IgG4-Related Disease with Negative IgG4 Immunohistochemistry

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Background:

Current literature on IgG4-related disease (IgG4-RD) includes rare reports in which IgG4 immunohistochemistry failed to demonstrate a significant number of IgG4-positive plasma cells despite classic clinical and histologic features, suggesting an "IgG4-negative" form of IgG4-RD exists (for example, *Mod Pathol* 2015;28:238-247). We present a case of a 62-year-old female with well-documented clinical and histologic evidence of IgG4-RD but in which IgG4+ plasma cells could not be demonstrated by immunohistochemistry but were present using in situ hybridization studies for IgG4 mRNA.

Methods & Materials:

A patient with a 9-year history of relapsing and remitting pancreatitis, salivary gland swelling, and ocular adnexal swelling was evaluated for possible IgG4-RD. Serum IgG4 measurements were obtained at multiple intervals, MRI and CT imaging was performed, and a biopsy of the lacrimal gland was obtained. Ancillary studies performed on the lacrimal gland biopsy included flow cytometry, immunohistochemistry, and mRNA in situ hybridization stains. Enzyme-linked ImmunoSpot (ELISPOT) assay was also performed.

Results:

Clinical and radiologic findings were classic for IgG4-RD. Serum IgG4 levels were persistently normal. The biopsy showed histologic features typical for IgG4-RD including a dense lymphoplasmacytic infiltrate with reactive lymphoid follicles, large areas of cellular fibrosis with focal storiform pattern, and occasional eosinophils. No granulomas, giant cells, neutrophil infiltrate, or obliterative phlebitis was seen. Flow cytometry showed no clonal B-cell populations. Immunohistochemical stains supported a reactive lymphoplasmacytic infiltrate and showed >200 IgG+ plasma cells per high power field (hpf) in numerous fields. IgG4 immunohistochemistry using 2 different monoclonal antibodies (HP6025 and MRQ-44) was completely negative (i.e. zero positive cells); IgG4 positive controls were reactive. However, in situ hybridization for IgG4 mRNA showed numerous positive plasma cells (140 per hpf; IgG4/IgG ratio = 42%). ELISPOT showed zero IgG4 antibody secreting cells per 10^6 peripheral blood mononuclear cells.

Conclusions:

The patient was diagnosed with IgG4-RD based on the classic clinical and histologic findings in conjunction with the positive IgG4 mRNA assay despite the negative immunohistochemistry results, normal serum IgG4 levels, and negative ELISPOT assay. We hypothesize that the lack of detectable IgG4 cells using multiple antibody-based assays may be due to lack of recognition of the target IgG4 protein by the antibodies utilized, which could be due to a genetic defect resulting in an epitope alteration, but this is unknown at present. Such false negative antibody test results could be an explanation for the rare cases of so-called "IgG4-negative" IgG4-RD.