Response to: 'Serum complement factor C5a in IgG4-related disease' by Fukui *et al*

We appreciate the interest shown by Dr S Fukui and colleagues¹ in our recent paper, 'How to diagnose IgG4-related disease (IgG4-RD)'.²

IgG4-RD is characterised by increased serum IgG4 concentrations and number of IgG4-positive plasma cells in affected lesions.³ However, its diagnosis can be difficult, because clinical signs vary depending on the organs affected.

A Japanese team established comprehensive diagnostic criteria for IgG4-RD, 2011 focusing on the concentration of serum IgG4 (>135 mg/dL), numbers of IgG4-positive cells (>10 cells/HPF) and ratio of IgG4-positive to IgG-positive cells (>40%) in affected tissues.⁴

However, many cases of IgG4-RD with low levels of IgG4 and mimickers of IgG4-RD with increased serum IgG4 have been reported and the concept of IgG4-RD has become blurred. Therefore, new specific markers or new criteria for IgG4-RD are required.⁵

Human IgG4 has a unique structure distinguished from the other IgG subclasses by lack of interaction with the complement system and inability to activate the classical complement pathway.^{6,7} However, hypocomplementaemia has been observed in IgG4-RD ever since the concept was first established⁸ and is in particular more frequent and sometimes severe in IgG4-related kidney disease.⁹ A recent study showed that non-IgG4 IgG such as IgG1, which can activate complement, might be involved in the activation of complement in IgG4-RD.¹⁰

Fukui *et al* reported the significant increase of C5a in IgG4-RD and suggested it for a therapeutic target.¹ However, serum C5a elevation is also a very important feature of active systemic lupus erythematosus (SLE). Since elevated C5a levels in IgG4-RD are much lower than in active lupus cases¹¹ and only some groups of patients with IgG4-RD have hypocomplementaemia, the production of C5a in SLE and IgG4-RD likely exhibits significant differences in both underlying mechanism and pathogenetic role.

Although the details of the pathogenesis of IgG4-RD are unclear at present, recent basic studies have implicated the toll-like receptor (TLR) signalling pathway.¹² Activation of C5aR in macrophages inhibits TLR-4 signals resulting in reduction of IL-12, IL-23 and IL-27 production by inflammatory macrophages.¹³ Thus, the role of cross-talk between innate and acquired immunity through the complement pathway and TLR system is attracting attention in the pathogenesis of IgG4-RD.¹⁴

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