

Letter to the editor regarding Immunoglobulin G4-related disease in a dog

Dear Dr DiBartola and Dr Hinchcliff,

We read with interest the case report “immunoglobulin G4-related disease (IgG4-RD) in a dog”.¹ We have been working on IgG4-RD in dogs for a number of years, specifically investigating it in English cocker spaniels (ECSs) and some other dogs with chronic pancreatitis. The authors could be forgiven for being unaware of this, because apart from an early paper describing the histology in affected ECSs,² our work has so far only appeared in the American College of Veterinary Internal Medicine (ACVIM) and the European College of Veterinary Internal Medicine-Companion Animals (ECVIM-CA) Forum abstracts.^{3–6} We have reported typical clinical and histological features with infiltration of IgG4-positive plasma cells into the pancreas, kidney, salivary gland, and lacrimal glands of affected dogs together with an association with a particular canine leukocyte antigen subtype in affected ECSs, and the histology was the subject of Fran Coddou’s MPhil thesis. An extensive histological study is currently undergoing review for publication in a pathology journal, which we hope will provide more details soon.

In the light of this background, we found that some features of this case report were not typical, either of the human disease or of the cases we have thus far recognized in dogs, which suggest perhaps a “crossover” autoimmune disease in this Husky.

The diagnostic criteria for IgG4-RD in humans remain a matter of discussion, but usually rely on typical clinical features of autoimmune disease in multiple organs combined with characteristic histological features or, in the absence of biopsy samples, increased circulating IgG4 concentration and an effective response to glucocorticotherapy.⁷ It is well recognized that serum and tissue IgG4 concentration increase in other inflammatory and neoplastic diseases in humans and also in dogs, where, for example, there is an increased concentration in dogs with pemphigus.⁸ Therefore, a diagnosis cannot be made on the basis of increased serum concentration of IgG4 alone. In the case reported in the Husky, cytology but not histology was available and neither this nor the clinical signs were typical of IgG4-RD in our experience or in the human literature.

Human IgG4-RD was initially reported as autoimmune pancreatitis. It then became apparent that other organs were often involved, particularly kidney, lacrimal glands, biliary tract, and salivary glands.

Affected individuals had keratoconjunctivitis sicca and xerostomia, but the typical mass-like lesions referred to by Colopy et al. were confined to the pancreas and not found in the salivary or lacrimal glands.⁹ This is also our experience in dogs—we have described pancreatic mass-like lesions in affected ECSs but their salivary glands appear grossly normal even in the face of a marked lymphoplasmacytic infiltrate on histology.² Colopy et al. did not convincingly demonstrate autoimmune disease in the salivary or lacrimal glands or kidneys; nor did they report the results of Schirmer tear tests, and the increase in urine protein:creatinine ratio (UPC) was mild. In dogs with IgG4-related kidney disease, the UPC is usually >2 (reference interval < 0.4).

The large number of plasma cells found in their cytological sample is also unusual—although by using immunohistochemistry on histological sections, we find that plasma cells are common, lymphocytes still predominate histologically and typically there are 10–50 plasma cells per high power field in affected tissues. A monoclonal gammopathy is also unusual—80% of affected humans show a polyclonal hypergammaglobulinaemia.⁹ The marked eosinophilia is also interesting: the authors cite this as support for their theory that this case had IgG4-RD based on a reporting peripheral eosinophilia in 38% of human patients with confirmed IgG4-RD compared with 9% of healthy humans.¹⁰ In that human study, the eosinophilia and serum IgG4 concentrations were investigated in the context of the hypothesis that underlying atopy may be a risk factor for IgG4-RD, which contrasts with the Husky.

Confirmation of increased serum IgG4 concentrations in this paper used an as yet unpublished immunofixation technique based on the use of a commercial polyclonal canine anti-IgG1 antibody which is suggested to cross-react with canine IgG4. Because measurement of canine IgG subclasses is problematic in the absence of commercially available reagents, we look forward to the publication of this new study.

The Husky responded clinically to glucocorticoid treatment, but this is not specific to IgG4-RD. The combination of clinical and hematological findings in this case lead us to consider that this dog may have had hypereosinophilic syndrome, which might also respond to glucocorticoid treatment. The clinical signs of coughing, inappetence

and vomiting were never really explained, but could also represent other parts of this syndrome. Increased serum concentration of IgG4 has also been reported in hypereosinophilic syndrome in humans.¹¹ From the evidence presented in this case report, we would suggest any increase in the serum concentration of IgG4 is likely to be secondary, rather than the primary disease, in this dog.

Immunoglobulin G4-related disease undoubtedly occurs in dogs, but we need to define the diagnostic criteria properly, and it is important we do not rush to diagnose all inflammatory and neoplastic diseases we investigate as primary IgG4-RD. It would be useful for researchers active in this new area to collectively produce some consensus recommendations in the near future.

Penny Watson¹

Fran Coddou¹

Barbara Blacklaws¹

Julien Bazelle²

Michael Day^{3,4}

Fernando Constantino-Casas¹

¹Department of Veterinary Medicine, Queen's Veterinary Teaching Hospital, Cambridge, UK

²Davies Veterinary Specialists, Manor Farm Business Park, Higham Gobion, Hitchin, UK

³Department of Pathology, Asia Veterinary Diagnostics, Kowloon, Hong Kong

⁴Department of Veterinary Pathology, Bristol Veterinary School, Bristol, UK

REFERENCES

- Lydia J, Colopy L, Shiu K, et al. Immunoglobulin G4-related disease in a dog. *J Vet Intern Med.* 2019;33(6):2732-2738.
- Watson PJ, Roulois A, Scase T, Holloway A, Herrtage ME. Characterization of Chronic Pancreatitis in English Cocker Spaniels. *J Vet Intern Med.* 2011;25(4):797-804.
- Watson PJ, Coddou MF, Capaldo F, Bazelle J, Constantino-Casas F, et al. Clinical features of English Cocker Spaniels with chronic pancreatitis mimic human IgG4-related disease. Research Communications of the 27th ECVIM-CA Congress: Intercontinental, Saint Julian's, Malta, 14th to 16th September 2017. *J Vet Intern Med.* 2018;32:525-609.
- Coddou MF, Constantino-Casas F, Blacklaws B, Scase T, Day MJ, Watson PJ. Identification of IgG4-related disease in the English cocker spaniel and dogs of other breeds. Research Communications of the 27th ECVIM-CA Congress: Intercontinental, Saint Julian's, Malta, 14th to 16th September 2017. *J Vet Intern Med.* 2018;32:525-609.
- Watson PJ, Constantino-Casas F, Saul CJ, Day MJ. Chronic pancreatitis in the English cocker spaniel shows a predominance of IgG4+ plasma cells in sections of pancreas and kidney. 2012 ACVIM Forum Proceedings; 2012 May 30-June 12; Greenwood Village, Colorado: ACVIM; 2012.
- Bazelle J, Aguirre-Hernandez J, Watson PJ, Kennedy LJ. Association between chronic pancreatitis and dog leukocyte antigen haplotypes in the English Cocker Spaniel. Proceedings of the ACVIM Forum, Seattle. *J Vet Intern Med.* 2013;27:696 GI-4.
- Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol.* 2012;25:1-12. <https://doi.org/10.1038/modpathol.2012.72>
- Day MJ, Mazza G. Tissue immunoglobulin G subclasses observed in immune-mediated dermatopathy, deep pyoderma and hypersensitivity dermatitis in dogs. *Res Vet Sci.* 1995;58(1):82-89. [https://doi.org/10.1016/0034-5288\(95\)90094-2](https://doi.org/10.1016/0034-5288(95)90094-2)
- Haldar D, Hirschfield GM. Deciphering the biology of IgG4-related disease: specific antigens and disease? *Gut.* 2018;67(4):602-605. <https://doi.org/10.1136/gutjnl-2017-314861>
- Culver EL, Sadler R, Bateman AC, et al. Increases in IgE, eosinophils, and mast cells can be used in diagnosis and to predict relapse of IgG4-related disease. *Clin Gastroenterol Hepatol.* 2017;15:1-46. <https://doi.org/10.1016/j.cgh.2017.02.007>
- Nagamura N, Ueno S, Fujishiro H, Oonuma H. Hepatitis associated with hypereosinophilia suspected to be caused by HES that also presented with the pathological features of IgG4-related disease. *Intern Med.* 2014; 53(2):145-149. <https://doi.org/10.2169/internalmedicine.53.0292>