IgG4-related disease: features and treatment response in a multi-ethnic cohort in Singapore

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ABSTRACT

Objective. *To describe the features and treatment outcomes of IgG4-RD in multi-ethnic patients in Singapore.*

Methods. *A retrospective study was performed on IgG4-RD patients identified from patient databases in a tertiary hospital.*

Results. *Fourty-two patients (76% male) were included; 79% fulfilled the 2011 comprehensive diagnostic criteria for IgG4-RD for definite IgG4-RD. 81% were Chinese and 19% were Malays. Common initial manifestations included jaundice (52%), abdominal pain (36%) and swollen salivary glands (26%). Only 36% had a history of allergy. 83% had ≥ 1 organ involvement. Erythrocyte sedimentation rate, immunoglobulin E, IgG2 and IgG4 levels were elevated in 84%, 100%, 70% and 44% of patients, respectively. The most common histopathological feature was >10 IgG4+ cells per high power field (66%). 94% (34/36) of patients were treated with moderate to high doses of glucocorticoids, including 17 patients with combination immunosuppressants. Of these, all patients responded to therapy by 3 months. With a median (range) follow-up of 4.1 (0.4-13.8) years, 69% (25/36) needed low dose of glucocorticoids to maintain disease remission. Twenty-six per cent had relapse of disease, of which 82% had disease recurrence in the same organs.*

Conclusion. *Pancreatitis, lymphoadenopathy and cholangitis were the commonest manifestations in Asians with IgG4-RD. All patients responded to glucocorticoid therapy by 3 months, two-thirds required maintenance therapy with glucocorticoids, and one-quarter developed relapse of disease.*

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a chronic inflammatory disorder, characterised by fibrosing and sclerosing lesions, dense lymphoplasmacytic infiltrates and infiltration of organs with IgG4+ plasma cells. Serum IgG4 levels are often elevated, but can be normal in a third of affected individuals. This disease entity was first recognised in a cohort of Japanese patients with autoimmune pancreatitis and raised serum levels of IgG4 (1). Since then, the disease has been described in multiple organ systems besides the pancreas (2). With the increasing use of FDG-PET CT in the diagnosis of IgG4-RD (3), common pathological features are now known to characterise IgG4-RD in different organ systems (4), and consists typically of mass lesions containing abundance of IgG4+ plasma cells. The pathogenesis of IgG4-RD is still not well understood, and increases in IgG4+ plasma cells appear to be a consequence of the inflammatory process rather than a primary disease driver. Previous studies have highlighted the possible role of B cells in the pathogenesis of IgG4-RD. B-cell depletion with rituximab had induced disease remission and resulted in improvement of tissue fibrosis (5). Furthermore, patients with active disease had oligoclonally expanded CD19+CD20-CD27+CD38+ plasmablasts, and treatment response correlated with depletion of this B-cell subpopulation (6). Recent investigations have focused on the interactions between plasmablasts and a novel CD4+ SLAMF7+ cytotoxic T cells capable of promoting fibrosis (7). Middle-aged and elderly males are often affected (8). Previous publications described the characteristics of patient cohorts from Japan (9), France (10), America (11) and China (12). Data from Asian countries is scanty. In this study, we aim to describe the disease characteristics of IgG4-RD in a multi-ethnic Asian country, Singapore.

Materials and methods

Patients and study design

Consecutive patients with IgG4-RD

diagnosed by gastroenterologists and rheumatologists with experience in IgG4-RD were identified from prospective databases in four departments (Gastroenterology, Rheumatology, Radiology and Pathology) of Singapore General Hospital, a tertiary referral centre from 2003 to 2015. Patient records were retrospectively reviewed. Sociodemographic, clinical and laboratory data were collected using a standardised data collection form. All archived pathological specimens and radiological images were reviewed and findings recorded using standardised data collection forms. Patients were re-evaluated with the 2011 comprehensive diagnostic criteria for IgG4-RD for definite and probable IgG4-RD (2). Briefly, definite IgG4-RD must have the following: (i) organ enlargement mass or nodular lesions, or organ dysfunction; (ii) a serum IgG4 concentration of >1.35 g/L; and (iii) histopathological findings of >10 IgG4 cells/HPF and an IgG4+/IgG+ cell ratio >40%. Possible IgG4-RD included patients who fulfilled criteria (i) and (ii), but without histopathological findings. A diagnosis of IgG4-RD is probable in patients who fulfilled criteria (i), but without increased serum IgG4. Disease activity at baseline, and follow-ups were assessed by the IgG4-RD Responder Index (IgG4-RD RI) where available (13). Follow-up data were reviewed for relapses, type of organ involvement during relapses and response to therapy. Malignant diseases and comorbidities were also recorded. The study was approved by the SingHealth Centralized Institutional Review Board (CIRB 2015/2811) with exemption of patient consent.

Statistical analysis
The results were described in standard summary statistics, including mean (standard deviation [SD]) or median (range) for normally and non-normally distributed data, respectively. Comparison between variables was performed using the chi-square, Fisher's exact test, Mann-Whitney *U*-test or *t*-test as appropriate. *P*-values <0.05 were considered statistically significant. Multivariate and univariate analysis was performed

to investigate factors that could correlate with disease severity or number of organs involved. Statistical analysis was performed using IBM SPSS Statistics 21 (IBM, Armonk, NY, USA).

Results
Patient demographics
Forty consecutive patients diagnosed to have IgG4-RD by consultant specialists experienced in IgG4-RD were identified. Thirty-five (87.5%) and five (12.5%) patients fulfilled the 2011 comprehensive diagnostic criteria for IgG4-RD for definite and probable IgG4-RD, respectively. The cohort consisted of 31

(77.5%) males, 82.5% Chinese and the remaining were Malay. Baseline demographics are described in Table I.

Clinical manifestations and organ involvement
Patients commonly presented initially with jaundice (50.0%), abdominal pain (35.0%) and constitutional symptoms (25.0%) (Table I). Common organ involvement included the pancreas (65.0%), lymph nodes (45.0%) and bile ducts (40.0%) (Fig. 1). 82.5% of patients had more than one organ involvement, with 27.5%, 30.0%, 22.5% and 2.5% of patients having 2, 3, 4 and
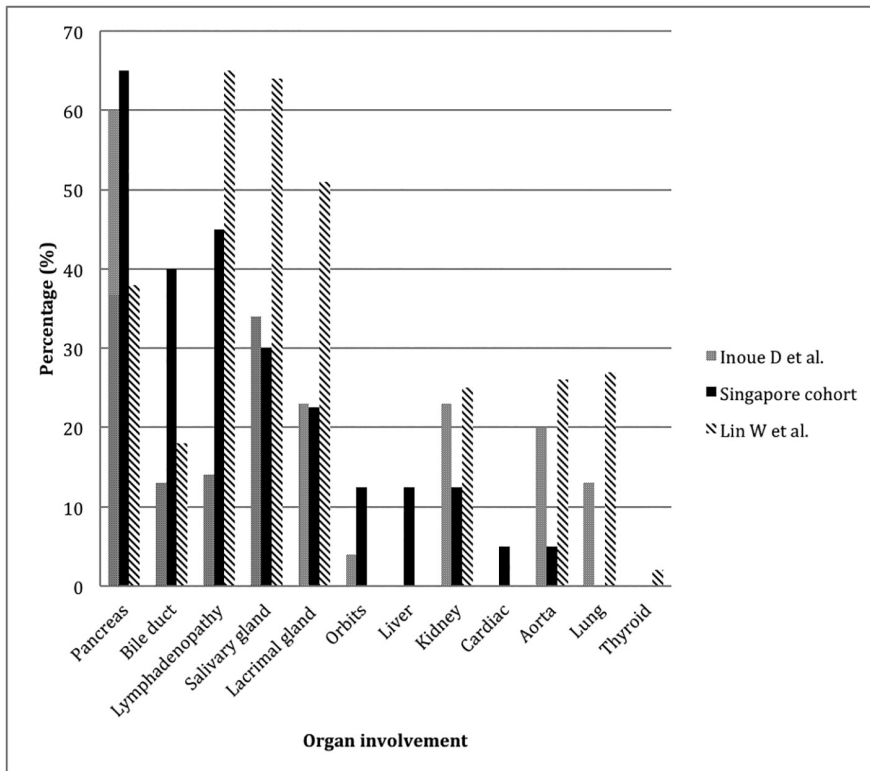
Table I. Baseline characteristics, clinical manifestations, laboratory and histological features in patients with IgG4-RD.

Baseline characteristics	Total	Definite IgG4-RD n=35	Probable IgG4-RD n=5
Males, n (%)	31 (77.5)	28 (80.0)	3 (60.0)
Current age, median (range), years	66.3 (26.8-86.8)	64.0 (26.8-86.8)	67.8 (53.4-75.9)
Age of symptom onset, median (range), years	59.0 (18.0-79.0)	56.0 (18.0-79.0)	65.0 (51.0-67.0)
Age of diagnosis, median (range), years	59.5 (18.0-80.0)	59.0 (18.0-80.0)	61.0 (51.0-71.0)
Duration of follow-up, median (range), years	3.6 (1.1-9.7)	3.7 (1.1-9.7)	2.9 (1.3-4.6)
Clinical manifestations			
Jaundice, n (%)	20 (50.0)	20 (57.1)	0 (0.0)
Abdominal pain, n (%)	14 (35.0)	14 (40.0)	0 (0.0)
Constitutional symptoms (loss of appetite and weight), n (%)	10 (25.0)	8 (22.9)	2 (40.0)
Submandibular gland swelling, n (%)	7 (17.5)	6 (17.1)	1 (20.0)
Parotid gland swelling, n (%)	7 (17.5)	4 (11.4)	3 (60.0)
Lymphadenopathy, n (%)	6 (15.0)	4 (11.4)	2 (40.0)
Lacrimal gland swelling, n (%)	6 (15.0)	4 (11.4)	2 (40.0)
Nausea, n (%)	3 (7.1)	3 (8.6)	0 (0.0)
Fever, n (%)	3 (7.1)	3 (8.6)	0 (0.0)
Nasal congestion, n (%)	3 (7.1)	2 (5.7)	1 (20.0)
Cough, n (%)	2 (4.8)	2 (5.7)	0 (0.0)
Diarrhoea, n (%)	2 (4.8)	2 (5.7)	0 (0.0)
Other*, n (%)	5 (12.5)	4 (11.4)	1 (20.0)
Laboratory features			
ESR, mean (SD) mm/hour	49.9 (35.2)	50.4 (39.1)	48.2 (22.6)
IgE levels, mean (SD) g/L	389.8 (230.5)	389.8 (230.5)	-
Total IgG levels, mean (SD) g/L	20.5 (11.6)	18.5 (9.0)**	33.5 (18.7)**
IgG1 levels, mean (SD) g/L	9.1 (4.7)	8.6 (3.1)	12.6 (10.3)
IgG2 levels, mean (SD) g/L	9.8 (5.6)	9.6 (5.8)	10.7 (5.3)
IgG3 levels, mean (SD) g/L	1.3 (1.1)	1.2 (1.0)	1.9 (1.6)
IgG4 levels, mean (SD) g/L	1.5 (1.2)	1.6 (1.2)**	0.5 (0.2)**
Absolute eosinophil count, mean (S.D.) x10⁹/L	0.6 (0.6)	0.6 (0.6)	0.8 (0.7)
Histological features			
Lymphoplasmacytic infiltration and ibrosis, f n (%)	20 (50.0)	15 (44.1)**	5 (100.0)**
Storiform fibrosis, n (%)	21 (52.5)	19 (55.9)	2 (40.0)
Obliterative fibrosis, n (%)	3 (7.5)	3 (8.8)	0 (0.0)
IgG4⁺: IgG⁺ cell ratio ≥40%, n (%)	16 (40.0)	11 (32.4)**	5 (100.0)**
More than 10 IgG4⁺ plasma cells per hpf, n (%)	27 (67.5)	23 (67.6)	4 (80.0)

*Other clinical manifestations included rashes over the lower limbs (n=1), angina (n=1), haematuria (n=1), hypopigmentation of skin (n=1), xerostomia and xerophthalmia (n=1). **$p<0.05$.
ESR: erythrocyte sedimentation rate; IgE: immunoglobulin E; IgG: immunoglobulin G; Hpf: high power field.

Fig. 1. Organ manifestations of patients with IgG4-RD in Singapore compared to other cohorts.

5 organs involved, respectively. Of those with isolated lesions, 85.7% (6/7) involved only the pancreas. Only 7.5%, 5.0% and 25.0% of patients had a history of asthma, skin sensitivity and drug allergy respectively. Clinical manifestations were not statistically different between genders and ethnicity. Organ involvement was not statistically different between the genders, whilst the liver was more commonly involved in Malays compared to Chinese patients (57.1% *vs*. 3.0%, *p*=0.002).

Laboratory and histological findings
Mean baseline levels (Table I) of total serum immunoglobulin G (IgG), IgG2, IgG4, immunoglobulin E (IgE), erythrocyte sedimentation rate (ESR) and absolute eosinophil counts were increased in patients with IgG4-RD, and did not differ between gender and ethnicity. Of all patients, 47.4%, 22.2%, 69.4%, 27.8% and 44.4% had increased serum levels of total IgG, IgG1, IgG2, IgG3, and IgG4 respectively. 83.9%, 100.0% and 65.2% had increased levels of ESR, IgE and absolute eosinophil counts respectively at baseline. The mean (S.D) levels of

IgG2 and IgG4 were 12.1 (5.2) g/L and 2.7 (5.1) g/L in patients with abnormal levels of IgG2 and IgG4 respectively. ESR did not correlate with baseline disease activity (r=0.037, *p*=0.845) and IgG2 levels (r=0.249, *p*=0.210), but correlated with IgG4 levels (r=-0.385, *p*=0.047). IgG2 levels correlated with baseline disease activity (r=0.368, *p*=0.027) and IgG4 levels (r=-0.433, *p*=0.008), but not multiorgan involvement (r=0.287, *p*=0.089). IgG4 levels at baseline did not correlate with baseline disease activity or multiorgan involvement.

Majority (97.5%) of patients underwent a biopsy. Histological findings are described in Table I. Of the 24 patients that had IgG4+: IgG+ cell ratio <40%, 21 fulfilled the criteria for autoimmune pancreatitis (14), whilst 3 fulfilled the IgG4+ Mikulicz's disease (15). There was no statistical difference in histological findings between gender and ethnicity.

Comorbidities and mortality
Hyperlipidaemia, hypertension and diabetes mellitus was present in 52.5%, 47.5% and 42.5% of our patients re-

spectively. Cardiovascular heart disease was present in 12.8% of patients, and 2.6% of patients had a history of stroke. Three patients had osteoporosis. One patient developed lung cancer 2.5 years after diagnosis of IgG4-RD. Comorbidities did not differ significantly between ethnicity and gender. One patient died of brain abscesses and acute myocardial infarction.

Disease activity
Mean (S.D.) IgG4-RD RI at baseline, 3 months and 6 months was 7.6 (3.8), 1.3 (1.5) and 0.4 (0.8) respectively in all patients. In six (14.3%) patients who declined treatment, the mean (S.D.) IgG4-RD RI was 8.5 (4.0), 1.8 (3.1) and 0.2 (0.4) at baseline, 3 months and 6 months respectively. There was no difference in the mean IgG4-RD RI between gender and ethnicity.

Treatment
Glucocorticoids were prescribed as initial treatment in 87.5% of the patients. Five patients declined treatment. 2.8%, 80.0% and 17.1% of patients were treated initially with low intensity (*i.e.* oral prednisolone ≤0.5mg/kg), moderate intensity (*i.e.* oral prednisolone 0.51-0.99mg/kg) and high intensity (*i.e.* oral prednisolone ≥1.0mg/kg) glucocorticoids respectively based on physician discretion. Intensity of glucocorticoid initiation did not differ between gender and ethnicity. Concurrent steroid-sparing agents including azathioprine, mycophenolate mofetil, and methotrexate were used in 27.5%, 10.0% and 2.5% of patients respectively. All treated patients responded to therapy by 3 months as reflected by a decrease in the IgG4-RD RI. After a median (range) follow-up of 3.6 (1.1-9.7) years, 60.0% of patients required a low intensity of glucocorticoids to maintain disease remission.

Relapse of disease
Eleven (27.5%) patients experienced relapse of their IgG4-RD. Of these, 88.2% experienced relapse of IgG4-RD in the same organs. Mean (S.D.) time to relapse of their disease was 2.0 (1.0) years. There was no statistical difference in time to relapse of disease

between gender and ethnicity. Seven patients experienced one relapse, whilst three patients experienced two relapses and one patient experienced three relapses of IgG4-RD. All patients experienced disease improvement with re-administration of moderate intensity oral glucocorticoids.

Discussion

This is the first study that describes the clinical, laboratory, histological features and treatment response in multi-ethnic Asian patients with IgG4-RD, and is the one of the largest Asian cohort described, apart from the cohorts from China (12) and Japan (9). Furthermore, our patients were identified from clinics dedicated to the treatment of patients with IgG4-RD. 97.5% of our patients had a biopsy performed, with 75.0% of patients having histological findings typical of IgG4-RD. Also, 87.5% of patients fulfilled the 2011 comprehensive diagnostic criteria for IgG4-RD for definite IgG4-RD.

The majority of patients were Chinese, and this was similar to the distribution of ethnicity in Singapore, with 74.1%, 13.4%, 9.2% and 3.3% of the population made up of Chinese, Malay, Indian and other races respectively (16). Mean age of diagnosis was in the 5th decade, while the mean (S.D.) age of symptoms onset were 0.8 (1.5) years earlier. There was a male predominance, which is similar to other described cohorts (9, 11, 12). In our cohort, only 35.0% of patients had a history of asthma, skin hypersensitivity or drug allergies, as compared to 61.9% described by Lin *et al.* (12) and 24.0% by Ebbo *et al.* (10). None of our patients reported a history of urticarial lesions. The majority of our patients also had multi-organ involvement, a similar observation noted in previously described cohorts (9, 12).

Abnormal levels of ESR, IgG2 and IgE levels was noted in a high proportion of patients, which is similar to another Chinese cohort described by Lin *et al.* (12). However, a smaller proportion (44.4%) of our patients had raised IgG4 levels, compared to 100.0% in Lin *et al.* (12) and 88.5% in Inoue *et al.* (9). A possible explanation for this is the prozone phenomenon, where the presence of large antigen excess can lead to underestimates of the serum IgG4 concentration. In our cohort, we did not progressively dilute the blood samples. Another possible reason is that sequential class switching is known to occur over the course of an immune response (17, 18), and since our patients were diagnosed relatively early in the course of their disease [mean (SD) of 0.8 (1.6) years], hence this might explain why IgG2 levels were significantly increased in our cohort, and correlated with baseline disease activity. IgG4 levels in our cohort did not correlate with the number of organs involved as previously described in other cohorts (9, 12), but this might be a limitation of our small cohort. Histologically, lymphoplasmacytic infiltration and fibrosis was not as common in our cohort of patients, as compared to the cohorts described by Lin *et al.* (12) and Ebbo *et al.* (10).

All of our treated patients responded to initial glucocorticoid therapy with a decrease in the IgG4RD-RI, with about two-thirds needing low dose of glucocorticoids to maintain disease remission, similar to the cohort described by Ebbo *et al.* (10). Relapses were also common, and often in the same organs. There are limitations to our study. This includes the retrospective study design, which can give rise to incomplete data with possible recall bias. We attempted to overcome this by reviewing all the imaging and patient charts to maximise the identification of organ involvement. Histological specimens were also reviewed to accurately describe histological characteristics. Patients were also identified from the gastroenterology, rheumatology, pathology and radiology department databases, which could result in our patient population being skewed towards patients with multi-organ manifestations or patients with predominant pancreatic manifestations, whilst patients with mild disease or single-organ involvement might be under-represented. Nonetheless, there was a wide range of organ involvement in the cases of IgG4-RD described in our cohort, and patients with IgG4-RD are often managed by the gastroenterologists or rheumatologists in our institution. There is strong collaboration between the radiologists and pathologists in our tertiary centre, and patients with isolated lesions are often referred to the rheumatologists or gastroenterologist for further management. Finally, due to the small cohort numbers, it is difficult to ascertain if there are distinct differences in clinical characteristics between different ethnicities. However, in comparison with other cohorts, there appears to be differences in the clinical manifestations, histological and immunoglobulin profile. Further research into possible genetic and geographic factors that lead to these differences is needed. Our small cohort numbers also precludes us from determining the relationship of IgG2 and baseline activity and IgG4 levels, and further research will be needed.

In conclusion, we have described the clinico-pathological features of a cohort of multi-ethnic Asian patients with IgG4-RD, which have differences from previously described cohorts. Long-term follow-up is underway to determine if these differences are unique to our study population and if they have prognostic significance.

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