Joint Pain and Sjögren's Syndrome

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In 1930, Henrik Sjögren, a Swedish ophthalmologist, examined a woman with rheumatoid arthritis who had extreme dryness of her eyes and mouth and filamentary keratitis, an eye condition related to her lack of tears (1). He became fascinated by this unusual debilitating condition and subsequently evaluated 18 additional women with the same combination of findings. He described this new syndrome as "keratoconjunctivitis sicca" in his postdoctoral thesis. Thirteen of the 19 women had chronic inflammatory arthritis. We would now classify these 13 women as having secondary Sjögren's syndrome (SS), occurring in the context of rheumatoid arthritis. However, joint pain constitutes one of the most common symptoms of the primary form of SS, defined as SS occurring in the absence of an underlying rheumatic disease. In a recent survey of SS patients belonging to the French Sjögren's Syndrome Society (Association Française du Gougerot-Sjögren et des Syndromes Secs), 81% reported significant joint and muscle pain (2). In this article, the joint manifestations of primary SS will be reviewed.

A few definitions are needed for the reader. Although the term "arthritis" was originally applied to conditions causing joint inflammation, it now includes disorders in which the joint has become damaged by degenerative, metabolic, or traumatic processes. Joint inflammation is characterized by warmth, redness, tenderness, pain with motion, and swelling. Joint swelling may arise from thickening of the normally thin membrane which lines the joint cavity (the synovium) or the presence of an increased amount of fluid within the joint space (joint effusion). Examples of inflammatory arthritis include rheumatoid arthritis, gout, and arthritis related to a joint infection (such as Lyme disease). The forms of arthritis characterized by joint damage often have minimal, if any, inflammation. On examination of the joint, there may be bony enlargement, malalignment, crepitus (a grinding sensation) with motion, and restricted motion. However, both inflammation and joint damage may co-exist in arthritis. Inflammatory arthritis can lead to permanent joint damage and degenerative joint processes can trigger inflammation. The term "arthralgia" refers to joint pain, irrespective of its cause. Importantly, patients may have joint pain, but lack signs of arthritis when examined by a physician. As will be described below, this is often true for primary SS patients.

There are many causes of arthritis. These include inflammation of the synovium, trauma, hormonal changes, or degeneration of the cartilage. A physician differentiates the various causes of arthritis with the aid of the history, physical examination, laboratory testing, and radiologic imaging. The potential causes of arthritis can be differentiated in part by determining how many and which joints are affected, how quickly the joint pain developed, and how the joints are affected over time. The physical examination helps to determine if there is inflammation, joint damage, or a combination of the two. Two blood tests, the erythrocyte sedimentation rate and C-reactive protein, are abnormal in inflammatory forms of arthritis. A positive rheumatoid factor test is present in up to 80% of patients with rheumatoid arthritis, but is also present in other forms of arthritis, including up to two-thirds of primary SS patients (3-5). A positive cyclic citrullinated peptide (CCP) antibody test is more specific for rheumatoid arthritis, but is also present in approximately 5-10% of SS patients (4-5). Imaging of the joints with X-ray, ultrasound and magnetic resonance techniques serves to define the presence of inflammation of the synovium as well as joint damage, evident as alterations of key structural elements, such as cartilage, ligaments and adjacent bone.

The joint manifestations of Sjögren's syndrome are listed in the Table. An inflammatory arthritis, defined by the presence of joint tenderness and swelling, usually affects many joints, particularly those of the fingers, the wrists and the ankles. The shoulders, hips and knees may also be painful. The arthritis usually "comes and goes" and affects the same joints in the right and left limbs in a "symmetric" fashion. Joint x-rays are usually normal. In a recent series, this type of arthritis was present in 35% of 188 primary SS patients (6). More severe forms of arthritis can occur rarely in primary SS and appear to be a true overlap of two distinct rheumatic diseases, namely rheumatoid arthritis and SS (7).

Joint pain is one of the most common symptoms of SS**.** Multiple joints are painful, usually episodically with periods of joint pain, known as "flares", followed by periods of little or no joint pain. Arthritis and/or arthralgia may develop before the onset of dryness of the eyes and/or mouth in SS patients and thus be the first manifestation of Sjögren's syndrome. The arthritis of SS is often associated with other features of SS not related to the salivary or tear glands, such as blood vessel inflammation (vasculitis), nerve damage (neuropathy), Raynaud's phenomenon, and kidney disease.

Some patients with SS may have joint pain as a result of fibromyalgia. In general, the pain of fibromyalgia arises from the muscles although it may be perceived as coming from the joints. Fibromyalgia and joint pain related to SS may be hard to differentiate. Fibromyalgia pain is present on a nearly daily basis, with flares of increased pain triggered by increased exertion, lack of sleep, and stress.

Patients with secondary SS have an underlying systemic rheumatic disease, such as rheumatoid arthritis, systemic lupus erythematosus, or scleroderma. Arthritis is a prominent feature of these systemic rheumatic diseases. The distinction between primary SS with arthritis and SS occurring in the setting of rheumatoid arthritis or systemic lupus can be difficult. Both sets of patients may have positive tests for rheumatoid factor and antinuclear antibodies, markers respectively of rheumatold arthritis and systemic lupus. Additionally, a positive CCP antibody test in a primary SS patient does not always imply the presence of rheumatoid arthritis (4). In general, secondary SS occurs in rheumatoid arthritis patients who have had the disease for many years. Systemic lupus is diagnosed when certain types of medical problems occur together, such as specific rashes, inflammation of the lung or heart lining (pleurisy and pericarditis), inflammation of the filtering portion of the kidney (glomerulonephritis), and blood abnormalities (such as low white counts, low platelets, or anemia). Some of these medical problems may also occur in SS patients, but an experienced rheumatologist can generally distinguish the two diseases.

Some patients have dryness of their eyes and mouth, but do not have any signs of an underlying autoimmune disease. They cannot be classified as having SS since they lack SS-A and/or SS-B antibodies and do not have a "positive" lip biopsy. Patients with these SS mimics often have joint pain. These mimics have been labeled the "dry eye and mouth syndrome", the "sicca, asthenia, and polyalgia syndrome", and "chronic sialoadenitis in association with nodal osteoarthritis" (8-10). The existence of these syndromes reflects the fact that dryness of the eyes and mouth may have a variety of origins, including aging, anxiety, and the use of certain medications. Menopause itself appears to be a cause of joint pain and sicca symptoms in some women (sometimes termed 'menopausal arthritis'). This has

become evident in studies of women who develop joint pain and sicca symptoms while receiving medicines that block estrogen production (aromatase inhibitors) as treatment for breast cancer (11).

The arthritis of primary SS is mildly inflammatory and a manifestation of the systemic autoimmune disease. The mechanisms responsible for this arthritis may include systemic factors which affect the joint tissue secondarily, such as immune complexes (which can induce inflammation in small vessels) or inflammatory mediators (such as cytokines, which induce physiologic changes in various tissues). Alternatively, the immune reaction may be directed specifically at a structural component of the joint, thereby inciting an inflammatory response.

Many treatment modalities are available to treat joint pain associated with SS. If the joint pain is mild and intermittent, acetaminophen or short courses of non-steroidal anti-inflammatory drugs (NSAIDs) available without prescription may suffice. If the joint pain is more persistent, prolonged use of prescription-strength NSAIDs may be required. Chronic therapy with prescription-strength NSAIDs has a risk of inciting potentially dangerous stomach ulcers in up to 4% of patients each year, particularly in elderly individuals as well as those who are taking blood thinners or corticosteroids or who have had a prior history of stomach or peptic ulcers (12). Steps can be taken to reduce this risk. These include using the lowest dose that controls the joint pain, taking the NSAID with food, choosing an NSAID with a lower risk of gastrointestinal side effects, and taking a proton-pump inhibitor, such as omeprazole or pantoprazole, along with the NSAID on a daily basis (13). Hydroxychloroquine (Plaquenil) is commonly used for treating joint pain in SS patients, based in part on its efficacy in treating the joint pain of patients with systemic lupus erythematosus and rheumatoid arthritis (14-15). It is generally well-tolerated but its use for a period of 10 years or more is associated with potential damage to the retina of the eye in 1 out of 1000 patients. Patients taking hydroxychloroquine for prolonged periods should thus have yearly eye examinations (16).

More severe forms of arthritis associated with SS may require treatment with disease-modifying anti-rheumatic drugs other than hydroxychloroquine. These include methotrexate, leflunomide, cyclosporine, TNF antagonists (such as etanercept, adalimumab, and infliximab), and rituximab. Prednisone can be a very effective and quick-acting treatment for arthritis, but chronic therapy, even in low doses, leads to an increased risk of osteoporosis. Higher doses should only be used for short periods of time, since these can result in so-called Cushingoid side effects, such as weight gain, diabetes, bruising, and an increased risk of infection.

Non-pharmacologic measures are also important aspects of the therapeutic program. The application of moist heat to the hands with a paraffin bath can help relieve stiffness of the fingers and wrists in the morning. Gentle exercise, including Tai Chi, yoga and dancing, can serve to strengthen muscles and preserve joint range of motion. Nutritional supplements, such as glucosamine or fish oils, may also help some patients. Finally, experimenting with one's diet may reveal certain foods that aggravate the joint pain. This is variable, but elimination of dairy, bread products, or excessive salt can reduce joint pain in some individuals.

In conclusion, joint manifestations are very common in primary SS and often relate to a mild inflammatory arthritis, affecting in particular the small joints of the fingers, wrists, and ankles. Some patients have more severe forms of arthritis, with features of rheumatoid arthritis or systemic lupus. Many different treatment modalities are available, and these serve to reduce the frequency of joint flares and control the joint pain and stiffness.

Table: Joint Manifestations of Sjögren's Syndrome and Related Entities

Primary Sjögren's syndrome
Polyarthritis
Arthralgia alone
Fibromyalgia
Secondary Sjögren's syndrome
The joint manifestations are those of the underlying rheumatic disease, such as rheumatoid arthritis, systemic lupus erythematosus, or scleroderma.
Sicca syndrome*
Nodal osteoarthritis with chronic sialoadenitis
Dry eye and mouth syndrome
Sicca, asthenia, and polyalgia syndrome
Menopausal arthritis

*defined by presence of dry eyes and mouth, but lacking evidence of autoimmune process as mandated by 2002 AECC classification criteria for SS

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