IBD – where are we 10 years after WSAVA standardisation?

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Inflammatory Bowel Disease (IBD)

In the dog and cat, IBD is the collective term for a group of chronic enteropathies characterized by persistent or recurrent gastrointestinal signs and inflammation of the gastrointestinal tract. As in humans, it is believed to result from predisposing genetic and environmental factors (e.g., specific antigens and MAMPs) acting on the immunoregulatory system and causing inflammation of the gastrointestinal mucosa. In dogs, mutations and polymorphisms in receptors of the innate immune system (e.g., TLRs, NOD2) as well as dysregulation of lymphocyte subpopulations (e.g., reduced apoptosis of mucosal lymphocytes) are well known. Furthermore, the breakdown of immunologic tolerance to luminal antigens (bacteria and dietary components) is thought to be critical, perhaps resulting from disruption of the mucosal barrier, dysregulation of the immune system, or disturbances in the intestinal microflora.

Chronic enteropathies are frequently encountered in dogs and cats, resulting in diarrhoea and occasionally vomiting. The clinician faced with a case usually performs an extensive workup to exclude extra-gastrointestinal causes for diarrhoea and vomitus (e.g., liver, kidney, hypoadrenocorticism (dogs), hyperthyroidism (cats)) as well as disorders such as pancreatic diseases, chronic parasitic or bacterial infections, and tumours. Diagnostics performed to rule out underlying disorders include a complete blood count (CBC), serum biochemical analysis (incl. bile acids/ammonium), urinalysis, hormonal testing (ACTH stimulation test in dogs, T4 in cats), parasitic and bacterial analysis of faecal samples, abdominal ultrasonography, and assessment of serum concentration of trypsin-like immunoreactivity (TLI), pancreatic specific lipase (PLI), serum cobalamin and folate concentrations. If there is no obvious underlying infectious, parasitic, pancreatic, neoplastic, endocrinologic or metabolic disease identified, these animals are mostly undergoing a trial therapy +/− endoscopy and are retrospectively diagnosed by the response to treatment as antibiotic-responsive diarrhoea (ARD; Tylosin-responsive diarrhoea (TRD); nowadays better dysbiosis), food-responsive diarrhoea (FRD) or IBD (also called steroid-responsive diarrhoea).

Histology and WSAVA standardisation

IBD is associated with histopathological evidence of inflammation in the intestinal mucosa with the infiltration of the gastric, small and/or large intestinal wall with inflammatory cells. The nomenclature reflects the predominant cell types present: lymphocytic-plasmacytic enteritis (LPE) is the form most commonly reported in dogs and cats, whereas eosinophilic or granulomatous (gastro-) enteritis is less common. However, a new study is pointing out some deficits in standard histology to detect eosinophils (1). Nevertheless, the eosinophilic form occurs uncommonly, and the animals affected tend to be younger. Endoparasites, infectious agents, and food allergy have all been incriminated in this form, but none has been proven. Regardless, it is prudent to investigate and eliminate these potential aetiologies first since treatment of eosinophilic enteritis tends to be more difficult than that of LPE. Granulomatous enteritis (defined by presence of periodic acid-Schiff negative macrophages) is rare and usually presents as a segmental, thickened, partially obstructed segment of bowel. The ileum and colon appear to be affected most commonly. It is important to eliminate inflammation secondary to fungal disease, intestinal parasites, feline infectious peritonitis, and foreign material. Treatment remains controversial, although most advocate surgical resection if possible.

Histology is an important tool to define chronic inflammation and is part of the diagnosis of IBD. Furthermore, intestinal neoplasia and especially intestinal lymphomas have to be excluded. However, the interpretation of biopsies leads often to problems even for specialists (2). Therefore, the World Small Animal Veterinary Association (WSAVA) conscripted a group of experts to solve this problem resulting in new histopathological standards for the diagnosis of gastrointestinal inflammation in endoscopic biopsy samples from the dog and cat (3). The initial euphoria rapidly had to give way to disillusion. Despite the very detailed and colourful description and characterisation as well as guidelines for endoscopy (4), the interpretation of the biopsies heavily depend on the quality of the samples (5,6). Even the experts of the WSAVA-group published disappointing results 2 years later (7), where they had to admit obvious differences amongst themselves, at least partially due to differences in handling of the biopsy samples. Furthermore, the agreement between biopsies from duodenum and Ileum in dogs suffering from small and large bowel diarrhoea is modest pointing towards the need of taking routine biopsies from duodenum and ileum (8).

Where are we in 2019?

Despite the somewhat deflating results, the WSAVA standardisation did raise the standards worldwide concerning biopsy techniques, their handling and interpretation as well as the comparability of the results. Nevertheless, we are still confronted with the question if intestinal samples are really needed and helpful to diagnose IBD. Furthermore, the jury is still out about the best methods to differentiate IBD from intestinal lymphoma (and other tumours). Finally yet importantly, it would be much easier to have biomarkers in blood and/or faeces at hand instead of taking endoscopic or surgical biopsies.

In the future, which diagnostics could potentially facilitate the diagnosis of IBD and the differentiation of IBD from other chronic enteropathies and intestinal lymphoma?

a. ileac biopsies
-often different to duodenum in dogs (8)
-in the cat better for the diagnosis of intestinal lymphoma (9)

b. immunohistochemistry (CD3, CD20, CD79, Ki-67)
-as a 2nd step after normal histology (10)
-Ki-67 significantly increased in lymphomas (10)

c. PCR for antigen receptor rearrangement (PARR)
-as a 3rd step after immunohistochemistry (10)
-unfortunately, results are not always clear…

d. biomarker
-in blood (CRP (11,12), α1-PI (11), marker of oxidative stress (13), others)
-in faeces (α1-PI, S100A12 (14), calprotectin (12), others)

e. faecal microbiome
-different in various diseases (15,16)
-dysbiosis index (17)

f. metabolome (18,19)

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