IgG4 levels and plasmablasts as a marker for IgG4-related disease (IgG4-RD)

Robert I Fox, Carla M Fox

Stone and his coworkers present two elegant papers on IgG4-related disease (IgG4-RD).

In The Diagnostic Utility of Serum IgG4 Concentrations in IgG4-Related Disease, Carruthers et al retrospectively analysed charts of 190 patients with elevation of IgG4. They also randomly selected 3360 charts with normal IgG4 levels and reviewed 190 cases for characteristics of IgG4-RD. They found:

- The specificity and positive predictive value of elevated serum IgG4 concentrations were only 60% (183/309) and 34% (65/190), respectively.
- When the IgG4 value ‘cut-off’ values were doubled so as to improve specificity, the sensitivity of IgG4 levels fell to an unacceptably low 35%.

In a closely related study by the same group, Wallace et al describe the ‘Diagnostic Utility of Plasmablasts as a Biomarker for IgG4 Related Disease (IgG4 RD)’ Independent of Serum IgG4 Levels’. They reported 37 patients with biopsy-proven IgG4-RD.

- Thirteen of these patients had normal IgG4 levels.
- But all 37 patients had elevated levels of plasmablasts (CD19 low, CD20 neg, CD38+ and CD27+).
- They also demonstrated that rituximab (anti-CD20 antibody) was beneficial, even though the plasmablasts were CD20 negative, indicating removal of plasmablast precursors.

Since we see patients with possible IgG4-RD in a variety of organs (table 1) that are often not easy to biopsy, serum IgG4 levels have incorrectly become a ‘surrogate’ marker for IgG4-RD in clinical practice. These articles will make us take a hard look at our current diagnostic approach to IgG4-RD.

The spectrum of IgG4-RD is remarkably complex (table 1) and it would be nice to simply think of this complex multisystem pathology as a single pathogenetic disorder occurring in a variety of target organs. Unfortunately, it may not be that simple.

In a critical evaluation of the evolving spectrum of IgG4-RD, Cheuk et al note that this condition is both ‘over-diagnosed’ and ‘under-diagnosed’.

- Under-diagnosis is due to the sheer lack of recognition of IgG4-RD.
- Over-diagnosis seems to result from the well-intentioned enthusiasm of physicians and pathologists to demonstrate that they recognise this new disease entity.

Thus in order to make rational therapeutic decisions, we need future studies from multicentre cohorts to determine:

1. What is the agreement among different pathologists in the diagnosis of IgG4-RD when slides are read in a blinded fashion?
2. What proportion of patients with consensus IgG4-RD pathology have elevated IgG4 levels and now plasmablasts?
3. What per cent of patients with clinical involvement of the target organs listed in table 1 do NOT have pathologic features of IgG4-RD on biopsy?
4. Among the patients lacking pathologic evidence of IgG4-RD, what percentage have the either elevated IgG4 or plasmablasts?

Still on a practical day-to-day level in clinic, we need to know:

- What are the potential pitfalls in measuring IgG4 levels or flow cytometry of plasmablasts for the practising rheumatologist?
- What information do we need to provide to the surgeon on obtaining the biopsy, or to the pathologist about the immunohistologic analysis of the biopsy?

Historically, Yoshida et al in 1995 reported autoimmune inflammatory pancreatitis (AIP) in elderly men with Sjogren’s Syndrome (SS). In the past decade, the literature on IgG4-RD has grown rapidly. In the past 2 years, a PubMed search reveals over 600 articles with IgG4-RD in their titles.

The diagnosis of IgG4-RD is based on a biopsy showing lymphoplasmacytic infiltrates enriched with IgG4 plasma cells, storiform (cartwheel) fibrosis, obliterative phlebitis and mild-to-moderate tissue eosinophilia (table 2). A consensus statement on the pathologic changes was presented by Deshpande et al in 2012.

However, the current criteria recognise that diagnosis cannot be made entirely upon the number of IgG4 plasma cells, because a number of other diagnostic entities can have increased IgG4 plasma cells. Histopathology trumps immunostaining when it comes to making this diagnosis (albeit the two generally complement each other). Most essential, perhaps, is the experience of both the clinician and the pathologist and the centrality of clinico-pathologic correlation to making this diagnosis appropriately.

Despite the large number of reports, the incidence and epidemiology of AIP and other IgG4-RDs remain unclear. In

<table>
<thead>
<tr>
<th>Table 1</th>
<th>IgG4-Related Diseases (IgG4-RD) are a Family Immuno-proliferative Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 autoimmune pancreatitis or AIP (IgG4-related pancreatitis)</td>
<td></td>
</tr>
<tr>
<td>IgG4-related sclerosing cholangitis</td>
<td></td>
</tr>
<tr>
<td>Mikulicz’s disease (IgG4-related dacryoadenitis and sialadenitis)</td>
<td></td>
</tr>
<tr>
<td>Sclerosing sialadenitis (Küttner’s tumor, IgG4-related submandibular gland disease)</td>
<td></td>
</tr>
<tr>
<td>Inflammatory orbital pseudotumor (IgG4-related orbital inflammation or orbital inflammatory pseudotumor)</td>
<td></td>
</tr>
<tr>
<td>Chronic sclerosing dacryoadenitis (lacrimal gland enlargement, IgG4-related dacryoadenitis)</td>
<td></td>
</tr>
<tr>
<td>A subset of patients with “idiopathic” retroperitoneal fibrosis (Ormond’s disease) and related disorders (IgG4-related retroperitoneal fibrosis, IgG4-related mesenteritis)</td>
<td></td>
</tr>
<tr>
<td>Chronic sclerosing aortitis and periaortitis (IgG4-related aortitis or periarteritis)</td>
<td></td>
</tr>
<tr>
<td>Riedel’s thyroiditis (IgG4-related thyroid disease)</td>
<td></td>
</tr>
<tr>
<td>IgG4-related interstitial pneumonitis and pulmonary inflammatory pseudotumors (IgG4-related lung disease)</td>
<td></td>
</tr>
<tr>
<td>IgG4-related kidney disease (including tubulointerstitial nephritis and membranous glomerulonephritis secondary to IgG4-RD)</td>
<td></td>
</tr>
<tr>
<td>IgG4-related hypophysitis</td>
<td></td>
</tr>
<tr>
<td>IgG4-related pachymeningitis</td>
<td></td>
</tr>
</tbody>
</table>

Department of Rheumatology, Scripps Memorial Hospital-XIMED, La Jolla, California, USA

Correspondence to Dr Robert I Fox, Department of Rheumatology, Scripps Memorial Hospital-XIMED, La Jolla, CA 92037, USA; RobertFoxMD@scripps.com
both the initial report and many of the reports of IgG4-RD, serum IgG4 level was elevated in more than 85% of patients inscribed with this diagnosis. Thus, elevated IgG4 levels have become a surrogate marker for IgG4-RD in clinical practice.

In Japan where most patients have been reported, the patients are predominantly men, and usually have a good general condition, with no fever or constitutional symptoms. Many of these patients had low titres of autoantibodies (such as antinuclear antibodies and rheumatoid factor) and this certainly provided an ascertainment bias for referral to rheumatology clinic.

Due to the high association of IgG4 levels and IgG4-RD (indeed the name alone implies a causal association), most rheumatologists exclude the diagnosis of IgG4-RD if elevations of this Ig were not present. The article by Wallace et al challenges us to question that assumption. In this journal in 2012, I wrote an editorial about the pathogenesis of Mikulicz’s disease (MD) as an IgG4-RD. Historically, MD had been considered a subset of SS. However, the clinical features (male predominance and unusual pattern of tissue fibrosis on biopsies) always hinted that at least a subset of patients with the Mikulicz’s syndrome was distinct from ‘garden variety’ SS.

An elegant series of studies by Maehara et al confirmed that clinical suspicion by demonstrating an increase in IgG4 plasma cells in MD tissue biopsies. Further, the pathogenesis could be partially explained by the release of interleukin 21 and interleukin 6 that promoted the differentiation of B cells towards IgG4 plasma cells and release of profibrotic tissue factors. Thus, we can hypothesise that a similar pathogenetic process is occurring in each of the tissues involved in IgG4-RD (table 1).

As rheumatologists, we face both a general philosophical dilemma and specific day-to-day practical issues in diagnosis and management of IgG4-RD.

In the philosophical area of diagnosis of a multisystem disorder such as IgG4-RD (table 1), will we become?

▸ ‘Lumpers’ (ie, putting too many diseases into same category based on a laboratory result), or

▸ ‘Splitters’ (ie, ignoring groups of apparently disparate diseases that share a common pathogenesis)?

This dilemma is present even in the current papers by Stone’s group. Serum IgG4 levels were significantly higher in patients with multiorgan involvement than in single organ (ie, AIP that was generally diagnosed by radiographic methods). More plasmablasts were also seen in the biopsies from multiorgan involved patients as well. Therefore, we must consider that the pathology in single organ may be different than in patients with multiorgan involvement.

In our practical daily clinics, what are the pitfalls in obtaining biopsies and laboratory measurements for the general rheumatologist?

▸ A recent report described a patient with IgG4-RD who had an apparently low IgG4 level due to ‘prozone’ effect and the serum sample needed to be diluted before nephelometry could reveal the true elevated level. Thus, the rheumatologist should order dilution of samples when clinically indicated. It is not clear from the Methods sections of the papers from the Stone group that such dilutions were performed, but it is my understanding from contacting the authors that the prozone effect was ruled out.

▸ The rheumatologist office should contact the local clinical laboratory that will collect and analyse the samples for flow cytometry (fluorescence activated cell sorting; FACS). Experience during clinical trials where FACS samples were sent to a ‘central laboratory’ has indicated the importance of fixative concentrations in antigen preservation.

▸ FACS samples are placed in different fixatives depending on whether surface markers only or internal cytoplasmic markers (ie, fixatives that make membranes permeable) are studied. At present, fixatives for surface markers appear to be preferred, since the latter fixatives may lead to loss of surface antigenicity.

▸ The rheumatologist needs to alert the surgeon obtaining the biopsy and the pathologist that special immunohistology will be required.

▸ The rheumatologist needs to evaluate the biopsy report according to the guidelines set out by the IgG4-RD consensus committee. The sample may need to be ‘sent out’ for a review at a tertiary centre.

CONCLUSIONS AND FINAL REMARKS

We can no longer simply use elevated IgG4 levels as a surrogate marker for IgG4-RD. The unexpected low predictive value of an elevated IgG4 level will certainly change the way rheumatologists approach diagnosis, and thus therapy. Indeed, we must even examine our terminology and whether it is misleading to designate these conditions as ‘IgG4-related disease.’

Plasmablasts may provide the surrogate marker with greater sensitivity and specificity for IgG4-RD, but larger multicentre trials are required to support both this hypothesis and rituximab treatment in refractory cases.

We must ask our clinical laboratory to perform dilutions of IgG4 in suspicious cases to avoid prozone effect that can lead to artificially low IgG4 levels.

Further, we have to be aware of the variations among pathologists in making the diagnosis of IgG4-RD and that we may need to send tissue biopsies for secondary review to tertiary centres with expertise in this disease.

Table 2  Diagnostic criteria for IgG4-Related Disease

A consensus statement from a multi-national, multi-disciplinary group of experts on IgG4-RD describes guidelines for the diagnosis of the disease and the histopathologic findings important in making the diagnosis. The histopathological findings include:

▸ a dense lymphoplasmacytic infiltrate,

▸ storiform fibrosis, and

▸ obliteratorive phlebitis

—all critical features for establishing the diagnosis in affected tissues other than lymph nodes.

The presence of these findings, together often with mild tissue eosinophilia, is strongly suggestive of IgG4-related disease if accompanied by increased numbers of IgG4-positive plasma cells. The number of IgG4-positive plasma cells per high-power field (HPF) regarded as sufficient, varies somewhat from tissue to tissue. Tissue IgG4-positive cell counts and the ratios of IgG4- to IgG-positive cells are considered secondary in importance.

Generally, the minimum for making the diagnosis for most tissues is from 30 to 50 IgG4-positive cells/HPF. However, in some organs or tissues, including the kidney and others, only 10 IgG4-positive plasma cells/HPF may be sufficient.

The diagnosis cannot be predicated entirely upon the number of IgG4-positive plasma cells because a large number of other entities can have such cells, nor can the diagnosis of IgG4-RD be based upon serum concentrations of IgG4 alone. Serum IgG4 concentrations are neither sufficiently sensitive nor specific for this disease. Thus, we strongly prefer confirmation of the diagnosis by biopsy of an involved organ whenever this is possible.
On an optimistic note, these articles provide hope that a surrogate non-invasive marker may allow us to provide earlier and less invasive diagnosis.

If this editorial sounds like the early days of achieving consensus about classification of lymphomas or monoclonal gammopathy, then I have made my point.

Competing interests None.

Provenance and peer review Commissioned; externally peer reviewed.


Received 18 August 2014
Revised 16 October 2014
Accepted 24 October 2014

REFERENCES