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ANEMIA IN CATS: IS IT MYCOPLASMA?
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Anemia is one of the most frequent hematological abnormalities found in cats. Both regenerative and non-regenerative anemia is commonly observed, associated to a myriad of infectious and non-infectious diseases. Non-regenerative anemia is associated to chronic inflammatory processes, neoplasias, endocrinopathies such as diabetes mellitus, renal diseases, and bone marrow diseases. It also occurs as a consequence of feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV) infection. Regenerative anemia usually develops after blood loss or hemolysis. The latter is frequently associated with oxidative damage of red blood cells (RBC), neoplasias and primary or secondary immune-mediated syndromes. Many infectious agents as Babesia felis, Cytauxzoon felis and hemoplasmas target RBC and infect them, leading to premature destruction of infected cells, either intravascular or extravascularly.

A careful examination of blood smear is the cornerstone for a successful diagnostic approach of anemia. Beside polychromatophilic RBC, finding hemoplasmas infected RBC is highly suggestive of infectious cause of anemia. Nevertheless, failure to find RBC parasites on blood smears does not exclude infectious origin of anemia.

### Hemotrophic mycoplasmas as cause of anemia

Hemotrophic mycoplasmas are pleomorphic bacteria that parasite red blood cells in a wide range of vertebrate animals. The bacteria may be rod, spherical or ring shaped and are found either singularly or in chains across the cell surface. The occurrence of an acute hemolytic syndrome in cats more likely of infectious origin has been known for a long time. Flint and Moss (1953) first described a parasite on RBC of anemic cats dubbing the disease feline infectious anemia (FIA) and the organism, *Haemobartonella felis*. Based on their small size, negative-Gram staining properties and apparent obligate parasitism of RBC, the newly described *Haemobartonella felis* was classified as a member of Family Anaplasmataceae, order Rickettsiales.

Ultra structural studies clearly showed that the parasites were on the surface of the red blood cells and did not appear to penetrate the cell. These organisms, usually less than 1 μm in size, were observed by electron microscopy in shallow depressions and deeper crevasses on the surface, with 15 to 25 nm clear zone separating the parasite from RBC. The parasite lacked cell wall, a characteristic that was largely responsible for negative Gram stain reaction and lack of susceptibility to many commonly prescribed antimicrobial agents, including penicillin. All attempts to cultivate the organism in vitro were unsuccessful and it still remains uncultured. Recently, sequence analysis of the 15SrRNA gene from *Haemobartonella* sp. showed that gene sequence of this organism was more related to the ones belonging to Class Mollicutes. *Haemobartonella felis* was transferred to genus Mycoplasma as *Mycoplasma haemofelis*.

Acute infection with *Mycoplasma haemofelis* is associated with a massive parasitemia of RBC causing a severe and sometimes fatal hemolytic anemia. The clinical signs of the disease include lethargy, anorexia, fever and anemia in naturally or experimentally infected animals. The pyrexia is intermittent and spikes when parasite number are highest in the peripheral blood. Splenomegaly and icterus are commonly seen in acute cases. The resulting anemia is typically regenerative as anisocytosis and polychromasia with an increase in the absolute number of reticulocytes are observed in the blood smears. However, the severity of anemia depends on the stage of infection and the hematocrit may fall to less than 20% at peak parasitemia. *Mycoplasma haemofelis* may rapidly and synchronously disappear from the RBC of the cat and cyclically reappear in vivo. This phenomenon may occur in less than one hour in both splenectomized and intact animals. It is possible that the organism changes or alters surface antigens allowing it to detach from the red blood cell. This temporary loss of adherence contributes to the survival of *Mycoplasma haemofelis* and is related to the development of a carrier state observed in many infected cats. This mechanism of evasion delays an immune response and
enables *M. haemofelis* to establish infection of new RBC or even another cell type. The return of adherence to the RBC may aid in the initiation of a new cycle infection, thereby facilitating the transmission of the *M. haemofelis* by a blood sucking vector.

PCR was used to correlate the presence of parasitemia with clinical disease in cats. Using *in situ* hybridization, the sequence used for PCR was also physically linked to the organism attached to the red blood cells. Thus, the molecular criteria for disease causation have been fulfilled, establishing that *Mycoplasma haemofelis* causes the disease known as feline infectious anemia. Chronic infection of cats is also described, with low or transient levels of parasites in peripheral blood. Such an infection is not easily detected by evaluation of blood smears. It might be revealed only by molecular tests.

**Other hemotropic mycoplasmas infection of cats**

For many years, feline infectious anemia was thought to be caused by a single infectious agent. However, recently two distinct genetic variant of *Haemobartonella felis* have been identified by molecular methods, a large one (Ohio variant) and the small one (California variant). The large form was consistently associated to hemolytic anemia whereas the small form produced only minimal-to-mild anemia in experimental infections. Based on the 16SrRNA gene sequencing, both forms were molecularly characterized as distinct parasites and named *Mycoplasma haemofelis* and *Candidatus* Mycoplasma haemominutum. Although *Candidatus* Mycoplasma haemominutum may be found in some anemic cats, the association between the organism and anemia is still controversy. Healthy cats experimentally infected with C. Mycoplasma haemominutum developed only minimal clinical signs of acute disease and negligible hematological changes. Despite the cat’s hematocrit declined throughout the course of infection, it never was below the reference range for the cat. Additional studies are needed to define the difference in the virulence between these two red blood cells parasites in the cat. The prevalence of both infections in cats throughout the world is variable on the dependence of the sample, geographic area and health status of the animals. Apparently, the prevalence of C. Mycoplasma haemominutum is higher, mainly in healthy animals, whereas infection of *Mycoplasma haemofelis* is more likely among anemic cats.

More recently, third specie of hemoplasma was described and named *Candidatus* Mycoplasma turicensis. Its pathogenicity is not clear, although intravascular hemolysis was associated to the organism in an experimental infection. The majority of prevalence study and risk factors analysis for this newly described hemoplasma showed that this organism alone has probably minimal clinical importance, is frequently found infecting healthy cats and the risk factors involved are co-infection with other hemoplasmas or retrovirus infections.

**Hemoplasmas and retrovirus. Is there a connexion?**

Several researches done in the last years showed that risk factors for hemoplasma infections are gender, older age and both FIV or/and FeLV infection. The prevalence of FeLV and FIV has been shown to be much higher in cats with clinical hemotropic mycoplasmosis than in the general population. Cats infected with FIV, FeLV or both, were at greater risk of being hemoplasma infected than retroviral negative cats. C. Mycoplasma haemominutum infection is more likely to occur in association to FIV infection. For many years it was known that cats infected with FeLV and *Mycoplasma haemofelis* develop more severe anemia than cats infected with *M. haemofelis* alone. Beside this, there are evidences that infection with *M. haemofelis* may induce myeloproliferative disease in FeLV infected cats. In the other hand, *Candidatus* Mycoplasma haemominutum, the small variant of *Haemobartonella felis* may lose its pathogenicity by passage through FeLV-free cats.

**Conclusions**

Although three variants of hemotropic mycoplasmas have been described, only *Mycoplasma haemofelis* has a clear potential for developing anemia in cats, either alone or associated to other hemoplasmas. Concurrent infections with retroviruses may predispose to more severe disease as well as enhance the potential for hemolytic anemia caused by infection of less pathogenic *Candidatus* M. haemominutum and *Candidatus* Mycoplasma turicensis.
References