LEAP ROUNDS

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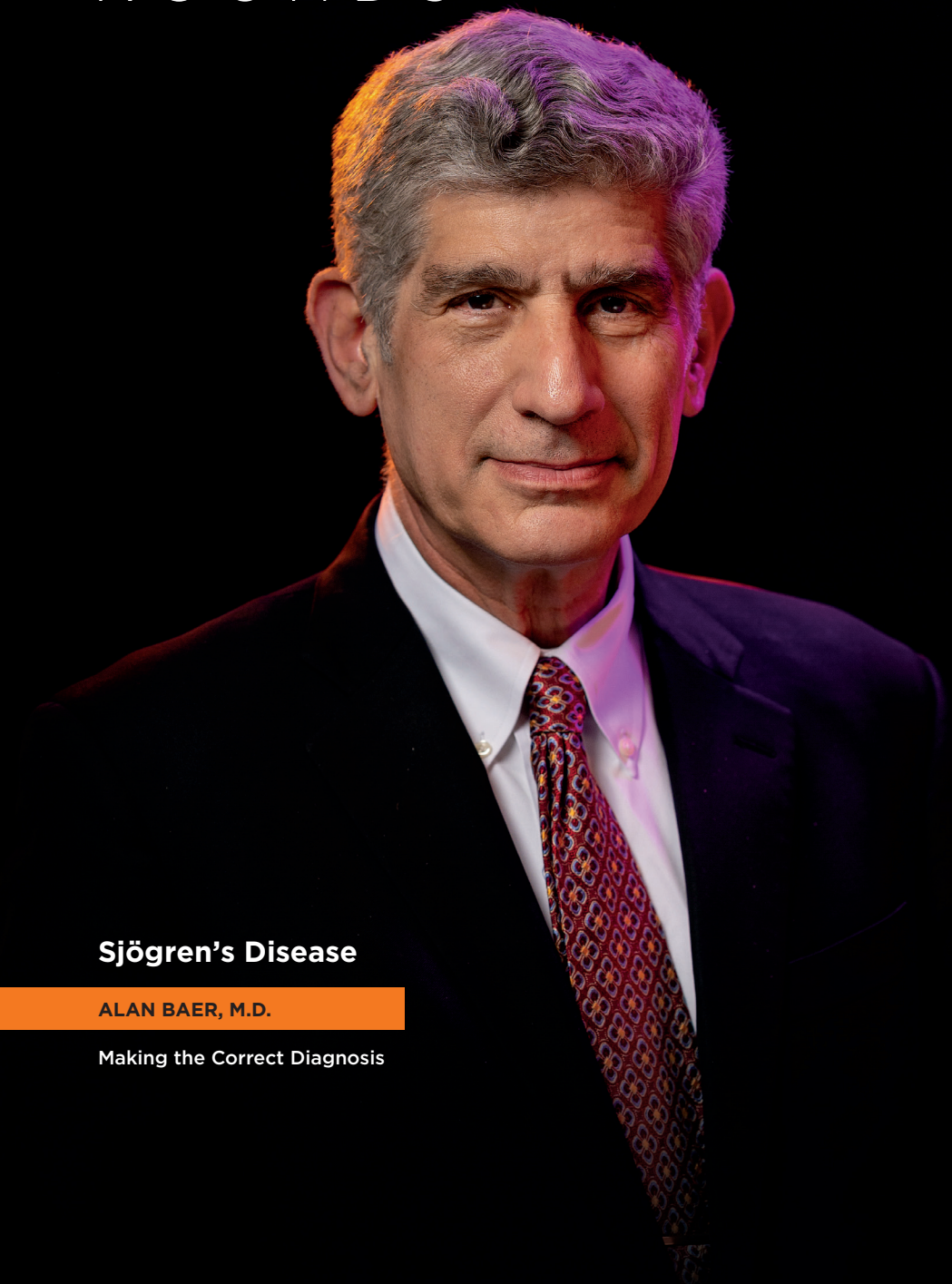

Sjögren's Disease

ALAN BAER, M.D.

Making the Correct Diagnosis

SJÖGREN'S

300

Number of patients enrolled in the Sjögren's International Registry (SICCA)

A prevalent belief among rheumatologists has been that an accurate diagnosis of Sjögren's is not essential because of the lack of disease-modifying therapies. But a correct diagnosis *is* very important to patients, who worry about a chronic illness marked by persistent fatigue, pain, progressive dryness of mucosal membranes, morbidity related to dental integrity, sexual dysfunction, internal organ involvement and the risk of lymphoma.

In fact, an effort is under way to change the name from Sjögren's Syndrome to Sjögren's Disease (SD), or simply, Sjögren's.

Labial Gland Biopsy: Tricky to Interpret

The characteristic histopathology of SD is focal lymphocytic sialadenitis, defined by tightly-aggregated mononuclear cells adjacent to striated ducts. These foci should contain 50 or more cells, predominantly lymphocytes. A high density — one or more foci per 4 mm^2 of glandular tissue — increases the specificity of this finding. Note: Accuracy of the focus score depends heavily on having enough tissue for analysis. A small sample can artificially inflate this assessment.

Damage of minor salivary glands is not uncommon, occurring focally in gland lobules as a result of ductal obstruction or more diffusely with aging. The signs are acinar loss, fibrosis, and ductal dilatation. Aggregates of lymphocytes can be seen in damaged portions of the gland, but should only be counted as foci if they are in areas of the glandular parenchyma that are *not* damaged.

Pitfalls: Beware the rough estimate! The total surface area of the glandular tissue really needs to be measured with precision; similarly, it is easy to miscount foci, and to misread glands that are dominated by damage as showing late stages of SD.

A careful surgical technique for the labial minor salivary gland biopsy can minimize postoperative bleeding and lip numbness. Dr. Jean Kim at the Johns Hopkins Sjögren's Center has established a surgical protocol that minimizes these complications (*Laryngoscope* 2016; 126:2041). For optimal histopathologic analysis, 4–7 glands should be collected.

What Can We Learn from Ultrasound of the Salivary Gland?

Salivary gland ultrasound allows us to stratify patients. It also reveals alterations in the gland indicative of inflammatory infiltrates or damage. Patients with multiple hypoechoic lesions are most often seropositive with a high likelihood of a positive lip biopsy; they are also more likely to develop lymphoma. In patients without sicca symptoms, the presence of multiple hypoechoic foci on salivary gland ultrasound strongly supports the diagnosis of SD, particularly if they have autoantibodies. This is particularly helpful in the evaluation of a child with recurrent parotitis or a young adult with overlap features of lupus and SD. The salivary gland ultrasound could thus be a substitute for the labial gland biopsy in certain patient groups. In patients with salivary gland enlargement, ultrasound-guided needle biopsies can be used for representative or targeted sampling of the parenchyma.

Many People Have Dry Eyes. Is it SD?

Dry eye can arise from *aqueous tear deficiency* (often due to lacrimal gland disease, such as occurs in SD) and also from *evaporative tear loss* (often due to meibomian gland dysfunction). The distinction between these two forms of dry eye requires testing by an ophthalmologist using a slit lamp. Many patients with SD also have *meibomian gland dysfunction*, and proper treatment of their dry eye requires attention to both disorders.

The advent of multiplex ANA panels has increased the detection of weak positive reactions for SSA/Ro or SSB/La antibodies. This increases the risk

SD-related dry eye should be managed by an ophthalmologist.

of an incorrect SD diagnosis, given the prevalence of dry eye symptoms (up to 30%) and autoantibodies (up to 1% for anti-SSA) in the healthy population. Findings that point specifically to SD include conjunctival staining with lissamine green, high ocular surface staining scores, and Schirmer test values of <5 mm/5 min.

When severe, the symptoms of SD-related dry eye — ocular pain, photophobia, and impaired vision — can have a profound impact on quality of life. Rarely, patients may develop corneal ulceration. Treatments are based largely upon severity, and in addition to tear supplements, include: medicated drops (corticosteroids for short-term use; cyclosporine and lifitegrast for long-term use), punctal occlusion, autologous serum tears, and scleral prostheses.

Is it Primary or Secondary SD?

We used to think this was a straightforward question; now we realize that it is not. For example, patients may initially present with SD and then develop systemic lupus years later. In addition, SD patients may have overlap features of another connective tissue disease. The best example of this is the subset of SD

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Respected for his contributions to the study and treatment of SD, Baer has been an Investigator in the Sjögren's Clinic at the National Institutes of Health since 2015. He is engaged in a number of research studies in SD at Johns Hopkins and the NIH. Baer was the principal investigator of the NIH subcontract to Johns Hopkins to conduct the Sjögren's International Registry (SICCA). With its enrollment of 300 patients, the SICCA registry has been a rich source of clinical data and biospecimens for research that Baer is conducting with colleagues at Hopkins and the University of California-San Francisco. He also is conducting a longitudinal observational study of patients with Sjögren's.

patients with anti-centromere antibodies, in whom Raynaud's phenomenon, nailfold capillary telangiectasia, and/or puffy digits are often present. With the advent of disease-specific antibodies, we now identify Sjögren's patients with non-specific interstitial pneumonitis who have a myositis-specific antibody and those with myelitis who have aquaporin-4 antibodies. Other non-rheumatic autoimmune diseases that can affect SD patients include pernicious anemia, celiac disease, and Hashimoto's thyroiditis.

Multifaceted Management of Salivary Hypofunction

Salivary hypofunction can lead to impaired taste, burning with spicy or acidic food, rampant dental decay, and even impaired sleep. There is a great need for treatments that reverse or ameliorate the glandular inflammation that is causing these manifestations. We don't have one. Thus, we rely on treatments that ameliorate symptoms and prevent complications such as dental decay. Whenever possible, patients should be given a trial of a sialogogue, to see if there is clinical benefit. Unfortunately, these drugs may have limited benefit in patients with more advanced salivary hypofunction, and side effects may prompt patients to stop the medication or limit the dose. We also prescribe nightly use of 1.1% neutral sodium fluoride toothpaste, or recommend professional fluoride treatments.

Management of candidal overgrowth: Symptoms include oral burning, sensitivity to acidic foods, and loss of taste. Examination findings include atrophic glossitis, angular cheilitis, and velvety erythema of the buccal mucosa or hard palate (particularly evident in the rugal folds). We typically initiate

Salivary hypofunction can lead to impaired taste and burning with spicy or acidic food.

treatment with oral fluconazole, 100 mg daily for the first 10–14 days of each month, but longer treatment periods may be necessary at first. An alternative is an oral anti-fungal troche or suspension, but these are flavored with sugar and their prolonged use can aggravate dental decay. Miconazole buccal tablets (Oravig) are sugar-free, but may be difficult to obtain or too costly.

Salivary and Lacrimal Gland Enlargement

Lacrimal gland enlargement is unusual in SD and should prompt concern for the presence of lymphoma. Involvement of *both* the salivary and lacrimal glands is more typical of IgG4-related sialadenitis and dacryoadenitis, sarcoidosis, and lymphoma. Persistent bilateral salivary gland enlargement can be an early manifestation of SD, especially in children and young adults. Patients with persistent salivary gland enlargement but *without* autoantibodies should be evaluated for other diseases, including sialadenosis, fatty infiltration of the

glands (with morbid obesity), IgG4-related sialadenitis (particularly if the submandibular glands are primarily involved), sarcoid, lymphoma, and rarely, benign salivary gland neoplasms involving both glands. Persistent salivary gland enlargement in a patient with known SD should prompt concern for intervening glandular lymphoma.

We use CT or MR imaging to evaluate the extent of the glandular enlargement (involvement of the deep lobe of the parotid can be a clue to malignancy); assess for regional lymph node involvement; and to evaluate lacrimal gland and orbital disease. Ultrasound may serve to distinguish fatty infiltration or sialadenosis from Sjögren's, and may sometimes reveal the enlargement to be related to masseter muscle hypertrophy. Whenever possible, we request an ultrasound-guided core needle biopsy to sample the parotid gland.

Recurrent salivary gland enlargement is a manifestation of SD, generally related to the formation of mucus plugs, stones, or worsening sialadenitis. In the absence of signs of infection (which should include an examination of the saliva extruded from Wharton's duct with glandular massage), treatment may consist of hot compresses, glandular massage, hydration, and sialogogues. A short course of steroids also may be helpful. We have had a few patients with paroxysmal parotid or submandibular gland enlargement, often in the context of significant atopic disease and peripheral eosinophilia. With glandular massage, mucus plugs can be extruded. Collection of these can reveal mucus plugs laden with eosinophils. Known as eosinophilic sialodochitis, this is likely an allergic disease of the salivary glands, and can be managed with antihistamines, leukotriene antagonists, and anti-IL5 inhibitors.

FURTHER READING

A validated method of labial minor salivary gland biopsy for the diagnosis of Sjögren's syndrome.
Laryngoscope
2016, PMID:27107215

Sjögren's Disease, Not Syndrome.
Arthritis & Rheumatology
2021, PMID:33559389

Eosinophilic sialodochitis: redefinition of 'allergic parotitis' and 'sialodochitis fibrinosa'.
Oral Disease
2017, PMID:27748012

Ultrasound-Guided Biopsy of Suspected Salivary Gland Lymphoma in Sjogren's Syndrome.
Arthritis Care & Research
2021, PMID:32248649

Ocular and systemic morbidity in a longitudinal cohort of Sjögren's syndrome.
Ophthalmology
2015, PMID:25178806

Relationship Between Neuromyelitis Optica Spectrum Disorder and Sjögren's Syndrome: Central Nervous System Extraglandular Disease or Unrelated, Co-Occurring Autoimmunity?
Arthritis Care & Research
2017, PMID:27696784

1,500 PATIENTS

enrolled in the longitudinal observation study at the Johns Hopkins Sjögren's Center.

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200-300

New patients with suspected SD evaluated yearly at Johns Hopkins Sjögren's Center.

HOPKINSSJOGRENS.ORG
PATIENTS: 410-550-1887