Nodular hyperplasia of lymphoglandular complexes in dogs—a potential diagnostic pitfall for rectal masses

Citation for published version: Stent, A, Kiupel, M, Dandrieux, J, Liffman, R & Bera, MM 2023, 'Nodular hyperplasia of lymphoglandular complexes in dogs—a potential diagnostic pitfall for rectal masses', Veterinary Pathology, pp. 1-5. https://doi.org/10.1177/03009858231190643

Digital Object Identifier (DOI): 10.1177/03009858231190643

Link: Link to publication record in Edinburgh Research Explorer

Document Version: Peer reviewed version

Published In: Veterinary Pathology

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
# Nodular hyperplasia of lymphoglandular complexes in dogs—a potential diagnostic pitfall for rectal masses

**Journal:** Veterinary Pathology  
**Manuscript ID:** VET-23-CR-0021.R2  
**Manuscript Type:** Case Report  
**Date Submitted by the Author:** 02-Jul-2023  
**Complete List of Authors:** STENT, ANDREW; Gribbles Veterinary Pathology Australia, Kiupel, Matti; Michigan State University Veterinary Diagnostic Laboratory, Veterinary Diagnostic Laboratory, Dandrieux, Julien; The University of Edinburgh Royal Dick School of Veterinary Studies, Hospital for Small Animals, Liffman, Rebekah; ASAP Laboratory, Bera, Monali; Asia Veterinary Diagnostics  
**Keywords:** Dog < Domestic Mammals < Species, Gastrointestinal < Digestive Tract < Tissue, Lymphoreticular < Tissue, Immunohistochemistry < Technology, Hyperplasia, Histology, Lymphoglandular complex  

**Abstract:** Lymphoglandular complexes are components of the gut-associated lymphoid tissue that are characterized by submucosal lymphoid aggregates invested by projections of mucosal epithelium. Reports of pathology involving these structures are rare in both human and veterinary literature. Here we report two cases of rectal masses excised from dogs following a period of tenesmus and haematochezia. In both animals the masses were composed of lymphoid tissue closely encompassing tubuloacinar structures. Immunohistochemistry and PARR testing demonstrated that the lymphoid population was polyclonal, comprising T and B cells arranged in loosely follicular aggregates centered on the epithelial foci. In light of these findings, a diagnosis of lymphoglandular complex nodular hyperplasia was reported. To the author’s knowledge, this is the first report of this condition in dogs.
Nodular hyperplasia of lymphoglandular complexes in dogs—a potential diagnostic pitfall for rectal masses

Andrew W Stent, Matti Kiupel, Julien R S Dandrieux, Rebekah Liffman, Monali M Bera

Institutions:
Faculty of Veterinary and Agricultural Sciences, The University of Melbourne, Australia (AS, JD, RL)
Veterinary Diagnostic Laboratory, Michigan State University, USA (MK)
Asia Veterinary Diagnostics, Singapore (MB)

Corresponding author:
Andrew Stent
Gribbles Veterinary Pathology
1868 Dandenong Road
Clayton, Vic, Australia 3168
P: (+613) 9538 6740
E: andrew.stent@gribbles.com.au
Abstract

Lymphoglandular complexes are components of the gut-associated lymphoid tissue that are characterized by submucosal lymphoid aggregates invested by projections of mucosal epithelium. Reports of pathology involving these structures are rare in both human and veterinary literature. Here, we report two cases of rectal masses excised from dogs following a period of tenesmus and haematochezia. In both animals, the masses were composed of lymphoid tissue closely encompassing tubuloacinar structures. Immunohistochemistry and polymerase chain reaction antigen receptor rearrangement testing demonstrated that the lymphoid population was polyclonal, comprising T and B cells arranged in loosely follicular aggregates centered on the epithelial foci. In light of these findings, a diagnosis of lymphoglandular complex nodular hyperplasia was reported. To the author's knowledge, this is the first report of this condition in dogs.

Keywords

Dog, gut-associated lymphoid tissue, histology, immunohistochemistry, lymphoglandular complex, nodular hyperplasia, rectum

Lymphoglandular complexes are components of the gut-associated lymphoid tissue, formed from a close association between lymphoid follicular tissue and epithelial diverticula projecting from the overlying mucosa. They are predominantly located within the distal small intestine, cecum, and colon and have been described in a wide range of mammalian species, including humans, dogs, cattle, horses, pigs, dolphins, and echidnas. While undoubtedly involved in immune surveillance of the gastrointestinal tract, the specific role of these structures in mucosal immunity is
unclear. Some researchers have speculated that they may be mammalian analogues of the bursa of Fabricius that act as secondary lymphoid organs. The clearest indication of their function is derived from studies in pigs, where they are the predominant site of IgA production during Campylobacter jejuni infection.

A range of proliferative lesions involving the gastrointestinal lymphoid tissue are recognized in humans and animals. Lymphoid follicular hyperplasia is a common endoscopic and histological observation in many chronic inflammatory enteropathies, reflecting expansion of the mucosa-associated lymphoid tissue (MALT) in response to persistent antigenic stimulation. While this is a non-specific finding seen with a variety of infectious and hypersensitivity diseases, gastrointestinal MALT hyperplasia is also closely associated with several immunodeficiency syndromes in humans, indicating that genetic predisposition may be a factor in some cases. Though hyperplastic foci are typically small, they can sometimes form larger masses up to several centimeters in size, and distinguishing these lesions from MALT lymphoma can be challenging. Indeed, progression from hyperplasia to neoplasia has been noted to occur in humans. Hyperplastic lesions of the lymphoglandular complexes are rarer still, and the incorporation of an epithelial component into these lesions introduces the risk of a misdiagnosis of both carcinoma and lymphoma. The following report describes nodular hyperplasia of lymphoglandular complexes within the rectum of two dogs.

In the first case, a 12-year-old, male Chinese crested dog was presented for acute large bowel diarrhea and tenesmus after 3 weeks of boarding. Similar episodes of diarrhea occurred over the previous two years after antibiotic or non-steroidal anti-
inflammatory treatment, with one episode of hematochezia. The dog was regularly
treated with anthelminthics.

Rectal endoscopic examination identified two large masses (each over 1 cm in
diameter) and three small masses (less than 5 mm in diameter), arising from the
dorsal and ventral rectal walls, 3–7 cm cranial to the anus. The masses were broad-
based with a sunken center and intact overlying epithelium (both with white light and
narrow-band imaging). The colon and distal ileum were assessed and no other
masses were noted. Needle aspirates were collected from one of the masses for
cytology. The samples contained cuboidal epithelial cells displaying mild to moderate
pleomorphism and arranged in tubular-type structures within a background of
lymphocytes and plasma cells. An epithelial malignancy was considered unlikely but
could not be entirely excluded.

In the second case, a 9-year-old, male neutered cross-breed dog presented with
frequent bleeding during defecation and tenesmus. The dog was originally treated
with antibiotics for a suspected anal gland infection, but the problem persisted.
Further endoscopic investigation of the rectum revealed a small pale raised polypoid
lesion arising from the rectal mucosa.

Masses from both cases were excised for histological examination. The lesions were
well-circumscribed and largely confined to the submucosa (Fig. 1a, b). Histologically,
the masses were essentially identical in composition, containing irregularly shaped
tubuloacinar structures lined by tall columnar epithelium. The epithelium was
crowded and sometimes displayed loss of polarity (Fig. 1c, d). The epithelial cells
displayed mild anisokaryosis, sometimes with hyperchromatic nuclei and prominent nucleoli, and frequent mitoses were present. Surrounding these glands, there were lymphocytes arranged in loosely follicular architecture with occasional germinal centers intermixed with plasma cells and histiocytes. The lymphoid cell population displayed a high mitotic rate. Immunohistochemical phenotyping (Fig. 2a, b) of the lymphocytes was performed as previously described, using normal canine lymph node as control tissue. Identified the lymphocytes immediately surrounding and adjacent to the glandular structures as predominantly CD20 and Pax-5 positive, consistent with a B-cell phenotype, and these foci were encircled by a population of CD3-positive cells, consistent with T-cells (Fig. 2a, b). Low numbers of both T- and B-cells infiltrated the epithelium of the glandular structures, and occasional intraepithelial clusters of B-cells were identified. In some areas, the epithelial lining of the tubuloacinar structures was discontinuous, with apparent protrusion of the lymphoid tissue into the lumen. In the first case, the overlying mucosa was inflamed and mildly eroded, while the mucosa in the second case was unremarkable. No infectious agents were identified in the tissues histologically, and bacterial culture of the tissue in the first case yielded only light growth of mixed gastrointestinal flora.

Polymerase chain reaction for antigen receptor rearrangement (PARR) testing was performed for both cases at the Michigan State University Veterinary Diagnostic Laboratory by extracting DNA from 5, serial 5-μm-thick sections (25 μm thickness total) from formalin-fixed, paraffin-embedded tissues. Rearrangements of the T-cell receptor gamma and the immunoglobulin heavy chain gene variable regions were assessed by amplifying the complementary determining region 3 (CDR3), as previously described. Clonality was not detected for either receptor and based on
In both cases the tenesmus resolved soon after surgery, with only a single small nodule of 2–3 millimeters in size palpated on rectal exam 4.5 months after surgery in the first dog and no further progression over a 4-year follow-up, while the second dog was clinically unremarkable through to 6-month follow-up.

Lymphoglandular complexes have been found throughout the intestinal tract of dogs, but occur with particular abundance in the duodenum, colon, and rectum. Two architectural forms of lymphoglandular complex have been described: Strauchdrüsen (shrub glands), which form from branching projections of a single epithelial tubule, and Büscheldrüsen (tufted glands), in which multiple adjacent epithelial tubules independently invest the lymphoid tissue. Büscheldrüsen were reported as most prevalent form in dogs, but it is uncertain which form of lymphoglandular complex these cases most closely resemble, as the communication between the epithelial structures and the overlying mucosa was unclear from the histological sections. Nevertheless, the masses described in this report displayed features broadly consistent with lymphoglandular complexes reported in dogs and other species—albeit of greater size and complexity—and are considered to represent hyperplastic enlargement of these structures. Lymphoid proliferation with prominent follicle formation has been reported in porcine lymphoglandular complexes in association C. jejuni infection, but no evidence of campylobacteriosis or any other infectious disease was identified histologically or by bacterial culture in the present cases.
Based on the history of previous episodes of acute diarrhea after medical treatment, the neutrophilic inflammatory component found on endoscopic biopsy and resolution without specific treatment, an episode of acute colitis was suspected to be the trigger for hyperplasia in the first case. No further information about the cause was determined as the dog was boarded when the tenesmus and diarrhea initially developed. However, the presence of multiple concurrent and persistent masses in the first case suggests this dog may have had an underlying predisposition to development of such lesions.

Similar masses containing varying proportions of epithelial and lymphoid components have been reported rarely in the human literature,\textsuperscript{9,15,19} though some of these cases are more consistent with inverted adenomatous polyps or submucosal hemiation of colonic glands than primary proliferation of the lymphoglandular complexes. The case documented by Zhou et. al., designated an inverted lymphoglandular polyp, bears closest resemblance to the lesions described here, but the arrangement of the epithelial component was slightly different, comprising sparse, irregular ectatic glandular structures rather than the small, contorted tubuloacinar foci observed in these dogs. This discrepancy may reflect anatomical differences in human lymphoglandular complexes, which typically contain relatively few, superficially distributed epithelial projections.\textsuperscript{14}

The distinctive histological features of this condition were rectal submucosal masses that were well-circumscribed and displayed integration of glandular structures into lymphoid tissue. Lymphoid follicles were centered on these glands and there was extension of the lymphocytic population into the gland lumina. Several notable
differentials were considered for this case. Submucosal herniation of crypts as seen in focal colitis cystica profunda could have a similar appearance, but while there may be secondary inflammation with this condition due to compression or rupture of crypts, it lacks the intimate association between lymphoid and glandular tissues seen in these cases. Furthermore, goblet cells typical of crypt mucosa were absent from the epithelium in the lymphoglandular complex. Lymphoma arising within a lymphoglandular complex was a concern due to the nests of lymphocytes in the glandular epithelium. However, the mixed population of inflammatory cells throughout the lymphoid tissue, the presence of recognizable follicular architecture, the lack of clinical progression, and the absence of detectable clonality with PARR testing makes this diagnosis highly improbable. An invasive adenocarcinoma was a further consideration, but the dispersed distribution of glands within the lymphoid tissue, close association between lymphoid and epithelial components, lack of stromal reaction or invasion outside of the mass, retention of basement membrane surrounding glands, absence of marked anaplasia within the masses or the overlying mucosa, and the lack of progression all refute a diagnosis of invasive adenocarcinoma. Failure to account for these factors engenders considerable risk of a misdiagnosis of malignancy, particularly as the submucosal location could make the procurement of truly representative samples problematic.

These two cases of lymphoglandular complex nodular hyperplasia demonstrate a non-neoplastic disease in the rectum that must be considered as a potential diagnosis for any submucosal mass containing both lymphoid and epithelial components. Considering the prognostic implications of possible differentials, such
as adenocarcinoma or lymphoma, it is imperative that biopsy samples are of sufficient depth and quality to allow careful scrutiny and recognition of this condition.

Acknowledgements

The authors would like to thank Annie M Zimmerman for her contribution to pathological assessment of these cases.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Authors’ Contributions

AWS, MK, RL, and MMB performed pathological evaluations; MK and MMB performed PARR analysis; JRSD performed clinical investigations; the manuscript was written by AWS with contribution from the other authors.

References


**Figure legends**

**Figure 1.** Lymphoglandular complex nodular hyperplasia, rectum, dog. Excisional rectal biopsies from case 1 (a and c) and 2 (b and d), both demonstrating well-demarcated submucosal masses containing a dual population of lymphoid and epithelial tissue. Hematoxylin and eosin.

**Figure 2.** Lymphoglandular complex nodular hyperplasia, rectum, dog. a) Photomicrograph of Pax-5 immunohistochemistry within the rectal mass, displaying aggregates of strongly Pax-5-positive cells surrounding tubuloacinar structures. Case 1. DAB chromogen, hematoxylin counterstain. b) Photomicrograph of CD3 immunohistochemistry within the rectal mass, demonstrating a cuff of CD3-positive cells that surround the central foci of B cells and tubuloacinar structures. Case 1. DAB chromogen, hematoxylin counterstain. c) Polymerase chain reaction (PCR) to
detect antigen receptor rearrangement (PARR) in the T-cell receptor gamma gene for case 1. The non-neoplastic lymphocytic (polyclonal) population presents as a smear (A4-A6) between 125 to 138 bp in the PCR gel and in the electropherogram produce multiple small, broad peaks rather than a single tall peak that is observed in clonal populations. Size markers are represented as peaks at 15 bp and 1000 bp in the electropherogram and green lines in the PCR gel.