Comment on: Beyond diagnosis: exploring the significance of IgG4+ plasma cell count through immunostaining in IgG4-related disease

Sir,

We deeply appreciate the insightful study by Martín-Nares *et al*. (1). This work offers valuable guidance and inspiration for advancing clinical understanding and improving the management of IgG4-related disease (IgG4-RD).

Upon careful review, we identified several points that could inspire future research and contribute to ongoing discussions in the field. The use of remission at last follow-up and relapse rates as prognostic indicators for patients with <100 IgG4+ plasma cells/HPF and ≥100 IgG4+ plasma cells/HPF is commendable. The observed correlation between ≥100 IgG4+ plasma cells/HPF and the proliferative phenotype, which is more responsive to treatment, aligns with previous findings (2). However, the data presented in Table I indicate that, among the 39 patients classified under the proliferative phenotype, 23 (59%) exhibited biopsy specimens with <100 IgG4+ plasma cells/HPF. This observation suggests that, even within the proliferative phenotype, fibrosis may have already begun, warranting heightened vigilance. The progression from the proliferative to the fibrotic phenotype, characterised by fibrosis and shifts in the cytokine milieu (*e.g*., increased TGF-β1) alongside reduced IgG4+ cell counts, underscores the need for advanced treatment strategies to prevent disease deterioration.

Patients with <100 IgG4+ plasma cells/HPF within the proliferative phenotype may signify disease progression and an increased risk of relapse. This finding underscores the critical need for proactive medical interventions to prevent irreversible fibrosis and enhance long-term outcomes.

In the discussion section, you highlighted a contrasting finding compared to prior research (3), which reported a higher relapse rate in proliferative patients compared to fibrotic patients (24% *vs*. 4.3%, respectively). This apparent discrepancy emphasises the need for further stratification of patients in follow-up studies to better understand these differences.

We propose constructing a two-way table (Table I) for clinical outcome tracking and statistical analysis, categorising patients by both phenotype (proliferative or fibrotic) and IgG4+ plasma cell counts (<100 or ≥100 cells/HPF). Longitudinal follow-up of these groups, supplemented by subgroup analyses based on clinical phenotypes (*e.g*., pancreato-hepato-biliary, retroperitoneal/aortic, head and neck-limited, and Mikulicz/systemic), could provide valuable insights into these relationships. This approach could also incorporate findings from IgG4-related ophthalmic disease (4), where an IgG4+ plasma cell count >150/HPF was identified as a relapse risk factor. The observed variation in clinical outcomes across phenotypes suggests that disease manifestations, such as head and neck-limited versus pancreato-hepato-biliary involvement, may result in different prognostic trajectories.

Table I. Two-way table for clinical outcome tracking and statistical analysis of patients categorised by proliferative or fibrotic phenotype and IgG4+ plasma cell counts.

	<100 IgG4+ cell/HPF	≥100 IgG4+ cell/HPF
Proliferative phenotype	• Might represent a later stage of the proliferative phenotype. • Relapse rates might be higher compared to the ≥100 IgG4+ cell/HPF group.	• Might represent an earlier stage of the proliferative phenotype. • Strong and active inflammatory disease state. If appropriate immunosuppressant treatment is provided, remission rates are good, and the relapse rate will be the lowest. • Conversely, inadequate treatment or abrupt discontinuation of medication can lead to relapse.
Fibrotic phenotype	• Fibrosis-related complications persist. • Might have poor treatment response and the highest relapse rate. • New treatment strategies might be needed (*e.g*., the use of JAK inhibitors could have potential in this group).	• Might represent an earlier stage of the fibrotic phenotype. • Continuous use of immunosuppressants can reduce the relapse rate.

Patients with <100 IgG4+ plasma cells/HPF within the fibrotic phenotype may represent a particularly high-risk group, indicative of advanced-stage IgG4-RD characterised by significant tissue fibrosis and suboptimal responses to treatment. In contrast, patients with ≥100 IgG4+ plasma cells/HPF within the proliferative phenotype likely reflect early-stage disease, which tends to respond more favourably to treatment. These findings underscore the importance of timely and appropriate therapeutic interventions to optimise patient outcomes.

Of particular interest is the article in the September issue of *Clinical and Experimental Rheumatology* by Cao *et al*. (5). This article discusses two cases (Case 1 and Case 3), both presenting with retroperitoneal fibrosis as the clinical manifestation and low serum IgG4 levels, yet experiencing disease relapse. These cases highlight the potential therapeutic value of tofacitinib in such populations, warranting further exploration in this context.

In conclusion, this pioneering study offers a novel perspective on clinical outcomes in IgG4-RD. Incorporating additional stratified analyses and longitudinal tracking could further improve diagnostic precision and enhance prognostic evaluations. We commend the authors for their valuable contribution to advancing the understanding of IgG4-RD and eagerly anticipate future studies that build on this important foundation.

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