Is it IBD or Lymphoma?

Craig Webb, PhD, DVM, DACVIM
Colorado State University
Ft. Collins, CO

The vast majority of cases of Inflammatory Bowel Disease in humans are either Ulcerative Colitis or Crohn's Disease, two reasonably well defined conditions. In contrast, as already mentioned, the term Inflammatory Bowel Disease in veterinary medicine refers to an Idiopathic condition that often serves as an umbrella term for a variety of clinical conditions – all of those for which we haven't found a cause. At the recent 2011 ACVIM meeting in Denver CO, Dr. Al Jergens defined feline IBD as having the following features: 1) the presence of persistent (> 3 weeks) gastrointestinal signs which are characterized by cyclic periods of active and inactive disease; 2) inadequate response to dietary trials and symptomatic therapies alone; 3) failure to document other causes for gastrointestinal inflammation; and 4) histopathologic evidence of mucosal inflammation.

The veterinary profession is undergoing a subtle but important shift in terminology. Whereas previously a diagnosis of "Inflammatory Bowel Disease" or IBD was often given to any cat or dog with diarrhea when time, patience, or finances precluded an actual diagnosis, we now tend to start with the term "Chronic Enteropathy". From there we move forward diagnostically and therapeutically in an organized manner that allows us to add important qualifiers, such as Chronic Enteropathy – Food Responsive Diarrhea. Only when we have exhausted the differential list and procured histopathology do we settle for a diagnosis of IBD (NOTE: the real name is *idiopathic* inflammatory bowel disease and it is a histopathologic diagnosis). Unfortunately even the most thorough work-up, including a histopathologic diagnosis, may still leave us wondering whether this patient has IBD or Lymphoma. The Gold Standard for the distinguishing diagnosis begins, and ends, with the Clinical Diagnostician, you!

Inflammatory bowel disease or lymphoma

1. Identify the patient as having a Chronic (you pick, 3 weeks, 2 months?) Enteropathy (diarrhea, vomiting, weight-loss, change in appetite, etc).; signs attributable to a dysfunction of the enteric system because non-enteric causes have been ruled-out (Diagnostic Step One, often referred to as the Minimum Data Base, with a number of tests thrown in for good measure; PLI, TLI, cobalamin, abdominal ultrasound, etc.). With a stable patient:
2. Fecal examination and prophylactic deworming (Step Two)
3. Diet trial (Step Three – ruling out an Adverse Reaction to Food)
4. Antibiotic trial (Step Four – ruling out an Antibiotic Responsive Condition)
5. The Chronic Enteropathy persists – Tissue Diagnosis (Step Five) to rule out Neoplasia.

Histopathology is/was/maybe considered the "gold standard" for diagnosis of Inflammatory Bowel Disease, although ironically, many studies show very little correlation between histopathologic severity and clinical reality, so what's the point? (Encourage your pathologist to look into the recent guidelines produced by the WSAVA, www.wsava.org). Perhaps the single most critical function of our pathologist is to distinguish between IBD and Neoplasia for us, our patient, and their owners. But even that distinction has clearly been shown to be a difficult one for the naked eye looking through a microscope – and it can be very difficult to get two eyeballs to agree (especially if they belong to two different pathologists). To make matters worse, the two may not be as separate and distinct as we would like. An overlap between IBD and alimentary lymphoma in cats has been suggested with some cases of IBD suspected of progressing to alimentary lymphoma (as has been demonstrated in humans). Fortunately, the information that can be derived from a piece of tissue is rapidly extending beyond a classical histopathologic description. Particularly relevant technological advances include immunohistochemistry and flow cytometry, both designed to more give much more detailed and sophisticated names to the cells that are present in the tissue specimen. Although currently of little practical importance, we are also able to identify differences at the biochemical level between cytokines and Toll-like receptors that likely have clinical implications. One of the more effective treatments for Crohn's disease is an antibody directed at TNF-alpha (tumor necrosis factor), a long way away from the non-specific biochemical atom bomb known as prednisone.

The major players in the etiopathogenesis of inflammatory bowel disease have seemingly been identified: Antigenic Stimulation, the Microbiota, the Enteric Architecture and Protective Functions, and the Immune System. New players are joining the ranks as research continues – particular enteropathic bacterial species, specific toll-like receptors, an array of cytokines and chemical messengers, breed-specific genetic mutations, etc. It makes for a fascinating quagmire of literature that renders us "idiopathic". To top off that quagmire, it is believed that chronic inflammatory conditions may progress to neoplastic disease (think feline vaccine-associated fibrosarcoma).

6. Diagnosis = Inflammatory Bowel Disease, GI Lymphoma, or a histopathologic surprise from a pathologist with a sense of humor that sends you reeling back towards square one.

IBD treatment – now that you've got it diagnosed, sort of, how to treat?

Diet

(There it is again and a crucial component of IBD therapy): novel protein, hydrolyzed, highly digestible diet, with dietary fiber, polyunsaturated fatty acids (n-3 FA), and prebiotic/probiotic supplements. There, did I leave anybody out? At various ends of the spectrum, an inappropriate immune response to dietary antigens may constitute an Adverse Reaction to Food, a Food Allergy, or simply an antigenic component of IBD. The only real way to tell is to rechallenge the cured cat with the previously offending diet and see if the diarrhea returns to the new carpet…sure.

Rx

Corticosteroids (prednisolone 2 mg/kg/day, taper over 6-12 weeks; budesonide 1-3 mg/day) and metronidazole (15 mg/kg BID) are the most frequently prescribed drugs for IBD. As an additional immune-modulator in cases that persist in the face of glucocorticoids, chlorambucil (2 mg every 4 days in cats > 2 kg) is gaining in popularity, and appears particularly important if the IBD is actually low-grade lymphoma – the two look disturbingly similar.

Cobalamin (vitamin B12 supplementation)

Because a healthy, functional GI tract is important in the processing and absorption of cobalamin, patients with chronic GI disease frequently have low levels of cobalamin. The concentration of cobalamin can be particularly in cases of GI lymphoma and so I would encourage clinicians to measure cobalamin levels prior to beginning supplementation, as another piece of the diagnostic puzzle. Few if any side-effects are seen with B12 supplementation, and the dose ranges from 250 µg (cats) to 500 µg to even 1000 µg per week as a starting dose, then tapered to once a month over the next several months, pending improvement in clinical signs or repeat measure of the patient's level.

Vomiting

Vomiting may be the only sign or a concurrent condition in cats with IBD. α2 adrenergic antagonists (chlorpromazine 0.2-0.4 mg/kg subQ or IM TID) and 5-HT_3 antagonists (ondansetron 0.1-1.0 mg/kg or dolasetron 0.5-1.0 mg/kg, orally or IV q12-24 h) act as effective anti-emetics in cats, while metoclopramide (dopaminergic antagonist, 1-2 mg/kg CRI) is less effective as an anti-emetic (although still a prokinetic, in theory at least). At CSU we frequently reach for the NK-1 receptor antagonist, maropitant 0.5 – 1.0 mg/kg q24 h intravenously, subcutaneously, or orally).

Comparison of treatment considerations: IBD vs. lymphoma and cat vs. dog

Signalment, History, Physical Examination An Effective Diagnostic Pathway is Dictated by a Sound Clinical Diagnosis The Use and Timing of Therapeutic Trials is Guided by the Severity of the Clinical Condition (dose recommendations can be highly variable; check current formulary prior to administration)	
Canine	**Feline**
Idiopathic Inflammatory Bowel Disease	
Dietary Intervention: Hypoallergenic or Hydrolyzed	
Antibiotics: Tylosin[#] 10 mg/kg q24hr Metronidazole***** 10 mg/kg q12hr	Antibiotics: Tylosin[#] 10 mg/kg q24hr Metronidazole***** 10 mg/kg q12hr
Prednisolone 1-2mg/kg BID, taper per clinical signs & side-effects	
Budesonide 1 mg (cats, toy breeds) – 3 mg (mid-lg breed) total dose q24hr, then taper	
Cobalamin (vit B12) Supplementation (see dose recommendations above)	
Cyclosporine 5 mg/kg PO q24hr Frozen, w/food if GI upset on empty stomach	Chlorambucil 2mg total/cat q4d If cat < 2kg, 2mg total/cat q1wk
Azathioprine 2 mg/kg PO q24hr then taper	Azathioprine not recommended in cats
GI Lymphoma	
Consult with an Oncologist	Chlorambucil 15 mg/m^2 PO q24hr for 4 days q3wks
	Prednisolone 3 mg/kg PO q24hr, then taper
Cobalamin (vit B12) Supplementation (see dose recommendations above)	
Additional Therapies to Consider as Warranted	
E-tube placement, Probiotics, canned Pumpkin, metamucil, *Helicobacter* Rx	
Mirtazapine 0.6 – 1.0 mg/kg BID	Mirtazapine 15mg tab, ¼ tab q24hr (1/8th in CKD)
Cerenia 1.0 mg/kg/day IV, SQ; 2.0 mg/kg/day PO (reduce dose 50% with liver failure); may be given for > 5 consecutive days may be given to young animals	Cerenia 1.0 mg/kg/day IV, SQ; 2.0 mg/kg/day PO (reduce dose 50% with liver failure)

[#]*Tylan®Soluble* = 100gms per bottle; 1 tsp (5ml) = 2.5-2.7gms; 1/8th tsp = 325mg; bitter, rec'd capsules

*1mg of metronidazole base = 1.6mg of metronidazole benzoate

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