Case Report

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Treatment of serologically negative Sjögren's syndrome with tacrolimus: A case report

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Abstract

We herein report an unusual case of primary Sjögren's syndrome in a 38-year-old woman with typical clinical symptoms (joint pain, dry mouth, and positive Schirmer test) and immunoglobulin G positivity but negativity for antinuclear antibody and all antinuclear antibody spectrum antibodies. Emission computed tomography demonstrated normal ingestion but impaired secretion by the submandibular and bilateral parotid glands. Labial gland biopsy revealed chronic tissue inflammatory changes and Chisholm grade 4 lymphocyte infiltration, confirming primary Sjögren's syndrome. The patient's condition was successfully controlled by nonsteroidal treatment with tacrolimus. Patients presenting with chronic dry mouth should be examined by a Schirmer test, lip gland biopsy, and salivary gland emission computed tomography for possible Sjögren's syndrome, even if serological autoantibodies are negative, to facilitate early intervention. Tacrolimus is a potential treatment option in patients intolerant of steroidal drugs.

Keywords

Antinuclear antibody, Sjögren's syndrome, labial gland biopsy, serologically negative, tacrolimus, case report

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Introduction

Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by destruction of exocrine glands by infiltrating lymphocytes, leading to chronic dry eyes and dry mouth.[1] It is a relatively common immune rheumatism, especially in females.[2] However, because of its nonspecific symptoms, diversity of clinical manifestations,

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The authors desire color illustrations.

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and lack of standardized diagnostic methods, the most appropriate diagnostic criteria are still being debated, and misdiagnosis rates are high in the early stages of the disease.

Previous diagnostic criteria for SS have emphasized the presence of anti-SSA/Ro-52 and anti-SSB antibodies, but it is now clear that both markers are more likely to be found in the late stage of the disease (probability of 30%–60% and 20%–40%, respectively).[4–10] Therefore, many patients with SS are not accurately diagnosed until the onset of more serious complications, such as dental caries, pulmonary interstitial fibrosis, B-cell lymphoma, kidney disease, and exocrine gland destruction. Indeed, the average patient with SS is not diagnosed or treated until 3.9 years after symptom onset, by which time there is often unexplained tissue damage and associated psychological distress.[11] Typical cases are characterized by dry mouth, dry eyes, and autoantibody abnormalities, and the condition is then confirmed by pathological examination of the labial glands. We herein report a case involving a 38-year-old woman who presented with joint pain and dry mouth but antinuclear antibody (ANA) and ANA spectrum (ANAs) negativity. Identification of exocrine gland secretion deficiency and tissue destruction at biopsy contributed to the diagnosis of primary SS (pSS) according to the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria.[3]

Case report

A 38-year-old woman was admitted to our hospital because of a 6-month history of joint pain and dry mouth causing her to wake up from thirst at night. She reported no history of dry eyes, blurred vision, abdominal pain, fever, or ecchymosis of the lower extremities. She had no history of head and neck radiotherapy and no relevant medical history. Laboratory tests showed negative rheumatoid factor, anticyclic citrullinated polypeptide antibody, ANA, and ANAs and a high C-reactive protein level and erythrocyte sedimentation rate. In view of her dry mouth, high immunoglobulin G (IgG) level (20.4 g/L), normal blood glucose level, normal submandibular gland and bilateral parotid gland function but impaired excretion function, positive Schirmer test (4.8 mm/5 minutes for the bilateral lacrimal glands), and negative upper abdominal computed tomography (CT) scan/enhancement, we considered the potential of SS despite her negative ANA and ANAs (Figure 1). The labial gland biopsy revealed multiple foci of lymphocyte infiltration, structural destruction of the parotid lobules, and partial atrophy of the acini (Figure 2). Pathological examination of the tissue showed chronic inflammatory changes and Chisholm grade 4 lymphocyte infiltration. These abnormalities combined with the patient's medical record and auxiliary examination findings led to a final diagnosis of pSS according to the 2016 ACR/EULAR classification criteria (score of 5 points).[3] After 3 months of tacrolimus treatment instead of steroid treatment, the patient's dry mouth was improved and her IgG level had decreased to normal.

Discussion

The precise etiology of SS is still unclear but may be related to immunological dysfunction, viral infection, an endocrine (sex hormone) disorder, genetic inheritance, or a combination of these factors.[12,13] At the initial stage, typical symptoms of SS are mainly manifestations of exocrine gland damage, such as dry mouth and eyes, and many patients choose to consult a dentist or ophthalmologist instead of a rheumatologist. Hence, improving physicians' awareness of SS and ensuring broader

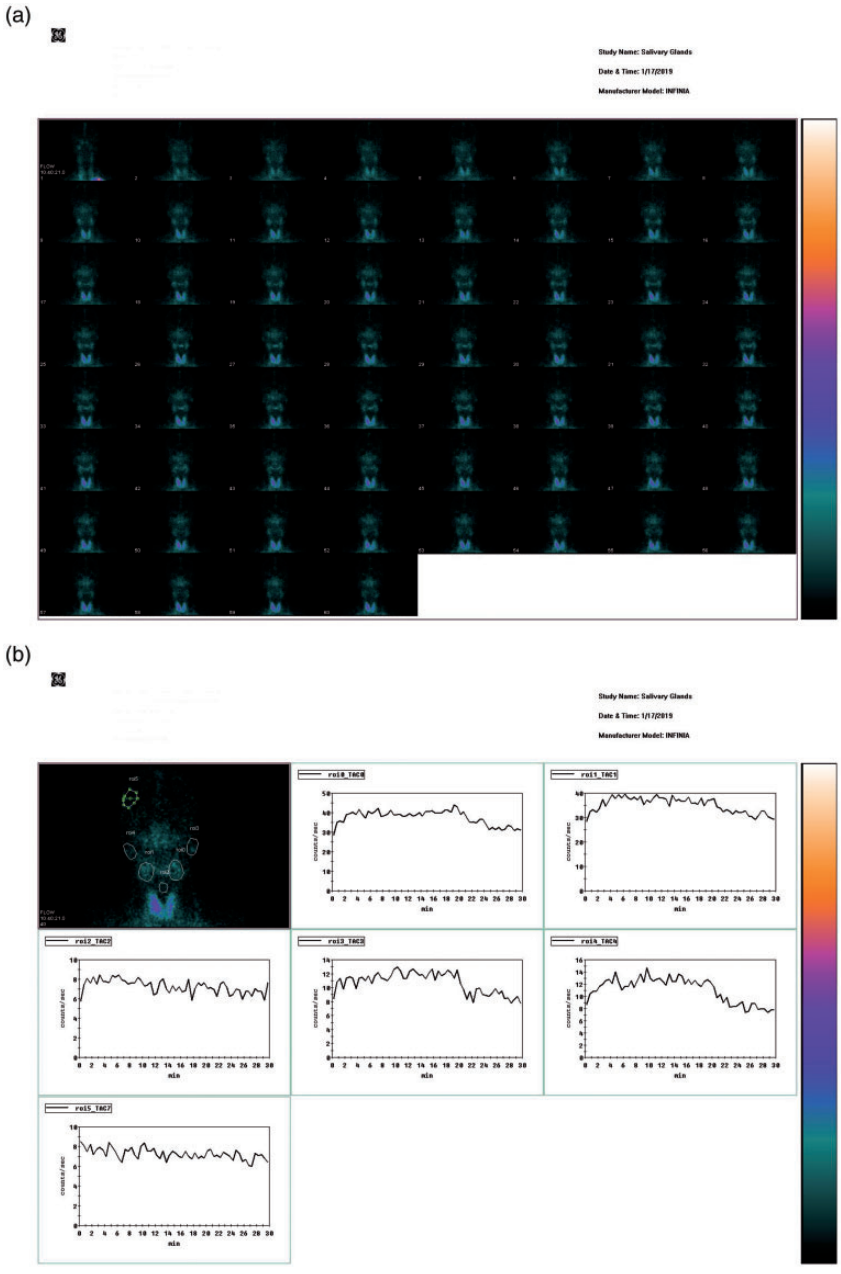

Figure 1. (a) Single-photon emission computed tomography of the salivary glands. (b) Salivary gland emission time curve.

application of auxiliary examinations can reduce diagnostic errors and omissions.

ANA and ANAs are important screening indicators for SS. In the present case, however, the patient presented with no specific serological evidence. Although autoantibodies indicative of possible SS were seronegative, the serum IgG level was high

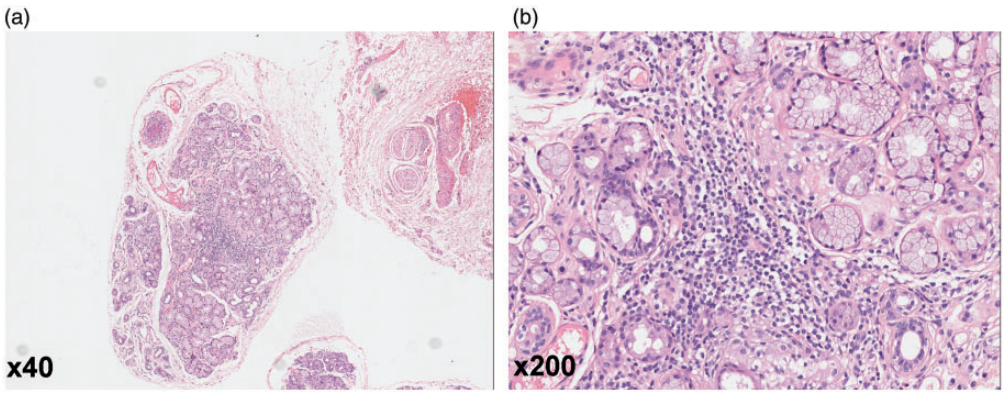

Figure 2. Hematoxylin–eosin stained labial gland sections (biopsy).

and a Schirmer test was positive. More importantly, salivary gland emission CT (ECT) showed exocrine gland dysfunction and biopsy revealed severe glandular destruction. We considered these to be signs of SS because the patient had no history or current evidence of hepatitis C virus infection, head and neck facial radiotherapy, acquired immunodeficiency syndrome, graft-versus-host disease, sarcoidosis, or IgG4-related disease. According to 2016 ACR/EULAR criteria for SS,[3] the patient's labial gland result score was 3 points and her Schirmer test score was 1 point (<5 mm/5 minutes). Salivary gland ECT allows for comparison of salivary gland uptake and secretion before and after vitamin C administration by nuclide measurement. Although we did not measure the salivary gland flow rate, salivary gland ECT examination showed impaired bilateral parotid gland and submandibular gland secretory function, which was scored 1 point. Therefore, the final diagnosis was pSS based on 5 points according to the ACR/EULAR criteria.

Our patient refused steroid therapy because of concern regarding adverse effects. Destruction of the exocrine glands is caused by infiltrating lymphocytes (T cells, B cells, and natural killer cells). Tacrolimus is a calcineurin inhibitor that can block T-cell nuclear factor activation, thereby acting as an immunosuppressive agent. In recent years, the safety and efficacy of tacrolimus for treatment of lupus nephritis have been confirmed.[14–16] Additionally, tacrolimus is reportedly effective against rheumatoid arthritis,[17] progressive interstitial pneumonia with systemic sclerosis,[18] SS complicated with meningoencephalomyelitis,[19] and interstitial cystitis.[20] Moreover, according to the 2017 British Society for Rheumatology guidelines on the management of adult pSS, external tacrolimus can be used as a substitute for hydroxychloroquine in patients with discomfort.[21] Tacrolimus at 1 mg twice a day is frequently prescribed for subsequent immunoregulatory treatment. In the current case, the patient's dry mouth was significantly improved and her IgG level was normal after 3 months of treatment.

Generally, SS is considered less likely in patients with negative ANA and ANAs. The new diagnostic criteria for pSS introduced by the ACR/EULAR in 2016 include the provision that serological anti-SSA/Ro seropositivity instead of anti-SSB/La seropositivity is still indicative of pSS. The most common ANAs in SS is a lack of either anti-SSA/Ro-52, anti-SSB, or ANA, but negativity for all three autoantibodies

has not been reported. Our patient had few clinical signs of pSS and was diagnosed only after ECT and labial biopsy.

In this case, early diagnosis of pSS allowed for timely treatment, which may prevent or delay progression of the disease and associated complications such as dental caries and kidney damage. Consequently, patients with chronic dry mouth or dry eyes should be made aware of potentially serious underlying pathologies such as pSS. Even if such patients are seronegative for autoantibodies, they should still undergo a Schirmer test, salivary gland ECT, and labial gland biopsy to reduce the risk of misdiagnosing pSS and to facilitate timely intervention.

This diagnostic regimen and our clinical conclusions have some limitations. First, while a radionuclide scan can reflect the uptake and secretory function of the salivary glands, its diagnostic specificity may be poor.[22] Second, while tacrolimus monotherapy demonstrated a curative effect, many additional cases are required to confirm its general efficacy for pSS.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Statement of ethics

The patient provided written informed consent for the publication of this case report. The study protocol was approved by the Medical Ethics Committee of the Affiliated Hospital of Zunyi Medical University.

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