

## **When answers create more questions – deciphering ferret GI pathology reports**

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It's hard enough being a practitioner – you have to anesthetize, incise, identify, excise, repair, and recover you shouldn't have to interpret the pathology report as well. “Mild diffuse lymphoplasmacytic enteritis” – “multifocal minimal lymphocytic portal hepatitis” – “diffuse severe mesenteric node hyperplasia” – all well and good, but how do you treat it, and what does it mean for the patient?

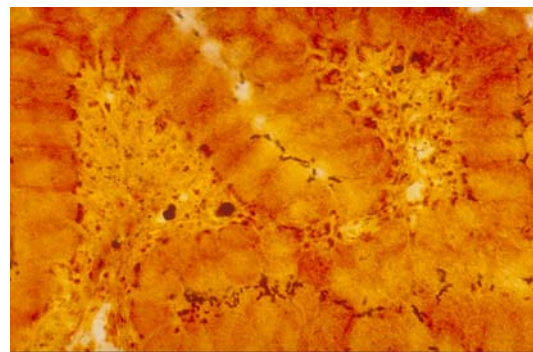
Almost every day, I receive a call from clinician asking me to interpret a pathology report on a ferret, and tell them what I think is going on. More often than not, it has to deal with GI biopsies – stomach, intestine, liver, and the regional lymph nodes. Another pathologist has left them hanging – describing what they see, but not interpreting the lesion in any context that the practitioner can use.

I can see how this happens. To start with, there actually just isn't a lot of pathologists out there with significant ferret experience – and even fewer familiar with the range of diseases to which this species is susceptible. As a consultant, the two main problems I see with these cases are a) the incorrect assumption that the ferret GI tract is susceptible to all of the same maladies as that of the dog or cat, and b) overinterpretation of normal findings in the GI tract.

Sending your samples to veterinary pathologists who specialize in exotic

species easily solves the first problem – there aren't a lot of them out there, but they'll work hard for your business. This is not meant as a slap to the larger commercial labs – I know a few pathologists working for them who are excellent at ferret tissues. However, there is no guarantee that the tissues will show up on their desk, and not someone else's. In large labs, ferrets comprise possibly 1% of total submissions, and probably less. For this reason, expertise in ferret tissues is not likely to be of major commercial value, either to the company or the individual pathologist. And, with the number of slides that they read (and reports that they write) each day, the opportunity to run off to the library each time a ferret case comes across their scope is just not there.

However, the second problem – that of ascribing pathologic significance to normal background findings - is likely far more pervasive among pathologists without extensive experience in this species. It takes review of many, many slides to know what normal ferret gut looks like, and more than that, what are normal changes as the animal ages.



**Close-up of *Helicobacter mustelae* in the gastric glands of a ferret. These bacteria live only in significant numbers in the pylorus, so all gastric biopsies should come from there. A silver stain (pictured) will easily demonstrate these organisms in cases of lymphoplasmacytic gastritis.**

At this point, let me provide you with a few hard “facts” which it has taken me many years and thousands of cases to learn. Perhaps this will be just that little bit of information you will need to “read between the lines” of that next report which has you scratching your head. I’ll try to break them down by organ – intestine first, then stomach, liver, and lymph nodes.

### *Intestine*

Inflammatory cells, especially lymphocytes, plasma cells, and in lesser numbers, eosinophils, are **normal** components of the ferret intestine. In fact, the gut-associated lymphoid tissues (GALT) comprises approximately 50% of the total lymphoid tissue in the body.<sup>1</sup> The ferret intestine is generally rife with foreign antigens, and a complex cast of lymphocytes and antigen-presenting cells continually sifts through them, gauging what is and is not a threat, and orchestrating a wide variety of inflammatory reactions against foreign invaders. Eosinophils also moderate proinflammatory (generally hypersensitivity) reactions, and are continually present in low numbers in the normal gut. Hence, a diagnosis of “mild lymphocytic and eosinophilic enteritis” likely reflects no actual pathologic change, but rather an “overinterpretation” of normal tissue. You should also be cognizant of the fact that over the course of a lifetime, as animals are exposed to a larger cumulative total of antigens through the intestinal tract, the numbers of resident inflammatory cells also increases. Hence, a 5-year-old would be expected to have more lymphocytes, plasma cells and eosinophils as part of its resident population in the gut than a 1-year old.

Today, inflammatory bowel disease (IBD) is a very common diagnosis in ferret surgical pathology. Truly, IBD is not a single entity, but the end result of a number of pathogenic mechanisms that result in a similar clinical and histologic picture. To the pathologist, IBD is represented by an influx of lymphocytes, plasma cells, and other inflammatory cells **to the detriment of the intestinal lining and its function.** (In truth, inflammatory bowel disease is a far more complex dysregulation of cell-mediated immunity characterized by features invisible to the microscope: derangement of mucosal permeability, upregulated inflammatory marker expression, and altered cytokine synthesis.)



The reddened GI tract of a ferret with ECE (bottom) compared with a normal one (top.) A diagnosis of ECE should always include a description of villar changes and marked lymphoplasmacytic inflammation in your pathology report.

The key to deciding whether the pathologist's diagnosis is consistent with IBD is based on a) the severity of the increase in the resident lymphocyte population, and b) the presence of villar damage. As a general rule, I usually ascribe little significance to minimal or mild changes in the resident lymphocyte populations; however, lymphocytic infiltrates described as moderate or severe should be viewed as potentially pathologic. Also, in most cases of chronic IBD, there is a significant and telling increase in the numbers of intraepithelial lymphocytes (IEL). In the normal state, very few IELs are seen in histologic preparations. More important, however, is the histologic presence of villar damage, usually manifested in IBD as atrophy, blunting, and/or fusion. These changes indicate significant prior damage to villar enterocytes, and coupled with an assessment of a moderate or severe accumulation of lymphocytes in the affected segment of gut, is highly suggestive of inflammatory bowel disease.

Likewise, the mention of a mild eosinophilic enteritis should always be viewed with caution. Small numbers of eosinophils are normally seen in the intestinal lamina propria. "Eosinophilic enteritis", a sporadic disease most commonly seen in young male ferrets, is characterized by **massive** influx of eosinophils into the intestine (as well as other abdominal organs in this poorly named disease). In long-standing cases, these eosinophils have often degranulated, forming a brightly colored extracellular compound known as "Splendore-Hoeppli material". Only a report of massive numbers or pure infiltrates of eosinophils with (or more commonly without) the presence of

Splendore-Hoeppli material should result immunosuppressive treatment for EE.

### *Stomach*

Diagnosis of lymphocytic or lymphoplasmacytic gastritis or duodenitis, on the other hand, should not be considered to represent the syndrome known as IBD. Until proven otherwise, all lymphocytic or lymphoplasmacytic lesions of the pylorus and proximal duodenum should be considered to be the result of infection with *Helicobacter mustelae*, a ubiquitous infection in ferrets. The organism is easily demonstrated in pyloric biopsies with a silver stain; however, many labs will not run this unless requested. Clinicians should also note that when biopsying the stomach, sampling should only be done from the pylorus, where organisms, ulcers, and inflammatory lesions are at their most profound.

### *Liver*

The liver is commonly biopsied in ferrets, as it is often discolored in animals with chronic GI disease. The yellowish discoloration so commonly seen in ferret livers at surgery is due to accumulation of fat within hepatocytes. This accumulation may be diffuse, resulting in an overall yellow color to the liver, or it may be nodular, resembling small dots throughout the liver. In many cases, the reporting of hepatocellular lipidosis may lead the practitioner to believe this to be a pathologic change – the equivalent of the syndrome of idiopathic hepatic lipidosis in the cat. However, this is not the case. Ferrets have a unique physiologic mechanism that allows rapid mobilization of peripheral fat stores in

times of inanition, sometimes “kicking in” as little as 6 hours following a meal. Hence, hepatic lipidosis in ferrets should not be interpreted as a pathologic finding, but simply a physiologic response.



**Hepatic lipidosis in a ferret. Yellow livers are extremely common in ferrets that have not been eating well, and are the result of mobilization of fat stores for energy rather than any particular disease state.**

Another extremely common finding in the liver is the infiltration of portal areas by lymphocytes and plasma cells. This finding results from chronic antigenic stimulation arising from the intestine and traveling up the portal triad. As one would expect, the severity of this common background finding increases with age, and becomes more pronounced in cases of chronic GI inflammation, as antigen absorption is increased across a mucosal barrier rendered more permeable to macromolecules. Lymphocytic portal hepatitis of this type should not be considered a disease requiring therapeutic intervention.

### *Mesenteric lymph nodes*

Mesenteric lymph nodes are commonly enlarged in ferrets with chronic gastrointestinal disease. In the vast majority of cases, this lymphadenomegaly is the result of

reactive hyperplasia. *Helicobacter mustelae* infection is the most common cause of this finding, but inflammation in any segment of the GI tract may cause secondary enlargement of draining nodes. The prevalence of hyperplastic mesenteric nodes in middle-aged and geriatric ferrets poses special problems for the pathologist. In many cases, the severity of the hyperplasia resulting from chronic GI inflammation may be quite difficult to differentiate from lymphoma. For this reason, the utilization of mesenteric nodes for the diagnosis of lymphoma in the ferret should be avoided if at all possible. Occasionally, malignant lymphoma may arise in the mesenteric nodes; however, the incidence and risk factors associated with malignant transformation in chronically stimulated nodes have yet to be elucidated. The presence of chronic inflammation in the GI tract or reactive hyperplasia in mesenteric nodes should not be considered a pre-neoplastic lesion in the ferret.

Finally, there are a few things that you can do to help the pathologist return the most specific diagnosis possible. These tips may seem a bit obvious, but they often “fall through the cracks” in a busy practice, especially when multiple individuals interact to ensure that the sample is collected, labeled, packaged, and mailed off.

- 1) Include as complete and accurate a clinical history as possible, to include clinical pathology data. In most cases of true IBD, while bloodwork is often not of great assistance in diagnosis, the presence of hypoalbuminemia and

lymphocytosis complement a suggestive pathologic description.

- 2) Sample logically. In cases of animals with chronic diarrhea, intestine and or colon is the appropriate submission rather than liver or lymph node. For biopsy, only the pyloric stomach should be taken – funding or antral specimens, although easier to harvest, will likely show little of what is going on in the pyloric area.

While there is no magic formula to ensuring that all of your GI surgical pathology specimens will come back with a useful diagnosis, an understanding of the basics of inflammation in this organ system, and attention to detail both in your submission and in reading the pathology report will markedly increase your ability to make accurate diagnoses and choose appropriate therapies for your ferret patients.

## **References**

1. Elwood CM and OA Garden. Gastrointestinal immunity in health and disease. *Vet Clin N A: Sm Anim Pract* 29(2):471-497, 1999.