

# AETC Fall 2011 Symposium

## Non regenerative anemia in the cat and dog

Topic outline with case illustrations

Jessica Larson, DVM, DACVIM (SAIM)

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**Goals for general practitioner:** This talk is designed to refresh the topic of non regenerative anemia in dogs and cats, provide discussion of mechanisms and treatment and to discuss specific parameters during diagnosis and monitoring. Several case examples with pathology and outcome are included to illuminate the topic.

### 1) Non regenerative anemia

- Typically normocytic normochromic with no to minimal morphology changes
- Characterized by absolute reticulocyte count
  - o In dogs: < 60,000 cells/ul, or < 1%
  - o In cats: < 15,000 cells/ul, or < 0.4% (aggregate reticulocytes)
  - o Persistence of non regenerative anemia > 5 days or so is real; most causes of regenerative anemia will respond by this time
- a) Classified by the 4 "H's"
  - i) Hemolysis, hemorrhage, hypoplasia or hemodilution
    - (1) Hemolysis and hemorrhage can be regenerative or non regenerative (typically thought of as regenerative)
    - (2) Hypoplasia, generally considered maturation defect anemias
    - (3) Hemodilution lowers Hct, Hb and RBC count but does not truly reduce red cell mass
  - ii) Red cell life span in cats vs. dogs
    - (1) Cat: ~73 days RBC; Dog: ~104 days
      - (a) Hypoplasia will cause anemia sooner in cats but cats are better able to tolerate severe chronic anemia
- b) Clinical signs of anemia: typically chronic anemias cause minimal clinical signs because of mechanisms to alleviate hypoxia
  - i) Non hemodynamic mechanism
    - (1) Increased production of 2,3-DPG: decreases affinity of Hb for oxygen thereby facilitating O<sub>2</sub> release to tissue
      - (a) This is main mechanism in dogs, not cats
        - (i) Cat Hb normally has reduced affinity for O<sub>2</sub> which allows them to tolerate more severe anemia
  - ii) Hemodynamic mechanism
    - (1) Increased cardiac output, due to decreased after load, increased preload, increased contractility and increased heart rate
    - (2) With chronicity anemia can cause "high output heart failure", which usually manifests as signs of RHF
      - (a) Not to be confused with typical "low output heart failure" of CHF
    - (3) Anemia cardiomyopathy usually does not cause arrhythmias
    - (4) Dogs with Hct <22-25% and cats with Hct <18-20% often develop a murmur because of lower blood viscosity
    - (5) Usually cardiomegaly and heart failure are reversible with treatment
  - iii) Odd tidbits:
    - (1) Cats are usually normotensive or hypotensive; may develop retinal bleeding
    - (2) Both cats and dogs may develop pica
- c) Symptomatic treatment
  - i) Often a transfusion is necessary before a definitive diagnosis/cause is achieved
  - ii) An anemic animal is at risk for volume overload; give fluids and transfusions slowly
    - (1) pRBC are usually preferred over FWB in chronic anemias
  - iii) Oxyglobin
    - (1) Hemoglobin-based oxygen carrier (HBOC), does not contain RBCs
    - (2) Monitor effectiveness by measuring Hb (other parameters do not change)

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- (3) Use care in patients with heart disease or known, or at high risk, circulatory overload disease states
  - (a) Especially use care in cats because of its colloidal volume expanding and nitric oxide scavenging effects, short duration of action – has been known to cause fatal pulmonary edema
- (4) Still not available to my knowledge (at least in US)
- iv) Erythropoiesis-stimulating agent (ESA) therapy {human terminology}
  - (1) Agents only labeled for CKD and some (limited) types of cancer in human therapy; not labeled for any veterinary use
    - (a) Recently released company statement outlining updated therapy guidelines and indications
    - (b) Still very risky to use – could make condition worse
  - (2) rhEPO (Procrit®, Janssen© LLC or Epogen®, Amgen© Inc.) – many other brand names and manufacturers around the world
    - (a) human recombinant form
  - (3) Darbopoyetin (Aranesp®, Amgen© Inc.)
    - (a) Synthetic form of erythropoietin
  - (4) Always give Fe (usually injectable) with erythropoietin compound – needs iron as substrate
  - (5) Use of an ESA is very strictly indicated when EPO level is known to be low – this requires measuring and monitoring
    - (a) This is difficult in the clinical veterinary setting; often forms of EPO are used without a firm indication in inappropriate circumstances
    - (b) In most forms of non regenerative anemia (that are not related to CKD) the EPO level will already be high so exogenous therapy is of no benefit
  - (6) In human medicine a definitive diagnosis/cause is identified; in veterinary medicine – despite dedicated owners and testing – a cause is not always identified, therefore some drugs are used empirically in the hopes that they will help
- v) Indications for transfusions, or “transfusion triggers”
  - (1) Review hemodynamic/cardiovascular status of patient: TYPE of blood loss (is it known?), specific clinical signs, perfusion status, ability of the lungs to oxygenate, chronicity of anemia, regenerative capacity of bone marrow
  - (2) Measure PCV, Hb, Hct; evaluate cardiac output status via blood pressure, peripheral perfusion, heart rate, respiratory rate, urine production, body temperature; measure oxygenation (SpO2 or arterial blood gas analysis); obtain pretransfusion testing including blood type and cross match compatibility
  - (3) Try to use component therapy when possible/advantageous as this maximizes the blood product
- d) Differential diagnoses: the 10 “D’s”
  - i) Detection
    - (1) Subtle or elapsed regeneration: can take a while for stimulus to regenerate
      - (a) Evaluate for increases in MCV and RDW
      - (b) In cats, an increase in punctuate reticulocytes will help identify a previous or ongoing regenerative response
      - (c) “Inappropriate regeneration”: where many anemias are hypo regenerative or inappropriately low for the degree of anemia
  - ii) Delay
    - (1) Often other major clinical signs will help determine acute pre regenerative anemia from chronic non regenerative anemia
  - iii) Destruction
    - (1) Cytotoxic drugs kill mitotically active cells and thereby cause transient injury to progenitor cells
      - (a) Acute bone marrow (BM) injury causes: neutropenia (most severe) > thrombocytopenia (more severe than anemia) > anemia

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- (i) Dogs: neutrophil lifespan = several hours to days, platelet lifespan = 5.5-6.5 days
- (b) Anemia from cytotoxic drugs in dogs is mild to moderate; more severe in cats
- (c) Estrogen toxicosis is possible but no longer common; consider Sertoli cell tumors and possibly Leydig cell tumors in male dogs (neutered or not)
  - (i) (Cats more sensitive to estrogen toxicosis than dogs but die from liver failure, not BM disease)
- (2) Bone marrow necrosis: vascular occlusion of small blood vessels and may lead to myelofibrosis
  - (a) Various causes: infectious, immunologic, neoplastic, drug
- iv) Deficiency – specifically iron
  - (1) Any cause of iron deficiency limits RBC regeneration; in the mature cat or dog it is due to chronic blood loss
    - (a) The anemia is initially regenerative but then the response becomes inappropriately low
  - (2) RBC indices: microcytic (low MCV) and hypo chromic (low MCHC) anemia
    - (a) In cats RBC indices changes are more difficult to detect: microcytosis is difficult to identify and hypo chromasia does not usually occur
    - (b)

Protein	Fe deficiency	AID	IMHA (immune mediated)	
Serum iron	Low to low-normal	Low to low-normal	Normal to increased	
Transferrin (TIBC)	High-normal to high	Low-normal to decreased	Normal to increased	Fe transport protein
Ferritin **	Low-normal to low	High-normal to increased		Intracellular Fe storage protein

- (c) In the future: reticulocyte Hb, MCV and other reticulocyte indices measurements will likely become more useful and available to assess iron deficiency
- (d) Bone marrow biopsy should reveal erythroid hyperplasia with expansion of late series (rubricytes, metarubricytes), often megakaryocytosis and the absence of storage iron in dogs; cats do not store iron in the bone marrow (usually easy to identify iron in BM samples of dogs with special stains)
- (3) Other causes of microcytic hypo chromic anemia include: anemia of inflammatory disease (AID), chronic liver diseases, lead poisoning and copper deficiency
  - (a) Portosystemic vascular anomaly (PSVA): cause defects in iron metabolism
- (4) Folate and cobalamin deficiency
  - (a) Necessary for normal RBC development; deficiency interferes with DNA synthesis causing delayed cell division and maturation (nuclear maturation defect)
    - (i) Results in dysplastic changes to RBCs rendering them very fragile, causing anemia and destruction within the bone marrow
  - (b) Dietary deficiencies in dogs and cats could theoretically occur but is not commonly reported; supplementation could help improve anemia in suspected cases (usually GI or pancreatic disease)
  - (c) Certain drugs can impair folate metabolism: azathioprine, methotrexate
- v) Deep development dam
  - (1) IMHA could occur “deep” in the bone marrow, attacking reticulocytes at various stages causing an apparent lack of regeneration
    - (a) Erythroid dysplasia may be prominent on bone marrow biopsy depending on the stages involved
    - (b) In dogs regenerative IMHA is more common; in cats NON regenerative IMHA is more common
  - (2) In most cases the anemia (of IMHA) is normocytic normochromic with normal to elevated serum iron and transferrin levels

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- (a) \*\* A lack of response to immunosuppression does not rule it out, as not all immune mediated diseases respond to therapy
  - (b) Other concurrent findings may be supportive (other immune mediated diseases, positive ANA and/or Coombs', spherocytes, thrombocytopenia, others)
  - (3) Cats with immune mediated dyserythropoiesis tend to occur in FeLV negative cases, causing non regenerative anemia (this is a more likely explanation than a false negative FeLV result)
    - (a) Aggressive immunosuppression is likely the key to treatment; > 70% of cats may respond
  - (4) Dogs with immune mediated dyserythropoiesis also may respond well (> 70% recover) although the prognosis tends to be better in dogs with sub acute to chronic disease; acute or per acute disease tends to increase risk of SIRS, PTE, DIC
- vi) Diversion
- (1) Hematopoiesis is diverted into production of malignant cells, with a resulting decrease in normal cell production \*\* marked non regenerative anemia is typical
    - (a) Acute myeloid leukemia (AML): neoplasia originating from any cell line in the bone marrow (RBC, platelet, granulocyte, monocyte or pluripotent stem cell)
      - (i) This is an evolving topic with many changes happening within specialty groups/discussions
      - (ii) Basically, it can be very difficult to tell between AML/acute erythroid leukemia and an immunohematologic disorder based on morphology alone – BM tissue culture, cytogenetic and molecular studies of clonality may become more available and useful
      - (iii) Be suspicious and talk to your lab/pathologist, another specialist to help differ and treat
    - (b) Myelodysplastic syndrome (MDS): typically involves peripheral blood cytopenias with normal to increased marrow cellularity with dysplastic changes
      - (i) Could progress to AML
      - (ii) Abnormal clone of hematopoietic progenitor cells that may suppress, displace and/or replace normal tissue
- vii) Displacement
- (1) RBCs may be “crowded out” by metastatic neoplasia, nonmyeloid hematopoietic neoplasia, granulomatous inflammation or myelofibrosis
    - (a) Acute lymphoid leukemia, multiple myeloma, mast cell neoplasia, histoplasmosis
    - (b) Neoplastic cells may also suppress erythropoiesis
    - (c) Neutropenia and thrombocytopenia may be more responsible for signs than anemia
    - (d) Bone marrow biopsy is diagnostic
  - (2) Myelofibrosis: *non specific finding*
    - (a) Causes include: idiopathic, FeLV infection, chronic inflammation (including IMHA), primary or secondary to neoplasia
    - (b) Non regenerative anemia is prominent finding and cause for clinical signs; WBC and platelet counts often normal
- viii) Depression by disease
- (1) “Anemia of chronic disease” is too broad a term – there are too many differences in mechanisms (although some are common)
  - (2) Common diseases associated with anemia include: infectious disease, non septic inflammation, cancer, chronic liver and kidney disease, some endocrinopathies, congestive heart failure
    - (a) Hypothesized that reduced activity associated with chronic illness may result in fatty replacement of hematopoietic tissue
  - (3) **Anemia of inflammatory disease (AID):** \*\* most common cause of mild to moderate anemia
    - (a) Caused by complex cytokine derangements that decrease EPO production, EPO function, iron metabolism and RBC lifespan
      - (i) \*\* *Iron sequestration is key*, renders the micronutrient unavailable to infecting organisms for use (an adaptive mechanism) ; also present in acute inflammation

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- (b) Causes lower Hb which initially causes a mild to moderate anemia but could cause severe anemia in cats (because of shorter RBC lifespan)
- (c) Bone marrow biopsy usually reveals normal to mildly reduced erythropoiesis and normal to increased iron stores (in dogs)

Protein	Fe deficiency	AID	
Serum iron	Low to low-normal	Low to low-normal	
Transferrin (TIBC)	High-normal to high	Low-normal to decreased	Fe transport protein (total iron binding capacity)
Ferritin **	Low-normal to low	High-normal to increased	Intracellular Fe storage protein
Marrow iron	Low	Normal to increased	

- (d) Ferritin is low in Fe deficiency anemia because not enough iron is available for use and high in AID because of sequestration of iron stores; transferrin is high in Fe deficiency anemia because there is not enough iron to transport for use and low in AID because the iron cannot be transported well (which makes it unavailable for use)
- (4) **Cancer-associated anemia:**
  - (a) Similar mechanisms to AID, assumed related to cancer after other causes ruled out
  - (b) Fe sequestration has been documented in dogs with LSA and OSA: this may be a protective mechanism as neoplastic cells have a higher iron requirement
    - (i) Although it is also known/accepted that mild to moderate anemia at diagnosis is a negative prognostic indicator, treatment with Fe and EPO may be detrimental
- (5) FIV
  - (a) \*\* Virus is not cytopathic, does not infect erythroid cells and does not suppress erythropoiesis
  - (b) Anemia can still be present due to concurrent hemotropic infection and cancer but could occur independently (affects about 1/3 of cats infected with FIV)
  - (c) Causes of FIV-associated anemia include infection of megakaryocytes, bone marrow stromal cells and T cells (could alter BM microenvironment and depress erythropoiesis)
    - (i) Contributes to AID
- (6) Chronic liver and kidney disease
  - (a) Anemia is common, multifactorial (AID, poor nutrition, shorted RBC lifespan, EPO deficiency, hemorrhage)
    - (i) Poikilocytosis is common (e.g. target cells in dogs), probably due to abnormal lipids in membrane
- (7) Endocrinopathies
  - (a) Hypothyroidism: anemia is a consequence, not a cause, of lethargy. It is considered an adaptation to decreased O<sub>2</sub> demand secondary to decreased basal metabolism.
    - (i) Thyroid hormone necessary for RBC synthesis
  - (b) Hypoadrenocorticism: anemia can occur in both typical and atypical Addison's. It is thought to occur because glucocorticoids enhance erythropoiesis.
    - (i) Anemia may be masked initially; anemia could also occur due to GI bleeding
- ix) Dilution
  - (1) Fluid therapy (pseudo anemia)
  - (2) Pregnancy: plasma volume expansion, minor erythropoiesis
- x) Drugs
  - (1) Idiopathic, immune-mediated or toxic to bone marrow
  - (2) Non cytotoxic drugs implicated in disease include: estrogens, phenylbutazone, meclufenamic acid, carprofen, captopril, quinidine, thiacetarsemide, albendazole, metronidazole and Phenobarbital
    - (a) Cats: griseofulvin and anti thyroid medications = higher risk

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- e) Pathology report language/terminology
  - i) Erythroid hyperplasia: presence or expansion of late erythroid series (rubricytes, metarubricytes), the maturation sequence should be orderly with a relative increase in early erythrocyte precursors
  - ii) Erythroid hypoplasia: immunologic attack occurs at the level of the earliest committed erythroid progenitor cells as evidenced by a lack of all stages of erythropoiesis; can also be seen with chronic inflammatory conditions that increase the M:E ratio (due to increased granulocyte production) and cause AID
    - (1) BM evaluation will also reveal increased iron stores (dogs) due to sequestration = hemosiderin
  - iii) Ineffective erythropoiesis: erythroid production tapers at the later stages of RBC development
  - iv) Maturation arrest: an attack on erythroid cells (the “second level” of attack in many immune mediated causes of anemia, e.g. not an attack on rubricytes)
  - v) Myeloid: erythroid ratio (M:E ratio)
    - (1) “A numerical estimate of the relative numbers of myeloid (granulocyte and monocyte) precursors and erythroid (RBC) precursors. Certain diseases may be associated with specific changes in the M: E ratio.”
    - (2) Normal: approximately 3:1, a higher ratio could indicate a relative increase in myeloid cells or decrease in erythroid cells; a lower ratio could indicate a relative decrease in myeloid cells or increase in erythroid cells
    - (3) Depends on species and case – call your pathologist!
  - vi) Trilineage hypoplasia or aplasia: immunologic attack at the level of pluripotent stem cells, revealing peripheral pancytopenia
    - (1) By convention aplastic anemia = trilineage bone marrow aplasia and pure red cell aplasia = only erythroid production is affected
  - vii) May comment on morphology, signs of infectious disease and iron stores (in dogs)
  - viii) \*\* Very important to discuss report and language with the pathologist in most cases to be sure to understand the findings and clinical implications (e.g. important to rule out erythroid or myeloid leukemia vs. exuberant non neoplastic BM response)
  - ix) *This is NOT an exhaustive list of common pathological terms and findings – call your pathologist!!*
- f) FeLV-associated anemias in cats
  - i) \*\* FeLV is not cytopathic – but infection of erythroid cells may alter or arrest their development, or lead to infectious causes of anemia (hemotropic mycoplasma infections), neoplasia, bone marrow changes and possibly IMHA
    - (1) Contributes to AID
  - ii) FeLV positive status is a proven cause of AML and MDS
  - iii) FeLV appears to cause a nuclear maturation defect by directly interfering with DNA synthesis

## 2) Case examples with discussion

- a) Cat #1: 9yr MN American Shorthair
  - i) CC: mild anemia, poor appetite, weight loss
  - ii) RDVM work up included: CBC, chemistry, urinalysis, three view thoracic radiographs, abdominal ultrasound, spleen aspirates, serum TLI/PLI/cobalamin/folate, buffy coat evaluation for systemic mast cell disease (history)
  - iii) RDVM work up revealed: moderate diffuse splenomegaly, spleen cytology suggestive of passive congestion and then mild reactive lymphoid hyperplasia (2 occasions), Hct 22%, and mildly low folate.
  - iv) AETC work up: bone marrow aspirate and biopsy
    - (1) Most suggestive of ineffective erythropoiesis; most consistent with anemia of chronic disease or AID
      - (a) Marked poikilocytosis and dacrocytosis were evident, suggesting hereditary defect resulting in cobalamin deficiency

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- (2) Absolute reticulocyte count: 10,860 cells/ul
- v) This cat ultimately went to exploratory laparotomy to try to identify underlying disease: multiple GI and spleen samples collected, placement of g-tube
- (a) (there were complications with the g-tube, which was then removed and an e-tube was placed)
- (2) Biopsies revealed: mild IBD and hepatitis, normal spleen
- vi) IRON PANEL \*\* was interpreted as most consistent with Fe deficiency even though ferritin and TIBC don't exactly fit
- |            |     |                 |        |
|------------|-----|-----------------|--------|
| SERUM IRON | 15  | 33 - 134 ug/dL  | LOW    |
| FERRITIN   | 760 | 31 - 144 ng/mL  | HIGH   |
| TIBC       | 237 | 169 - 325 ug/dL | NORMAL |
- vii) With this evidence one pathologist thinks that (this cat's) chronic non reg anemia is a congenital genetic malformation or metabolic error in RBC membrane metabolism
- viii) First hematology specialist consultation: seemed to be on good path, using appropriate drugs/therapy and monitoring, he was more suspicious of unidentified GI disease causing ACD (not bone marrow failure)
- i) Second hematology specialist consultation: probably not genetic, or iron deficiency; he was more concerned about underlying immune-mediated disease (despite treatment with steroid) and/or unidentified GI or splenic disease. Recommended Coombs testing and/or osmotic fragility testing (very specialized test that assesses red blood cell membrane function or "toughness")
- ii) Coombs' negative, FeLV negative, mycoplasma negative, slide agglutination negative
- COMMENTS / INTERPRETATION:
- (1) *Compared to control (this cat) has a normal osmotic fragility curve. There was no baseline hemolysis and thus the blood remained stable throughout shipping and storage. This excludes increased osmotic fragility as a cause of the anemia.*
- iii) Second bone marrow sample revealed: erythroid hyperplasia with mild left shifting of red cell line suggested – typical response (not supportive of ineffective erythropoiesis)
- iv) Conclusion: Second hematology consultant agreed: running out of alternative diagnoses and treatment, other than periodic blood transfusions.
- v) Tentative diagnosis: most likely "ineffective erythropoiesis", benign dyserythropoiesis or possibly myelodysplasia of erythrocyte line – *ultimately there was not a clear answer*
- vi) A second pathologist reviewed all clinical pathology data: basically agreed with our assessment of ruling out main causes (IMHA, cancer, MDS, Fe deficiency, myelofibrosis, heritable genetic abnormalities (causing abnormal morphology), increased osmotic fragility and infectious disease)
- vii) Treatment:
- 1) Prednisolone daily
  - 2) Metronidazole twice daily
  - 3) Iron dextran IM every 2 weeks
  - 4) Cobalamin (vitamin B12) SQ every 2 weeks
  - 5) Darbopoeitin SQ once weekly
- viii) Outcome: euthanized 5 months after diagnosis, did have a period of "better" quality of life with e-tube removed
- b) Cat #2: 1 ½ yr old MN Bengal
- i) CC: lethargy and anorexia
- ii) RDVM work up included: CBC, chemistry, FeLV/FIV testing (historical note: presented 1 year earlier for GI signs and possible toxin exposure, Hct 54%, recovered uneventfully)
- iii) RDVM work up revealed: CBC revealed: Hct 9-14%
- Initial working problem list:
- FeLV +**

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- Non regenerative anemia
- Probable neutropenia and thrombocytopenia
- Weight loss
- Reduced appetite
- Heart murmur – uncharacterized
- iv) RDVM performed bone marrow aspirate:
  - (1) Suspect marrow hypoplasia associated with FeLV infection (vs. hemodilution); FeLV PCR not performed on sample (to my knowledge)
    - (a) Few hematopoietic precursors are present, mostly erythroid precursors. These appear morphologically normal.
  - v) Then cat developed heart failure; this was not formally evaluated (to my knowledge) but suspected mechanisms could include myocardial failure from chronic hypoxia and/or FeLV myocarditis, other
  - vi) Treatment:
    - (1) Fe dextran injections weekly
    - (2) Erythropoietin injections SQ weekly
  - vii) Outcome: probable euthanasia (owner was considering)
- c) Cat #3: 5 yr MN Black DSH
  - i) CC: pancytopenia, hematochezia, large bowel diarrhea and oral bleeding
    - (1) Previously diagnosed with ulcerative colitis via endoscopic biopsy, current multi drug therapy
  - ii) RDVM work up included current CBC, physical exam, referral
    - (1) Hct 17%, TS 7.6 g/dL, slide agglutination positive
  - iii) AETC work up revealed: Hct 13%, WBC 54 K/ul, plts 431 K/ul (previously 43K/ul)
  - iv) Additional work up revealed: retroviral (current) status negative, Parvovirus negative, heartworm negative (unknown whether antibody or antigen testing or both), continued pancytopenia (CBCs varied with respect to automated platelet count on in-house labs); relatively normal abdominal radiographs and ultrasound
    - (1) During hospitalization patient developed severe ecchymoses along ventrum/inguinal region and continued to have profusely bloody diarrhea
    - (2) Send out CBC supported severe pancytopenia with zero evidence of regeneration
    - (3) Bone marrow sample collected 13 days after initial presentation:
      - (a) CYTOLOGICAL INTERPRETATION Marked hypo plastic marrow with suggested dysmyelopoiesis. Mildly increased plasma cells.
      - (b) COMMENTS The dysmyelopoiesis here appears to potentially affect all marrow cells with the remaining cells being myeloid series and the erythroid and megakaryocytic (series) are mostly absent. Potential causes include viral, toxic, neoplastic (no obvious evidence found), or idiopathic. The increased plasma cells suggest an immune stimulatory process here.
      - (c) (biopsy) MICROSCOPIC INTERPRETATION Erythroid and myeloid hypoplasia with apparent left shifting.
      - (d) COMMENTS Overall, changes are consistent with a severely hypo plastic bone marrow, and are suggestive of dyserythropoiesis/dysmyelopoiesis. These findings are consistent with those described in the bone marrow aspirate. Evidence of neoplasia, fibrosis, or necrosis was not noted.
  - v) Outcome: He was euthanized about 3 weeks after initial presentation due to progressive decline (despite initial response to supportive care) and continued need for transfusion therapy
    - (1) Suspect toxic BM insult – drug related
- d) Cat #4: 16 yr FS Ragdoll \*\* regenerative anemia but used as example of challenges in diagnosis

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- i) CC: lethargy (pallor noted on examination)
- ii) RDVM work up: CBC, chemistry, urinalysis, radiographs, blood type
- iii) RDVM work up revealed: PCV 12%, TS 5.3 g/dL, probable UTI, normal radiographs, FIV/FelV negative
- iv) AETC work up: abdominal ultrasound, send out CBC
- v) AETC work up revealed: proximal GI/duodenal abnormality, strong regeneration on CBC
  - (1) Reticulocyte counts: initial > 90,000/ul, 4 days later > 200,000/ul
  - (2) Suspect GI bleeding secondary to proximal duodenal abnormality but required further investigation and ongoing therapy (multiple transfusions)
  - (3) Cat presented again for 3<sup>rd</sup> transfusion: CBC suggested minimal regeneration
    - (a) Could represent bone marrow exhaustion or lab error
  - (4) GI endoscopy performed concurrent with BM sampling
    - (a) MICROSCOPIC INTERPRETATION (GI lesion): Adenomatous polyp, duodenal mucosal origin, benign, with attendant lymphoplasmacytic and eosinophilic inflammation.
    - (b) MICROSCOPIC DESCRIPTION (bone marrow aspirate) - Cellular slides: The M: E ratio is approximately 0.36: 1.00. The granulocytic series is complete to the mature segmented neutrophil. Eosinophils are 1 to 2% of the cellularity. The red cell series is complete to increased numbers of polychromatophils. No hemoparasites identified. Lymphocytes are roughly 3% of the cellularity and plasma cells are less than 1% of the cells seen. Megakaryocytes are adequate in numbers. There also are numerous red blood cells and small numbers of broken cells.
    - (c) CYTOLOGICAL INTERPRETATION Marked erythroid hyperplasia
- vi) Treatment: GI protectants, continued therapy for mild renal disease, hypothyroidism
  - (1) Recommended surgical excision of polypoid lesion as could represent carcinoma in situ
- vii) Outcome: waiting to consult another specialist, cat well clinically
- e) Dog #1: 8 yr FS, black and white mixed breed dog, medium size
  - i) CC: presented for lethargy, pale gums, reduced appetite
  - ii) RDVM work up included: PCV/TS
  - iii) RDVM work up revealed: PCV 21%, TS 8.0 g/dL, referred for further care
  - iv) AETC work up included: CBC, abdominal and thoracic radiographs, abdominal ultrasound
  - v) AETC work up revealed: largely unremarkable findings, stable cardiovascular system, moderate anemia with mild morphology changes (spherocytosis) and no evidence of agglutination
    - (1) Treatment plan included supportive care with oral medications, presumed IMHA
    - (2) Transfusion not indicated
  - vi) Follow up revealed worsening anemia with minimal regeneration
    - (1) Hct 14-15%, moderate mature neutrophilia with mild left shift, reticulocyte counts 22,000-27,000 cells/ul
  - vii) Bone marrow evaluation revealed:
    - (1) Hemodilution of aspirate sample, non diagnostic
    - (2) Core biopsy:
      - (a) MICROSCOPIC INTERPRETATION Bone marrow core: Moderate myelofibrosis, and multifocal bone marrow hyperplasia, and increased M:E ratio (myeloid hyperplasia, 4:1)
      - (b) COMMENTS Histologic evaluation of the excellent core biopsies submitted reveals prominent replacement of areas of bone marrow by myelofibrosis. In those areas where bone marrow is

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still evident there is evidence of hyperplasia of the bone marrow, with an increase in the M: E ratio, primarily due to myeloid hyperplasia. Microorganisms and inflammation are not identified. There is no evidence of a neoplastic process. The myelofibrosis present in these sections is likely to be secondary, and can be associated with neoplastic conditions, irradiation, and in many cases unknown etiologies. Although there is no obvious evidence of bone marrow necrosis in this section, it is often shown that myelofibrosis occurs concurrently with bone marrow necrosis. Bone marrow necrosis can be seen in patients with Ehrlichiosis and septicemia, and also associated with various drug treatments including estrogens and cephalosporins. The etiology for the myelofibrosis in this sample is unclear.

- (i) Contacted the pathologist on this case and she was very helpful in further interpretation, basically her written report *underestimated* her concern with these findings – very grave prognosis in this case
- viii) Treatment continued to consist of supportive care
  - (1) First and only transfusion about 3 weeks post diagnosis
- ix) Overall the prognosis for myelofibrosis is variable but often not very successful, continued management involves immunosuppression and transfusions as indicated
  - (1) Some folks feel that myelofibrosis is most often associated with immune-mediated non regenerative anemia and that there can be significant erythroid hyperplasia but it is ineffective
  - (2) Can sometimes resolve with long term immunosuppression
- x) Outcome: presented again for pale gums, lethargy
  - (1) Hct 10%, retics 11,000 cell/ul
  - (2) Elected euthanasia about 4 weeks post diagnosis

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