Imaging of Sjögren Syndrome and Immunoglobulin G4-Related Disease of the Salivary Glands

Akifumi Fujita, MD, PhD

KEYWORDS

• Sjögren syndrome • Immunoglobulin G4-related disease • Salivary glands • Autoimmune disease • CT • MR imaging

KEY POINTS

- MR imaging of chronic Sjögren syndrome shows a salt-and-pepper appearance of the parotid gland, and atrophy of the submandibular glands can be commonly detected incidentally with computed tomography and MR imaging in daily clinical practice.
- MR sialography can be replaced with conventional invasive sialography and is useful for grading Sjögren syndrome.
- Immunoglobulin G4-related disease (IgG4-RD) is a recently established disease that commonly shows involvement of the salivary glands. Mikulicz disease, Küttner tumor, and some inflammatory pseudotumors of the orbit are now considered to represent IgG4-RD.
- Bilateral symmetric diffuse swelling of the salivary glands (parotid, submandibular, and sublingual) and lacrimal glands is the classic finding of IgG4-RD.
- Isolated lesions of IgG4-RD are difficult to differentiate from tumors, especially malignant lymphoma, and usually require histopathological biopsy.

INTRODUCTION

Although salivary gland pathologic complications are relatively uncommon overall, the salivary glands are commonly affected in systemic autoimmune disease and diseases of unknown pathogenesis.[1,2] Bilateral symmetric involvement of multiple major salivary glands can easily result in suspicion of systemic disease; however, isolated salivary gland lesions often need to be differentiated from tumors, including malignancies. Imaging findings of salivary gland involvement in systemic disease is usually nonspecific; however, radiologists should be familiar with the clinical and imaging manifestations to avoid delays in diagnosis. Sjögren syndrome (SjS) is the most well-known autoimmune disease of the salivary glands, which can be affected both primarily and secondarily with other systemic diseases. Immunoglobulin (Ig)G4-related disease (IgG4-RD) is a recently introduced systemic inflammatory disease, now also considered an autoimmune disorder, that commonly affects salivary glands, as well as the pancreas, kidneys, lacrimal glands, and retroperitoneal periaortic lesions. This article discusses the details of SjS and IgG4-RD.

SJÖGREN SYNDROME

Background

SjS is a relatively common systemic autoimmune disease that is histologically characterized by

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Department of Radiology, Jichi Medical University School of Medicine, 3311-1, Yakushiji, Shimotsuke, Tochigi 329-0498, Japan
E-mail address: akifuji@jichi.ac.jp

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lymphocytic infiltration and destruction of the salivary and lacrimal glands, leading to secretory dysfunction. Sicca syndrome is the term for the resulting dryness of the mouth and eyes. SjS is referred to as primary in patients who do not have any additional systemic disease, and secondary when sicca syndrome coexists in patients with other systemic diseases such as systemic lupus erythematosus, scleroderma, and rheumatoid arthritis, or other organ-specific autoimmune diseases such as Graves disease and Hashimoto thyroiditis. The diagnosis of SjS is often delayed for years after symptom onset owing to underestimation of the significance of sicca symptoms.[3–5]

Because cross-sectional imaging techniques such as ultrasonography (US), computed tomography (CT), and MR imaging now play an important role in daily clinical practice, radiologists may come across various imaging manifestations of SjS incidentally.[6–8] Although imaging results are not included in the diagnostic criteria and are not necessary for diagnosis, radiologists should be familiar with the imaging findings of SjS to avoid delaying the diagnosis. In particular, radiologists should be aware of associations with acute inflammation and secondary lymphoma in SjS patients.

Pathogenesis

The pathogenesis remains incompletely clarified; however, SjS is considered an autoimmune systemic disease. The characteristic lymphocytic infiltrates were initially observed to be proximal to salivary gland epithelial cells, which were subsequently shown to express numerous immunomodulatory molecules, such as cytokines, chemokines, adhesion molecules, and apoptosis-related molecules, as well as autoantigens and functional innate immunity receptors. Salivary gland epithelial cells seem to be able to function as professional antigen-presenting cells and to mediate the exposure of intracellular autoantigens to the immune system. Salivary glands are sites of autoantigen presentation and initiation of the autoimmune response in SjS.

Histopathology

SjS is characterized by lymphocytic infiltration of the exocrine glands, primarily the salivary and lacrimal glands. The principal pathologic lesion in SjS is focal lymphocytic sialadenitis, predominantly consisting of CD4-positive T cells and CD20-positive B cells, in the salivary glands. Analogous lesions may occur in the lacrimal glands. In the absence of SjS-associated serum autoantibodies, a positive labial salivary gland biopsy is a mandatory criterion for the classification of SjS.

Clinical Manifestations

Sicca syndrome and glandular enlargement represent the 2 major symptoms of SjS and are seen in more than 80% of patients at the time of diagnosis. Other systemic manifestations may also be seen, such as articular, cutaneous, Raynaud phenomenon, pulmonary, nervous system, renal, genitourinary, and hematologic findings.[3–5] The greatest concern for SjS patients is that SjS carries a substantially increased risk for the development of non-Hodgkin lymphoma.[4]

In the early phase, the parotid glands are diffusely enlarged with normal parenchyma (stage 0). In the intermediate phase, the salivary glands are diffusely enlarged with multiple, scattered cysts and solid masses. These cysts range in size from less than 1 mm (microcysts) to macrocysts and mixed solid-cystic masses of more than 2 cm (stage I–III). In the chronic phase, atrophy of the glands becomes evident (stage IV).[2]

Diagnostic Criteria

Several diagnostic classification criteria for SjS have been described by organizations in different countries[9,10]; however, none have been validated or universally accepted. **Box 1** shows the classification criteria recently described by the American College of Rheumatology.[11]

Imaging Modality for Diagnosis

Typically, histopathological examination of the labial gland is considered as the most promising method of diagnosis for SjS. Imaging is still not included in the diagnostic classification criteria; however, various imaging modalities have been recognized as useful for diagnosing and grading SjS. Because the subjective complaints of patients with xerostomia do not necessarily reflect salivary gland disease, more objective and reliable methods are necessary. Until the 1980s, conventional radiographic sialography and radionuclide scintigraphy were the typical imaging methods used for diagnosing SjS.[12] However, these examinations are invasive and require exposure to radiation. Recent noninvasive imaging modalities such as US and MR imaging, including MR sialography, might offer advantages for the diagnosis and management of SjS patients.

MR Imaging

In the early 1990s, Takashima and colleagues[13] compared MR imaging findings with the results of conventional sialography and histopathological examination. They reported heterogeneous signals on both T1-weighted and T2-weighted