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Differential diagnosis of IgG4-related sialadenitis, primary Sjögren syndrome, and chronic obstructive submandibular sialadenitis

X. Hong [a,1], W. Li [a,1], X.-Y. Xie [b], Z.-Y. Zhang [b], Y. Chen [c], Y. Gao [c], X. Peng [a], J.-Z. Su [a], Y.-Y. Zhang [a], Z. Wang [a], Z.-G. Cai [a], L. Zhang [a], Y.-Y. Liu [d], J. He [d], L.-M. Ren [d], Z.-G. Li [d], G.-Y. Yu [a,*]

[a] *Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, Beijing 100081, China*
[b] *Department of Oral Radiology, Peking University School and Hospital of Stomatology, Beijing 100081, China*
[c] *Department of Oral Pathology, Peking University School and Hospital of Stomatology, Beijing 100081, China*
[d] *Department of Rheumatology and Immunology, Peking University People's Hospital, Beijing 100044, China*

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Abstract

Our aim was to differentiate IgG4-related sialadenitis, primary Sjögren syndrome, and chronic obstructive submandibular sialadenitis by analysing clinical, radiographic, and pathological features. Fifty-five patients, 50, and 50 were enrolled, respectively and their baseline characteristics and serological, sialographic, and pathological findings compared. The male:female ratio for IgG4-related sialadenitis was 1:1.2 for primary Sjögren syndrome 1:15.7, and for chronic obstructive submandibular sialadenitis1:0.92. Numbers with enlarged salivary glands were 55, 16, and 50; with xerostomia 26, 48, and 0; with a history of allergy 26, 4, and 6, and with coexisting systemic disease 12, 19, and 0 ($p = 0.14$). Mean (SD) serum IgG4 concentrations were 109.1 (97.9), 4.9. (1.9) g/L, and 5.3 (1.6) g/L, $p < 0.001$ in all cases. Sialography showed enlargement of the gland, dilatation of the duct, and slightly decreased secretory function in IgG4-related disease; obvious sialectasia and decreased secretory function in Sjögren syndrome; and dilatation of Wharton's duct and filling defects in obstructive sialadenitis. Histopathological examination showed lymphoplasmacytic infiltration with storiform fibrosis, lymphoplasmacytic inflammation and lymphoepithelial lesions, and dilatation of the duct with epithelial metaplasia in the three groups, respectively. The number of IgG4-positive plasma cells was 123 (45)/HPF, 8 (3)/HPF, and 5 (4)/HPF, while the IgG4-/IgG-positive cell ratio was 71.7 (13.9)%, 4.6 (2.5)%, 18.9 (19.7)%, respectively ($p < 0.001$). The three conditions have different clinical, radiographic, and pathological features that provide important clues to the differential diagnosis. Serological and histological tests are important, and comprehensive consideration is necessary.

Keywords: Salivary glands; IgG4-related sialadenitis; Primary Sjögren syndrome; Chronic obstructive submandibular sialadenitis; Differential diagnosis

Introduction

Immunoglobulin G4-related disease is an increasingly-recognised, systemic, immune-mediated disease that is characterised by dense lymphoplasmacytic infiltrates, storiform fibrosis, and raised serum IgG4 concentrations.[1] Immunoglobulin G4-related sialadenitis is a part of it, and is characterised by enlargement of single or multiple salivary or lacrimal glands, or both, with reduced secretion of saliva.[2]

Because of its close relation to Mikulicz disease, IgG4-related sialoadentitis was thought to be identical to primary Sjögren syndrome,[3] which is characterised by xerophthalmia

* Corresponding author. Tel.: 0086 10 62195245.
E-mail address: gyyu@263.net (G.-Y. Yu).
[1] Equal contributors.

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and xerostomia as a result of immune-mediated destruction of the exocrine glands and enlargement of the salivary glands.[4]

Chronic obstructive submandibular sialadenitis is one of the most common disorders of the submandibular glands, and is characterised by obstruction of the ductal system by various factors.[5] Though a sialolith is the most common cause, radiolucent sialoliths are hard to detect. There is an ill-defined group with intermittent swelling of the gland but not typical obstruction or infection, which shares the histological features of chronic obstructive submandibular sialoadenitis. Clinically, advanced disease may manifest itself as a firm submandibular gland, and might be identified as a tumour or Küttner tumour.[6] However, recent studies have indicated that some patients with Küttner tumours develop high serum concentrations of IgG4, together with IgG4-positive plasma cell infiltration, indicating a strong resemblance between IgG4-related sialoadenitis and chronic obstructive disease.[7]

The three conditions are therefore completely different, but they do have several similarities, and differential diagnosis is important for treatment and evaluation of prognosis.[8] We have therefore retrospectively analysed their clinical, radiographic, and pathological features, with the aim of establishing clear distinctions between them.

Patients and methods

The study protocol was approved by the Ethics Committee for Human Experiments of the Peking University School of Stomatology (Beijing, China). Informed consent was obtained from all patients.

We reviewed the data for 55 patients with IgG4-related sialadenitis, 50 with primary Sjögren syndrome, and 50 with chronic obstructive submandibular sialadenitis who were diagnosed between August 2011 and May 2015 at Peking University School of Stomatology. IgG4-related sialadenitis was diagnosed from the serological and histological findings in patients with persistent (>3 months) swelling of the major salivary glands,[9] and primary Sjögren syndrome from the revised European criteria.[10] Chronic obstructive submandibular sialadenitis was diagnosed according to the following criteria: history of recurrent painful and periodical swellings of the involved gland; radiopaque appearance of submandibular calculi or filling defects and dilatation of Wharton's duct; and histopathological appearances with periductal lymphocytic, plasma cell, neutrophilic, and eosinophilic infiltration.

We recorded personal and clinical information including age and sex; clinical signs and symptoms including enlargement of the lacrimal or salivary glands, or both; xerophthalmia or xerostomia; history of allergic diseases (including asthma and allergic rhinitis); associated systemic coexisting diseases; and duration of symptoms.

The total serum concentrations of IgG and its subclasses were measured in all patients with IgG4-related sialadenitis, 12 with Sjögren syndrome, and nine with chronic sialadenitis. Serum antinuclear antibody (ANA) and anti-SS-A/Ro and anti-SS-B/La antibodies were measured in all patients in the first two groups, and nine with chronic sialadentitis. Detailed information is given in Supplementary information.

Thirty-three glands in 22 patients with IgG4-related sialadenitis were examined by parotid sialography, as were 42 patients with Sjögren syndrome, while 14 glands in 12 IgG4-RS patients with IgG4-related disease and eight with submandibular sialadentis were examined by submandibular gland sialography (Supplementary information). Occlusal projections and lateral submandibular gland projections were obtained for 36 patients with submandibular sialadenitis.

Histopathological and immunohistochemical examinations of the major salivary glands were made for all patients with IgG4-related disease and submandibular sialadenitis, together with 12 patients with Sjögren syndrome (Supplementary information), and reviewed by two pathologists. Three identical HPF with the greatest density of IgG-positive and IgG4-positive plasmacytes were quantified, and the IgG4-positive:IgG-positive plasmacyte ratio was calculated.

Student's *t* test, analysis of variance, and the chi square test were used to assess the significance of differences, as appropriate, with the aid of IBM SPSS Statistics for Windows (version 20.0 IBM Corp, Armonk, NY), and probabilities of less than 0.05 were accepted as significant.

Results

Clinical features

There were 25 men and 30 women in the IgG4-related sialadenitis group, all of whom had enlargement of the salivary glands (Tables 1 and 2). Only one patient gave a history of periodic swellings and remissions of the involved gland. Xerostomia and xerophthalmia were complained of by 26 (supplemental Fig. 1A) and 10 patients, respectively. An allergic disease history was reported by 26 patients. The systemic comorbidity rate included autoimmune pancreatitis (n = 5), sclerosing cholangitis (n = 1), interstitial pneumonia (n = 6), and a lesion in the cardia (n = 1).

There were three men and 47 women in the primary Sjögren group. Moderate to severe xerostomia was complained by 48 patients (supplemental Fig. 1B) and xerophthalmia by 28. Recurrent enlargements of the submandibular, parotid, and lacrimal glands were found in 2, 14, and 2 patients, respectively (Table 1). A history of allergic disease was reported by 4 patients. The number with coexisting systemic disease included disorders of the joints (n = 15), kidneys (n = 3), liver (n = 2), and the haematopoietic system (n = 1).

There were 26 men and 24 women in the group with chronic obstructive submandibular sialadenitis, but only one had bilateral swelling. Thirty-two gave a history of swelling after meals, while 11 had persistent swelling without discomfort. There were no other signs of exocrine gland swelling. No patient had xerostomia (supplemental Fig. 1C), except the