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Letter to the Editor

Applying the consensus statement on the pathology of IgG4-related disease to lacrimal gland lesions

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To the Editor: We read with interest the recent consensus statement by Deshpande *et al*.[1] The proposed diagnostic criteria require characteristic histological features, an IgG4+/IgG+ ratio >40%, and an intensity of IgG4+ staining that is organ-specific. For lacrimal lesions, a cutoff of 100 IgG4+ cells/hpf is proposed, markedly higher than the cutoff of 10 suggested in the comprehensive diagnostic criteria by Umehara *et al*.[2]

We recently undertook a meta-analysis of all published cases of IgG4-related orbital disease ($n=133$) and classified them using a cutoff of 10 IgG4+ cells/hpf.[3] When the cases were reclassified using the diagnostic criteria proposed by Deshpande *et al*,[1] the resultant cohort had some interesting characteristics. Of the lacrimal cases with an IgG4+/IgG+ ratio >40% ($n=72$), 23 (32%) had >100 IgG4+ cells/hpf. This group includes 10 males and 13 females and has an average age of 53.0 years. Twelve patients were from South Korea, six from Hong Kong and five from Japan; no patients were Caucasian. Of the cases that did not satisfy the diagnostic criteria, 24 had an IgG4+ count between 10 and 100, and 25 cases used non-specific descriptors such as 'abundant', 'numerous' or 'more than 10'.

Conditions that are clearly not manifestations of IgG4-RD occasionally feature moderately intense IgG4+ infiltration, certainly more than 10 IgG4+ cells/hpf.[4] Improving the specificity of the diagnostic criteria by setting higher organ-specific cutoffs for IgG4+ staining may therefore be useful. As is emphasized in the consensus statement by Deshpande *et al*,[1] it is important to cautiously interpret IgG4+ counts in the context of clinical and histological features.

It is likely that some of the 25 lacrimal cases reported with non-specific descriptors would have exceeded 100 IgG4+ cells/hpf; however, the fact that the true nature of one-third of all reported IgG4-related lacrimal disease specimens will forever remain speculative underscores the importance of investigators quantifying the IgG4+ stain precisely. None of the lesions staining for >100 IgG4+ cells/hpf were Caucasian, which supports the possibility of racial variation in IgG4-related orbital disease.

Deshpande *et al*[1] note that obliterative phlebitis is uncommon in lacrimal lesions and this is supported by our findings. To our knowledge, only five lacrimal cases featuring obliterative phlebitis have been reported,[3] and only two of these had >100 IgG4+ cells/hpf. Obliterative phlebitis and storiform fibrosis are rare in both lacrimal and salivary IgG4-related disease,[1] and this distribution of organ involvement often occurs concurrently.[3] Considering that these histological features are ubiquitous in disease affecting other organs, it is interesting that they should be so rare in the lacrimal and salivary groups. However, it is possible that the low rate of obliterative phlebitis is artifactual. Lacrimal biopsies are typically very small and obliterative phlebitis is often not detected in small specimens.[5] Further, as opposed to a much larger organ like the pancreas, the tiny veins of the lacrimal gland may be difficult to identify when obliterated. A larger number of meticulously reported cases may be required to explain the histological variations seen in IgG4-related disease.

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The authors declare no conflict of interest.

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