

Dear Editor-in-Chief,

We sincerely appreciate the time and effort that you and the reviewers have invested in evaluating our manuscript, “Comment on ‘Immunoglobulin G4-related Spinal Pachymeningitis: A Case Report’” (Manuscript ID: 105331). We are grateful for the constructive feedback, which has helped us improve the quality of our work. Below, we provide a point-by-point response to each comment. All required changes are highlighted in red in the manuscript.

Response to Reviewer #1 :

1. Clarification of the Letter's Novelty

Comment:

While the commentary is informative and contributes to the ongoing discourse in the field, the authors would benefit from more explicitly articulating how their insights provide new perspectives. A clearer delineation of how these insights transcend a mere reiteration of known limitations regarding serum IgG4 measurement would enhance the letter’s contribution to the existing literature.

Response:

We sincerely appreciate the reviewer’s insightful feedback. To clarify the letter’s novelty, we have revised the manuscript to emphasize how our work advances beyond existing literature. In particular, we have highlighted the following points:

- The integration of cerebrospinal fluid (CSF) IgG4 indices and oligoclonal bands as novel, non-invasive tools that complement serum IgG4 measurements, thereby addressing limitations in specificity and diagnostic reliability.
- A critical analysis linking intrathecal IgG4 synthesis with disease activity, offering a mechanistic connection between CSF findings and clinical outcomes—a perspective that has not been thoroughly explored in the case reported by Chae TS et al.
- New insights into the TGF- β 1/SMAD2/3 pathway as a driver of fibrosis in meningeal inflammation, thereby bridging gaps in the understanding of IgG4-related spinal pachymeningitis (IgG4-RSP) pathogenesis.

These revisions clarify that our commentary goes beyond reiterating known limitations and instead offers actionable insights for diagnosis and monitoring.

2. Expansion on Biopsy and Pathology Interpretation Recommendations

Comment:

Although the importance of histopathology is acknowledged as a cornerstone of accurate diagnosis, the letter could be significantly strengthened by including practical approaches for conducting biopsies, detailed examples of pathological morphology, and guidance on the interpretation of histological slides. Such information would be invaluable for clinicians navigating differential diagnoses and would provide concrete recommendations for obtaining and analyzing meningeal biopsies in suspected cases of IgG4-RSP.

Response:

Thank you for this constructive suggestion. We have expanded the section on histopathological evaluation to include:

- **Practical Biopsy Approaches:** We now emphasize the importance of obtaining adequate meningeal samples to ensure sufficient IgG4+ plasma cell counts (e.g., >10 per high-power field) and to minimize sampling errors.
- **Pathological Morphology Examples:** Detailed descriptions of hallmark features—such as storiform fibrosis and obliterative phlebitis—are now provided, along with references to prior cases that confirmed the diagnosis of IgG4-RSP.
- **Guidance on Slide Interpretation:** We have included recommendations for using immunohistochemistry to identify IgG4+ plasma cells and strategies to differentiate IgG4-RSP from conditions with similar presentations, such as ANCA-associated vasculitis.
- **CSF Analysis as an Alternative:** In cases where biopsy is contraindicated, we offer guidance on utilizing CSF IgG4 analysis.

These additions are designed to equip clinicians with clear, actionable protocols for diagnosing complex cases.

3. Provision of Evidence for Proposed Explanations

Comment:

While the suggested explanations for the observed phenomena are intriguing, their overall value remains limited without supporting evidence. Supplementary data or references to clinical studies that bolster these explanations would significantly enhance their credibility and clinical applicability.

Response:

We acknowledge the need for a stronger evidential basis for our hypotheses. To address this:

- **Autoimmune Hypothesis:** We have added references to studies that demonstrate clinical and serological responsiveness to treatments such as steroids and rituximab, thereby supporting the autoimmune nature of IgG4-RSP.
- **TH2-Driven Inflammation:** We now cite studies (e.g., Zhang et al. and Carruthers et al.) showing elevated IL-4/IL-10 levels in the CSF, which play a role in B-cell class switching.
- **Treatment Response:** The observed reduction in serum IgG4 levels following treatment with IL-4/IL-13 inhibitors (such as dupilumab) further supports the TH2-driven inflammation hypothesis.
- **Fibrotic Mechanisms:** We have expanded our discussion on TGF- β 1's role in activating the SMAD2/3 pathway, citing Cui et al., and have discussed its therapeutic implications.
- **Limitations:** We explicitly note gaps in the current evidence (e.g., regarding antigen specificity of IgG4) and propose future studies to validate these hypotheses.

Response to Reviewer #2:

1. Lack of Substantial New Insights

Response:

We appreciate the reviewer's critique and have revised the letter to emphasize its novel contributions. Specifically, our letter highlights:

- The use of CSF IgG4 indices and oligoclonal bands as non-invasive, cost-effective diagnostic alternatives to biopsy. For example, when CSF IgG4 is >2.27 mg/dL and the IgG4 Loc is >0.47, these markers provide high sensitivity and specificity.
- The identification of TGF- β 1/SMAD2/3 pathway activation as a driver of fibrosis in meningeal inflammation, which links directly to potential therapeutic targets such as TGF- β inhibitors.

2. **Alternative Biomarkers**

Response:

To address this point, we have expanded our discussion to include: The quantitative evaluation of the IgG4 index and CSF IgG4 levels, which provide evidence of intrathecal IgG4 production and help distinguish IgG4-RSP from similar conditions.

3. **Histopathological Criteria**

Response:

We have clarified the specific diagnostic thresholds for meningeal biopsy interpretation:

- More than 10 IgG4+ plasma cells per high-power field and an IgG4+/IgG+ ratio exceeding 40%.
- Identification of hallmark morphological features, such as storiform fibrosis and obliterative phlebitis, which are critical in differentiating IgG4-RSP from other forms of hypertrophic pachymeningitis (e.g., ANCA-associated vasculitis).

4. **Immunopathogenesis Depth**

Response:

We have strengthened our mechanistic discussion by:

- Linking IL-4/IL-13-driven TH2 inflammation to B-cell class switching and increased IgG4 production.
- Explaining how TGF- β 1 activation promotes fibroblast proliferation via the SMAD2/3 signaling pathway—a process that may be targetable by therapies such as rituximab.

5. **Treatment Strategies**

Response:

We have provided additional details on therapeutic approaches, including:

- **First-line Corticosteroids:** Although effective, their long-term use is limited by issues such as relapse and fibrosis.
- **Rituximab:** This B-cell depleting therapy reduces both IgG4 and IgE levels; however, challenges remain regarding blood–brain barrier penetration, which might necessitate intrathecal administration.
- **Emerging Therapies:** We discuss the potential of IL-4/IL-13 inhibitors (e.g., dupilumab) and TGF- β blockers as targeted treatment options.

Editorial Office's comments

Response: All comments have been addressed.

We thank the reviewers and editor for their rigorous critique, which has significantly strengthened the manuscript. The updated content now provides clearer novelty, practical clinical guidance, and robust evidence to support proposed mechanisms, aligning with the goal of advancing IgG4-RSP diagnosis and management.