CHAPTER

Unusual cases
A case of primary sialoangiectasia, which in this case was initially misdiagnosed as Sjögren’s syndrome, is described. Other diseases, including HIV-infection, psoriatic arthritis and acute parotitis, may cause glandular changes similar to the changes found in the syndrome. Therefore, sialography always must be combined with other methods of assessment of the oral cavity when suspicion is high for Sjögren’s syndrome. Properly applied, sialography provides essential information regarding the severity of glandular damage and the progression of the disease.
PRIMARY SIALOANGIECTASIA: A DIAGNOSTIC PITFALL IN SJÖGREN’S SYNDROME. CASE REPORT

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INTRODUCTION

Sialography is still a frequently applied tool in the diagnosis of Sjögren’s syndrome (SS), disclosing changes in the ductal and acinar system of the salivary glands as a result of disease activity. Several other methods are used to examine the oral component of SS, including salivary flow measurement (sialometry), salivary composition analysis (sialochemistry), salivary gland scintigraphy, ultrasonography, and histopathology. Despite controversy regarding the value of these methods, sialography has been used for decades and has been proposed as a criterion for the oral component of SS in 5 of the 9 sets of diagnostic criteria (revised criteria included) that are currently in use worldwide.¹⁻³

The first radiographic demonstration of salivary glands in vivo was performed in 1913. After the use of lipiodol was introduced in 1926, the procedure was named sialography.⁴ It was not until 1964 that the sialographic changes on the sialogram were classified by Blatt into punctate, globular, cavitary and destructive sialectasia (dilatation) of the acinar and ductal system; through use of this system, the progression of glandular damage caused by chronic inflammation could be graded.⁵ In 1965, results from the famous study of Bloch and co-workers demonstrated the high sensitivity of this diagnostic tool; 36 out of 37 patients with SS showed such sialectasia.⁶ In addition, more recent studies on sialography have shown that the demonstration of sialectasia is highly specific for SS. In a study that compared sialography and salivary gland biopsy in a series of 150 patients with SS, it was concluded that sialography has been unduly overlooked as a diagnostic tool and should be reconsidered as a useful and noninvasive procedure.⁷ In another study, sialography was shown to be a better indicator of the presence of SS than labial salivary gland biopsy, flow measurement of whole saliva, and scintigraphy.⁸ In a
review article on the effectiveness of sialography, the method appeared to be less sensitive but more specific than flow measurements of whole saliva, and more sensitive but less specific than labial salivary gland biopsy.9
Not surprisingly, the presence and severity of sialectatic changes in the parotid gland is paralleled by the degree of hyposalivation; this is in contrast to only a weak or absent relationship between a positive labial salivary gland biopsy and the degree of hyposalivation.10-12 Furthermore, in comparison with labial salivary gland biopsy, sialography has the advantage of being a relatively noninvasive technique.
Although it was stated that (non-obstructive) sialectatic changes in the salivary glands are pathognomonic for SS5, 3 other diseases, unrelated to SS, have been reported to cause similar glandular changes; they are HIV-infection, psoriatic arthritis, and acute (bacterial) parotitis.13-15 Sialectasia has also been identified in 9% of control subjects with supposedly normal parotid glands; this condition is called primary (idiopathic) sialoangiectasia.16-18 A congenital developmental disorder might cause this condition.16,19
The following case report describes a patient with primary sialoangiectasia who was originally misdiagnosed, mainly on the basis of sialography, as having SS.

CASE REPORT
In October 1997, a 56-year-old homosexual man was referred to the Department of Oral and Maxillofacial Surgery and the Department of Ophthalmology by his rheumatologist for confirmation of a diagnosis of primary Sjögren's syndrome. Eleven years earlier, the diagnosis of primary Sjögren's syndrome had been made at another institution on the basis of clinical complaints, parotid gland sialography demonstrating globular sialectasia, and a positive Schirmer's test. At that time, serologic findings were negative for rheumatoid arthritis factor, antinuclear antibodies, SSA-antibodies, and SSB-antibodies, and labial salivary gland biopsy showed no lymphocytic infiltration. The patient’s medical history included tuberculosis during infancy, recurrent peri-anal herpetic infections since 1986, mild psoriasis since 1987 and a neuropathy of the phrenic nerve since 1996. The patient had stopped working as a male nurse 9 years earlier because of complaints attributed to his diagnosis of primary Sjögren's syndrome.
On admission at our outpatient department, the patient complained of chronic fatigue, arthralgia, tendinomyalgia, and ocular dryness. The patient had no complaints of oral dryness, nor did he have a history of recurrent parotitis. Physical examination showed a patient with general adiposity and a diffuse symmetrical,
nontender enlargement of both parotid glands. No palpable lymph nodes were found in the head and neck region.

Intraoral examination showed a normal oral mucosa, salivary pooling in the floor of the mouth, and a well-preserved dentition. Sialometrical analysis showed normal resting and 2%-citric-acid-stimulated flows of whole saliva. Gland-specific sialometry showed normal secretion values for the submandibular and sublingual salivary glands and slightly decreased values for the parotid glands. Sialochemical analysis revealed normal values for electrolytes, total protein, and amylase in acid stimulated parotid and submandibular saliva (table 7.1.1). Sialography of the right parotid gland, repeated to examine the disease progression, showed globular sialectasia (figure 7.1.1). This sialographic image was similar to the one that was made eleven years before; no progression was noted. An incisional biopsy of the right parotid gland showed fatty serous glandular tissue without pathological changes.

| Table 7.1.1. Findings of sialometry (salivary flow rates) and sialochemistry (saliva composition). |
| SM/SL = submandibular / sublingual. |
| Salivary gland | Right parotid | Left parotid | SM/SL |
| Flow | | | |
| Unstimulated flow (ml/min) | 0.05 | 0.02 | 0.40 |
| Stimulated flow (ml/min) | 0.16 | 0.24 | 1.26 |
| Chemistry | | | |
| Sodium (mmol/L) | 7 | 5 | 6 |
| Potassium (mmol/L) | 23 | 21 | 17 |
| Chloride (mmol/L) | 17 | 16 | 17 |
| Total protein (g/L) | 1.41 | 1.25 | 1.88 |
| Amylase (10^3 U/L) | 275 | 320 | - |

Laboratory investigations revealed a normal full blood count, a normal white blood count differentiation and erythrocyte sedimentation rate, and normal levels of C-reactive protein, amylase, lactic-acid dehydrogenase, alkaline phosphatase, transaminases, and immunoglobulins (IgG 12.8, IgA 2.4, IgM 0.9 g/L). Immunologic tests showed negative serology for rheumatoid arthritis factor, antinuclear antibodies, SSA-antibodies, and SSB-antibodies. Furthermore, the patient tested negative for HIV.

Ophthalmologic examination in the Department of Ophthalmology showed a negative Schirmer’s test (8/10 mm, right and left eyes), a negative Rose Bengal staining of both eyes, and a positive break-up time (3 seconds).

Physical examination in the Department of Rheumatology showed tender points (11/18) according to the American College of Rheumatology criteria in the absence of signs of arthritis.

Because the patient did not fulfil any of the nine currently proposed sets of diagnostic criteria for SS, the diagnosis primary Sjögren’s syndrome was rejected.
Some of the patient’s complaints - i.e. tendinomyalgia and fatigue – might be related to the diagnosis of psoriasis; others remained unexplained, however. The sialographic findings were defined as primary sialoangiectasia.

**DISCUSSION**

A patient is presented showing evident sialectatic changes on the sialogram, supporting the diagnosis of SS as a possible explanation for his complaints of chronic fatigue, arthralgia, tendinomyalgia, and ocular dryness. Despite these findings, it seems that this patient had not had Sjögren’s syndrome for the past 11 years, for both the serologic findings and the histopathologic findings were negative for SS, as were the findings of sialometry and sialochemistry. Moreover, the sialogram showed no further glandular destruction with time. In addition, the absence of oral complaints argues against the diagnosis of SS. With a decreased break-up-time and globular sialectasia on the sialogram as the only objective signs, sufficient evidence for the diagnosis of primary Sjögren’s syndrome is lacking.

The complaints of chronic fatigue, arthralgia, tendinomyalgia, and ocular dryness and the abnormal sialographic findings make a striking combination. After the diagnosis of SS was ruled out, the question of whether these symptoms and signs share another common cause was raised. An HIV-infection would have been a logical explanation for several reasons. It is known that HIV can cause swelling of the parotid glands and sialectasia of the ductal and acinar system (HIV-salivary gland disease), mimicking changes that are seen in SS. The chronic fatigue, the
arthralgia, the tendinomyalgia and the ocular dryness all are common manifestations of AIDS related complex.\textsuperscript{25-31} Moreover, as a homosexual the patient belonged to a high-risk group for infection with HIV. However, although HIV-infection was in theory a logical explanation, the patient tested negative for HIV. Other diseases that might have caused the observed sialectasia were also ruled out. No signs of arthritis were found during rheumatologic examination; the patient therefore could not be classified as having psoriatic arthritis, a diagnosis that has been associated with sialectasia in the parotid glands.\textsuperscript{13} Furthermore, the patient did not have a history of acute parotitis, which is another possible cause for sialectasia in the parotid glands. The patient did have a history of tuberculosis during infancy, a disease that is known to cause specific changes in the salivary glands\textsuperscript{16,32}; however these changes, described as complicated patterns that are difficult to distinguish from malignant tumors, are not compatible with the sialographic findings observed in the reported case. Apparently, none of the diseases known to cause sialectasia in the salivary glands can be held responsible for the sialographic findings in the reported case. Therefore, as a diagnosis of exclusion, the observed sialectasia was defined as primary or idiopathic sialoangiectasia.

Because the sialographic findings in the reported case initially led to a misdiagnosis, the value of sialography as a pathognomonic diagnostic tool is questionable. Sialography is certainly not a pathognomonic diagnostic tool in SS, because other conditions can cause similar sialograms, as previously mentioned. However, to assess the oral component of SS, sialography provides relevant information regarding disease activity and progression by showing ductal and acinar changes in the salivary glands that are related to the degree of hyposalivation. If sialography is combined with other methods in assessment of the oral component, the risk of an unfortunate misdiagnosis caused by primary sialoangiectasia is eliminated. Although it is less invasive than salivary gland biopsy and although it is competitive with respect to diagnostic value (sensitivity and specificity), sialography should not be used to replace the histopathologic analysis for confirmation of the diagnosis of SS.

**References**


SUMMARY

A 32-year-old woman is demonstrated who presented with sarcoidosis and Sjögren’s syndrome. Diagnoses of both diseases were based on current internationally accepted criteria. Furthermore, histopathological findings characteristic for both diseases were present in salivary gland biopsies. As sarcoidosis is considered an exclusion criterion for Sjögren’s syndrome in current sets of diagnostic criteria we propose that these criteria should be reconsidered with respect to the exclusion of sarcoidosis.
SIMULTANEOUS PRESENTATION OF SARCOIDOSIS AND SJÖGREN’S SYNDROME. CASE REPORT

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INTRODUCTION

Coexistence of sarcoidosis and autoimmune diseases has been described in several case reports.¹⁻⁵ Simultaneous presentation of sarcoidosis and Sjögren’s syndrome has been suggested in several reports¹⁻⁴,¹⁸, but internationally accepted criteria for the diagnosis of Sjögren’s syndrome¹⁹⁻²⁵ were not met. We present a case in which both disease entities, sarcoidosis and Sjögren’s syndrome, presented simultaneously and were diagnosed based on accepted criteria. Although sarcoidosis is generally considered an exclusion criterion for the diagnosis of Sjögren’s syndrome, this exclusion criterion needs critical reconsideration as demonstrated by the following case report.

CASE REPORT

A 32-year-old woman was referred to the outpatient clinic because of pretibial painful red nodules. She had a 6-month history of migratory pain and swelling of several joints. She had daily complaints of progressive oral dryness, thirst, impaired swallowing and blurred vision with a feeling of dry eyes for more than three hours a day. She did not feel dyspneic. Past medical, family, occupational and environmental history were non-contributory. She used an oral contraceptive and ibuprofen. Physical examination, which was otherwise not remarkable, showed edema of the ankles and erythema nodosum on both legs. The parotid glands were not enlarged or painful.
Laboratory investigations revealed an ESR of 44 mm/h (n: <10), a CRP level of 42 mg/l (n: < 3). Haemoglobin concentration, leukocyte and thrombocyte count, glucose, electrolytes, creatinine level, liver and thyroid function, Ca, total protein, protein electrophoresis and 1.25(OH)₂-vitamin D₃ were all within the normal range. Urine analysis showed no erythrocytes. Creatinine clearance and urinary Ca-excretion were normal, slight proteinuria of 300 mg of protein/24 h was present. Serum lysozyme was elevated at 9.7 mg/l (n: 0.6-2.6), angiotensin-converting-enzyme (ACE) was 134 U/l (n: <45). Antinuclear antibody (ANA), antibodies to extractable nuclear antigens (ENA) and anti-dsDNA (Farr-assay) were all negative. Antibodies against SS-A were positive. IgM-rheumatoid factor was elevated at 105 kilo-U/l (n: <15). Levels of IgG were 19.2 g/l (n: 8.5-15.0); IgA 5.4 g/l (n: 0.9-4.5) and IgM 2.2 g/l (n: 0.6-2.6). No cryoglobulins were found. A tuberculin test with purified protein derivate (PPD) was negative.

A chest radiograph showed extensive mediastinal and bilateral hilar lymphadenopathy with tracheal displacement to the left and increased interstitial lining. Pulmonary function tests (lung volumes and diffusing capacity for carbon monoxide) were normal. Radiographs of hand and feet showed bilateral cystic lesions and small erosion of the left basisphalanx (hand) of the third generation. Ophthalmologic examination demonstrated a normal Schirmer’s tear test of 10 and 9 mm/5 min of the right and left eye, respectively (n: ≥5.5 mm/5 min) but a decreased tear film break-up time of 2 seconds for both eyes (n: ≥10 s before the tear film breaks) and a positive Rose Bengal staining (score of 5 and 3 according to Van Bijsterveld, of the right and left eye, respectively; n: ≤3.5), consistent with keratoconjunctivitis sicca.²⁶

Sialometrical analysis showed a reduced unstimulated and stimulated (2% citric acid) flow of whole saliva (unstimulated flow n: >0.1 ml/min; stimulated flow n: > 0.7 ml/min).²⁷ In detail, the reduced unstimulated flow of whole saliva was caused by a very low secretion of all individual salivary glands (<0.01 ml/min), whereas the reduced stimulated flow of whole saliva was mainly caused by very low secretion of the parotid glands (0.02 ml/min/gland; n ≥0.05-0.5 ml/min).²⁸⁻³⁰ Sialochemistry revealed elevated sodium concentrations and a normal amylase content in both whole, parotid and submandibular/sublingual saliva. Sialography of the right parotid gland showed punctate sialectasia, characteristic for Sjögren’s syndrome (figure 7.2.1).³¹
To differentiate between Sjögren's syndrome and sarcoidosis as cause of the observed salivary gland dysfunction, an incisional parotid biopsy was taken. Histopathological examination of parotid tissue showed epithelioid cell granuloma as well as periductal lymphocytic infiltration and epimyoepithelial islands (figure 7.2.2). Immunohistochemical staining showed a polyclonal plasmacytic infiltrate and a shift in the relative number of IgA bearing plasma cells in favour of IgG bearing plasma cells. These histopathological findings, which are in part suggestive for Sjögren's syndrome, asked for an additional labial salivary gland biopsy, in order to meet the current international standard for histological confirmation of Sjögren's syndrome. This revealed extensive epithelioid cell granuloma and lymphocytic infiltration with a positive focus score of 1 (n: <1; focus defined as ≥50 mononuclear cells/4 mm²) (figure 7.2.3). Since Sjögren's syndrome is associated with an increased incidence of malignant lymphoma, (a relative risk ratio of 44), the extensive mediastinal lymphadenopathy prompted us for additional histologic examination. Cervical mediastinoscopy of the lymphnodes revealed epithelioid
cell granuloma, with a negative auramine staining, and without evidence of malignant lymphoma.

The patient was diagnosed as having sarcoidosis, presenting as Löfgren's syndrome, with coexisting Sjögren's syndrome. Six months after the first presentation she developed a transient nontender bilateral cervical and supraclavicular lymphadenopathy. During a two years follow-up, laboratory investigations revealed a normalisation of CRP (<3 mg/l) and ACE-activity (31 U/l). IgM-rheumatoid factor was elevated to 210 k-U/l and stabilised to 115 k-U/l with persistence of SS-A antibodies. Repeated sialometrical analysis showed persisted reduction of unstimulated and stimulated flow of whole saliva with further reduction of the submandibular/sublingual salivary secretion. Sialochemistry revealed persisted elevation of sodium concentration compatible with chronic inflammation. Finally, a chest radiograph showed a major reduction in mediastinal and hilar lymphadenopathy. Until now, she has been treated symptomatically for her sicca complaints.

**DISCUSSION**

A patient is described with migratory symmetrical polyarthritis, erythema nodosum, extensive generalised lymphadenopathy, and sicca syndrome, in which two disease entities, sarcoidosis and Sjögren’s syndrome presented simultaneously. The diagnosis of sarcoidosis (Löfgren's syndrome) was confirmed by the presence of epithelioid cell granuloma in mediastinal lymph nodes, parotid and labial salivary glands, according to recommendations for the clinical evaluation of granulomatous diseases. Currently, seven sets of international criteria for the diagnosis of Sjögren’s syndrome are being used which apply the exclusion criterion of sarcoidosis. Nevertheless, the present case demonstrates that sarcoidosis and Sjögren's syndrome can coexist. The diagnosis of Sjögren’s syndrome was based on signs and symptoms of keratoconjunctivitis sicca and xerostomia, presence of SS-A antibodies and histological conformation of Sjögren's syndrome in both parotid and labial
salivary glands. Although the reduced stimulated secretory function of the parotid glands observed in our patient could also be caused by sarcoidosis, the observed elevation of salivary sodium concentration and the punctate sialectasia on the sialogram are distinctive features in Sjögren's syndrome and have not been described previously in association with sarcoidosis. The normalisation of ACE-activity, the persistence of sialometrical and sialochemical abnormalities and SS-A antibodies during a two years follow-up support the remaining presence of Sjögren's syndrome that initially presented in coexistence with sarcoidosis. Erythema nodosum could be caused either by sarcoidosis, by leukocytoclastic vasculitis associated with Sjögren's syndrome, as well as by hypergammaglobulinemic purpura.

Histopathological examination of salivary gland specimens revealed periductal lymphocytic infiltration as well as epimyoepithelial islands, besides clear evidence for sarcoidosis. These epimyoepithelial islands and periductal lymphocytic infiltration are both common features of major salivary glands in Sjögren’s syndrome. Only occasionally, epimyoepithelial islands were found in association with sarcoidosis. The decreased percentage of IgA bearing plasma cells further supports coexisting Sjögren’s syndrome. However, it is unknown whether an increased percentage of IgG and/or IgM bearing plasma cells may occur in salivary glands of patients with sarcoidosis.

The possibility of a common immunopathogenic pathway for sarcoidosis and Sjögren's syndrome is suggested by several observations. The presence of SS-A antibodies, which are rarely found in healthy individuals or in patients without connective tissue diseases has been associated with sicca complaints in systemic lupus erythematosus (SLE) and with Sjögren's syndrome. The presence of SS-A antibodies has further been shown to define a subset of patients with Sjögren's syndrome with lymphadenopathy and polyclonal hyperglobulinemia. Furthermore, the HLA-DR3 phenotype is associated with primary Sjögren’s syndrome, a subgroup of patients with SLE with the presence of SS-A antibodies as well as with a subgroup of patients with sarcoidosis with a specific antigen-driven overexuberant cellular immune response. In our patient sarcoidosis with coexisting Sjögren's syndrome was diagnosed in the presence of SS-A antibodies. However, the HLA-DR3 phenotype was absent in our case.

Several reports have shown overlap between sarcoidosis and autoimmune disorders including rheumatoid arthritis, SLE, systemic sclerosis, CREST syndrome and spondylarthropaties. In the majority of cases sarcoidosis is associated with SLE in which predominance exists for pulmonary symptoms. In addition, some cases have
been reported suggestive for sarcoidosis and coexisting Sjögren’s syndrome.\textsuperscript{1,4-18}

The incidence of sarcoidosis and Sjögren’s syndrome may be much higher than is suggested by this relatively small number of case reports since presence of sarcoidosis is one of the exclusion criteria for diagnosing Sjögren’s syndrome. In defining exclusion criteria for diseases with similar clinical presentations there might be a risk of underdiagnosis of overlap syndromes. We emphasise that in a subset of patients both disease entities might be present as illustrated in this case with possibly common immunopathogenic mechanisms. Furthermore, the presence of Sjögren’s syndrome may be easily underdiagnosed since extensive epithelioid cell granuloma may dominate the histopathological specimen, especially in minor salivary gland biopsy.

In conclusion, a patient with sarcoidosis and coexisting Sjögren’s syndrome is described suggesting shared immunopathogenic mechanisms. Careful use of exclusion criteria for Sjögren’s syndrome is warranted to define subgroups of patients with overlapping clinical syndromes. We propose that the exclusion criteria currently applied in diagnostic criteria sets for Sjögren’s syndrome need to be reconsidered with regard to the exclusion of sarcoidosis.

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**REFERENCES**