

A review of *Toxoplasma gondii* and muscular toxoplasmosis

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Abstract

Toxoplasma gondii is an important protozoal pathogen of man and animals. Infection is acquired by ingestion of infected tissue, ingestion of oocysts, or by maternal transmission. The protozoan develops in a parasitophorous vacuole in the myocyte and other host cells. Tissue cysts can remain viable in muscles for several years. *Toxoplasma gondii* infection of cardiac muscle is more frequent, and clinically more important, than infection of skeletal muscle.

Key words: toxoplasma gondii, tissue cyst, tachyzoite, bradyzoite.

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Infection and disease caused by intracellular parasitism with the protozoan *Toxoplasma gondii* have been known since the early 1900's. Nicolle and Manceaux described fatal infections in 2 North African rodents (the gundi, *Ctenodactylus gundi*) from the Pasteur Institute in Tunis in 1908 and latter that year, Splendore described a similar parasite from a laboratory rabbit in San Paulo, Brazil [40]. The life cycle of *T. gondii* is complex and it took nearly 60 years before the complete life cycle was elucidated. There are three infectious stages, sporozoites (within oocysts), tachyzoites and bradyzoites (within tissue cysts) present in the life cycle. The rapidly multiplying tachyzoite stages and slowly multiplying bradyzoites stages within latent tissue cysts have been observed in most organs and cell types of the human body including cardiac, skeletal and smooth muscle cells.

Infection with *T. gondii* is prevalent in humans and most infections in immunocompetent adults are asymptomatic [23]. *Toxoplasma gondii* is usually acquired either by ingestion of undercooked meat or by ingestion of oocysts (stages excreted in the feces of cats). Congenital infections can occur if the mother is infected during pregnancy and are due to tachyzoites crossing the placenta. Infections are most severe in transplacentally infected, young, or immunocompromised individuals. The clinical manifestations most frequently observed in immunocompetent humans are fever, lymphadenopathy (posterior cervical lymph nodes), headache, myalgia, and anorexia. Congenitally infected infants usually do not show signs of disease at birth; however most will develop ocular disease (blindness, retinochoroiditis) or will suffer slight to moderate

mental retardation later in life [47]. Few congenitally infected infants will present with the triad of hydrocephalus, blindness, and intracerebral calcification at birth. *Toxoplasma gondii* infection in humans immunocompromised for organ transplantation, during cancer chemotherapy or by AIDS can be life threatening [23, 36]. Disease in these individuals can be due to recently acquired infection or to recrudescence of a latent infection acquired prior to the immunosuppression. Encephalitis is the most common form of toxoplasmosis seen in AIDS patients and is due to relapse of existing latent infection.

Toxoplasmosis can be a serious disease of animals; however, as with humans, most infections are asymptomatic. Abortions are common in sheep and goats, but occur less frequently in other domestic and companion animals. *Toxoplasma gondii* infections in animals are most severe in transplacentally infected, young, or immunocompromised animals.

Toxoplasma Gondii Life Cycle

Life cycle of T. gondii in the intermediate hosts

When infected muscle or organ meats containing tissue cysts are ingested, the bradyzoites are liberated from the tissue cysts (Figure 1) after exposure to the acid conditions of stomach. Bradyzoites penetrate the mucosa of the small intestine and begin asexual multiplication within cells in the lamina propria. Bradyzoites convert to tachyzoites (Figure 2) within a few days [5, 44]. Tachyzoites are disseminated throughout the body by the lymphatic and vascular system. Tissue cysts containing bradyzoites are then produced in a variety of tissues including cardiac and

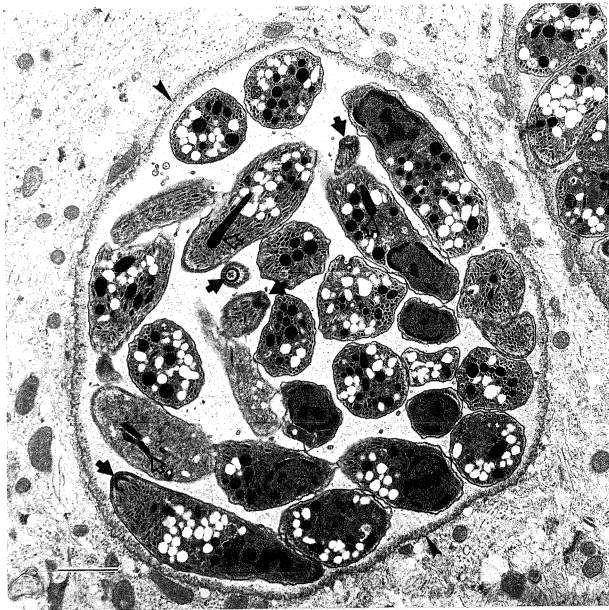


Figure 1. *Toxoplasma gondii* tissue cyst in the brain of a mouse 28 days after inoculation of heart tissue from a naturally infected wild turkey. Note the tissue cyst wall (arrowheads) enclosing bradyzoites and the conoid (arrows) and rhoptries (open arrows) of the bradyzoites. Bar = 1 μ m.

skeletal muscles. These tissue cysts remain viable for several months to life of the infected human or animal [8, 10, 11, 12, 17, 19].

When sporulated oocysts are ingested, sporozoites are liberated from oocysts in the duodenum. Sporozoites penetrate the mucosa of the small intestine and begin multiplication as tachyzoites within cells in the lamina propria. The fate of these tachyzoites is the same as those resulting from tissue cyst- induced infections.

Life cycle of T. gondii in the felids

In the cat, *T. gondii* undergoes a coccidia-like life cycle in the epithelial cells of the small intestine [9]. All members of the felidae are suitable definitive hosts for *T. gondii*, but domestic cats produce the greatest numbers of oocysts. Five distinct asexual types are present in enterocytes of the feline intestine. These stages eventually produce the sexual stages that give rise to the oocysts [14]. Oocysts are excreted in the feces for several weeks, but high numbers are only excreted during the first week of patency. Oocysts then develop (sporulate) outside in the environment within 2 to several days, depending on environmental conditions. Sporulated oocysts contain 2 sporocysts that each enclose 4 infective sporozoites.

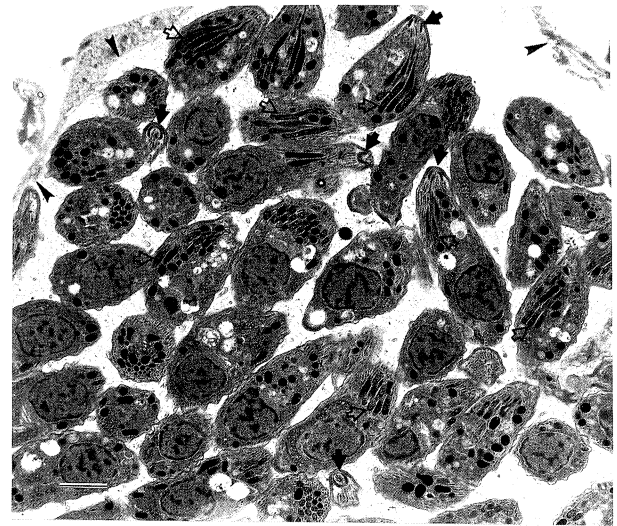


Figure 2. Portion of an infected cultured human fibroblast cell containing numerous *Toxoplasma gondii* tachyzoites (WTD-3 strain) 4 days after inoculation. Portions of the parasitophorous vacuole membrane (arrowheads) surrounding this group of tachyzoites is visible. The conoids (arrows) and rhoptries (open arrows) of several tachyzoites are labeled, Bar = 1 μ m.

The period of time required before oocysts are excreted (prepatent period) varies depending on the stage of *T. gondii* that is ingested by the cat [25]. Oral inoculation of bradyzoites/tissue cysts is most efficient in inducing oocyst- producing infections in cats, with 97% excreting oocysts with a short 3-6 day prepatent period [15]. Oral inoculation of tachyzoites or oocysts is less efficient because only the bradyzoite stage can undergo development in the enterocytes and produce the stages that eventually terminate in oocyst excretion. Oral inoculation of cats with oocysts or tachyzoites produces oocyst excreting infections in only 16% and 20% of cats, respectively. The prepatent period of these infections is 21-40 days [15, 25].

Toxoplasma gondii in laboratory systems

Tachyzoites can be continuously grown in cell cultures (Figure 2) or in the peritoneal cavities of mice. Large numbers of these stages can be obtained for laboratory studies and most of our knowledge of the molecular and cell biology of *T. gondii* is based on this stage. The same is true for immune responses of the host against *T. gondii*.

It is difficult to obtain large numbers of bradyzoites/tissue cysts for laboratory studies because these stages must be obtained from the brains chronically infected mice (Figure 1). Progress is being made at in vitro cultivation of the tissue cyst stage [35, 44] and, in the future, more will be known about this important stage of the life cycle.

The *T. gondii* stages present in the feline intestine have not been grown in cell culture. Cats excrete few oocysts in their feces and collection of usable numbers of oocysts is a difficult task.

It should be noted that continuous passage of *T. gondii* in mice or in cell cultures can alter its biology. The ability to produce infections in the feline intestine is lost after 30-35 passages in mice, or 40 passages in cell cultures [24, 35].

Muscular Toxoplasmosis in Humans

Cardiac toxoplasmosis in immunocompetent humans

Little is known about the importance of cardiac toxoplasmosis in immunocompetent patients [3]. *Toxoplasma gondii* was isolated following mouse inoculation of acid-pepsin digested heart tissue from 1 of 51 hearts from humans with antibodies to *T. gondii* [42]. These findings reflect the difficulties associated with making a definitive diagnosis of cardiac toxoplasmosis. Positive serological results may or may not be important because many people have chronic asymptomatic infections and are *T. gondii* antibody positive. Cardiac biopsy would probably be of little diagnostic value because the numbers and distribution of *T. gondii* stages in the heart are highly variable. In a study of 18 patients believed to have cardiac toxoplasmosis, the disease was characterized by arrhythmias, atypical chest pain, pericarditis, and cardiac failure [34]. One of the 18 patients was believed to have had acute toxoplasmosis while the remaining patients had chronic toxoplasmosis. Chronic, severe pericardial effusion caused by *T. gondii* has been documented in 2 patients [43]. *Toxoplasma gondii* was demonstrated in pericardial fluid in both cases.

Cardiac toxoplasmosis in transplantation recipients

Heart transplantation recipients are at risk for developing toxoplasmosis [2, 32, 37, 39]. Toxoplasmosis in these patients can be due either to primary infection acquired from the transplanted heart, or less frequently, from reactivation of latent *T. gondii* tissue cysts already present in the recipient. Toxoplasmosis in seropositive patients usually is mild [39]. However, the patient is at great risk of developing life threatening toxoplasmosis if the donor is positive for *T. gondii*. For example, 4 of 7 (57%) patients developed toxoplasmosis and 2 (29%) died in one study [46]. In another study, 3 of 4 (75%) patients developed toxoplasmosis and 2 (50%) died [37] when the donor was positive for *T. gondii*. The onset of clinical toxoplasmosis in these patients was 25 to 195 days [39]. Diagnosis of toxoplasmosis in transplant patients is made by demon-

strating *T. gondii* tissue cysts in biopsies of the transplanted heart, on samples taken at autopsy, or by serological testing. Current recommendations are that serum from both the donor and the recipient be examined for antibodies to *T. gondii* [32]. Several cases have occurred where serological examinations failed to detect *T. gondii* positive donors [2, 30]. Despite difficulties in diagnosis, it is recommended that serologic tests for IgG and IgM antibodies to *T. gondii* be conducted weekly for 8 weeks and then monthly for 4 months following heart transplantation in seronegative patients who receive a heart from a seronegative donor [32]. When seropositive donors are identified, prophylactic treatment with 25 mg/kg pyrimethamine a day for 6 weeks appears to prevent the development of disease [2, 32]. Sulfadiazine is an effective treatment for toxoplasmosis and is often combined with pyrimethamine because of synergism. However, sulfadiazine treatment has been shown to decrease the levels of cyclosporine in transplant recipients and careful monitoring is needed to make sure cyclosporine concentrations do not drop too low [46]. Trimethoprim-sulfamethoxazole, which is often given as prophylaxis for *Pneumocystis carinii*, does not appear to be as effective as pyrimethamine.

Cardiac toxoplasmosis in AIDS

Toxoplasma gondii induced myocarditis is recognized with increasing frequency in AIDS patients [29]. It is usually associated with reactivation of a chronic infection that the patient had acquired prior to developing AIDS. In a study of 80 cases of toxoplasmosis in AIDS patients, 15% (12 of 74 hearts) had infection in the heart based on examination of hematoxylin and eosin stained sections or by immunohistochemistry [31]. Cerebral toxoplasmosis is often present concurrently in AIDS patients with cardiac toxoplasmosis [6, 31], but cases where infection is observed only in the heart [1] or in heart and lungs [27] have been reported. Toxoplasmic myocarditis and resulting cardiac decompensation was the immediate cause of death in 1 of 54 AIDS patients [41]. Toxoplasmic myocarditis in AIDS patients responds well to treatment with pyrimethamine and sulfadiazine or pyrimethamine and clindamycin [27].

Skeletal muscle toxoplasmosis in humans

Clinical myositis due to *T. gondii* is rare in humans and is usually observed in immunocompromised individuals [4]. *Toxoplasma gondii* was isolated following mouse inoculation of acid-pepsin digested skeletal muscles from 3 of 51 humans who had antibodies to *T. gondii* indicating that tissue cysts are present in human skeletal muscle [42]. A diagnosis of toxoplasmic myositis is often based on serological testing for *T. gondii* antibodies and then demonstrating a decrease in antibody titer after treatment for toxoplasmosis. Stages of *T. gondii* are rarely observed in sections of skeletal muscle biopsies or tissues obtained at autopsy [38]. However, toxoplasmic myositis may be an overlooked condition in AIDS patients. *Toxoplasma gondii* was not observed in tissue sections of skeletal muscle

from 92 [48] or 7 patients [28] with AIDS. A much higher frequency was observed by Gherardi et al. [26] in their studies. *Toxoplasma gondii* was observed in 3 of 75 (4%) of consecutive muscle biopsies from patients with AIDS and neuromuscular disease and in 2 of 46 (4%) autopsies of AIDS patients. Muscular involvement in these patients included weakness and wasting, myalgias, and elevated serum creatine kinase levels. Skeletal muscle toxoplasmosis in AIDS patients is most likely due to reactivation of chronic infection already present in the muscle. A small number of skeletal muscle infections may arise at other sites (i.e. brain, heart) and be born to the skeletal muscles via the blood vascular or lymphatic systems.

Muscular Toxoplasmosis in Animals

Muscular toxoplasmosis in cats and dogs.

Clinical toxoplasmosis in cats is usually characterized by generalized infection or respiratory disease. Myocarditis is clinically more important in cats than is skeletal muscle infection. *Toxoplasma gondii* and associated lesions were observed in 63% of 59 hearts from cats with clinical toxoplasmosis [13]. Severe cardiac toxoplasmosis was only seen in 2 of these cats. Skeletal muscle toxoplasmosis is apparently not common in cats, even in those with disseminated infections. Toxoplasmosis involving skeletal muscles has been observed in congenitally infected kittens with disseminated toxoplasmosis [16].

Clinical toxoplasmosis in dogs usually is associated with the immunosuppression caused by concurrent canine distemper virus infection [21] and is probably due to reactivation of chronic infections. Cardiac lesions are much more common than skeletal muscle lesions in dogs with confirmed cases of toxoplasmosis. Many cases of polymyositis attributed to *T. gondii* in dogs are probably caused by a structurally similar protozoan, *Neospora caninum* [20]. Immunohistochemical methods using a *N. caninum* specific monoclonal antibody are needed to accurately distinguish the 2 parasites [7]. Until additional studies are conducted, the importance of toxoplasmic myositis in dogs will remain unclear.

Muscular toxoplasmosis in domestic farm animals

Domestic farm animals are generally resistant to toxoplasmosis. Cattle for example demonstrate a remarkable degree of resistance to *T. gondii* infection. Toxoplasmic abortion is the main clinical sign of toxoplasmosis and it is a significant production problem world-wide in the sheep and goat production industries. Although toxoplasmic abortion can occur in swine, it occurs less frequently than in sheep or goats. Cardiac and skeletal muscle infections can be observed in aborted fetuses or congenitally infected young with disseminated infections. However, muscular toxoplasmosis is not recognized as a significant or frequent problem in weaned or adult animals.

Inactivation of Toxoplasma gondii tissue cysts in meat of food animals

Adequate cooking will kill *T. gondii* tissue cysts in meat. A recent study demonstrated that tissue cysts are killed by exposure to 58°C for 9.5 minutes and that temperatures of 61°C or greater for 3.6 minutes or longer will kill *T. gondii* tissue cysts in meat [22]. Freezing meat is also effective in killing *T. gondii* tissue cysts in meat. However, *T. gondii* tissue cysts will survive for up to 22 days at -1 or -3.9°C and up to 11 days at -6.7°C [33]. It is believed that exposure of tissue cysts in meat to -12.4°C would instantaneously kill all tissue cysts [33]. Gamma irradiation is effective in killing *T. gondii* tissue cysts in meat. An absorbed dose of 0.4 kGy is lethal [18]. Temperatures between -4 and 16°C do not markedly influence killing by gamma-irradiation.

Presently no strains of *T. gondii* resistant to high or low temperatures or irradiation have been documented. In the few cases where suspected resistance to freezing [33] or irradiation [18] was critically examined, no resistance was found.

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