG, salivary gland.
[a]Hilar and/or mediastinal lymphadenopathy on chest radiograph.

presentation at our clinic, the patient reported dryness of the mouth, eyes, nose, skin, and vagina. She also reported recurrent sinusitis, nasal congestion, cough, bronchitis, shortness of breath, skin rash, fatigue, fibromyalgia, muscle, and joint pain. Salivary evaluation revealed low salivary output and her serologic profile was consistent with the diagnosis of SS (Table 2). No complication was developed during 6 months of follow-up.

Patient 3 is a 42-year-old white female. Her medical history revealed the diagnosis of sarcoidosis when she was 35 years old. Four years later, she developed a swelling in the sublingual salivary gland, which did not respond to treatment with antibiotics. A biopsy of the sublingual gland revealed a NCG and grade IV focal sialadenitis consistent with the diagnosis of sarcoidosis and SS, respectively (Table 2). No serious complication was reported during a 1-year follow-up.

Patient 4 is a 55-year-old African-American female who was referred by her dentist for evaluation of dry mouth symptoms. Her medical history revealed hepato/spleenomegally for the past 4 years. Laboratory tests showed abnormal liver function and elevated ACE levels. Biopsies of the liver and the lung were consistent with the diagnosis of sarcoidosis (Table 2). A minor salivary gland biopsy was consistent with the diagnosis of SS (Table 2). During a 4-year clinical follow-up period, the patient was diagnosed with hepatitis C, had serious inflammatory pancreatitis, and developed severe upper respiratory infection that required hospitalization.

Patient 5 is a 79-year-old white female who was referred by her dentist for evaluation of burning mouth symptoms. She was diagnosed with both SS and sarcoidosis during routine clinical evaluation at the Salivary Dysfunction Clinic (Table 2). No serious complication was reported during the 4-year clinical follow-up.

Discussion

Sjögren's syndrome is a chronic inflammatory disease characterized mainly by sicca-related symptoms, but it may also have systemic manifestations. Sarcoidosis is a chronic granulomatous disease that mainly affects the lungs, but it may have systemic manifestations as well. Both disease entities have neither pathognomonic features nor a specific diagnostic test, which leaves the clinician with a challenge. The diagnosis of either one is based on a combination of clinical and laboratory findings. Several criteria have been proposed for the diagnosis of SS, yet SS continues to be underdiagnosed (3), which is attributed to the vague onset and course of the disease (3, 4, 6). The same is true for sarcoidosis with its vague and nonspecific symptoms (9, 10).

Although most of the diagnostic criteria of SS exclude sarcoidosis, a coexistence of both entities has been reported in the literature (13–15). It is possible that the actual incidence of coexistence could be even higher than reported because of the exclusion of sarcoidosis from the current criteria for the diagnosis of SS. When both diseases do coexist, no specific marker allows for the distinction of one vs. the other during an exacerbation. However, some systemic manifestations are more commonly encountered in one disease compared with the other, and that could be a guide for the clinician. A higher prevalence of systemic symptoms was observed in patients with coexisting sarcoidosis and SS (13, 14). For example, our cases had a higher prevalence of nasal, respiratory, ear, skin, vaginal, gastrointestinal, and joint and muscle symptoms (Table 3) when compared with those reported in patients with SS alone (16) or patients with sarcoidosis alone (17).

Sicca symptoms are typical of SS; however, sarcoidosis may affect the exocrine glands producing sicca symptoms that are difficult to distinguish from those caused by SS (18). Cases where the sicca symptoms are the only presenting features in sarcoidosis are rare but they have been increasingly reported (13–15, 19, 20). Ocular involvement was reported in 25% of patients with sarcoidosis, anterior uveitis being the most common feature. Although involvement of the lacrimal gland was reported in 3% of the cases, gallium uptake was noted in about 80% of the time with keratoconjunctivitis sicca manifesting in about 16% of the cases (19). The salivary glands could be affected by sarcoidosis as well and was reported in 6% of the cases. Parotid gland enlargement was detected in 6% of the patients, but increased gallium uptake was noted in about 75% of the patients (20). Parotid gland enlargement in patients presenting with sicca symptoms is believed to be of clinical significance. Such finding might be more likely associated with sarcoidosis, especially in patients presenting with negative serologic profiles (15, 20). Two of our cases had enlarged salivary glands, one with enlarged parotid glands who also tested positive for ANA while the other had enlarged sublingual glands and a negative serologic profile.

Pulmonary involvement could be evident in either condition, but it is considered more typical and more common in sarcoid patients. However, pulmonary manifestations of SS are very similar to those of sarcoidosis. Both conditions share very similar clinical, pathologic, radiographic and physiologic features, preventing the differentiation in diagnosis solely on clinical grounds; however, differentiating between the two conditions is of prognostic significance. Sarcoidosis may present as an auto-limiting process and frequently resolves spontaneously without significant residual functional impairment. SS, on the other hand, often causes permanent defects and may progress to incapacitating disease. Nevertheless, the available literature is not consistent regarding the frequency, the pattern of physiologic abnormalities, and the clinical significance of the respiratory involvement in SS. Depending on the sensitivity of the diagnostic parameters and the criteria used to define the abnormalities, the prevalence of pulmonary involvement varies from 2% to 75% of patients, being most common and severe in secondary SS (21, 22). It is believed that up to 30% of SS patients have subclinical pulmonary involvement (4). Although histologic examination of the lung may show similarities

between sarcoidosis and SS, lymphocytic interstitial pneumonitis (LIP) is considered a manifestation of SS but not sarcoidosis (14). Actually, 25% of interstitial pneumonitis cases are associated with SS, and 1% of SS patients acquire LIP during the course of their disease (23). Bi-hilar lymphadenopathy, which is more common in sarcoidosis (more than 90% of the cases), could be interpreted as a sign indicating lymphoma associated with SS (13). Pulmonary function tests are helpful in detecting the pulmonary involvement but not in differentiating between the two conditions.

Other potentially shared features are the involvement of the joints and skin (13, 24). Ankle swelling, for example, might be caused by arthritis of the ankle joints associated with either condition (19, 24). Although the two diseases share many similarities, indicating a common or a similar pathophysiological mechanism, they show a different serologic profile. While SS patients are usually positive for autoantibodies, sarcoidosis patients are negative (13, 14). ANA is detected in more than 90% of SS patients, RF in more than 60%, and SSA and SSB in more than 50% (3). SSA may identify a subset of SS patients with greater frequency of extraglandular manifestations. SSB, on the other hand, is particularly associated with the sicca syndrome (14). Immunologic examination for SSA or SSB in sarcoidosis patients is usually negative, whereas some patients may show low titers of ANA or RF (13, 14). In sarcoidosis patients presenting with sicca symptoms, the existence of a positive immunologic marker would indicate a coexisting SS condition (13, 24). Such patients would have higher frequency of ANA, RF, SSA, and SSB autoantibodies. However, the differentiation between SS and sarcoidosis may still be difficult, especially when the patient presents with negative serologic profile and normal serum ACE level. Although ACE levels are elevated in sarcoidosis, such a finding may be masked by commonly used medications such as ACE inhibitors. This may warrant a microscopic examination of a tissue specimen of either the salivary gland or the lung to establish a definitive diagnosis. The histologic finding of NCG is considered diagnostic in a clinical setting of sarcoidosis. However, whether the presence of this feature in a clinical SS setting is indicative of a true coexistence with sarcoidosis, or whether it is a mere unusual manifestation of SS in the absence of sarcoidosis, are questions yet to be answered (14). In the minor salivary gland biopsies, the dilemma is faced when only nonspecific findings are present. Focal sialadenitis is considered the histologic hallmark of SS; however, mild or scattered infiltrates are not diagnostic, and further investigation is required to confirm the diagnosis. Furthermore, extensive epithelioid cell granuloma may dominate the histopathologic specimen making it easy to underdiagnose SS (13–15). When both features (focal sailadenitis and NCG) are present in the histologic specimen, the clinical features as well as the immunologic profile should be considered. When the two conditions coexist, their histologic features may be apparent in the same histologic specimen from the salivary gland or the NCG characteristic of sarcoidosis may ensue in a different organ, simultaneously or at different times. In addition to three of our cases, 28 cases of coexistence described in the literature showed histologic features of both diseases. Seven of these cases (including one of our case) showed both features in minor salivary gland biopsy. The remaining cases showed focal sialadenitis in salivary gland biopsy, whereas the NCGs were shown extraglandularly, mostly in the lungs (13).

In the literature, the coexistence of sarcoidosis with SS can only be confirmed when the patient shows the histopathologic features of both diseases, simultaneously or at different times (13, 14). However, we believe that the current criteria are too strict and may exclude certain cases of SS patients where they meet the relatively less stringent 1993 European criteria without having the characteristic histopathology, thus contributing further to the underestimation of the prevalence of sarcoidosis in SS patients.

Conclusion

Despite the fact that sarcoidosis and SS are multi-system diseases with similar clinical features, we have never understood the logic of suggesting that if a patient has sarcoidosis, he/she cannot develop SS. Clearly, there is no limit to the number of unrelated disease a patient may develop. Our clinical observation and those of several others provide clear evidence of a true coexistence of both SS and sarcoidosis in the same patient. Based on these observations, we suggest removing sarcoidosis from the exclusion criteria for the diagnosis of SS.

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