Web Supplement: Fever of Unknown Origin in Cats*

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Identifying the cause of a fever of unknown origin (FUO) in cats is a considerable diagnostic challenge. As in dogs, the diagnostic workup can be frustrating, but most causes of FUO can eventually be determined. Below is some updated information on FUO in cats and up-and-coming techniques in veterinary medicine that may be valuable in diagnosing cats with FUO in the future.

Differential Diagnosis

The top diagnostic differentials in feline FUO are infectious disease, neoplasia, immune-mediated disease, and noninfectious inflammatory disease. The following examples are known to cause fever in cats:

Infectious diseases[1,2]
- Localized bacterial infections (e.g., pleuritis, osteomyelitis, periodontal abscess, metritis)
- Pyelonephritis (the kidneys are a common source of occult infection)
- Infections with organisms that are not typically sensitive to common antibiotics (e.g., *Mycobacterium* spp, *Mycoplasma* spp, L-form bacteria)

Viral infections[1,3]
- Feline infectious peritonitis (FIP)
- FIV
- FeLV
- Feline calicivirus

Systemic mycotic diseases[1]
- Histoplasmosis
- Blastomycosis
- Coccidiomycosis

Protozoal and rickettsial diseases[1]

Parasitic infections[1]
- *Haemobartonella felis*
- *Toxoplasma gondii*
- Aberrant parasite migration
- Pulmonary embolism by *Dirofilaria immitis*

Tumors[1]
- Lymphoma
- Myeloproliferative diseases
- Pulmonary adenocarcinoma

Noninfectious inflammatory diseases[1]
- Cholangiohepatitis
- Inflammatory bowel disease
- Pancreatitis
- Pansteatitis

Drugs
- Tetracycline
- Sulfonamides
- Penicillins
- Levamisole

Immune-mediated diseases rarely cause FUO in cats; however, these diseases are not well described in cats, and their true incidence is unknown.[1]

Repeated fundic examination should be performed in cats with FUO because numerous infectious diseases cause ocular changes in cats (e.g., FIP, FIV, FeLV, feline rhinotracheitis, feline bartonellosis, tularemia, toxoplasmosis, systemic mycoses).[4]

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Absence of ocular changes does not rule out infection with these diseases.[4]

Clinical Approach

FeLV and FIV Testing

FeLV antigen and FIV antibody tests should be conducted on every febrile cat. The FeLV ELISA and the FeLV immunochromatographic assay are rapid, reliable screening tests and can be conducted using serum or plasma from cats of any age.[5] A positive FeLV test result usually correlates with viremia, but technical and user errors can lead to false-positive results; therefore, cats should be retested immediately (with the same test) to confirm a positive result.[5] To distinguish between transient and persistent viremia, cats should be retested in about 10 weeks.[5] A second positive result usually indicates persistent viremia.[5] Direct fluorescent antibody testing can also be used on monolayer fresh blood or bone marrow smears for prognostic purposes or to confirm positive results.[5]

Cats with positive FIV ELISA antibody test results should be retested by Western blot to confirm the diagnosis.[6] Positive results of the FIV ELISA antibody test confirm infection in an unvaccinated cat older than 5 months (maternal antibodies can be present in kittens up to 16 weeks of age) but do not necessarily correlate to disease induced by the virus.[6] Diagnostic testing for other opportunistic infections is advisable with both positive FeLV and FIV test results.[6] Unfortunately, the Western blot test cannot discriminate between infection and vaccination. New PCR tests that may be helpful are becoming available.[6]

Cytology

Cats with cytauxzoonosis occasionally present with fever, anorexia, and lethargy before they become anemic and icteric, so blood smears are extremely important.[7] Anemic cats should be evaluated for mycoplasmosis using fresh, thin blood smears and a PCR assay.[8] However, 50% of negative blood smear results for mycoplasmosis are false negatives.[8] Cats with submandibular lymphadenopathy and fever or signs of pneumonia should undergo fine-needle aspiration of the affected lymph node, with samples evaluated for characteristic bipolar rods in areas endemic for *Yersinia pestis*.[8]

Serologic Testing

Serum samples should be submitted for testing for FIP virus only if this disease is suspected because the test cannot distinguish FIP virus from feline coronavirus (FCoV).[9] Lymphopenia, neutrophilia (with or without a left shift), polyclonal hypergammaglobulinemia, and an albumin:globulin ratio of <0.4 in effusion or serum can be suggestive of FIP infection.[9] Measuring α_1–acid glycoprotein (AGP; an acute-phase protein) in plasma or effusions can be helpful; this protein is moderately elevated in FIP patients (AGP >1500 µg/mL) but is a nonspecific marker for infectious disease.[9] AGP can help differentiate FIP from other noninflammatory diseases such as cardiomyopathy and neoplasia.[9]

Currently, there is no single diagnostic test for FIP, and histopathology and antigen detection in tissue or effusion samples is still the gold standard.[9] Positive antigen staining of FCoV-infected macrophages is diagnostic for FIP, but a negative result does not rule out FIP.[9] The mRNA reverse transcriptase polymerase chain reaction (RT-PCR) assay has been investigated for use in the diagnosis of FIP. In one study,[10] 93% (75 of 81) of cats diagnosed with FIP on histopathology had positive mRNA RT-PCR results, and 17 cats without FIP had negative results. However, another recent study[9] showed that mRNA RT-PCR may detect FCoV in blood samples from healthy cats as well as FIP virus in cats with clinical signs of FIP.[11] RT-PCR testing may be valuable in the future.

Samples may be submitted for blood culture, PCR assay, or serologic testing for cats with suspected bartonellosis (e.g., a febrile cat with uveitis, lethargy, lymphadenopathy, gingivitis, or neurologic disease).[8] If the results of these tests are positive, bartonellosis should remain on the list of differentials, but other causes should still be investigated.[8] A positive PCR assay result for *Bartonella*, hemoplasma, *Rickettsia, Ehrlichia*, or *Anaplasma* infection does not equate to a diagnosis of clinical illness from these agents.[8]

Arthrocentesis

Immune-mediated polyarthritis is classified into erosive (periosteal proliferative form

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and rheumatoid arthritis) and nonerosive (systemic lupus erythematosus and idiopathic polyarthritis) forms.[12,13] These conditions are not well documented or described in cats. A recent study[12] showed that 12 cats were diagnosed with rheumatoid arthritis over a 3-year period, which suggests that this disease may not be as rare as previously thought. Siamese cats were overrepresented in this study. Periosteal proliferative polyarthritides are apparently more common in cats, particularly young, male, neutered cats.[12] Rheumatoid factor testing is not definitive; cats with polyarthritis are not always rheumatoid factor positive, and other disease states may cause positive results.[12,13]

Advanced Imaging

Computed tomography (CT) and magnetic resonance imaging can be used to help delineate conditions found via the use of other techniques or when the diagnosis remains uncertain.[14] In humans with FUO, nuclear scintigraphy with gallium 67, technetium (Tc) 99m, or indium-labeled leukocytes is commonly used for detecting inflammatory conditions and neoplastic lesions that are frequently missed by CT.[14] Nuclear scintigraphy is being used more frequently in veterinary medicine, and there are reports of its use in dogs and cats for evaluation of thyroid diseases, mammary lymphoscintigraphy, gastric emptying, glomerular filtration rate, portosystemic shunts, reverse patent ductus arteriosus, and pancreatitis.[15–24] It may also be a valuable tool in investigating FUO through the use of radiolabeled leukocytes or antibiotics to detect sources of occult inflammation or infection (abscesses).[25]

One of the newest imaging modalities being used in investigating human FUO is called *image fusion* or *coregistration*. It combines positron emission tomography (PET; a type of nuclear imaging) and CT,[14] allowing one continuous body scan that simultaneously captures PET images of tiny changes in the body's metabolism caused by abnormal cells (infection or neoplasia) and CT images of abnormal tissue.[26] One nonspecific tracer of increased glucose metabolism that is commonly used with PET is called *18F-fluorodeoxyglucose* (*FDG*), which accumulates in neoplastic and activated inflammatory cells.[27] The increased glycolytic activity of these cells causes increased 18F-FDG uptake at the site of inflammation and infection.[28] Essentially, coregistration detects small lesions or tumors with PET and precisely locates them with CT.[26] The human medical literature states that PET has a high negative predictive value in ruling out inflammatory causes of fever.[14] Absence of areas of increased uptake with PET/CT may rule out infection.[28]

Three case reports on the use of PET/CT in dogs[29–31] and one report on the use of this technology in cats[32] demonstrate that this imaging modality could play an important role in diagnostic imaging in veterinary medicine. The report on the use of PET/CT in cats describes normal uptake of a radiotracer in the head.[32] One of the problems with interpreting some of the more advanced imaging techniques is obtaining proof that the documented abnormality is the cause of the fever.[33] PET/CT seems promising as a noninvasive diagnostic technique, but because of its limited availability in humans and, therefore, small animals, it is too early to tell.[14]

Brief Tips for Handling Fractious Febrile Cats

Mild sedation may be necessary for the handling of fractious cats to enable physical examination as well as perform minor diagnostic procedures. The choice of sedative agent will depend on the patient's clinical status as well as the procedure to be performed.[34] Butorphanol, a K–agonist and μ-antagonist (dosed at 0.2 mg/kg IV, IM, or SC), or buprenorphine, a partial μ-agonist (dosed at 0.01 mg/kg IV, IM, or SC), are good choices because they cause less respiratory depression and can be reversed with naloxone, if needed.[34] The dose of naloxone used to reverse the effects of butorphanol is 0.01 to 0.02 mg/kg IV, IM, or SC. To reverse the effects of buprenorphine, a dose 10 times greater may be required (i.e., 0.1 to 0.2 mg/kg).[34] If deemed necessary, a small amount of acepromazine can be added (0.005 to 0.02 mg/kg IV or 0.01 to 0.05 mg/kg IM) if the cat is normovolemic and has stable cardiovascular function.[34] C

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