

CLINICAL PRACTICE

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Primary Sjögren's Syndrome

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 52-year-old woman presents with a 2-year history of an extremely dry mouth. She has difficulty swallowing dry food and has to drink water throughout the night. She also reports having episodes of fatigue and pain in her hands and wrists, particularly in the morning. Ten years before presentation, ocular discomfort and dryness caused her to discontinue the use of contact lenses. She has had several episodes of swelling of the parotid glands during the past 2 years. The physical examination reveals dry mouth, palpable purpura on the legs, three swollen joints, and bilateral swelling of the parotid glands. Laboratory studies reveal lymphocytopenia (850 cells per cubic millimeter) without other abnormalities in the blood count, a serum creatinine level of 1.6 mg per deciliter (140 µmol per liter; as compared with 0.7 mg per deciliter [60 µmol per liter] 1 year earlier), polyclonal gammopathy, positive rheumatoid factor, the presence of antinuclear antibodies (including antibodies against Sjögren's syndrome-related antigen A [anti-SSA antibodies]), and a low C4 level without cryoglobulinemia. How should this patient's case be managed?

THE CLINICAL PROBLEM

PIMARY SJÖGREN'S SYNDROME IS A COMMON SYSTEMIC AUTOIMMUNE disease, with a female-to-male predominance of 9:1 and peak incidence at approximately 50 years of age.¹ The hallmark of the disease is exocrinopathy, which often results in dryness of the mouth and eyes, fatigue, and joint pain. These three symptoms are present in more than 80% of the patients with this disease and have a major effect on quality of life, primarily because of disabling fatigue, with associated loss of work productivity.² This condition may occur in isolation or in association with organ-specific autoimmune diseases, such as thyroiditis or primary biliary cirrhosis or cholangitis, in which case the disease is referred to as primary Sjögren's syndrome. In contrast, the term secondary, or associated, Sjögren's syndrome has been used when the disease occurs in association with another systemic autoimmune disease, such as rheumatoid arthritis, systemic lupus erythematosus (SLE), scleroderma, or dermatomyositis.

On the basis of formal criteria for the diagnosis,³ which require the presence of immunologic abnormalities (the presence of serum anti-SSA antibodies or focal lymphocytic sialadenitis on biopsy of labial salivary glands), the estimated prevalence is 0.3 to 1 per 1000 persons.¹ The major diagnostic challenge relates to the fact that mouth and eye dryness, limb pain, and fatigue are very common in the general population and may be associated with fibromyalgia or other pain syndromes, whereas primary Sjögren's syndrome is relatively rare. Although the

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N Engl J Med 2018;378:931-9.

DOI: 10.1056/NEJMcp1702514

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KEY CLINICAL POINTS

PRIMARY SJÖGREN'S SYNDROME

- A diagnosis of primary Sjögren's syndrome is often made on the basis of a classic triad of symptoms: dryness of the mouth and eyes, fatigue, and pain. Systemic complications, which are present in 30 to 40% of patients, may provide the first clues to the disease.
- The risk of B-cell lymphoma is markedly increased (by a factor of 15 to 20) among patients with primary Sjögren's syndrome, as compared with the general population.
- Treatment relies on muscarinic agonists (pilocarpine hydrochloride and cevimeline hydrochloride). The main adverse effect of these agents is sweating, which can be minimized by gradual escalation of the dose.
- Hydroxychloroquine is often used for arthralgia with or without synovitis and purpura, although benefits have not been shown in a randomized, controlled trial.
- In the absence of trials involving patients with primary Sjögren's syndrome, severe organ manifestations are treated with immunosuppressive agents (including prednisone, methotrexate, mycophenolate sodium, azathioprine, and cyclophosphamide), in accordance with guidelines for systemic lupus erythematosus and other connective-tissue diseases.

recently validated American College of Rheumatology (ACR)–European League against Rheumatism (EULAR) criteria were designed for the purposes of classification,³ they may also be useful in establishing a diagnosis of primary Sjögren's syndrome in the context of these common symptoms (Table 1).

SYSTEMIC COMPLICATIONS

Systemic manifestations occur in approximately 30 to 40% of the patients with primary Sjögren's syndrome (Fig. 1).^{4,5} Lymphocytic infiltration of the epithelia of organs beyond the exocrine glands can cause interstitial nephritis, autoimmune primary biliary cholangitis, and obstructive bronchiolitis. Immune complex deposition as a result of the ongoing B-cell hyperreactivity can result in extraepithelial manifestations, such as palpable purpura, cryoglobulinemia-associated glomerulonephritis, interstitial pneumonitis, and peripheral neuropathy. Renal involvement in primary Sjögren's syndrome differs from that in SLE, since it is typically characterized by interstitial nephritis and associated with systemic acidosis, low levels of proteinuria, and progressive loss of renal function. Glomerulonephritis occurs more rarely in primary Sjögren's syndrome than in SLE and is most often associated with cryoglobulinemia.⁶

PATHOPHYSIOLOGICAL FEATURES

Current models of the pathophysiological features of this disease implicate the activation of mucosal epithelial cells, possibly from viral stimulation or from abnormal production of endogenous

viral elements. This process leads to the activation of the innate and adaptive immune systems with the secretion of autoantibodies. These autoantibodies constitute immune complexes that maintain and amplify the production of interferon alpha, resulting in a cycle of immune-system activation that leads to tissue damage.

Data to support such models are derived from studies of innate immunity, genetics, and B-cell activation in primary Sjögren's syndrome. The increased expression of genes related to interferon (either type I or type II) can be detected in salivary glands and blood in more than half the patients with this disease.⁷⁻¹¹ Consistent with this finding, multiple viral agents have been hypothesized to have a role in the disease, although none have been shown to be causal.¹² Genomewide association studies have shown associations between the syndrome and genes linked to interferon pathways.¹³⁻¹⁵ The presence of ectopic germinal centers in salivary glands highlights the B-cell activation that is characteristic of primary Sjögren's syndrome. Recent studies have suggested the presence of plasma-blasts in the blood and plasma cells in the salivary glands¹⁶ and of activated CD8 T cells in the blood and glands.¹⁷ The level of B-cell activating factor of the tumor necrosis factor family (BAFF), a cytokine that promotes B-cell maturation, proliferation, and survival, is increased in primary Sjögren's syndrome, both in the serum and in salivary glands.¹² BAFF, induced by interferon type I and type II, provides a link between innate immunity and autoimmunity in disease pathogenesis.¹²

Table 1. 2017 ACR–EULAR Classification Criteria for Primary Sjögren's Syndrome.*

Item	Description	Score
Focus score of ≥ 1	A score determined by the number of mononuclear-cell infiltrates containing ≥ 50 inflammatory cells per 4 mm^2 of minor labial salivary gland obtained on biopsy	3
Presence of anti-SSA antibodies†	Measured in serum; only anti-Ro60 antibodies have to be considered; isolated anti-Ro52 antibodies are not specific for Sjögren's syndrome	3
SICCA ocular staining score of ≥ 5	A score determined by an ophthalmologist on the basis of examination with fluorescein and lissamine green staining; scores range from 0 to 12, with higher scores indicating greater severity	1
Schirmer test of $\leq 5 \text{ mm}$ per 5 min	An assay for measuring tear production by inserting filter paper on conjunctiva in the lower eyelid and assessing the amount of moisture on the paper	1
Unstimulated whole salivary flow of $\leq 0.1 \text{ ml}$ per min	An assay for measuring the rate of salivary flow by collecting saliva in a tube for at least 5 min after the patient has swallowed	1
Total score		9

* On the basis of the listed classification criteria, a diagnosis of primary Sjögren's syndrome is defined as a score of 4 or more. These criteria apply to patients who have at least one symptom of ocular or oral dryness or the presence of systemic manifestations suggestive of primary Sjögren's syndrome. Exclusion criteria include active hepatitis C virus infection on polymerase-chain-reaction assay, radiotherapy of the cervical spine, sarcoidosis, graft-versus-host disease, receipt of anticholinergic drugs, and IgG4-related disease. ACR denotes American College of Rheumatology, EULAR European League against Rheumatism, SICCA Sjögren's International Collaborative Clinical Alliance, and SSA anti-Sjögren's syndrome-related antigen A.

† Positive serologic results for anti-SSB/La antibodies in the absence of anti-SSA/Ro antibodies is not specific and is no longer considered to be a criterion for the diagnosis.

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

A diagnosis of primary Sjögren's syndrome is often considered on the basis of the classic symptoms of mouth and eye dryness, fatigue, and pain. However, systemic complications sometimes provide the first clues to the disease. Patients presenting with such complications should routinely be queried about manifestations of primary Sjögren's syndrome and about the presence of other autoimmune diseases among family members.

LABORATORY TESTING

Anti-SSA antibodies (often associated with antibodies against Sjögren's syndrome-related antigen B [anti-SSB antibodies]) are present in two thirds of patients and should be assessed when primary Sjögren's syndrome is suspected. Rheumatoid factor is present in approximately half of the patients, whereas antibodies against double-stranded DNA (important in the diagnosis of SLE) are typically absent. Biopsy of minor salivary

glands is typically recommended for establishing a diagnosis of primary Sjögren's syndrome in the absence of anti-SSA antibodies. Such a biopsy procedure is usually performed by an oral medicine specialist or another clinician with specialized training.

Measures of oral and ocular dryness may also be useful. Among such measures, Schirmer's test of ocular dryness and determination of the unstimulated salivary flow rate to assess oral dryness can be performed by any clinician with appropriate training. Ultrasonography of the major salivary glands may reveal multiple hypoechoic or anechoic areas in the four main salivary glands (parotid and submandibular glands) and may be helpful in diagnosis or longitudinal assessment, although such evaluation is not formally included among the classification criteria (Fig. 2).¹⁸

Two indexes for the assessment of disease activity in primary Sjögren's syndrome have been validated by EULAR. The EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) is the mean of three visual-analogue scales that assess

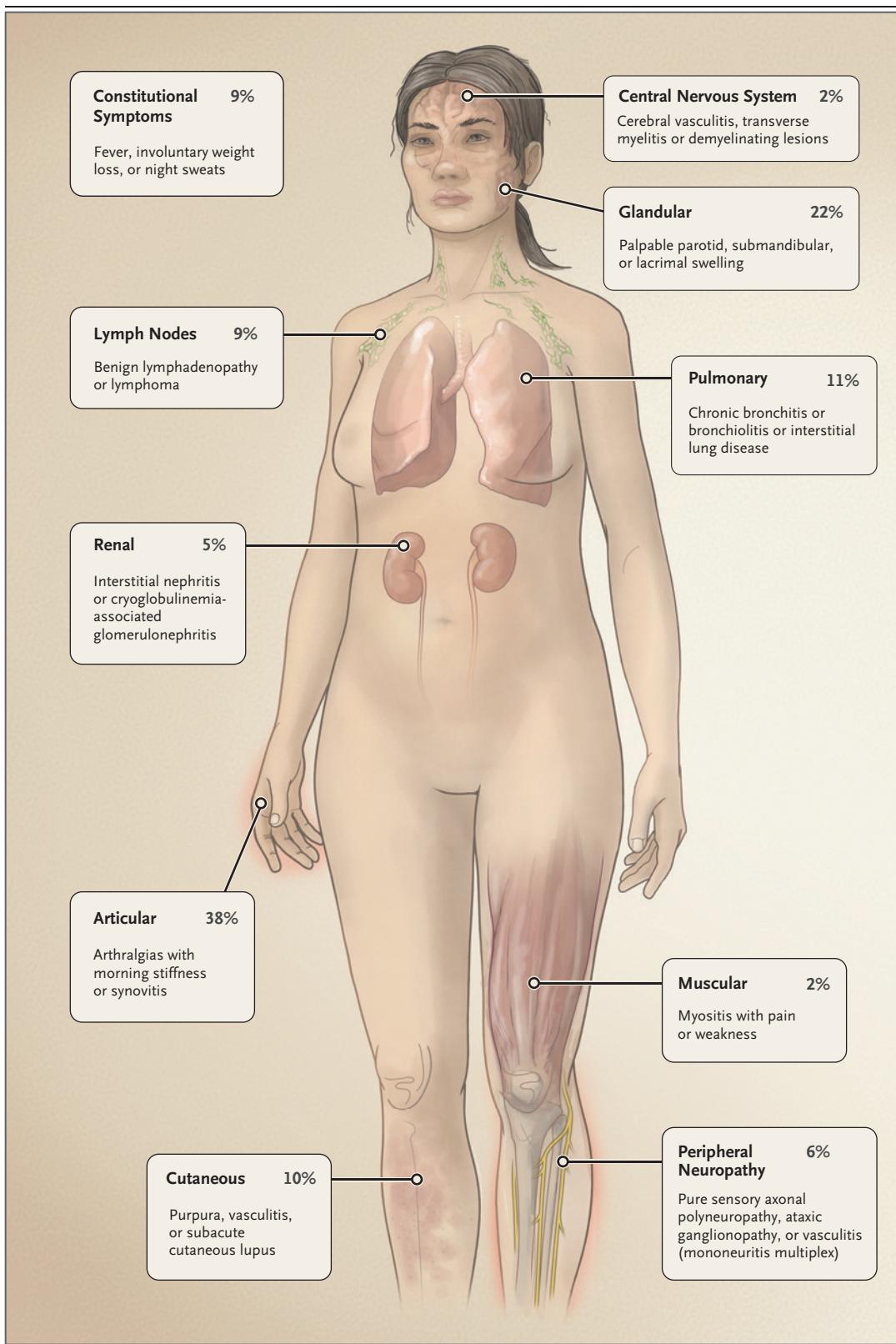


Figure 1 (facing page). Systemic Manifestations of Primary Sjögren's Syndrome.

The percentages of patients with the various manifestations of primary Sjögren's syndrome were derived from reports in the Sjögren Big Data project,⁴ which includes information on more than 10,000 patients with primary Sjögren's syndrome from 22 countries. The patients were classified according to the domains on the Sjögren's Syndrome Disease Activity Index of the European League against Rheumatism.

mouth and eye dryness, fatigue, and pain in a simple patient-administered questionnaire¹⁹ (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI)²⁰ assesses systemic complications of the disease in 12 domains and is used only in clinical trials (Table S1 in the Supplementary Appendix).

RISK OF LYMPHOMA

The risk of B-cell lymphoma is 15 to 20 times as high among patients with primary Sjögren's syndrome as in the general population (lifetime risk, 5 to 10%),^{21,22} a finding that has been attributed to the chronic B-cell activation in this condition. These lymphomas are mostly B-cell non-Hodgkin's lymphomas, with a predominance of the low-grade, marginal-zone histologic type. Lymphomas often develop in organs in which primary Sjögren's syndrome is active, such as the salivary glands, and thus are primarily mucosa-associated lymphoid tissue (MALT) lymphomas.²²

Features that are associated with an increased risk of lymphoma among patients with primary Sjögren's syndrome are listed in Table 2; most of these features are assessed by clinical examination or by readily available blood tests. The simplest of these tests (lymphocyte count, protein electrophoresis, rheumatoid factor, C3 and C4 protein, and cryoglobulin) are recommended every 1 to 2 years. In patients who are considered to be at higher risk, assessments every 6 months may be appropriate, although data that show improved outcomes with close surveillance are limited. When lymphoma is suspected, imaging studies such as positron-emission tomography may be helpful, although diagnosis requires tissue biopsy.

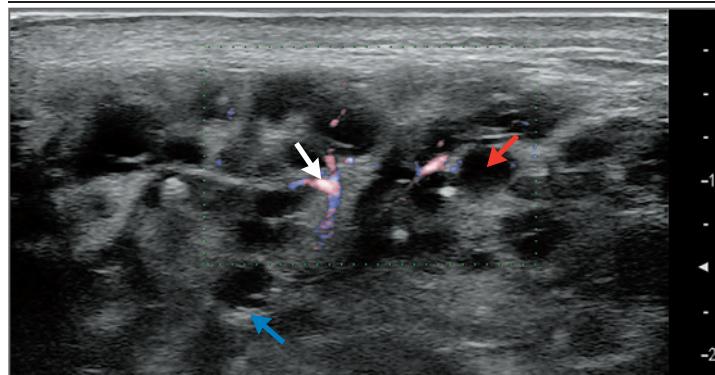


Figure 2. Ultrasonography of a Parotid Gland in a Patient with Primary Sjögren's Syndrome.

The main ultrasonographic characteristics of the disease are the multiple hypoechoic or anechoic areas (>10 in this scan) (red arrow), hyperechoic reflections at the border of these anechoic areas (blue arrow), and sometimes hypervascularization (white arrow). All these abnormalities are usually present in the four main salivary (parotid and submandibular) glands. Courtesy of Dr. Gilles Gailly, Hôpitaux Universitaires Paris Sud.

MANAGEMENT

A systematic review of randomized clinical trials has shown the benefit of muscarinic agonists (pilocarpine hydrochloride and cevimeline hydrochloride) for the treatment of oral dryness and, to a lesser extent, ocular dryness in patients with primary Sjögren's syndrome.²³ A placebo-controlled trial evaluating two doses of pilocarpine (2.5 mg and 5 mg every 6 hours) in 373 patients showed that the 5-mg group had a higher frequency of improvement than the placebo group in dry mouth (61% vs. 31%, $P<0.001$) and dry eye (42% vs. 26%, $P=0.009$); there was no significant effect of the 2.5-mg dose on these outcomes.²⁴ The main side effect of cholinergic agonists is sweating, which can be minimized by a gradual increase in the dose. (For example, pilocarpine could be started at 2 mg once or twice a day, with progressive dose escalation to 5 mg three or four times per day.) The use of topical cyclosporine eyedrops (0.05% or 0.1% concentration) has been shown to result in better tear production than placebo and in improvement in symptom scores among patients with moderate or severe ocular dryness and inflammation, although such findings have been mixed.²⁵ Ocular glucocorticoid drops are not recommended in such patients, since they are not very effective²³ and are associated with adverse effects, including cornea dam-

Table 2. Risk Factors for the Development of Lymphoma in Patients with Primary Sjögren's Syndrome.*

Risk Factor
Recurrent swelling of parotid glands
Splenomegaly, lymphadenopathy, or both
Purpura
Score of >5 on the ESSDAI†
Rheumatoid factor
Cryoglobulinemia
Low C4 level
CD4 T-cell lymphocytopenia
Presence of ectopic germinal centers
Focus score of >3‡
Germinal mutations in TNFAIP3

* TNFAIP3 denotes tumor necrosis factor alpha-induced protein 3.

† Scores on the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) range from 0 to 123, with a score of 5 indicating moderate activity and a score of 13 indicating high activity.

‡ The focus score is the number of mononuclear-cell infiltrates containing at least 50 inflammatory cells per 4 mm² of labial salivary gland obtained on biopsy. A score of 1 or more is indicative of primary Sjögren's syndrome.

age and increased intraocular pressure. Regular dental examinations and oral hygiene are crucial for reducing the risks of caries and periodontal disease associated with xerostomia.

Randomized trials assessing the efficacy of analgesic drugs in primary Sjögren's syndrome are lacking. On the basis of clinical experience, simple analgesics (e.g., acetaminophen) may be used as first-line therapy for pain; nonsteroidal antiinflammatory drugs may be appropriate for joint pain. Neuropathic pain in patients with primary Sjögren's syndrome is typically treated with gabapentin, pregabalin, or duloxetine, which are associated with less dryness of the mouth and eyes than small doses of amitriptyline. No drug has been shown to be effective for the fatigue that is so common among patients with primary Sjögren's syndrome.

To date, no immunomodulatory drug has proved to be efficacious in primary Sjögren's syndrome. Severe organ manifestations are treated in accordance with guidelines for SLE or other connective-tissue diseases. Agents that are commonly used include hydroxychloroquine (which has interferon activity), prednisone, methotrexate,

mycophenolate sodium, azathioprine, and cyclosporine; of these, only hydroxychloroquine has been studied in a randomized trial involving patients with primary Sjögren's syndrome. Although open-label studies have suggested improvement in symptoms with hydroxychloroquine, a randomized trial of the drug, as compared with placebo, showed no significant between-group difference in the primary outcome of improvement of 30% or more in at least two of three patient-reported outcomes (mouth and eye dryness, fatigue, and pain), with rates of 17.9% and 17.2%, respectively (odds ratio, 1.01; 95% confidence interval, 0.37 to 2.78).²⁵ Hydroxychloroquine was associated with a lower level of IgM than was placebo, but the difference was not significant after adjustment for multiple comparisons. However, patients who were enrolled in the trial had low systemic disease activity at entry, and the wide confidence interval around the odds ratio for the primary outcome means that substantive benefit cannot be ruled out. Given these observations as well as the similarities between Sjögren's syndrome and SLE, hydroxychloroquine is still used in patients with primary Sjögren's syndrome, particularly in patients with purpura and articular symptoms.

Few biologic agents have been rigorously studied in primary Sjögren's syndrome, and none have shown significant efficacy in multiple studies. Randomized, controlled trials of infliximab and etanercept showed no significant improvement in a composite primary outcome on a visual-analogue scale of joint pain, fatigue, and dryness.^{26,27}

Four randomized, controlled trials have assessed the efficacy of the monoclonal anti-CD20 antibody rituximab. The first trial, involving only 17 patients, showed significant improvement from baseline on a visual-analogue scale for fatigue in patients assigned to a single course of rituximab (two doses) but not in the placebo group.²⁸ In another small trial involving 30 patients, a course of rituximab was associated with significant improvement in the primary end points of stimulated salivary flow, as compared with placebo, and also in patient-reported improvement in fatigue and oral and ocular dryness.²⁹ However, a larger trial involving 120 patients showed no significant improvement with rituximab in a composite primary end point that included clinically significant improvement on at least two of four visual-analogue scales (assessing global dis-

ease, pain, fatigue, and dryness) at 24 weeks, although improvement was noted on earlier assessments of some measures.³⁰ Similarly, in TRACTISS (Trial of Anti-B-Cell Therapy in Patients with Primary Sjögren's Syndrome), which involved 110 patients, there was no significant benefit of rituximab for fatigue or oral dryness, but the drug was associated with lesser deterioration in salivary flow than placebo.³¹ A study of data derived from the French Autoimmune and Rituximab (AIR) registry, which involved 78 patients with primary Sjögren's syndrome who had primarily systemic manifestations, showed systemic improvement in approximately two thirds of the patients treated with rituximab, especially those with cryoglobulinemia-induced vasculitis or persistent or recurrent parotid swelling.³² Thus, rituximab may be useful for the treatment of some systemic manifestations. Data are limited with respect to the effectiveness of this drug for the prevention of lymphoma in the presence of risk factors for lymphoma.

An open-label study suggested the efficacy of belimumab, an inhibitor of B-cell activating factor (which is approved for the treatment of SLE), in 60% of patients, as assessed by an improvement in at least two of five disease indicators, including dryness, pain, fatigue, systemic activity, and B-cell biomarkers.³³ However, there was no significant improvement in salivary flow or tear production, as assessed by Schirmer's test; controlled trials of this agent are needed.

GUIDELINES

Guidelines for the management of primary Sjögren's syndrome have been published by the clinical practice guidelines committee of the Sjögren's Syndrome Foundation.³⁴ Recommendations in this article are generally concordant with these guidelines.

AREAS OF UNCERTAINTY

Recent pathophysiological studies have shown a number of similarities between primary Sjögren's syndrome and SLE, which suggests that primary Sjögren's syndrome may represent a form of SLE affecting the mucosa. Type I interferon, B cells, plasmablasts, and plasma cells are all involved in the pathogenesis of both primary Sjögren's syndrome and SLE. The role of drugs that target

these cells (bortezomib, atacicept, daratumumab, and other anti-CD38 antibodies) warrants further study. Also promising are other types of B-cell-targeted therapies, including agents that target molecules such as CD40 and inducible T-cell costimulator (ICOS) ligand, along with agents that target both CD20 and BAFF, which could modulate the hyper B-cell activation that is observed in primary Sjögren's syndrome^{35,36} (Table S2 in the Supplementary Appendix). In a preliminary randomized trial, patients with primary Sjögren's syndrome who received the higher dose of a selective anti-CD40 antibody had significantly lower disease activity, as measured on the ESSDAI at 12 weeks, than did those receiving placebo.³⁷

The heterogeneity of the disease, in conjunction with varied results of therapeutic trials, suggests that a more individualized approach to therapy will be required in order to achieve improved long-term outcomes in patients with primary Sjögren's syndrome. Future studies will also benefit from the increasing availability of validated measures of disease activity and outcome, such as the ESSDAI and ESSPRI.

CONCLUSIONS AND RECOMMENDATIONS

The woman described in the vignette has a classic case of primary Sjögren's syndrome on the basis of clinical findings of dryness of the mouth and eyes, fatigue, and pain, along with the presence of anti-SSA antibodies; a biopsy of the minor labial salivary glands is not necessary for diagnosis, given these findings. Treatment for this patient would typically include pilocarpine, with a gradual increase in the dose to 5 mg three or four times daily, depending on side effects, and ocular gel lubricants for symptoms of dryness.

The patient has some features predictive of an increased risk of lymphoma, including high disease activity, rheumatoid factor positivity, a low C4 level, recurrent parotid swelling, and purpura. We would generally recommend close follow-up in patients with these features, although in the present case such follow-up will definitely be needed, given the presence of purpura and renal dysfunction, which are among the recognized systemic complications of primary Sjögren's syndrome. We would be especially concerned about

interstitial nephritis associated with this disease; further evaluation is needed, including renal biopsy. If interstitial nephritis is present, we would initiate treatment with glucocorticoids. An immunosuppressive agent might also be useful in patients with inadequately controlled disease or to facilitate reduction of the prednisone dose.

If the use of immunotherapy is considered, we would favor the choice of rituximab on the basis of the evidence of B-cell activation and the predominance of B cells in the lymphoid infiltrate. In addition, open-label studies of rituximab have shown benefit for the treatment of

interstitial nephritis in patients with SLE and primary Sjögren's syndrome,^{6,32} although data regarding its effectiveness have been inconsistent.

Dr. Mariette reports receiving grant support from Biogen and Pfizer, fees for serving on advisory boards from Pfizer, UCB, Bristol-Myers Squibb, GlaxoSmithKline, MedImmune, Novartis, and Janssen, and fees for serving on a scientific council from Laboratoire Français des Biotechnologies. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Manel Ramos Casals, Department of Systemic Autoimmune Diseases, Instituto Clínic de Medicina y Dermatología, Hospital Clinic, Barcelona, for creating an earlier version of Figure 1.

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