Concise report

Necessity of early intervention for IgG4-related disease—delayed treatment induces fibrosis progression

Yui Shimizu¹, Motohisa Yamamoto¹, Yasuyoshi Naishiro¹, Gohta Sudoh¹, Keisuke Ishigami¹, Hidetaka Yajima¹, Tetsuya Tabeya¹, Mikiko Matsui¹, Chisako Suzuki¹, Hiroki Takahashi¹, Nobuhiko Seki², Tetsuo Himi², Ken Yamashita³, Hiroko Noguchi⁴, Tadashi Hasegawa⁴, Yasuo Suzuki⁵, Saho Honda⁶, Takashi Abe⁷, Kohzoh Imai⁸ and Yasuhisa Shinomura¹

Abstract

Objective. Despite ongoing research, the clinical and histopathological natural history of immunoglobulin (Ig) G4-related disease (IgG4-RD) remains unclear and the optimal time to initiate treatment is unknown. A focus on clinical symptoms rather than image finding is recommended for therapeutic initiation in autoimmune pancreatitis, but evidence for this approach is lacking. We aimed to retrospectively analyse disease duration, efficacy of treatment with glucocorticoids and results of histopathological examination of submandibular gland specimens to clarify the necessity for early intervention in IgG4-RD.

Methods. Salivary secretions were assessed before and after treatment in 26 cases of IgG4-related Mikulicz’s disease (IgG4-MD). Relationships between disease duration, amount of salivary secretion before treatment, improvement of salivary secretion and ratios of areas of residual acini, fibrosis and lymphoid follicles in the involved submandibular gland specimens were analysed.

Results. Salivary secretions were significantly reduced in cases with illness of >2 years (P < 0.05). An inverse correlation was seen between improved amount of salivary secretion and amount of salivary secretion before treatment (r = −0.60). Improved amount of salivary secretion was also associated with each histological factor (acini, r = 0.29; fibrosis, r = −0.23; lymphoid follicles, r = −0.31), which showed interrelationships (acini and lymphoid follicles, r = −0.23; acini and fibrosis, r = 0.42; lymphoid follicles and fibrosis, r = 0.30).

Conclusion. Salivary secretion can be improved even in cases with lower levels of salivary secretion before treatment in IgG4-RD, but improvements in the amount of salivary secretion decrease with histological changes with delayed therapeutic intervention. These data suggest that early intervention is needed to improve outcomes in patients with IgG4-MD.

Key words: autoimmune pancreatitis, early intervention, fibrosis, IgG4, Mikulicz’s disease.

Introduction

Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a chronic inflammatory disorder characterized by elevated levels of serum IgG4 and by swollen organs with fibrosis and infiltration of abundant IgG4-positive plasmacytes. It is considered to be a systemic disorder and can affect various organs, including the lacrimal and salivary glands [IgG4-related Mikulicz’s disease (IgG4-MD)] [1, 2], pancreas [autoimmune pancreatitis (AIP)] [3, 4], kidneys...
(IgG4-related tubulointerstitial nephritis) [5] and lung [6]. Despite ongoing research, the clinical and histopathological natural history of this disease remains unclear, and the optimal time at which to initiate treatment remains unclear. This study retrospectively analysed the duration of illness, efficacy of treatments and results of histopathological examination of specimens of submandibular glands from patients with IgG4-MD in order to provide data regarding the necessity of early intervention.

Methods

Patients

The study population comprised 26 subjects with IgG4-MD who had been diagnosed according to the Japanese diagnostic criteria for IgG4-MD [7] and who were registered in the Sapporo Medical University and Related Institutes Database for Investigation and Best Treatments of IgG4-RD (SMART) database. Written consent to use case information was obtained from all patients prior to enrolment, in accordance with the Declaration of Helsinki. This study was conducted with the approval of our institutional review board (Sapporo Medical University Hospital, SMU 22-57).

Clinical assessments

Stimulated salivary secretion was evaluated by the Saxon test before and after treatment [8]. Saxon tests after treatments were performed while patients were receiving 10 mg/day of prednisolone. The duration of illness was also reviewed, and the relationship between duration of illness, amount of saliva secretion and levels of serum IgG4 before treatment and improved amount of saliva after treatment was analysed. Duration of illness was defined as the period from first awareness of glandular enlargement to the diagnosis of IgG4-MD. Treatment consisted of 0.6–0.8 mg/kg/day of prednisolone for 4 weeks, with 10% dose reductions every 2 weeks thereafter.

Histopathological evaluation

Ratios of areas of residual acini, fibrosis and lymphoid follicles were assessed in specimens from whole submandibular glands from 26 cases. Biopsies were performed to diagnose IgG4-RD and exclude the possibility of lymphoma. Microscopic images of specimens were digitized (DP Controller version 2.3.1.231; Olympus, Tokyo, Japan) and then Scion Image version 4.0.3.2 software (Scion Corporation, Frederick, MD, USA) was used to assess the variables described above. Relationships between these results, duration of illness, amount of saliva and levels of serum IgG4 before treatment and amount of saliva after treatment were analysed.

Statistical analysis

The Mann–Whitney U-test was used to compare amounts of saliva before and after treatment, and values of $P < 0.05$ were considered significant. Statistical processing was performed using StatView version 5.0 software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The 26 participants in this study comprised 15 men and 11 women. Mean (s.d.) age at onset was 57.7 (12.3) years and the mean age at diagnosis was 58.9 (11.9) years. Duration of illness was 1.3 (1.6) years (maximum, 5 years). Mean amount of salivary secretion before treatment and improved amount of salivary secretion after treatment were 1.84 (1.65) g/2 min and 0.83 (1.47) g/2 min, respectively. The mean level of serum IgG4 was 776.4 (635.3) mg/dl.

Salivary reversibility and disease duration

Mean changes in the amount of salivary secretion after treatment were 1.16 (1.28) g/2 min in patients treated ≤2 years after onset and −0.24 (1.65) g/2 min in patients treated >2 years after onset ($P < 0.05$) (Fig. 1). Mean improvements in amount of salivary secretion also correlated negatively with the amount of salivary secretion before treatment ($r = −0.60$) (supplementary Fig. S1, available as supplementary data at Rheumatology Online). Serologically, the longer the disease duration, the higher the serum levels of IgG4 ($r = 0.42$).

Histopathological factors

Histopathological results showed close correlations with each factor. The greater the area of lymphoid follicles, the lower the area of acini ($r = −0.23$) (supplementary Fig. S2A, available as supplementary data at Rheumatology Online). Lymphoid follicles also correlated with fibrosis ($r = 0.30$) (supplementary Fig. S2B, available as supplementary data at Rheumatology Online). Furthermore, area of

**Fig. 1** Relationship between duration of illness and improvement in amount of salivary secretion after treatment.
Fig. 2 Relationship between improved amount of salivary secretion and histopathological factors.

(A) Relationship between area of residual acini and improvement in amount of saliva secretion. (B) Relationship between lymphoid follicle and improvement in amount of saliva secretion. (C) Relationship between fibrosis and improvement in amount of saliva secretion. Area of residual acini showed a positive correlation, and areas of lymphoid follicle and fibrosis showed an inverse correlation with improvements in the amount of salivary secretion.
fibrosis showed an inverse correlation with area of residual acini ($r = -0.42$) (supplementary Fig. S2C, available as supplementary data at Rheumatology Online).

**Improved amount of salivary secretion and histopathological factors**

With regard to improved salivary secretion and histopathological factors, area of residual acini correlated with improved amount of saliva secretion ($r = 0.29$) (Fig. 2A). The area of lymphoid follicle and fibrosis correlated negatively with improved amount of saliva secretion ($r = -0.31$ and $r = -0.23$, respectively) (Fig. 2B and C). The more levels of serum IgG4 decreased, the larger the area of residual acini.

**Discussion**

IgG4-RD is a new disease entity. Despite ongoing research, the clinical and histopathological natural history of this disease remain unclear. Cases presenting with spontaneous regression or remission in AIP have recently been reported [9–11]. In the Japanese therapeutic guidelines for the management of AIP, indications for glucocorticoid treatment thus include obstructive jaundice due to stricture of the bile duct, abdominal or back pain and complications of extra-pancreatic lesions [12]. On the other hand, almost no cases have presented with spontaneous regression or remission in IgG4-MD according to the SMART database. We therefore analysed whether early treatment of the disease can be expected to result in improved/preserved clinical function of affected organs.

In IgG4-RD, the potential for reversibility of clinical glandular function is known to be very good in the short term [13], thanks to the low frequency of glandular apoptosis despite the presence of severe inflammation [14]. Actually, evaluations of submandibular gland specimens in IgG4-MD have revealed that the glands remain almost entirely intact despite severe inflammation with fibrosis. Particularly in areas showing prominent fibrosis, the glands appear atrophic. Even in IgG4-MD, gland function was considered to be gradually decreased due to glandular destruction in the medium to long term.

The present study disclosed that duration of illness $\geq 2$ years led to reductions in the improvements that can be expected in the amount of salivary secretion. We divided cases into two groups according to disease duration and analysed improvements in the amount of saliva secretion. Separation using a cut-off of 2 years was considered the most significant. Two years after onset thus appears to represent a branch point in the prognosis of IgG4-MD. This suggests that early therapeutic intervention is necessary for the preservation of salivary function. Interestingly, salivary gland function was reversible even in cases presenting with severe sicca symptoms before treatment. The amount of saliva secretion before treatment was not a predictive factor for reversibility.

We performed histopathological analyses to clarify reasons for these clinical findings. The development of lymphoid follicles is considered to reflect the degree of inflammation, because antigen presentation is performed in the lymphoid follicle. This study revealed the close interrelationship between inflammation, fibrosis and residual acini. The inflammation was found to be associated with the progression of fibrosis, and both fibrosis and inflammation decreased the area of residual acini. Contrasting with MD, inflammation in SS directly destroys the ducts and acini through the actions of Fas or cytolytic granules [15]. SS thus represents a fundamentally different pathogenesis from MD due to lack of a role for fibrosis, and the rate of disease progression in SS may be faster than that in MD.

With regard to the relationship between clinical features and histopathological results, we found that a large area of residual acini was associated with greater improvements in the amount of salivary secretion. On the other hand, large areas of lymphoid follicle and fibrosis were associated with decreased improvements in the amount of saliva. A direct correlation between the above histological factors and response to treatment was evident. Subjects in this study showed MD, but similar phenomena would occur in AIP and other IgG4-RDs. Early therapeutic intervention has been clinically and histopathologically demonstrated to be important for the retention of glandular function in IgG4-RD.

We examined the relationship between levels of serum IgG4 and clinical and histopathological factors. The results showed positive correlations with disease duration and negative correlations with percentage area of residual acini. While the present analysis was limited due to the two-dimensional nature of histopathological examination, serum IgG4 values are suggested to reflect histological destruction of the glands in MD.

In conclusion, salivary secretion can be improved even in cases of IgG4-RD with relatively low amounts of salivary secretion before treatment, but the improvements that can be obtained decrease with the histological changes that result from delays in therapeutic intervention. These data suggest that early intervention is needed to achieve optimal outcomes in patients with IgG4-MD.

**Rheumatology key message**

- Early intervention is needed to improve outcomes in patients with IgG4-related MD.

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**Supplementary data**

Supplementary data are available at Rheumatology Online.
References