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Ocular toxoplasmosis in the immunocompromised host

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Abstract

Disseminated toxoplasmosis is a well-known complication of immunodeficiency states, including those induced by malignancies, steroid and cytotoxic drug therapy, and AIDS. In immunodeficient patients, toxoplasmic infections of the eye are less common than toxoplasmic infections of other organs for unknown reasons. When ocular toxoplasmosis does occur in the immunodeficient host, or if immunosuppressive therapy is administered to patients with active disease, widespread tissue destruction by proliferating organisms may result. Immunodeficiency alone may not be sufficient, however, to cause reactivation of encysted organisms in retinochoroidal scars.

Ocular toxoplasmosis in the immunocompromised host presents difficult problems in diagnosis and management. There may be a variety of clinical lesions, including single foci of retinochoroiditis in one or both eyes, multifocal lesions, or diffuse areas of retinal necrosis. The majority of lesions do not arise from the borders of preexisting scars, which suggests that they result from acquired infection or dissemination of organisms from nonocular sites of disease. *Toxoplasma gondii* may infect iris, choroid, and vitreous – tissues that are not usually infected in the immunocompetent host. Ocular lesions appear to respond to standard antiparasitic drug therapies, but continued treatment is probably necessary to prevent reactivation of disease in the most immunocompromised patients. The best treatment regimens have yet to be determined. Histopathologic studies show little retinal inflammation; therefore anti-inflammatory drugs, such as oral steroids, probably have no role in the management of infection.

Introduction

Toxoplasma gondii is an important opportunistic pathogen of immunocompromised individuals. Patients receiving immunosuppressive drugs, those with malignancies involving the reticuloendothelial system, and those with the acquired immunodeficiency syndrome (AIDS) are at risk for serious disseminated toxoplasmosis. Although ocular toxoplasmosis is believed to the most common infectious disease of the retina in the general population, it has been reported infrequently among patients who are immunosuppressed. Nevertheless, the dramatic rise in the number of patients with AIDS and the continued use of immunosuppressive drug therapies for a variety of disorders make ocular toxoplasmosis in immunocompromised hosts an increasingly important problem. It can be a particularly severe disease, but recent studies show that it can be successfully treated if recognized early and treated appropriately.

Ocular toxoplasmosis and immunosuppression

Cellular immunity plays an important role in host defenses against *Toxoplasma gondii*. Largely on the basis of animal studies, it is believed that tissue destruction in toxoplasmic retinochoroiditis results from proliferation of organisms, and not from an immunological reaction to toxoplasmic antigens. An association therefore could be expected between ocular toxoplasmosis and immunosuppression, attributable to the body's impaired ability to fight organisms.

The immunosuppressive effect of large doses of steroids (when administered without concurrent antimicrobial therapy) has been associated with deterioration of ocular toxoplasmosis, and destruction of the eye in some cases [1, 2]. Less clear is the association between steroid use and the recurrence of inactive toxoplasmic lesions. Tabarra reported a 28-year-old male with a history of a retinochoroidal scar, consistent with ocular toxoplasmosis, who underwent renal transplantation followed by treatment with azothiaprine and prednisone to prevent allograft rejection. He developed a focus of retinochoroidal inflammation adjacent to the preexisting scar. A diagnosis of recurrent ocular toxoplasmosis was made and was attributed to the immunosuppressive therapy [3]. There are, however, few other cases in the ophthalmic literature where recurrence of ocular toxoplasmosis has been attributed to administration of immunosuppressive therapy.

In recurrent ocular toxoplasmosis, the source of proliferating organisms is encysted parasites in retinochoroidal scars. Immunodeficiency alone may not cause reactivation of encysted organisms [4]. It is possible that release of viable organisms requires one or more mechanisms unrelated to the host's cellular immune system. A number of other factors have been hypothesized to play a role in the reaction of parasites: spontaneous degeneration of the cyst wall over time, trauma, hormonal influences, and changes in circulating anti-*Toxoplasma* antibodies. Following reactivation, the immune response may then determine the extent of *Toxoplasma gondii* proliferation and the severity of recurrent disease.

Toxoplasma gondii is a common opportunistic pathogen in immunocompromised hosts, in whom it has a propensity for central nervous system infections [5, 6, 7]. Infections of the eye, however, has been reported only rarely, primarily in patients with disorders characterized by cellular immunodeficiency. Nicholson and Wolchok reported a women with a lymphoproliferative disorder of unknown type who developed widespread bilateral retinal necrosis while receiving prolonged systemic steroid therapy [8]. Histopathologic examination revealed trophozoites and cysts with little inflammatory reaction. Early lesions were primarily perivascular in location, suggesting that organisms reached the eye via the blood stream. Hoerni and associates reported 2 patients with Hodgkin disease who developed focal inflammatory chorioretinal lesions consistent with *Toxoplasma gondii* infection after being treated with chemotherapeutic agents [9]. Yeo and associates reported a patient with lymphoma treated by irradiation and chemotherapy who developed a focal retinochoroidal lesion in one eye that spread to involve the entire posterior pole [10]. Examination at autopsy also revealed retinal necrosis but little inflammation in this patient. In none of these cases were there retinochoroidal scars at the time disease developed.

Toxoplasmosis and AIDS

The understanding of toxoplasmosis in the immunocompromised host has increased greatly in recent years because of the AIDS epidemic. Toxoplasmosis is the most common nonviral intracranial infection among patients with AIDS, [11–13] but as with other immunocompromised patients, ocular toxoplasmosis has been reported infrequently [14–19]. In various reports of the neurological manifestations of AIDS, only 10 to 20% of patients with intracranial toxoplasmosis have eye involvement. It has been hypothesized that only 1 to 3% of ocular infections in patients with AIDS are due to *Toxoplasma gondii* [20].

A variety of clinical manifestations have been reported in patients with ocular toxoplasmosis. In a

series of 8 patients with ocular toxoplasmosis and AIDS, 4 patients had a single focus of ocular toxoplasmosis in one or both eyes; 1 had multifocal disease; and 3 had diffuse areas of retinal necrosis [19]. None had preexisting retinochoroidal scars. Hemorrhage was uncommon. Vitreous and anterior chamber inflammatory reactions were prominent, a finding that helps to distinguish cases of diffuse ocular toxoplasmosis from CMV retinopathy. Disease was located primarily of the inner retina in one patient and primarily in the outer retina of another. Most patients, however, had full-thickness retinal necrosis. Retinal detachments or tears occurred in 3 patients.

As in other immunosuppressed patients, ocular toxoplasmosis in patients with AIDS frequently begins adjacent to retinal blood vessels, suggesting that parasites reach the eye via the blood stream. Direct extension from the brain via the optic nerve is another possibility in selected patients [19].

The AIDS epidemic has also shown that with severe immunosuppression, organisms can infect and proliferate in tissues other than the retina. In the immunocompetent host, infection of the choroid and iris either do not occur or are extremely rare. The iridocyclitis that accompanies retinal infections in these patients is believed to be a secondary, immunological reaction, and destruction of choroid is probably related to inflammation stimulated by the adjacent retinal infection. In contrast, organisms were found in an iris biopsy specimen from a patient with AIDS [21]. Other, similar cases have been suspected [19].

Anti-*Toxoplasma* IgG antibodies are almost always present in patients, but antibody titres are rarely helpful in diagnosis. Anti-*Toxoplasma* IgM antibodies are uncommon.

Toxoplasma gondii may co-infect the retina with other organisms. CMV retinopathy and toxoplasmosis in the same eye has been reported in a patient with AIDS [19]. It has been known for many years that concomitant parasitic and viral infections in immunosuppressed patients have a higher incidence than would be expected from random occurrence, but the reasons for this apparent synergism are not known [6, 7].

There appears to be a clear role for antiparasitic drug therapy in the treatment of ocular toxoplasmosis in immunosuppressed patients. Resolution of retinal disease activity has been seen following treatment with pyrimethamine (either alone or in combination with sulfadiazine, clindamycin, or tetracycline), and to spiramycin [19]. Reactivation of disease is common when therapy is discontinued. Continued treatment with at least one antiparasitic drug appears to be necessary to maintain disease quiescence. Continued therapy is difficult in patients with AIDS, however, because of preexisting marrow suppression and the frequent allergies that occur to sulfonamides.

Although patients may have prominent vitreous and anterior chamber inflammatory reactions, histopathologic examination reveals little or no retinal inflammation in areas of necrosis. The absence of inflammation within the retina supports the conclusion that tissue damage occurs because of proliferating organisms and suggests that steroids should not be used in the treatment of ocular toxoplasmosis in patients with AIDS.

Conclusions

Ocular toxoplasmosis in immunocompromised hosts is an important although uncommon disease. Experience shows that it can have a variety of clinical manifestations, which often makes diagnosis difficult. Although the infection can be confused with other disorders, such as CMV retinopathy, the presence of pain, redness, and prominent anterior chamber and vitreous inflammatory reactions should make one suspicious of toxoplasmosis. Immunocompromised hosts have severe infections, and in contrast to immunocompetent hosts, they may have infection of the iris, choroid, and vitreous.

Immunosuppressed patients do not appear to be at increased risk for *recurrent* ocular infections; evidence is lacking to support the hypothesis that immunological alterations initiate recurrent ocular toxoplasmosis. Ocular disease in these patients may be new to the eye, resulting from acquired infection or from organisms newly disseminated to the eye from nonocular sites of disease. When or-

ganisms reach the eye, the immunodeficiency allows widespread tissue destruction.

Ocular lesions appear to respond to antiparasitic drug therapy, but continued treatment, at least in lower dosages, is probably necessary to prevent reactivation of disease in the most compromised patients. The best treatment regimens have yet to be determined.

Ocular toxoplasmosis may be the first manifestation of a life-threatening but treatable disorder in immunosuppressed hosts. Accurate diagnosis can allow early treatment with preservation of vision. In addition, the study of these patients may allow a better understanding of the pathophysiology of both acquired and recurrent ocular toxoplasmosis among all patients.

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