Fe - Feline Medicine
THE DIFFERENTIAL DIAGNOSIS OF FELINE ANAEMIA

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CLASSIFICATION OF FELINE ANAEMIA

Anaemias can be broadly divided into regenerative (blood loss or haemolytic) and non-regenerative types. In cats the majority of anaemias are non-regenerative in contrast to the dog. However multiple causes of anaemia can be present concurrently. This can lead to difficulties in classification of the anaemia resulting in a diagnostic challenge.

DIFFERENTIATING REGENERATIVE AND NON-REGENERATIVE ANAEMIAS

Haematology

The mean cell volume (MCV) indicates the average size of red blood cells (RBCs). Regenerative anaemias are usually macrocytic because reticulocytes have high MCVs. However, macrocytosis is not just a feature of regenerative anaemias since non-regenerative anaemias associated with FeLV infection or myelodysplasia can be associated with macrocytosis (Shimoda, et al 2000, Weiss 2006b).

The red cell distribution width (RDW) is an estimate of the degree of anisocytosis in a blood sample and is available on some haematology analysers. A high RDW can indicate the presence of increased number of macrocytes, microcytes or both.

The mean cell haemoglobin concentration (MCHC) indicates the average concentration of haemoglobin per RBC. A reduced MCHC is termed hypochromic. Regenerative anaemias are usually hypochromic because reticulocytes have higher MCVs and lower haemoglobin content than mature RBCs.

Nucleated RBCs (NRBCs) can indicate active regeneration but are also seen with splenic dysfunction, shock, heavy metal toxicity and bone marrow disorders.

The presence of polychromasia, anisocytosis and NRBCs on blood smears may indicate regeneration.

Reticulocyte Count

This quantifies the RBC regenerative response. A vital stain such as new methylene blue (NMB) allows the identification of reticulocytes. Reticulocytes correspond to polychromatic cells on a Romanowsky-stained blood smear. Cats have two types of reticulocytes; punctate and aggregate. Feline aggregate reticulocytes are identical in appearance to canine reticulocytes, with multiple basophilic granules, and these only last in the circulation for about a day before maturing further. Punctate reticulocytes have only a few basophilic granules and are more mature reticulocytes that survive in the circulation for up to 10 days. Since only aggregate reticulocytes accurately reflect recent bone marrow RBC production, these should be counted when evaluating moderate to marked anaemia. With mild anaemias, punctate reticulocyte counts may be of benefit. Calculation of the absolute reticulocyte count allows assessment of the degree of regeneration for the anaemia present.

Absolute reticulocyte count (x 10^9/l) = % reticulocytes x RBC count (x 10^{12}/l) x 10

Regenerative response	Absolute reticulocyte count (x10^9/l)
Negligible	< 50
Mild	50-100
Moderate	100-200
Substantial	>200

REGENERATIVE ANAEMIAS: HAEMORRHAGE

Causes of Haemorrhage in Cats

Haemorrhage is the most common indication for feline blood transfusions (Weingart, et al 2004). Acute haemorrhage is relatively common in cats, particularly after trauma (including surgery). Haemostatic disorders can arise with conditions such as liver disease or inherited coagulopathies. Systemic amyloidosis can cause spontaneous hepatic rupture and abdominal haemorrhage in Siamese and related cats. Chronic haemorrhage is uncommon in cats but can occur due to severe ectoparasitism in kittens or urogenital tract/gastrointestinal bleeding. Gastroduodenal ulceration/bleeding can arise due to neoplasia, NSAID toxicity and inflammatory bowel disease, but cats tend to present in a critical condition due to shock and severe anaemia. Chronic external haemorrhage may eventually lead to iron deficiency.

Diagnostic Features of Haemorrhage

Reticulocytes appear in the circulation after 3-5 days and peak at 5-7 days, although PCV may take up to 2-3 weeks to return to normal. Regeneration is evidenced by anisocytosis, polychromasia and sometimes NRBCs on blood smear examination. Hypoproteinaemia may be present in the first week after bleeding. Persistent anaemia and hypoproteinemia suggest ongoing blood loss. Iron deficiency anaemia is a non- or poorly regenerative microcytic hypochromic anaemia.

REGENERATIVE ANAEMIAS: HAEMOLYSIS

Haemolysis arises due to extravascular or intravascular RBC destruction. Extravascular haemolysis usually occurs by macrophage phagocytosis in the spleen, liver and bone marrow. Intravascular haemolysis is less common and occurs within the vascular system. Haemolysis may be mediated by antibodies bound to the surface of RBCs in immune-mediated haemolysis (IMHA).

Causes of Haemolysis in Cats

- Infections – FeLV, haemoplasmosis, Babesia, Cytauxzoonosis,
- Oxidant injury such as exposure to chemicals or toxins (onions) and some disease states (diabetic ketoacidosis, hyperthyroidism and lymphoma) – oxidant injury can result in a Heinz body haemolytic anaemia. Feline haemoglobin is particularly sensitive to oxidation. Anaemia is more likely to result if the Heinz bodies are large and affect >30% RBCs.
- Secondary IMHA – can arise secondary to infectious agents such as FeLV, haemoplasmas and feline infectious peritonitis (FIP), drugs (such as methimazole, trimethoprim-sulphonamides), neoplasia (such as lymphoma)
- Primary IMHA – in some cases no underlying causes of IMHA can be identified and such cases are referred to as primary IMHA. This is a common form of IMHA in the dog, and was thought to be rare in the cat, but recent reports (Husbands, et al 2002, Kohn, et al 2006) suggest it is more common than previously believed
- Haemolytic blood transfusion reactions and neonatal isoerythrolysis are mediated by haemolysis of RBCs which arises due to incompatibility of donor and recipient, or queen and kitten, blood types respectively
- Hypophosphataemia (<0.35 mmol/l) – can result in haemolysis of RBCs, due to depletion of energy supply to the RBCs and has been associated with diabetes mellitus, hepatic lipidosis, refeeding syndrome and oral administration of phosphate-binding antacids
- Microangiopathic haemolytic anaemia – disseminated intravascular coagulation, trauma
- Inherited RBC defects – osmotic fragility of Abyssinians and Somalis, pyruvate kinase (PK) deficiency in Abyssinians, Somalis and DSHs

Diagnostic Features of Haemolysis

Haemolytic anaemias are usually strongly regenerative after 3-5 days with anisocytosis, polychromasia, reticulocytosis and sometimes NRBCs. In IMHA, if the immune response is directed at RBC precursors in the bone marrow, as well as peripheral RBCs, the anaemia may be non-regenerative. Unlike anaemia due to external blood loss, serum protein concentrations remain normal with haemolysis. Bilirubinaemia and bilirubinuria indicate acute, severe haemolysis (intra- or extravascular), while haemoglobinemia and haemoglobinuria specifically indicate intravascular haemolysis. The presence of large numbers of Heinz bodies (precipitated haemoglobin) suggests exposure to oxidant damage. Heinz bodies are colourless with Romanowsky stains but blue-green with NMB. In cats Heinz bodies tend to be single and uniform in size and can become very large. IMHA cases may show autoagglutination on a blood smear. Positive slide agglutination (following washing of RBCs) or Coombs' tests indicate the presence of RBC-bound antibodies in IMHA cases.

Feline Haemoplasmosis

See notes on feline haemoplasma infections.

PK Deficiency

PK is an enzyme critical to energy metabolism in RBCs. If deficient in PK, RBC haemolysis occurs. PK deficiency is an autosomal recessive inherited trait in Abyssinians and Somalis. A molecular screening test is available to identify affected and carrier cats.

NON-REGENERATIVE ANAEMIAS

Non-regenerative anaemias develop as the diseased bone marrow fails to replace ageing erythrocytes.

Diagnostic Features of Non-regenerative Anaemias

There is minimal anisocytosis and polychromasia with a low reticulocyte count. RBCs are usually normocytic and normochromic although FeLV infection and myelodysplasia can cause a macrocytosis. Iron deficiency anaemia will typically be microcytic and hypochromic with a mild degree of regeneration. Concurrent leukopenias and thrombocytopenias may occur.

Causes of Non-regenerative Anaemias

Systemic disorders tend to produce mild subclinical anaemia whereas primary marrow disorders tend to cause moderate to severe anaemia.

- *Primary Bone Marrow Disorders*
  - Pure red cell aplasia (PRCA)
  - Aplastic anaemia/pancytopenia
  - Myelodysplastic syndromes (MDS)
  - Myeloproliferative diseases
  - Myelophthisis – filling of the marrow space with neoplastic cells or fibrous tissue (myelofibrosis)
- *Systemic Causes of Bone Marrow Suppression*
  - Anaemia of inflammatory disease (AID)
  - Chronic renal failure (CRF)
  - Retrovirus-associated

PRCA

Selective erythroid bone marrow depletion causes anaemia. It can arise secondary to FeLV subtype C infection which is invariably fatal, or can be immune-mediated, as reported in young FeLV negative cats (Stokol and Blue 1999) in which some cats were Coombs' test positive and immunosuppressive treatment was often effective.

Aplastic Anaemia/Pancytopenia

All cell lines in the bone marrow are affected. FeLV, FIV, parvovirus, toxoplasmosis, ehrlichiosis and FIP are potential causes. Agents such as griseofulvin (particularly in FIV positive cats), chloramphenicol and some chemotherapy agents can also induce pancytopenia. Some cases are idiopathic. More recently a report found aplastic anaemia arose in association with CRF in cats and it has been suggested that starvation may contribute to the development of marrow aplasia (Weiss 2006a).

MDS

Maturation defects of one or more of the haematopoietic cell lines are known as MDSs. These are usually characterized by hypercellular marrow with concurrent cytopenias in the peripheral blood. Dyshaematopoiesis is evident and a macrocytosis may be present. Myelodysplasia is often associated with FeLV (Shimoda, et al 2000) although a recent report found only 36% of cats with MDS were FeLV positive (Weiss 2006b). Secondary dysmyelopoiesis can arise due to IMHA in which the immune system targets the bone marrow resulting in a non-regenerative anaemia, and differentiation of secondary dysmyelopoiesis from primary MDS can be difficult as both can show autoagglutination. MDS cases tend to have higher numbers of blast cells in the bone marrow. Some MDS cases respond to differentiating agents (such as cytosine arabinoside), anabolic steroids or haematopoietic growth factors. Some go on to develop leukaemia.

Myeloproliferative Disorders

Neoplastic proliferation e.g. in a leukaemia, can result in inhibition of haematopoiesis.

AID

AID is a very common cause of anaemia in the cat, occurring in association with many diseases including infections and neoplasia. The anaemia is mild to moderate (PCV >17%), normocytic and normochromic. Clinical signs are rare. AID can develop quite rapidly in the cat (within 3-4 days) suggesting that a shortened RBC lifespan, as well as reduced RBC production, contributes to the development of anaemia. Iron sequestration by the macrophage system, erythrocyte sequestration and impaired bone marrow response to EPO are all thought to contribute to the development of AID.

CRF

Up to 40% of cats CRF are anaemic due to decreased renal EPO production, bone marrow inhibition by uraemic toxins, decreased RBC survival, blood loss due to gastrointestinal ulceration or thrombocytopathia, and impaired iron utilization (a component of AID). Aplastic anaemia has recently been reported in association with CRF (Weiss 2006a).

Retrovirus Infection

Several mechanisms (e.g. PRCA, IMHA, AID) can contribute to retrovirus anaemia but most cases show evidence of non-regenerative anaemia. FeLV and FIV testing can be done on blood and bone marrow samples.

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