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LETTER TO THE EDITOR

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Response to letter to editor regarding Immunoglobulin G4-related disease in a dog

Dear Dr DiBartola and Dr Hinchcliff

Thank you for the opportunity to address the points made by Drs. Watson et al on our recent case of immunoglobulin G4-related disease (IgG4-RD) in a dog. We agree that development of diagnostic criteria of IgG4-RD in dogs deserves attention, should be based on evaluation of a broad case set, and should involve a consensus opinion from multiple clinicians and researchers, as was done in human medicine.[1] We look forward to being part of that conversation.

The consensus comprehensive diagnostic criteria for IgG4-RD in humans involve a combination of (1) characteristic diffuse/localized swelling or masses in single or multiple organs; (2) increased serum IgG4 concentrations (>135 mg/dL); and (3) histopathologic examination with (3.1) marked lymphocyte and plasmacyte infiltration and fibrosis, (3.2) infiltration of IgG4+ plasma cells: ratio of IgG4+/IgG+ cells >40% and >10 IgG4+ plasma cells/high-power field (HPF), or (3.3) both.[1] Specific combinations of these findings lead to a more certain diagnosis and not all lesions are expected to have every finding.[1,2] Our published work addresses these criteria with open discussion of both the strengths and weaknesses of our assertion that our case is consistent with the diagnosis of IgG4-RD.

Several of the claims made by Drs Watson et al regarding IgG4-RD in humans are not supported by the cited references and do not agree completely with the literature. Review of human literature reveals:

1. Immunoglobulin G4-related disease in humans can be divided into subgroups or phenotypes; mass-like lesions of the lacrimal or salivary gland are a predominant finding in some phenotypes of IgG4-RD in humans and less prominent in others.[3,4] One study grouped cases into phenotypes of pancreatohepatobiliary disease; retroperitoneal fibrosis and/or aortitis; head and neck-limited disease; and classic Mikulicz syndrome with systemic involvement. Mikulicz disease is defined as swelling of 2 pairs of the lacrimal, parotid, or submandibular glands and the head and neck-limited disease is expected to have mass-like lesions; these 2 phenotypes were present in 46% of 765 human patients.[3] The parotid and salivary gland enlargement in our case is consistent with IgG4-RD in humans.
2. Descriptions of humans with IgG4-RD indicate that phlebitis and fibrosis are uncommon or unexpected in involved lymph node, lacrimal gland, and salivary glands.[2] Although, we would have liked to demonstrate fibrosis and phlebitis in our case, their presence or absence in our case of IgG4-RD would have fit with reported findings in humans.
3. Diagnostic criteria used in humans recommend histologically counting IgG4+ plasma cells.[1] These histologic IgG4+ plasma cell counts should not be confused with total plasma cell counts in fine needle aspiration cytology. A review of fine-needle aspiration cytology from 10 human patients with IgG4-RD found that plasma cells were variable and made up as much as 15% of the non-epithelial inflammatory and fibroplastic component.[5] For reference, the cells interpreted as plasma cells in lymph node flow cytometry of our case made up 12.7% of the counted population. The IgG4-RD cytology affected human cases also had a variable but occasionally marked eosinophilia, lower numbers of neutrophils and macrophages, and a lymphocyte predominance, similar to what we describe in our case of IgG4-RD in a dog.[5] The cytologic features in our IgG4-RD are consistent with cytologic findings in humans with IgG4-RD.
4. Multiple studies confirm that the incidence of peripheral eosinophilia in all humans with IgG4-RD, including both atopic and nonatopic cases, is ~40%.[6] The eosinophilia of IgG4-RD in humans is commonly of the same magnitude as was observed in our dog with IgG4-RD case and responds well to steroids, similar to our IgG4-RD case.[6] Description of atopy is not needed to explain peripheral eosinophilia and lack of findings of atopy does not rule out IgG4-RD in our case.
5. Immunoglobulin G4-related disease in humans has been misdiagnosed as hypereosinophilia syndrome but the two diseases are not mutually exclusive; concurrent hypereosinophilia syndrome and IgG4-RD have been reported in humans.[6] Bone marrow evaluation in our dog with IgG4-RD case was inconsistent with a myeloid clonal process and a T-cell clone was not found by polymerase chain reaction (PCR) for antigen receptor rearrangements (PARR) to support a paraneoplastic cause of the hypereosinophlia.[6] Additionally, lesion distribution in our case was inconsistent with hypereosinophilia syndrome in dogs, in our experience. We do not

know the relationship of IgG4-RD in dogs and cases previously diagnosed as hypereosinophilia syndrome but suspect that at least some cases of canine IgG4-RD have been diagnosed as idiopathic hypereosinophilia syndrome in the past.

6. Serum IgG4 concentration is significantly higher in humans with IgG4-RD than in other diseases with increased serum IgG4 concentrations, including cancer (excluding IgG4-producing myeloma), autoimmune disorders, vasculitis, infections, and other causes such as hypereosinophilia syndrome.[7] Our lab has documented IgG4 by immunofixation in cases with a history of parasitic infections, inflammation, cancer, and atopy/allergy, among other causes. Except for the two cases of IgG4-producing multiple myeloma published as part of our evaluation of the immunofixation protocol,[8] serum IgG4 increases in dogs have been much lower in the non-IgG4-RD cases than was observed in our IgG4-RD case, as judged by the electrophoretogram changes. Documentation of increased serum IgG4 concentration is a diagnostic criterion of IgG4-RD in humans and may help solidify the association of IgG4-RD and dogs with chronic pancreatitis.
7. A marked polyclonal serum IgG4 increase can appear as a monoclonal band by electrophoresis and cause a misdiagnosis of a monoclonal gammopathy of neoplasia in humans, as referenced in our IgG4-RD case manuscript. We demonstrated a similar electrophoretic morphology in the dog and ultimately classified the case as a polyclonal increase. This point is important as it highlights that IgG4-RD in dogs can be mistaken for a plasma cell neoplasm with a monoclonal gammopathy.

It is not surprising that differences are present between our dog with IgG4-RD and English Cocker Spaniels with chronic pancreatitis. Both phenotyping studies of IgG4-RD in humans segregated the pancreatic predominant disease phenotype from other phenotypes and documented distinct differences of signalment, risk factors, clinical findings, and clinical progression between phenotypes.[3,4] The observations provided by Dr Watson et al are very useful as they suggest that a similar breadth of presentations may be found in dogs with IgG4-RD. We expect that their in-review manuscript lays out data from English Cocker Spaniels with chronic pancreatitis fully and provides useful information on the pancreatic predominant phenotype of IgG4-RD in the dog. Rigorous comparison of our dog with IgG4-RD with chronic pancreatitis cases in dogs with IgG4-RD should be delayed until a full evaluation of that data can be made.

We find IgG4-RD in humans a fascinating disease and are intrigued by the potential that it shares as diverse a presentation in dogs as it does in humans. We expect that as awareness of this disease process increases, more cases will be described and further clarification of the diagnostic criteria for IgG4-RD in dogs will be possible.

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