Serum complement factor C5a in IgG_4-related disease

We read with great interest the correspondence by Umehara *et al*[1] which discussed the difficulties in the diagnosis of IgG_4-related disease (IgG_4-RD). They mention that increased IgG_4 concentration is not a specific marker for IgG_4-RD. Therefore, the markers for the diagnosis and the disease activity of IgG_4-RD are demanded.

Approximately a quarter of patients with active IgG_4-RD have hypocomplementaemia defined by the lower normal limit of C3 or C4 levels.[2] Complement pathways consist of three pathways: classical, alternative and lectin pathways.[3] Here, we focus on complement factors as makers of IgG_4-RD and attempt to evaluate the entire complement system in IgG_4-RD.

We enrolled 28 patients with active and untreated IgG_4-RD, diagnosed based on the 2011 comprehensive diagnostic criteria[4] and 28 sex-matched and age-matched healthy donors. We evaluated the characteristics of patients with IgG_4-RD, the number of affected organs and the IgG_4-RD Responder Index (IgG_4-RD RI).[5] None of the healthy donors had a history of inflammatory disease.

In the sera of the patients with IgG_4-RD and the healthy donors, we measured the levels of complement factors, C1q, C2, C3, C3b/iC3b, C4, C4b, C5, C5a, C9, factor D, factor I, mannose-binding lectin (MBL), factor B, factor H and properdin, using the MILLIPLEX MAP Human Complement Panel 1 and Panel 2 (Merck Millipore, Darmstadt, Germany). Written informed consent was obtained from all patients and donors.

Table 1 summarises the characteristics of patients with IgG_4-RD. The patients with IgG_4-RD at diagnosis had significantly higher levels of C5 and C5a (figure 1A) and significantly lower levels of C4, C4b and factor D compared with the healthy donors (online supplementary table 1). C5a had a significant correlation with C3 (figure 1B) but not with C4 (figure 1C).

The levels of C5a in remission were significantly changed compared with the levels of C5a at diagnosis (16 305 pg/mL to 10 030 pg/mL, p=0.0043) (figure 1H). Other complement factors showed no significant change between the levels at diagnosis and the levels in remission (figure 1D–G,1I).

We divided the patients with IgG_4-RD into two groups by the median of C5a: high-C5a and low-C5a groups. The high-C5a group had significantly higher IgG (figure 1J) and IgG_4 (figure 1K) levels compared with the low-C5a group, but the IgG_4/IgG ratio was not significantly different (figure 1L). The high-C5a group also had significantly higher levels of soluble IL-2 receptor (figure 1M). There were no significant differences in the number of affected organs or in the IgG_4-RD RI (figure 1N,O).

Our finding that C5a is negatively correlated with C3 may indicate that patients with hypocomplementaemia as shown in a clinical study[2] have higher C5a levels. In addition, the absence of a correlation between C4 and C5a levels suggests that it is not appropriate to bracket C3 and C4 as the same component of hypocomplementaemia.

C5a has a strong inflammatory potency through binding to C5a receptor (C5aR).[6] Considering the reduced C5a levels observed in patients with IgG_4-RD in remission, C5a-C5aR-targeted drugs may be effective against IgG_4-RD. With the success of the C5 inhibitor eculizumab for paroxysmal nocturnal haemoglobinuria[7] and the progression of a number of novel C5a-C5aR1-targeted drugs including the C5aR1 antagonist avacopan for antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis,[8] complement therapeutics have shown great promise.[9]

Based on the high serum circulating immune complex in autoimmune pancreatitis, the classical pathway is thought to be involved in IgG_4-RD.[10] Our findings of decreased C4 and C4b and normal MBL levels in the patients are compatible with this supposition. However, because IgG_4 is ineffective at activating complement (in contrast to IgG_1 and IgG_3),[11] the mechanisms underlying complement activation remain a mystery. A limitation of our study is that we are unable to answer this question based on our results.

In conclusion, the serum C5a level has been high in active disease and low in remission in IgG_4-RD. Our data suggest that C5a may be a therapeutic target for IgG_4-RD.

Table 1 Demographic, clinical and laboratory characteristics of patients with IgG_4-RD

Clinical parameter	Value
Age at diagnosis, years, median (IQR)	64 (56–73)
Females, n (%)	7 (25)
BMI, kg/m^2 (IQR)	20.9 (19.3–23.0)
History	
Allergy, n (%)	11 (39)
Asthma, n (%)	3 (11)
Organ involvement, n (%)	
Lacrimal gland and orbit	10 (36)
Salivary gland	15 (54)
Lymph node	18 (64)
Thyroid	2 (7)
Lung	5 (18)
Pancreas	4 (14)
Bile duct	1 (4)
Kidney	4 (14)
Aorta	4 (14)
Prostate	2 (7)
Retroperitoneum	5 (18)
No of affected organs, median (IQR)	2 (1–3)
IgG_4-RD Responder Index, median (IQR)	9 (6–15)
Laboratory test results, median (IQR)	
White cells, ×10^9/μL	6.4 (5.4–7.4)
Eosinophils, %	5.0 (2.0–6.4)
Haemoglobin, g/dL	13.1 (12.1–14.5)
Platelets, ×10^9/μL	230 (195–260)
C-reactive protein, mg/dL	0.19 (0.05–0.77)
Erythrocyte sedimentation rate, mm/hour	41 (10–63)
Creatinine, mg/dL	0.83 (0.61–0.95)
Estimated GFR, mL/min/1.73 m^2	71.9 (60.2–81.0)
Soluble IL-2 receptor, U/mL	584 (454–1261)
IgG, mg/dL	1985 (1494–3039)
IgG_4, mg/dL	393 (175–876)
IgG_4/IgG ratio, %	18.3 (11.1–34.0)
IgE, IU/mL	632 (203–1435)

BMI, body mass index; GFR, glomerular filtration rate; IgG_4-RD: IgG_4-related disease; IL-2, interleukin-2.

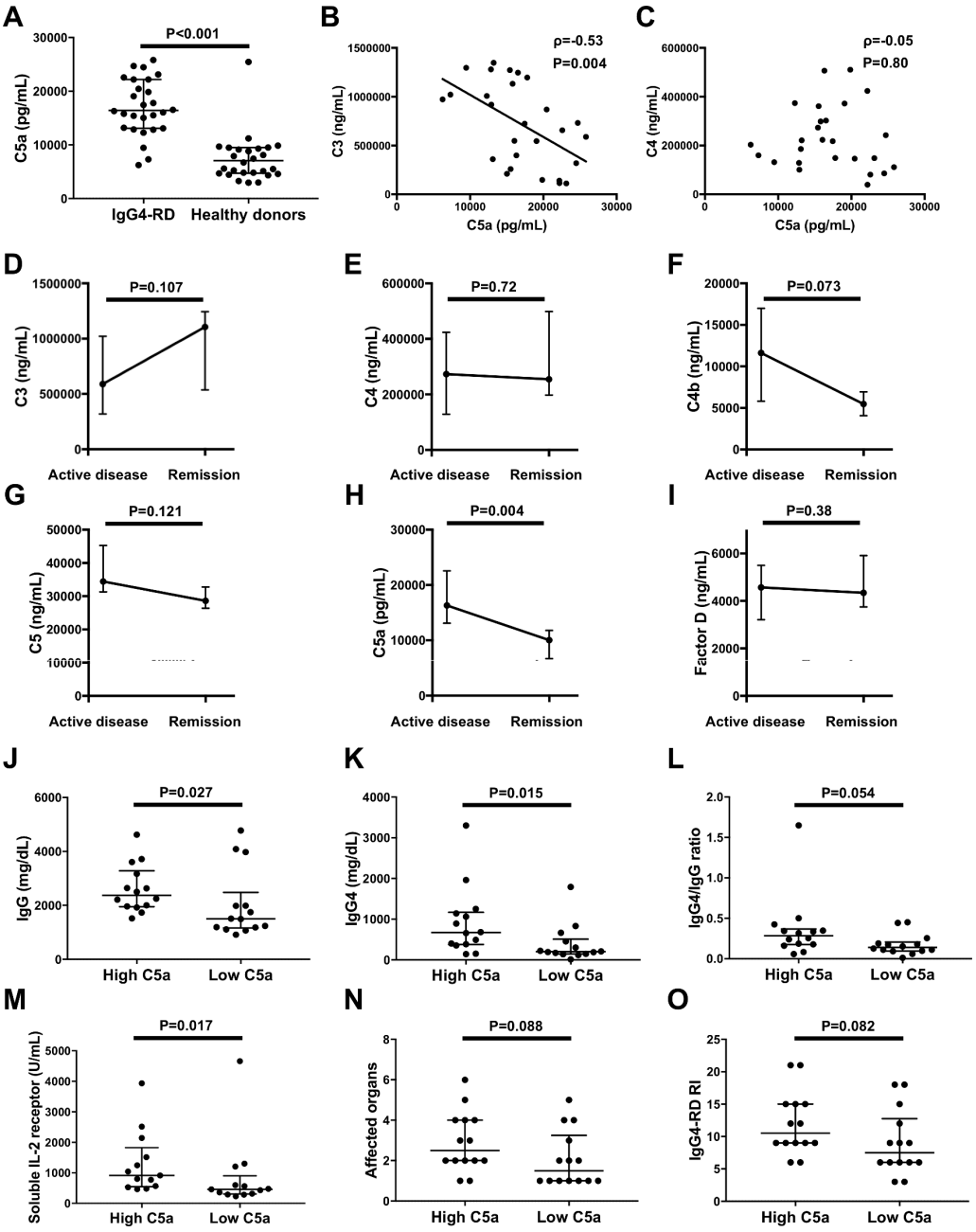

Figure 1 The patients with IgG_4-RD at diagnosis had significantly higher levels of C5a compared with the sex-matched and age-matched healthy donors (A). C5a had a significant correlation with C3 (B) but not with C4 (C). The level of C5a in remission was significantly changed compared with the level of C5a at diagnosis (H), but other complement factors showed no significant change (D–G, I). The high-C5a group had significantly higher IgG (J) and IgG_4 (K) levels compared with the low-C5a group, but the IgG_4/IgG ratio was not significantly different (L). The high-C5a group had significantly higher levels of soluble IL-2 receptor (M). There were no significant differences in the number of affected organs or in the IgG_4-RD RI (N, O). IgG_4-RD, IgG_4-related disease; IgG_4-RD RI, IgG_4-RD Responder Index; IL-2, interleukin-2.

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Contributors All authors were involved in drafting this letter or revising it critically for important intellectual content, and all authors approved the final version for publication. SF had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; internally peer reviewed.

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2018-213705).

To cite Fukui S, Fujita Y, Origuchi T, *et al*. *Ann Rheum Dis* 2019;**78**:e65.

Received 3 May 2018
Accepted 6 May 2018
Published Online First 6 June 2018

► http://dx.doi.org/10.1136/annrheumdis-2018-213729

Ann Rheum Dis 2019;**78**:e65. doi:10.1136/annrheumdis-2018-213705

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