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Predicting therapeutic response in IgG4-related disease based on cluster analysis

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ABSTRACT

To bring the clinical practice of immunoglobulin (Ig)G4-related disease (IgG4-RD) close to personalized medicine, we classified the patient groups and clarified the therapeutic responses of each group. A total of 147 patients enrolled in our registry were classified into four groups by cluster analysis with the software. The therapeutic responses and prognosis of each group were examined. The cluster analysis classified the subjects into four groups: Cluster 1, patients who presented with prominent hypergammaglobulinemia, elevated levels of serum IgG4, and hypocomplementemia; Cluster 2, patients who presented with eosinophilia, elevated concentrations of serum IgG, IgG4, and IgE, and in whom CRP tended to be positive; Cluster 3, patients with younger onset and serum levels of IgG, IgG4, and IgE and peripheral eosinophil counts lower than the other clusters; and Cluster 4, patients with elder onset and low peripheral eosinophil counts. The amounts of glucocorticoid for maintenance treatment were from 5 to 7 mg/d in all groups, but the amounts were significantly greater in Cluster 1 (patients with hypergammaglobulinemia, elevated levels of serum IgG4, and hypocomplementemia) than in Cluster 4 (elder onset patients, relatively low concentrations of peripheral eosinophils). With regard to the use of immunosuppressants and the relapse rate, there were high frequencies in Cluster 1 and Cluster 3 (younger onset patients who presented with mild elevations of serum IgG and IgG4). On the other hand, Cluster 4 showed a low rate of relapse and often could discontinue steroids. The present results suggest that personalized medicine could be provided in IgG4-RD by classifying patients based on their clinical features.

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Autoimmune pancreatitis; cluster analysis; IgG4-related disease; precision medicine; personalized medicine

1. Introduction

It was confirmed that glucocorticoid is the first-line induction therapy for immunoglobulin (Ig)G4-related disease (IgG4-RD) at the 2nd International Symposium on IgG4-RD & Associated Conditions [1]. It was found that glucocorticoid has efficacy in all patients with IgG4-RD, but most patients cannot discontinue steroid and require maintenance treatment [2,3]. Furthermore, relapse can easily occur with steroid tapering [4], and there are often patients who need immunosuppressants or biologic agents for disease control [5,6]. However, when we analyzed the patients enrolled in the SMART (Sapporo Medical University and related institutes

database for investigation and best treatment for IgG4-RD) registry cohort [2], it was found that they were a fairly diverse group in their clinical features and laboratory data even though they met the comprehensive diagnostic criteria for IgG4-RD [7]. Currently, we are in the era where personalized medicine or, furthermore, precision medicine, presented by former US President Obama [8], should be the aim. Of course, this also applies to IgG4-RD. To begin to address this challenge, the aim of the present study was to examine the therapeutic responses and the prognosis of patients enrolled in the SMART registry cohort by cluster analysis of clinical factors.

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2. Methods

2.1. Study population

A total of 147 cases diagnosed with IgG4-related dacryoadenitis and sialadenitis (IgG4-RDS) were selected from the SMART registry, which was a multicenter cohort. They were definite cases according to the diagnostic criteria for IgG4-RD, 2011 [7], and their treatment periods were over a year. The treatment protocol involved starting prednisolone at a dose of 0.6 mg/kg/d for patients with only lacrimal and salivary gland involvement and 0.8 mg/kg/d in patients with multiple organ lesions. The initial dose of prednisolone was continued for 4 weeks, and was tapered by 10% every 2 weeks. When the levels of serum IgG4 were increased twice consecutively, steroid tapering was stopped, and that the dose was used for maintenance treatment. For patients with a maintenance dose over 10 mg/d of prednisolone, immunosuppressants were prescribed concurrently at the discretion of the attending physician.

2.2. Cluster analysis

Hierarchical cluster analysis was performed with the following continuous variables: age at onset, peripheral eosinophil count, and serum C-reactive protein (CRP), IgG, IgG4, IgE, and complement levels at the first visit. It was performed using Cluster 3.0 with centroid linkage method after transforming these values into *z*-scores [9].

The patients were classified into four groups. Clinical characteristics were extracted, and the maintenance dose of glucocorticoid, the frequency of concomitant use of immunosuppressants, and the relapse rate were analyzed in each group. With regard to the maintenance doses in cases

treated with immunosuppressants, the doses of glucocorticoid just before the addition of immunosuppressants were tentatively taken as the maintenance doses, to exclude the effects of the immunosuppressants.

2.3. Statistical analysis

p Values < .05 were considered statistically significant. All statistical analyses were performed using Multivariate analysis for Mac version 3 software (ESUMI Co. Ltd., Tokyo, Japan).

3. Results

3.1. Patient profile

The 147 cases consisted of 79 males and 68 females, with an average age of onset of 58.85 ± 11.40 (mean $\pm$ SD) years. With regard to the diagnosis according to the main organ lesions, there were 96 cases with IgG4-RDS, 35 cases with only IgG4-related sialadenitis, and 16 cases with only IgG4-related dacryoadenitis. The mean follow-up period was 5.84 ± 3.91 years.

3.2. Clinical characteristics of each cluster

The cluster analysis classified the subjects into the following four groups (Figure 1): Cluster 1, patients who presented with prominent hypergammaglobulinemia, elevated levels of serum IgG4, and hypocomplementemia; Cluster 2, patients who presented with eosinophilia, elevated concentrations of serum IgG, IgG4, and IgE, and in whom CRP tended to be positive; Cluster 3, patients with younger onset and serum levels of IgG, IgG4, and IgE and peripheral eosinophil counts lower than the other clusters; and

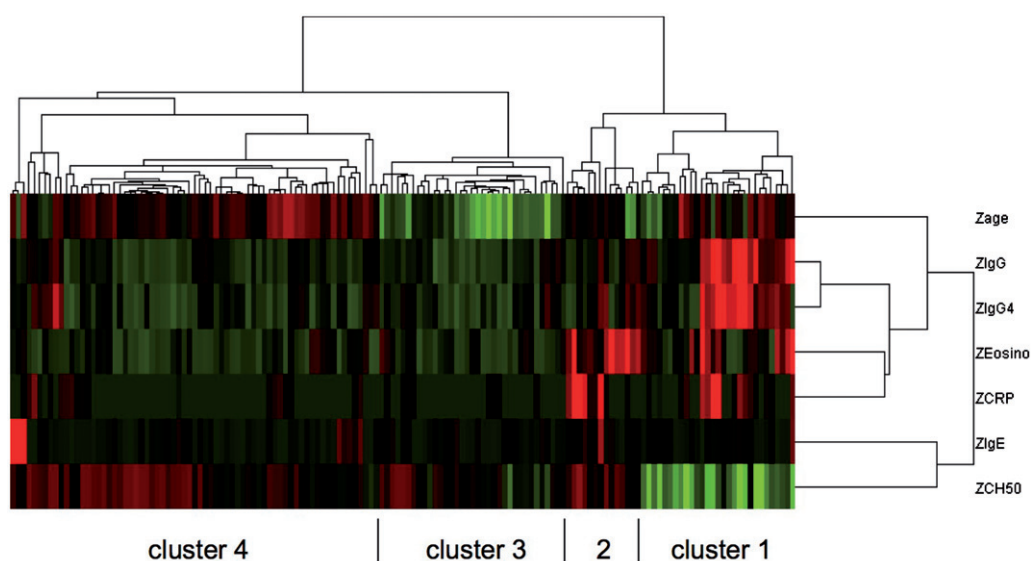


Figure 1. Heat map of the four clusters. The patients are clustered into four groups by the clustering analysis with clinical continuous variables, consisting of age at onset, serum levels of IgG, IgG4, CRP, IgE, and complement, and the peripheral eosinophil count.

Table 1. Clinical features of each cluster.

	N	Age of the onset (years)	IgG (mg/dL)	IgG4 (mg/dL)	IgE (IU/mL)	CH50 (U/mL)	Eosino (/μL)	CRP (mg/dL)
Cluster 1	29	60.55 ± 9.55	3849.07 ± 1777.57	1401.62 ± 935.05	343.56 ± 400.54	24.25 ± 10.94	408.79 ± 337.99	0.26 ± 0.40
Cluster 2	14	57.43 ± 8.08	2224.29 ± 632.14	793.36 ± 451.83	641.46 ± 648.37	51.04 ± 7.79	723.43 ± 340.96	0.54 ± 0.76
Cluster 3	35	45.00 ± 8.92	1719.63 ± 433.31	483.21 ± 271.93	294.38 ± 277.83	43.99 ± 8.44	167.77 ± 118.23	0.04 ± 0.07
Cluster 4	69	65.45 ± 6.68	1840.04 ± 434.84	524.79 ± 363.40	579.32 ± 1669.42	49.63 ± 7.87	149.28 ± 102.30	0.06 ± 0.12

Table 2. Sex ratio and the rate of organ involvement in each cluster.

	Sex	Lac.	Sub.man.	Panc.	Kidney	Lung	Aorta	R. pelvis	Malig.
Cluster 1	0.586	0.828	1.000	0.310	0.345	0.207	0.103	0.069	0.241
Cluster 2	0.786	0.857	0.857	0.500	0.286	0.429	0.214	0.143	0.143
Cluster 3	0.343	0.771	0.829	0.171	0.257	0.114	0.057	0.057	0.057
Cluster 4	0.565	0.710	0.899	0.290	0.116	0.145	0.130	0.101	0.145

Lac: lacrimal gland; Sub. man: submandibular glands; Panc: pancreas; R. pelvis: renal pelvis; Malig: malignancies.

Cluster 4, patients with elder onset and low peripheral eosinophil counts (Table 1). Table 2 shows the frequencies of organ involvement and malignancies in each cluster.

3.3. Therapeutic responses and prognosis

The mean amount of glucocorticoid used for maintenance in all subjects was 5.59 ± 2.82 mg/d. The maintenance doses for each cluster were from 5 to 7 mg/d (Table 3). There was a significant difference between Clusters 1 and 4 ($p = .016$). The frequency of concurrent use of immunosuppressants in all patients was 8.84%; the rates in Clusters 1 and 3 were higher (17.24% and 11.43%, respectively). There was no patient treated with immunosuppressants in Cluster 2. The relapse rate in all subjects was 20.41%. The rate in Cluster 1 was the highest, at 34.48%. There was a significant difference between Clusters 1 and 4 ($p = .0034$). On the other hand, the drug-free remission rate in all subjects was 7.48%. The rate in Cluster 4 was the highest, at 13.04%. There was no significant difference between Clusters 2 and 4, but there was a significant difference between Clusters 1 and 4 ($p = .041$).

4. Discussion

IgG4-RD is a fibro-inflammatory disorder that can cause irreversible organ involvement [10]. Because only 10 years have passed since the development of this disease concept [11,12], there continue to be many unmet medical needs in IgG4-RD. On the other hand, the concept of IgG4-RD has spread worldwide, and the diagnostic criteria for IgG4-RD have been established [7]. With regard to the treatments for IgG4-RD, it was confirmed that glucocorticoids are the first-line treatment for induction in the International Symposium held in 2014 [1]. However, the treatment regimen was not discussed, and the long-term prognosis was not evaluated in this statement. Furthermore, there are several

Table 3. Therapeutic responses and prognosis in each cluster.

	Amounts of maintenance (mg/day)	Rates of IS (%)	Relapse rates (%)	Rates of DFR (%)
Cluster 1	6.71 ± 2.80	17.24	34.48	0.00
Cluster 2	6.07 ± 2.50	0.00	14.29	0.00
Cluster 3	5.26 ± 2.88	11.43	25.71	5.71
Cluster 4	5.20 ± 2.77	5.80	13.04	13.04

IS: immunosuppressants; DFR: drug-free remission.

difficulties in clinical practice with IgG4-RD. The biomarkers that reflect completely disease activity have not been identified, and excessive tapering of steroids can easily lead to recurrence. Therefore, hierarchic cluster analysis was performed with the IgG4-RD patients enrolled in the SMART registry cohort, and predictors of therapeutic responses and recurrence rates were analyzed. The initial analysis was performed with clinical factors including sex and each organ lesion, but it was not well separated. Therefore, cluster analysis was performed only with continuous variables, and good and poor response groups were identified in the registry.

It was found that patients in Cluster 1 needed a large amount of glucocorticoid and immunosuppressants to maintain remission. The relapse rate in this cluster was the highest, and no patient achieved steroid-free remission. On the other hand, Cluster 4 was the group characterized with the lowest doses of glucocorticoid for maintaining remission, the lowest relapse rates, and the highest rates of discontinuing glucocorticoid because of cure. These findings suggest that disease activity was very high in Cluster 1. In this type, enhancement of induction therapy with immunosuppressants to prevent recurrence must be considered. The results also showed that the rates of relapse and the use of immunosuppressants for maintenance treatment were higher in Cluster 3. We previously identified the relapse predictors in IgG4-RD using multivariate analysis of clinical data at the first visit and initial treatment; they were male sex and younger onset in cases without organ involvement at diagnosis, and low levels of serum

IgG4 in cases with organ dysfunction at diagnosis. Autoimmune pancreatitis and low steroid dose at initial treatment also tended to be associated with recurrence [13]. In the present analysis, it was difficult to interpret the results because sex and organ involvement were excluded, but Cluster 3 had features similar to those described above, younger onset, and low levels of serum IgG4. It was considered that these factors were associated with high disease activity, because the relapse rate in Cluster 3 was also very high, at 25.71%. On the other hand, Cluster 4 showed the highest drug-free remission rate. This cluster was characterized by elder onset, lower levels of serum IgG and IgG4, and a low frequency of eosinophilia. We might be able to aim for discontinuing glucocorticoid, in other words, cure, in patients with these clinical features.

Even in IgG4-RD diagnosed by the comprehensive diagnostic criteria [7], the patients are quite varied. We consider that we can provide better precision medicine by classifying the patients scientifically. Although treatment should aim to target molecules directly associated with the pathogenesis, it is best to carry out treatments in anticipation of therapeutic responses and prognosis at this point when the pathogenesis has not been elucidated. We believe that our research will be a starting point for personalized or precision medicine in IgG4-RD.

This analysis has several limitations. All the subjects had IgG4-RDS. Although the results are useful for rheumatologists, their value for other clinicians is unknown. Other registry cohorts including autoimmune pancreatitis or IgG4-related kidney diseases need to be validated.

5. Conclusions

Cluster analysis of IgG4-RD patients enrolled in the SMART registry cohort was performed, and patients were classified into four groups. Cluster 1, with prominent hypergammaglobulinemia, elevated levels of serum IgG4, and hypocomplementemia, was characterized by large amounts of steroid to maintain remission, a high rate of immunosuppressant use, and a high relapse rate. On the other hand, glucocorticoid could easily be withdrawn because the relapse rates were lowest in Cluster 4.

Ethical approval

The protocol was approved by Sapporo Medical University Hospital Institutional Review Board subject to applicable laws and regulations and ethical principles consistent with the Declaration of Helsinki. Informed consent has been obtained from the subjects.

Disclosure statement

All authors have declared no conflicts of interest.

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