Clinical and Experimental Rheumatology 2013; 31: 773-775.

IgG4-related Mikulicz's disease: ultrasonography of the salivary and lacrimal glands for monitoring the efficacy of corticosteroid therapy

Y. Takagi[1], H. Nakamura[2], T. Origuchi[2], T. Miyashita[3], A. Kawakami[2], M. Sumi[1], T. Nakamura[1]

[1]*Department of Radiology and Cancer Biology, Nagasaki University School of Dentistry, Nagasaki, Japan;*
[2]*Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan;*
[3]*Department of Rheumatology, NHO Nagasaki Medical Center, Omura, Japan.*

Yukinori Takagi, DDS, PhD
Hideki Nakamura, MD, PhD
Tomoki Origuchi, MD, PhD
Taiichiro Miyashita, MD, PhD
Atsushi Kawakami, MD, PhD
Misa Sumi, DDS, PhD
Takashi Nakamura, DDS, PhD

Please address correspondence to:
Prof. Takashi Nakamura,
Department of Radiology and Cancer Biology,
Nagasaki University School of Dentistry,
1-7-1 Sakamoto,
Nagasaki 852-8588, Japan.
E-mail: taku@nagasaki-u.ac.jp

Received on January 18, 2013; accepted in revised form on April 8, 2013.

Key words: IgG4, Mikulicz's disease, ultrasonography, salivary gland, lacrimal gland, corticosteroid, treatment

Competing interests: none declared.

ABSTRACT

Objective. *IgG4-related Mikulicz's disease (IgG4-MD) has been recently established as a subtype of IgG4-related diseases involving the salivary and lacrimal glands, and the diseased glands are characteristically and highly responsive to corticosteroid therapy. We retrospectively evaluated ultrasonography (US) of the salivary and lacrimal glands for monitoring the efficacy of corticosteroid treatment in patients with IgG4-MD.*

Methods. *US features of the salivary and lacrimal glands were assessed and compared with the serum IgG4 levels in 8 patients with IgG4-MD before and at various stages after initiation of oral corticosteroids.*

Results. *US features of the lacrimal and salivary glands of patients with IgG4-MD were characterised by multiple hypoechoic areas with varying sizes in enlarged glands. The submandibular glands were most frequently involved by the disease, and bilateral glands of the same type were similarly affected exhibiting the same hypoechoic pattern. Alleviations of abnormal gland architecture and size in response to corticosteroid therapy were effectively detected with US. The US findings of the involved glands were proportional to the serum IgG4 level before and during the corticosteroid therapy.*

Conclusion. *US helps monitor the efficacy of corticosteroid treatment in patients with IgG4-MD.*

Introduction

Mikulicz's disease (MD) is characterised by symmetrical swelling of the salivary and lacrimal glands and has recently been proposed as a subtype of IgG4-related diseases. A good response to corticosteroids is a characteristic clinical feature of IgG4-related disease (1, 2). However, the optimal imaging techniques for the diagnosis of the gland disease and assessment of treatment efficacy in IgG4-MD patients have not been established (3). In the present study, we retrospectively evaluated the use of ultrasonography (US) for assessing the efficacy of corticosteroid treatment in IgG4-MD patients.

Patients and methods

US findings from 8 patients with IgG4-MD (3 women and 5 men; average age, 67±7 years) who received oral doses of corticosteroid and underwent periodical US follow-ups for at least 1 month were studied to compare with the changes in serum IgG4 levels of the patients. The diagnostic criteria for the disease were previously described (2). US of the lacrimal and salivary glands were performed before and various times after the initial doses of predonisolone (15–35 mg). Some patients (n=3) received conventional MR imaging and MR sialography. The study was approved by the institutional review board and informed consent was obtained from all patients.

Results

Serum IgG4 levels in the 8 patients were elevated 5- to 15-fold above the upper limit (135 mg/dL) during the pretreatment periods. Serum IgG4/IgG ratios were 0.46±0.09 (range, 0.32–0.57). Elevated serum IgG4 level rapidly responded to treatment as early as 1 week after initiating corticosteroid treatment. However, serum IgG4 levels did not decrease below the upper limit (135 mg/dL) in 7 out of the 8 patients with IgG4-MD after varying treatment periods (1–140 months).

US features of the lacrimal and salivary glands of patients with IgG4-MD were characterised by multiple hypoechoic areas with varying sizes, probably representing accumulation of lymphoid tissues and/or fibrosis in the glands (Fig. 1) (2, 5-7). The submandibular glands were most frequently involved (8/8). US revealed that the involved glands rapidly responded to corticosteroids in line with decreases in serum IgG4 levels. However, abnormal parenchymal architecture and gland size on US were still present in many cases. Notably, all the submandibular glands with multiple large-sized hypoechoic areas on US (n=3) were still hypoechoic and atrophic even at the last follow-up examination.

Discussion

Although we did not measure the gland size, decreases in size in response to

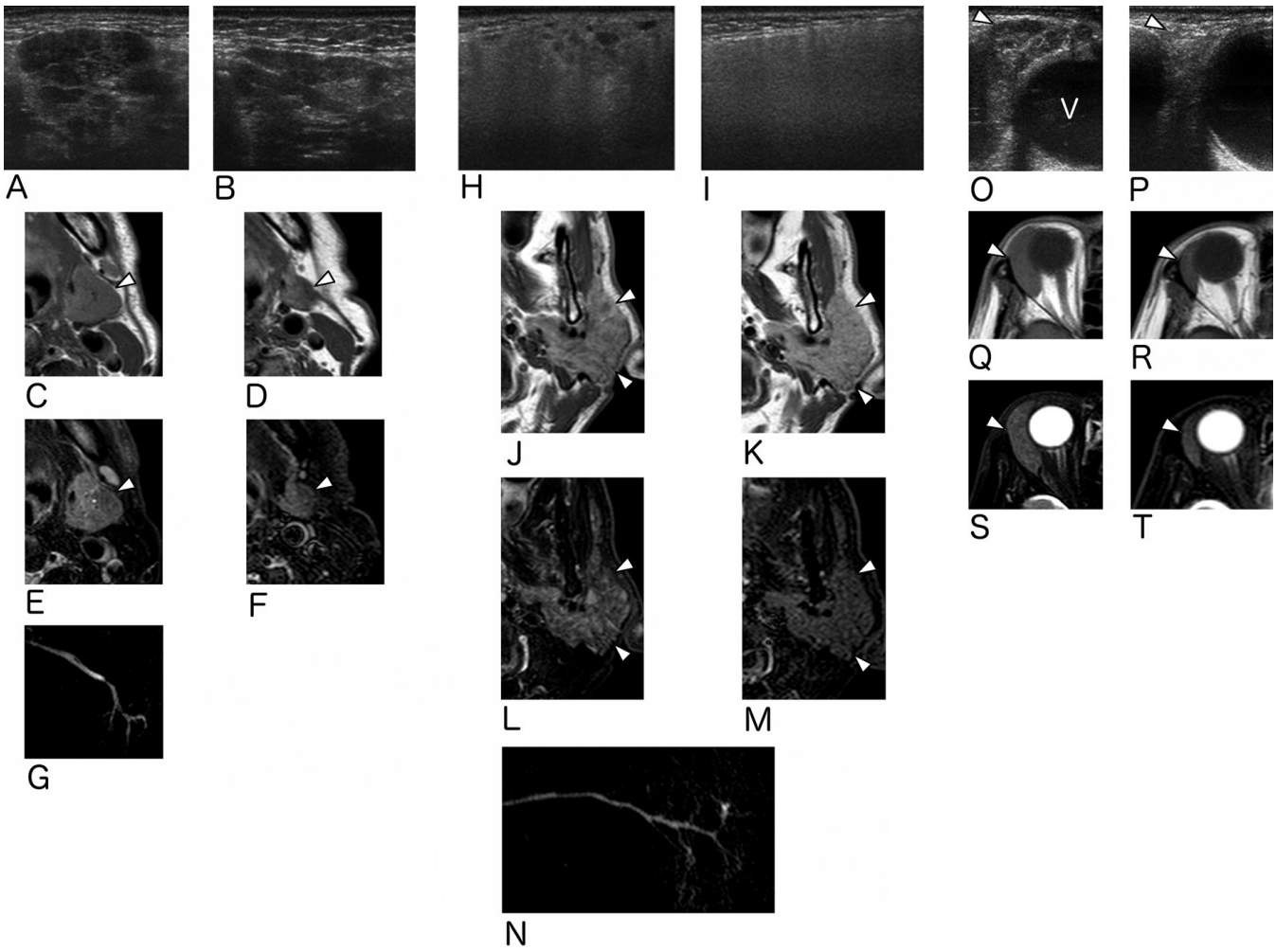

Fig. 1. US and MR imaging features of the salivary and lacrimal glands in a 72-year-old man with IgG4-MD.
A, **B**, US shows left submandibular gland before therapy (A) and 12 weeks (B) after initiation of oral corticosteroids. The gland exhibits multiple, large-sized hypoechoic areas (A), which remains in atrophic gland 12 weeks after initiation of oral corticosteroids (B).
C-**F**, Axial T1-weighted (C, D) and fat-suppressed T2-weighted (E, F) MR images show left submandibular gland (arrowheads) before therapy (C, E) and 12 weeks (D, F) after initiation of oral corticosteroids. Fat-suppressed T2-weighted MR images show hypointense areas suggestive of extensive fibrosis in the gland parenchyma (E, F).
G, MR sialography of left submandibular gland shows normal duct ramification.
H, **I**, US shows left parotid gland before therapy (H) and 12 weeks (I) after initiation of oral corticosteroids. Characteristic multiple, small-sized hypoechoic areas (H) disappear in response to corticosteroid 12 weeks after initiation of oral corticosteroids (I).
J-**M**, Axial T1-weighted (J, K) and fat-suppressed T2-weighted (L, M) MR images show left parotid gland (arrowheads) before therapy (J, L) and 12 weeks (K, M) after initiation of oral corticosteroids. Note multiple hypointense (J) and hyperintense (L) areas in gland parenchyma before the therapy suggesting the presence of extensive lymphoplasmacytic infiltration and/or enlarged lymph nodes in the gland parenchyma.
N, MR sialography of left parotid gland shows normal duct ramification.
O, **P**, US shows right lacrimal gland (arrowheads) before therapy (O) and 12 weeks (P) after the initial dose of corticosteroid. Note that multiple, medium-sized hypoechoic areas (O) almost disappears 12 weeks after initiation of oral corticosteroids, but the gland remains enlarged (P). V, vitreous body.
Q-**T**, Axial T1-weighted (Q, R) and fat-suppressed T2-weighted (S, T) MR images show right lacrimal gland (arrowheads) before therapy (Q, S) and 12 weeks (R, T) after initiation of oral corticosteroids. Gland enlargement is obvious, but a faint trace of irregular intensity is noted in the gland parenchyma (Q, S).
Serum IgG4 = 1900 mg/dL before the oral corticosteroid treatment and 401 mg/dL 12 weeks after the initiation of therapy.

corticosteroid therapy were well delineated on MR images; however, changes in gland architecture were minimal on MR images (Fig. 1).

Different types of glands responded differently to corticosteroids. For example, the involved parotid and lacrimal glands were well restored to near normal appearance after the corticosteroid treatment on US. In contrast, the submandibular glands were more resistant to corticosteroid therapy.

Hypoechoic spots are also characteristic of the glands in SS patients (8). However, in the glands of IgG4-MD fat infiltration does not occur, and fibrosis and acinar destruction are minimal (4). These differences in histololical components of the affected glands between SS and IgG4-MD patients may cause different MR imaging features of the 2 distinctive gland diseases.

Alleviations of the abnormal architecture and size of the affected glands in response to the therapy were steadily traceable with US, and the scoring system used for SS would be useful for evaluating gland status of patients with IgG4-MD (9). US examination is non-invasive and inexpensive for

routine evaluation of the gland status of patients with IgG4-MD who need long-term corticosteroid therapy (10). Therefore, US may be a useful adjunct to monitoring the efficacy of corticosteroid therapy in these patients.

References

1. FRAGOULIS GE, MOUTSOPOULOS HM: IgG4 syndrome: old disease, new perspective. *J Rheumatol* 2010; 37: 1369-70.
2. MASAKI Y, DONG L, KUROSE N *et al*.: Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. *Ann Rheum Dis* 2009; 68: 1310-5.
3. FUJITA A, SAKAI O, CHAPMAN MN, SUGIMOTO H: IgG4-related disease of the head and neck: CT and MR imaging manifestations. *Radiographics* 2012; 32: 1945-58.
4. TAKAGI Y, SUMI M, SUMI T, ICHIKAWA Y, NAKAMURA T: MR microscopy of the parotid glands in patients with Sjögren's syndrome: quantitative MR diagnostic criteria. *AJNR Am J Neuroradiol* 2005; 26: 1207-14.
5. MASAKI Y, SUGAI S, UMEHARA H: IgG4-related diseases including Mikulicz's disease and sclerosing pancreatitis: diagnostic insights. *J Rheumatol* 2010; 37: 1380-5.
6. TAKAHIRA M, KAWANO M, ZEN Y, MINATO H, YAMADA K, SUGIYAMA K: IgG4-related chronic sclerosing dacryoadenitis. *Arch Ophthalmol* 2007; 125: 1575-8.
7. YAMAMOTO M, HARADA S, OHARA M *et al*.: Clinical and pathological differences between Mikulicz's disease and Sjögren's syndrome. *Rheumatology* 2005; 44: 227-34.
8. TAKAGI Y, KIMURA Y, NAKAMURA H, SASAKI M, EGUCHI K, NAKAMURA T: Salivary gland ultrasonography: Can it be an alternative to sialography as an imaging modality for Sjögren's syndrome? *Ann Rheum Dis* 2010; 69: 1321-4.
9. DE VITA S, LORENZON G, ROSSI G, SABELLA M, FOSSALUZZA V: Salivary gland echography in primary and secondary Sjögren's syndrome. *Clin Exp Rheumatol* 1992; 10: 351-6.
10. DELLE SEDIE A, BALDINI C, DONATI V, MOSCA M: Mikulicz's disease: a long-term follow-up case report. *Clin Exp Rheumatol* 2012; 30: 596.