SOME ASPECTS OF THE PATHOGENESIS AND COMPARATIVE PATHOLOGY OF TOXOPLASMOsis

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Some aspects of the pathogenesis and comparative pathology of toxoplasmosis are described. The general pattern of infection, with or without necrosis, and tissue cyst formation as it occurs in all species is dealt with. The wide pathological manifestations of toxoplasmosis as seen in sheep, cattle, pigs, horses, dogs, cats, chinchillas and man are reviewed.

INTRODUCTION

Toxoplasmosis is a disease entity caused by the protozoan parasite Toxoplasma gondii. T. gondii was first reported simultaneously in 1908 by Nicolle and Man­ceaux in a North African rodent, Ctenodactylus gondii, and by Spendore in São Paulo in the rabbit[20 40 56]. The name of the parasite is derived from the Greek toxon, meaning bow or arc, alluding to their lunate shape and from the North African rodent. T. gondii has a world wide distribution and has been isolated from the tissues of many species of mammals and birds[3 4 6 7 10 13 16–18 20 23 28 30–32 44 50 51 56 57 61 64 67 70 74].

Numerous serological surveys have been carried out in various parts of the world, the findings of which confirm the high prevalence of toxoplasma antibodies in animals and man[1 5 9 23 29 32 36 51 52 56 57 61 64 67 70 74].

Both in animals and man, toxoplasmosis covers a wide clinical spectrum and occurs either as a congenital or an acquired infection. There is also a high incidence of asymptomatic infections in mammals and birds[8 9 18 22 24 29 32 40 45–49 52 56 58 63 66 72]. The various clinical manifestations of toxoplasmosis with its concomitant pathology can be regarded as being of interest, not only to the protozoologist and pathologist, but to the veterinary and medical professions in general.

For a better understanding of the pathogenesis and pathology of toxoplasmosis it is necessary to outline the life cycle of T. gondii.

LIFE CYCLE

The life cycle of Toxoplasma is divided into 2 separate cycles, namely an enteric-epithelial cycle and an extra­intestinal (tissue) cycle. The coccidian-type entero­epithelial cycle with oocyst production occurs only in cats and other feline species[14 19 20 28 32 40 43 59]. The extra­intestinal cycle occurs in both feline and non-feline hosts and constitutes the entire cycle in non-felines[12 18 20 25 50]. The three known infective stages of Toxoplasma are bradyzoites (tissue cysts stage), tachyzoites (proliferative forms in tissue during acute infection) and sporozoites (in sporulated oocysts).

Enteric-epithelial cycle:

The feline host is infected by the ingestion of tissue cysts (containing bradyzoites) or proliferative forms (tachyzoites) in tissues during acute infection or by the ingestion of sporulated oocysts originating from feline faeces. Multiplication takes place in the epithelial cells of the small intestine with the eventual formation of oocysts. The oocysts are detached from the intestinal epithelium and are discharged with the faeces. The oocysts are non-infective when unsporulated, with sporulation taking 1 to 5 days[11 12 19 20 25 27 28 32 50 68 70 71]. Millions of oocysts may be shed in a single stool and may remain infective for a year in warm, moist climates or longer in cooler climates[20 21 28 32 40 53 75].

Extra-intestinal cycle:

Infection can occur from the ingestion of sporulated oocysts of feline origin or the ingestion of tissue cysts or the transplacental infection of the foetus with proliferative forms (tachyzoites) after ingestion of sporulated oocysts or encysted tissue organisms by the pregnant female[20 24 25 28 31]. A parasitaemia then occurs with cyst formation taking place as the host's immunity builds up[20 28 32 33]. Tissue cysts are characteristic of the chronic infection and may occur in any tissue[37]. The tissue cysts may persist for the life of the host[11 20 24].

PATHOGENESIS

When a mammalian or avian host is infected by the ingestion of sporulated oocysts or tissue cysts toxoplasmosis begins with the development of tachyzoites in the lamina propria of the intestine[32]. A parasitaemia then develops with the tachyzoites being disseminated to various organs (including the placenta) in macrophages, lymphocytes, granulocytes and in free forms in the circulation[20 24 28 33 37 59]. T. gondii, according to some authors, does not appear to show a special affinity for any particular tissue or cell type[27].

The tachyzoites localize intracellularly in various tissues and begin to proliferate. The localization may be followed by active lesions in the affected tissue or encystment of the Toxoplasma organisms in which form
they may remain viable for a long time. From about 8 to 16 or more tachyzoites accumulate in the host cell before it disintegrates and new cells are infected.

The typical response of all tissues to proliferating organisms is necrosis. In certain cases T. gondii appears to actively invade the vascular walls resulting in early damage to capillaries, arterioles and venules, with increased vascular permeability and perivascular oedema. Plasma cells are not uncommon in the perivascular infiltrates, and some authors think that an allergic response may play a role in the pathogenesis of toxoplasmosis.

This general pattern of infection and cyst formation occurs in all species. The severity of the infection is determined by the degree of cellular necrosis, which will depend on the virulence of the strain; the organ or tissue involved; the number of proliferating organisms; the species of animals infected; its age and resistance; and the degree of hypersensitivity, if any.

The tissue-cysts may persist for the life of the host as a sub-clinical infection. Should, for various reasons, the host's immunity wane, cyst organisms may be released and a renewed proliferation of tachyzoites will be initiated, causing a localized or generalized relapse. Increasing numbers of cases of toxoplasmosis are being recorded in humans undergoing therapy for malignancies, in patients on immuno-suppressive agents and in people suffering from an immunodeficient disease.

Information concerning the pathogenesis of placental and foetal toxoplasmosis in humans and animals is scant. The infection in the dam is usually asymptomatic. It may be assumed that placental and foetal infection can occur at any time during an active infection where tachyzoites are in the general circulation. Whether the female host chronically infected with tissue cysts can give rise to placental and foetal infection is a controversial point. Some workers, however, claim that premunition prevents infection of placenta and foetus during successive pregnancies.

It has been claimed that invasion of the placenta may occur in a chronic infection due to rupture of endometrial cysts during implantation. It is noteworthy that occasional cases of toxoplasmosis have occurred in lambs of ewes that had high antibody levels to Toxoplasma at mating.

**PATHOLOGY**

In animals, such a wide diversity of pathological manifestations has been attributed to infection with T. gondii that it is difficult to ascribe limits to this condition. The organs and tissues most often affected are the brain, myocardium, lymph nodes, lung, intestinal muscularis, pancreas or liver. A high incidence of asymptomatic infections occur.

In tissue sections, tachyzoites and bradyzoites of Toxoplasma may be crescent-shaped, but also occur in rounded and ovoid forms. They are most frequently found in the cytoplasm of cells but may be free. A large number of the organisms may be encountered in a single cell or may be contained by a thin membrane which is believed to be the remnant of the wall of a host cell by some who speak of the structure as a "pseudo-cyst". Others consider the membrane to be a product of the parasite and regard it as a true cyst.

**Toxoplasma** organisms are not always readily demonstrable but may be seen in microscopic sections of animal tissues in which the injury to the host is severe, minimal or even non-recognizable. In active toxoplasmosis the microscopic findings in a particular organ are reasonably characteristic and diagnosis is therefore not entirely dependent on the demonstration of the parasite.

In the brain, active infection is indicated by diffuse non-suppurative infiltration of the brain parenchyma; lymphocytic cells accumulate within the Robin-Virchow spaces and are scattered throughout the parenchyma. Vacuoles may occur in the white matter. Toxoplasma organisms may be found scattered singly or in pairs in the parenchyma. Focal areas of necrosis are seen in the grey and white matter. After glial activation has taken place nodules form. Proliferation of perivascular reticuloendothelial cells is prominent and tends to make the vessels very obvious. They contribute to the scarring of the necrotic foci so that both glial and fibrous elements are present in the nodules.

Affected liver often shows large sharply delimited areas of coagulation necrosis involving any part of the hepatic lobules. Small numbers of organisms may be found singly or in pairs within liver or Kupffer cells and later in cysts containing large numbers of organisms.

The lung, when involved, exhibits rather striking changes, particularly in the alveolar walls; the lining becomes cuboidal or columnar and very rich in cells, suggesting in this respect the appearance of foetal lung. The alveoli are filled with large mononuclear cells and leukocytes with aggregations of Toxoplasma organisms in the cells lining the alveoli. These lesions have a nodular distribution throughout the lung, appearing grossly as small, grey, tumour-like masses scattered throughout one or all the lobes.

The lymph nodes, particularly those draining an affected organ or area, are commonly involved in active cases of toxoplasmosis. They are usually enlarged, firm in consistency and congested. Extensive coagulation necrosis is seen microscopically and organisms may be found adjacent to these necrotic areas, particularly in endothelial cells of veins, but may be with the cytoplasm of mononuclear cells or free in the tissues.

Ulcers in the intestine, presumably resulting from necrotic changes in sub-mucosal lymph nodules have been described. Toxoplasma may invade the muscularis of the intestine where a necrotizing lesion followed by production of granulation tissue results in large, grossly detectable granulomatous nodules. Toxoplasma organisms are noted in small or large groups in the muscularis and the granulation tissue.

In the affected pancreas, acute necrosis, intense lymphocytic infiltration, oedema and swelling may be seen. Numerous organisms in both duct and acinar cells are seen.

The myocardium is frequently invaded by Toxoplasma with small or large groups of organisms within the cytoplasm of the cardiac muscle cells. Focal necrosis with severe lymphocytic infiltration or very little signs of inflammation may be seen.

It is apparent that Toxoplasma infections may be manifested in a variety of forms. This is illustrated by the pathology of toxoplasmosis in domestic animals and man.
Spleen. Proliferative form of *T. gondii*.

Brain. *Toxoplasma* tissue cysts with no cellular reaction.

**Fig 3** Brain. Severe vasculitis associated with *Toxoplasma* cysts in the perivascular tissue.

**Fig 4** Lung. Infiltration of alveoli with macrophages and neutrophils (from confirmed case of toxoplasmosis).
Sheep:
Abortion due to toxoplasmosis is probably more important in sheep than in any of the other animals. Abortions often occur late in pregnancy.

Affected foetuses show no significant gross lesions. But histologically the parasites can be demonstrated and isolated from the myocardium, lung and brain. The foetal placenta bears what are probably characteristic lesions. The cotyledons are bright to dark red as compared with a normal deep purple colour; scattered amongst the foetal villi are numerous white flecks or small soft white nodules 1-3 mm in diameter. The villi are oedematous and there is focal necrosis and desquamation of trophoblastic epithelium. In more extensive cases there may be casueous and calcified cotyledonary nodules. The organisms are readily identified microscopically from the placental material, either free or in cysts. The intercotyledonary placenta usually only shows oedema.

The neuropathology of ovine toxoplasmosis has been described in detail by Koestner. Twenty-five sections at various levels of the central nervous system (CNS) were taken. The lesions in the CNS were found to be equally distributed and no predilection site was found. Foci of necrosis with numerous extracellular proliferating organisms were seen.

Microglial proliferation occurs with glial nodules being formed in the subacute and chronic stages. Glial nodules basically consist of microglia, activated oligodendroglia, astrocytes and monocytes. The Toxoplasma organisms occur intracellularly and in cysts at this stage. A striking feature is the mineralization of the vascular walls of the cerebral and meningeal vessels.

There are very few reported cases of clinical forms of toxoplasmosis in adult sheep, other than outbreaks of abortion and perinatal mortality. McErlean reported a case of two sheep showing progressive paralysis. No macroscopic lesions were noted at post mortem examination but extensive perivascular cuffing in the spinal cord associated with several Toxoplasma cysts was observed.

Cattle:
Toxoplasmosis is exceptionally rare in cattle. Cattle are very difficult to infect with T. gondii and the CNS seems to be particularly resistant. Koestner claims that the neuropathology in cattle is the same as that described for sheep.

Congenital toxoplasmosis has been known to occur in calves. Affected calves showed occasional CNS lesions which were accompanied by oedema and perivascular gliosis.

Pigs:
Although Toxoplasma infection is prevalent in pigs in all parts of the world, the infected host seldom shows any pathological changes. Organisms in pigs without obvious lesions are frequently isolated from striated muscle, brain, lung, stomach and large intestine.

Experimental evidence suggests that infection during the 3rd month of pregnancy will result in foetal death and congenital toxoplasmosis in any piglets born alive. Clinical cases of toxoplasmosis have been reported in pigs, occurring mainly below the age of 9 weeks. The pathological changes in these particular cases were as follows: hydrothorax, hydropericardium, ascites, focal necrosis of liver, fibrinous peritonitis, catarrhal pneumonia and enteritis. Parasites were easily demonstrated in wet or stained preparations of the affected organs.

Horses:
Not much is known about toxoplasmosis as a disease entity in horses. Cusick et al. described toxoplasmosis in two horses that showed progressive paralysis of the hindquarters and a marked myelomalacia of the spinal cord at autopsy.

Dogs:
A large number of dogs are regarded as having benign asymptomatic infections.

Congenital toxoplasmosis has been reported in dogs.

There is evidence that both immaturity and a concurrent distemper infection increases the susceptibility to toxoplasmosis. Whether distemper lowers the resistance of the host to enable primary toxoplasmosis to become established or whether it encourages reactivation of a latent infection is not known.

There is a considerable variation in the severity of toxoplasmosis when seen in dogs.

The following pathological lesions have been recorded in dogs:

Lungs – are usually affected and often manifest the most pronounced lesions. The lesions vary from small irregular areas which are grey in colour and firm in consistency, to interstitial pneumonia or focal fibrinous pneumonia. The acute interstitial pneumonia which frequently occurs strongly suggests the diagnosis. There is a adenomatoid hyperplasia of the alveolar cells, many of which contain organisms.

Liver – numerous areas of focal necrosis may occur. Lymph nodes – these are often enlarged and are congested with focal areas of necrosis. Spleen – enlarged, with numerous foci of necrosis in the parenchyma in which organisms can be demonstrated. Pancreas – haemorrhages and necrosis. Intestine – acute duodenal ulcers, the involved segment of intestinal wall being thickened with haemorrhages and oedema. Retina – in the dog inflammatory changes have been reported as being predominantly in the retina rather than in the choroid (opposed to the classic chorioretinitis seen in man). Haemorrhages and inflammatory exudate with mononuclear cells and small foci of necrosis in the retina are seen adjacent to Toxoplasma organisms. Perivascular cuffing with mononuclear cells in the retina and its optic fibre and ganglion cell layers may also occur.

Brain and spinal cord – Koestner considers the incidence of brain and cord lesions in canine toxoplasmosis to be high and of great diagnostic significance. Toxoplasma cysts may also occur in the CNS with no signs of any tissue response. Young dogs appear to be more susceptible and congenital infections result in the most severe and extensive lesions. Koestner describes the neuropathology of canine toxoplasmosis in great detail. Lesions are found in all parts of the CNS. Acute cases...
are characterised by vascular damage and focal necrosis; by glial nodules and repair in chronic cases. Glial nodules contain microglia, oligodendroglia, astrocytes and monocytes.

Toxoplasma organisms appear to actively invade the vascular walls the Virchow-Robin spaces and the adjacent nervous tissue. The parasitic invasion results in necrosis. At the margin of the lesion numerous cysts, ruptured cysts and extracellular proliferating organisms can be seen. The meningitis may show a slight infiltration of lymphocytes and plasma cells.

Cats:

Apart from playing a role as the source of Toxoplasma oocysts, the cat can also develop the extra-intestinal form of the infection and show signs of acute toxoplasmosis as well as chronic and asymptomatic infections.

The lungs are the most frequently and most severely affected organs and at post-mortem examination these show nodular necrotic lesions, interstitial pneumonia and oedema. The CNS may also be affected. The liver, myocardium and lymph nodes show focal areas of necrosis.

In young kittens the infection may be fatal. Ocular lesions have also been described in cats.

Impression smears from affected lungs may in some instances reveal organisms.

Chinchillas:

In an outbreak of toxoplasmosis in chinchillas in South Africa with a 17% mortality the following lesions were recorded: focal necrosis of liver and myocardium, interstitial pneumonia and, in the brain, parasitic cysts associated with focal gliosis and perivascular infiltration by plasma cells.

Man:

Both congenital and acquired forms of human toxoplasmosis occur. The acquired form covers a wide clinical spectrum. Lymphadenopathy is a frequent manifestation and toxoplasmosis is accepted by many as the most frequent cause of lymphadenopathy in which the Paul-Bunnell test for glandular fever is negative.

Ocular lesions (especially chorioretinitis), encephalitis, chorioretinitis, hydrocephalus, pancreatitis, myositis, necrosis of lymph nodes and various osseous changes may cause obstructive hydrocephalus. Radiologic examination of affected bones reveals abnormalities in the process of enchondral ossification. It appears as if, in these particular cases, the inflammatory cells interfere with the blood vessel invasion of the spaces between the calcified cartilage cores, and the remodeling by osteoclasts is impeded.

CONCLUSION

Although toxoplasmosis is a clinical disease that occurs rather sporadically, the clinical and pathological manifestations can be severe in the congenital and acquired forms. In domestic animals the disease is of the greatest economic importance in sheep.

From the foregoing it is apparent that both medical and veterinary clinicians and pathologists should include toxoplasmosis in their differential diagnosis where an immediate diagnosis is not possible.

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