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Toxoplasmosis of the Domestic Feline

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This article will review toxoplasmosis in the domestic feline from a practical, clinical standpoint. Aspects of transmission of infection, the life cycle of the organism, clinical signs and lesions will be discussed along with diagnosis, treatment and prevention of the disease.

Toxoplasma gondii is an obligate intracellular protozoan. Its name comes in part from the word "toxon", meaning bow or arc and describing the shape of the proliferative form of the organism. The name also comes, in part, from the North African rodent, the gondii, in which the organism was first discovered in 1908. The length of T. gondii is 47 microns with a width of two to four microns. When stained using Wrights stain, one-fourth of the total area of the organism is occupied by the nucleus which is reddish or purplish in color. The cytoplasm is bluish with small granules being present.

There are three known infective stages of Toxoplasma gondii in mammals and birds. These include bradyzoites from tissue cysts, sporozoites from cat feces, and tachyzoites. Infection occurs from ingestion of infected tissues, by consuming substances from the environment that have been contaminated by cat feces, and also by a transplacental route. Another possible route of transmission involves the mechanical transport of the organism by coprophagous invertebrates such as cockroaches and filth flies.

The route by which a given mammal or bird is infected varies with the species involved. The cat, for example, is primarily infected by consuming infected tissues. It has been demonstrated that cats can be more easily infected with mice, birds and meat than with oocysts. Also, the infective stage ingested determines to a great extent the likelihood of a given cat becoming infected. In one study, less than 50% of cats shed oocysts after ingesting tachyzoites or oocysts, whereas nearly all cats shed oocysts after ingesting cysts. Cats differ from other species in that they are not believed to transmit toxoplasmosis transplacentally.

The life cycle of Toxoplasma gondii is divided into two separate cycles. The enteroepithelial cycle occurs only in felines and involves the production of oocysts. The extraintestinal cycle occurs in other mammals and birds as well as felines.

The entero-epithelial cycle begins with a feline ingesting an infective stage of Toxoplasma. If infection occurs via a cyst, dissolution of the cyst wall by proteolytic enzymes in the stomach and small intestine must initially occur. This breakdown results in release of bradyzoites which penetrate the epithelial cells of the G.I. tract. These penetrating organisms initiate the formation of numerous asexual generations. This process of asexual reproduction may occur as early as twelve hours after ingestion and may continue for as long as sixteen days. Sexual division begins with fertilization of the female gamete by the male gamete. Two walls are laid around the fertilized gamete and oocysts are excreted, unsporulated, in the feces. Sporulation doesn’t occur until the oocysts have been one to four days at room temperature. During sporulation, the oocyst condenses its cytoplasm to form the sporoblast, from which arises two sporocysts each with four sporozoites. The oocysts may remain infective for more than a year in warm, moist soil.

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After shedding for one to two weeks following initial infection, the cats become carriers and shedding ceases. Reactivation of shedding can occur after induction of hypercorticism or after superinfection with other feline microorganisms such as *Isospora fels*.4

The extraintestinal (tissue) cycle in the cat occurs simultaneously with the enteroepithelial cycle. What triggers this extraintestinal development in the cat is unknown.7 The bradyzoites or other infective forms penetrate the lamina propria of the intestine and multiply as tachyzoites. After a few hours the organisms may disseminate through the bloodstream or through the lymphatic channels to extraintestinal tissues and organs.3 Pseudocysts, which are clusters of dividing tachyzoites within cells, are soon formed. True cysts are also formed which measure up to 100 microns and are most common in brain, skeletal and cardiac muscle.9 In the not too distant past, it was believed that cysts developed as a result of antibody production which killed the extracellular forms and slowed intracellular development resulting in cyst formation.1 Recent evidence suggests that cysts form under the influence of factors other than the developing immune mechanism. Cysts can develop as early as eight days after infection, before humoral antibody or any cellular immune response can be demonstrated.9 Also, cysts can form in tissue cultures, away from the influence of any immune mechanism.9 This evidence suggests that cysts are a stage in the life cycle of the parasites and their production is independent of the host’s immune response. Cysts may persist for long periods of time, even years, in a host. Under the right conditions, and no one is sure what these are, the walls of the cysts are destroyed and toxoplasma organisms emerge and penetrate new cells.5 One theory suggests that the release of organisms may be due to waning immunity.11 A renewed proliferation of tachyzoites occurs resulting in a localized or generalized relapse.

Even though the entire life cycle is completed only in the feline, about 200 species of mammals and birds can serve as intermediate hosts.5 The routes of infection are the same as in the cat with the addition of the transplacental route. The infective stage that is the major source of infection differs from that seen in the cat. The oocyst shed in cat feces may be the major source of infection to the intermediate host due to the fact that as many as ten million oocysts may be shed in a single day.9 After the ingestion of sporulated oocysts, sporozoites excyst in the intestine. From the intestine they enter any cell in the body, by the same routes as in the cat. Once inside the cells, multiplication is by endodyogeny, a process unique to *Toxoplasma*.9 This is a process of internal budding in which the daughter organisms enlarge and break out of the maternal cell, destroying it. Once outside the maternal cell, division is completed. The development of pseudocysts and true cysts occur as they do in the cat.

Toxoplasmosis in cats is mainly subclinical. The lesions resulting from the enteroepithelial cycle usually are not serious and do not produce clinical signs.10 Therefore, when present, clinical signs are produced by the lesions from the extraintestinal cycle.

As *Toxoplasma* disseminates and multiplies in the various organs and tissues of the body, necrosis is the major lesion observed. Some authors believe that an allergic response may play a role in the pathogenesis of the disease.11

The clinical syndromes produced are extremely variable due to the number of different organs and tissues that can be involved. A common finding, however, is a concurrent immunosuppression.2 Those tissues most frequently affected include the lung, brain, myocardium, lymph nodes, intestinal muscularis, pancreas and liver.11

The lung is the most frequent and severely affected organ. The respiratory signs observed are due to an acute and sometimes fatal adenomatous pneumonia. Interstitial and fibrinous pneumonia as well as focal granulomas occur.10 Grossly, small nodular pulmonary lesions have been reported. Microscopically alveolar walls are thickened with an increased number of cuboidal to columnar cells. Alveoli are filled with large mononuclear cells and leukocytes and aggregates of *Toxoplasma* are present in the cells lining the alveoli.11

Temperatures of 104°F or higher and dyspnea are common signs. As the pneumonia progresses, respiration becomes rapid, deep and abdominal. In severe cases, lethargy and anorexia are consistent signs with death following within seven days of onset.10
The radiographic appearance of toxoplasmal pneumonia is considered unique and highly indicative of the disease. Blotchy or mottled, ill-defined, coalescing alveolar densities are seen. These densities are particularly prominent in the caudal lobes. The CNS lesions seen with toxoplasmosis depend on the nervous structure involved. Spinal cord infection produces a myelitis which may result in a partial or complete, transverse or disseminated myelopathy. Upper or lower motor neuron damage may be seen depending on the level of the lesion. Infiltration of the brain parenchyma produces a diffuse non-suppurative infection with focal areas of necrosis in both the white and grey matter. Other lesions frequently seen are the development of vacuoles in the white matter, glial nodule formation and a proliferation of perivascular reticuloendothelial cells. Clinical signs of CNS involvement are more common in chronic toxoplasmosis than in acute cases. Signs may include seizures, blindness, incoordination, tremor, hemiparesis or paraparesis.

Intraocular lesions may involve the uveal tract, retina, or extraocular muscles. The retina appears to be the structure most frequently involved, with the production of an inflammatory retinopathy which may be focal or diffuse. An exudative retinal detachment and retinal necrosis may result.

Focal areas of coagulation necrosis are produced in the liver resulting in hepatitis with hypobilirubinemia in advanced cases. Coagulation necrosis is also produced in the myocardium and in the lymph nodes, especially those nodes draining infected organs. Infiltration of the pancreas results in acute necrosis with high lymphocyte infiltration, edema and swelling.

Ulcers have been described in the intestines. Invasion of the muscularis may cause a necrotizing lesion, followed by production of granulation tissue, resulting in the formation of large granulomatous nodules. These nodules have frequently been seen in older cats, probably as a result of immunosuppression and recurrent infection. If large enough, intestinal obstruction may be produced.

Diagnosis of the disease based on the clinical appearance is not practical due to the wide range of syndromes possible. However, antemortem diagnosis is aided by the identification of oocysts in the cat's feces, by isolation of the organism, and by demonstration of a rising antibody titer. When infected tissues are injected into laboratory mice, a peritoneal exudate sometimes forms within four to six days in which tachyzoites can be seen developing in macrophages. More often, however, the inoculation of suspect material into mice produces an asymptomatic infection which must be diagnosed histologically from the finding of cysts or serologically by the development of antibodies.

Serologic tests include the Sabin-Feldman dye test, indirect fluorescent antibody, indirect hemagglutination and complement fixation. A four-fold rise in antibody titer determined on paired serum samples taken two weeks apart is indicative of acute infection but not necessarily of clinical disease. These serologic tests are of limited value in the cat. The antibody titer rises slowly in the infected cat so that at the time there is shedding of oocysts in the feces, the tests are still negative. Thus, during the period of time diagnosis is most crucial, the desired information cannot be obtained from these tests.

As you have probably already concluded, a definitive diagnosis is often made only on postmortem examination. Impression smears and histologic sections are frequently used to demonstrate organisms. The appearance of gross and microscopic lesions may also help in making a final diagnosis.

Treatment involves using a combination of sulfadiazine and pyrimethamine (Daraprim). These drugs act synergistically to inhibit sequential steps in the biosynthesis of folinic acid. Humans and other mammals can directly incorporate folinic acid from the diet, something Toxoplasma gondii cannot do. Thus, folinic acid, baker's yeast or brewer's yeast can be added to the diet to alleviate possible toxic side effects caused by the treatment without interfering with the action of the drugs.

Sulfadiazine is quickly excreted and the daily dose must be given in four to six divided doses in order to maintain therapeutic levels. Pyrimethamine, on the other hand, is slowly excreted and can be given once daily. For suppression of oocyst shedding, sulfadiazine is given at the level of 120 mg% or half this dose combined with pyrimethamine at 0.5% in the

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*Daraprim, Burroughs Wellcome, Research Triangle Park, NC.*
diet. For the treatment of illness, a combination of 100 mg/Kg b.w./day sulfadiazine given either orally or by injection and 1 mg/Kg b.w./day pyrimethamine given orally has been used. Since all clinical syndromes indicate deficient immunity, chemotherapy should be continued beyond abatement of symptoms for a period of two weeks. Since the treatment is only suppressive and not curative, it has been seriously questioned whether or not treatment should even be attempted. Those cats that are treated are still potential shedders if reactivation of infection occurs.

From the public health standpoint, prevention of infection is extremely important. Humans, especially pregnant women, are at risk of being infected by animals, especially the cat. Preventive measures which should be undertaken to decrease exposure include cooking meat thoroughly to a temperature greater than 140°F and washing hands after handling raw meat to remove cysts from the skin. “Indoor” cats should be restrained from hunting birds and mice. Also, litterpans should be cleaned daily and sterilized with boiling water or dry heat at 150°F or higher. Flies, cockroaches and other coprophagous invertebrates should be controlled and access to food prevented. The development of a vaccine, now in progress, and a better understanding of the disease process itself will hopefully lead to a decreased incidence of toxoplasmosis in the future.

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