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# Bilateral ocular toxoplasmosis in a returning traveller: age and route of infection as potential risk factors

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## SUMMARY

We report the case of a 69-year-old man, who presented in the UK with a short history of deteriorating vision and clinical features of bilateral atypical retinochoroiditis, after travelling to South America. Vitreous samples demonstrated *Toxoplasma gondii* DNA by PCR. Serology tests demonstrated recent acquired *Toxoplasma gondii* infection with IgM antibodies. He responded well to treatment with trimethoprim-sulfamethoxazole, azithromycin and oral steroids. This case is a reminder of the global importance of *Toxoplasma* related eye disease, and its uncommon bilateral severe presentation in a returning traveller, where the risk factors were age and the route of infection likely to be a virulent parasite oocyst from vegetables or water rather than undercooked meat or direct contact with cats.

## BACKGROUND

*Toxoplasma gondii* is a highly-endemic mammalian parasite, which commonly causes sub-clinical or mild disease in immunocompetent humans. More severe disease is associated with the elderly population, and the more virulent strains found in Latin America, which can be potentially life-threatening.<sup>1</sup> Ocular demonstrations of *T. gondii* are frequently seen as a manifestation of primary/acquired, or reactivation of latent disease. The diagnosis of typical congenital Toxoplasmic chorioretinitis reactivation is usually made after observing a solitary focus of active chorioretinitis adjacent to a pigmented healed chorioretinal scar ophthalmoscopically. Here, we describe a case of bilateral *T. gondii* atypical retinochoroiditis in an elderly traveller returning from Latin America with no history of contact with cats.

## CASE PRESENTATION

A 69-year-old man was referred to his local district general hospital in the North-West of England (UK) having seen his optometrist for a 3-week history of bilateral blurred vision. He had bilateral anterior and intermediate uveitis with raised intraocular pressures (IOP) at 38 mm Hg (normal range 11–21) in each eye. He was initially treated with intensive steroid drops and IOP-lowering drops. At a follow-up 1 week later, he was found to have active retinochoroiditis and was referred to a tertiary centre. On presentation, his acuity was 0.9 logMAR in the right and 0.5 logMAR in the left eye. He had mild anterior uveitis (anterior chamber faint flare and grade 1+cells with 6–15 cells in 1×1 mm slit-lamp beam),<sup>2</sup> mild vitritis (score of 2 with slightly hazy details of the posterior pole)<sup>3</sup> and

active retinochoroiditis in each eye. There was an area of active necrotising chorioretinitis along the inferotemporal arcade in the right eye with very mild signs of localised retina vasculitis (figure 1A) and a large lesion of retinitis in the superior far peripheral retina in the left eye (figure 1B). There were no retinal haemorrhages, optic disc swelling, macular oedema (figure 2A,B), retinal detachment or previous retinal scars in either eye. Optical coherence tomography images of the lesion in the right eye showed thickening and inflammation extending to all retinal layers with colocalised increased choroidal thickness (figure 2C,D). He was diagnosed with atypical bilateral retinochoroiditis. On the day of his presentation, intravitreal vancomycin and ceftazidime were given to cover for a potential bacterial aetiology and risk of rapid progression. In addition, he was treated with oral ciprofloxacin until we received the results of our investigations. The vitreous PCR demonstrated *T. gondii* DNA. The serology tests identified anti-*Toxoplasma* IgM and IgG. The rest of the investigations came back as normal.

He had no history of immunosuppression or weight loss. Three weeks before his initial presentation to his optometrist, he had been treated for a presumed lower respiratory tract infection with a flu-like illness. His chest X-ray at the time was not reported as showing acute infective changes. His symptoms transiently improved with a 5 day course of erythromycin but had not done so with a course of amoxicillin previously provided by his general practitioner. We hypothesise that treatment with a short course of erythromycin for a presumed lower-respiratory tract infection probably provided some partial treatment for his underlying *Toxoplasma* infection.<sup>4</sup> The general feeling of unwellness commenced soon after his return from a 3-week cruise around Brazil and Argentina. Following a detailed travel history, the patient recalled visiting a local restaurant in Rio de Janeiro where he ate salad during a night ashore. He denied contact with any animals or soil and did not eat any undercooked meat during his trip. He spent the majority of the remaining time of his cruise aboard the ship.

## INVESTIGATIONS

Ocular fluid (aqueous and vitreous humour) sample analyses showed scanty white cells, but no organisms on Gram staining or following culture. Aqueous PCR detected *T. gondii* DNA. There was no evidence of cytomegalovirus, herpes simplex virus or varicella zoster virus infection



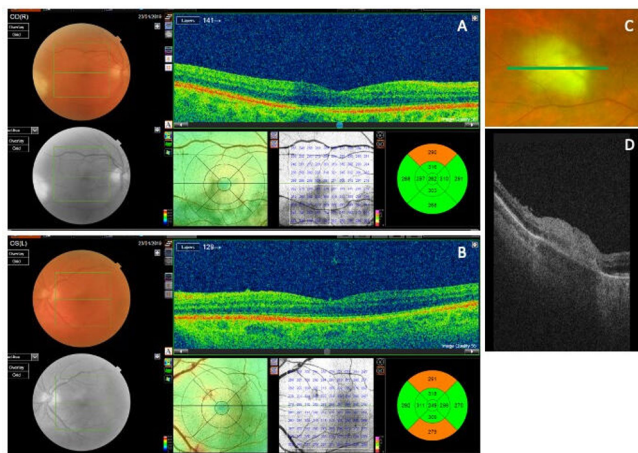
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**Figure 1** (A) Coloured photo of the right fundus at presentation showing haziness in the vitreous from mild vitritis, a temporal focus of retinochoroiditis with very mild focal vasculitis overlying the focus in the absence of haemorrhages, disc swelling or retinal detachment. (B) Left fundus at presentation showing vitritis and a large focus of retinochoroiditis superiorly. (C) Right and (D) left fundi 6 months later showing response to anti-*Toxoplasma gondii* treatment combined with oral prednisolone. No evidence of vitritis or active retinochoroiditis in either eye. The lesions are well demarcated with pigmentation in the border in left superior lesion.

on a pan-viral PCR. Serological testing was positive for both IgM and IgG antibodies against *T. gondii*. His peripheral blood cultures, Treponemal serology, as well as beta-glucan, galactomannan, interferon-gamma release assay and angiotensin converting enzyme (ACE) tests were all normal. HIV screening was negative. We tested immunoglobulin (A and G) levels and serum electrophoresis, which were normal. An immunodeficiency panel demonstrated a marginal reduction in CD16 B cells (87, normal range 100–500), which has been associated with *T. gondii* infection in vivo.<sup>5</sup>



**Figure 2** (A) Optical coherence tomography of the right eye and (B) left eye macula with no signs of macular oedema. (C) Right eye temporal retinochoroiditis lesion at the time of presentation. The Optical coherence tomography (OCT) scan across the green line can be seen (D) with a hyperreflective area affecting all the layers of the retina in the absence of subretinal fluid.

Within 1 week, wide field imaging of both retinæ showed a good response to treatment with reduced vitritis and the retinochoroidal lesions becoming more well defined, reduced in size and starting to scar.

### DIFFERENTIAL DIAGNOSIS

A range of infectious and non-infectious diseases should be included in the differential diagnosis of bilateral atypical retinochoroiditis. We excluded infective causes such as acute retinal necrosis syndrome, other necrotising herpetic retinopathy, cytomegalovirus retinitis, bacterial and fungal (candidiasis and blastomycosis) infections, syphilis and tuberculosis, as well as inflammatory causes such as sarcoidosis and intraocular lymphoma. In our patient, PCR testing of ocular fluid was vital for early diagnosis and initiation of treatment in the absence of positive cultures. Any unusual or severe presentation of a common infection should prompt consideration of an underlying immune pathology.

### OUTCOME AND FOLLOW-UP

Six months later, the patient's vision had improved to corrected logMAR of  $-0.04$  in the right eye and  $+0.14$  in the left eye, and the condition was inactive in both eyes (figure 1C,D). His co-trimethoprim and sulfamethoxazole had been stopped after 3 months, and he remained on azithromycin at a dose of 500 mg once a day with a low dose of oral prednisolone.

### DISCUSSION

Toxoplasmosis by *T. gondii* is one of the most common parasitic infections. Nearly one-third of the population<sup>6</sup> has been exposed worldwide through ingestion of tissue cysts containing bradyzoites in undercooked meat or food/water contaminated with sporozoites contained in environmentally resistant oocysts from infected cat faeces.<sup>7</sup> In the UK, seroprevalence-based studies estimate 350 000 people become infected annually, with 10%–50% being symptomatic.<sup>8</sup> Most will have mild self-limiting low fever, flu-like illness, lymphadenopathy, generalised malaise and muscle pain. However, in vulnerable groups such as the elderly, pregnant women or immunocompromised (eg, fetus, cancer, HIV/AIDS, on systemic immunosuppressants) more severe disease might develop. The overall burden in the UK is unknown. In the Netherlands, Toxoplasmosis is the highest foodborne disease burden due to stillbirths and retinochoroiditis (both in congenital and acquired infections) with potential severe symptoms and long-term sequelae.<sup>9</sup> The estimated lifetime risk of eye disease following acquired *T. gondii* infection for British-born individuals is 18 per 100 000.<sup>10</sup> In comparison, in Canada,<sup>11</sup> the risk of ocular toxoplasmosis (OT) after acquired toxoplasmosis is estimated to be 0.3% and as high as 25% in certain regions of Brazil.<sup>12 13</sup>

Typical OT findings include white focal retinitis with overlying vitreous inflammation ('the headlight in the fog'), adjacent pigmented retinochoroidal scar, vitreous inflammation (mild, moderate or severe), secondary non-granulomatous iridocyclitis, granulomatous and stellate keratic precipitates, inflammatory ocular hypertension and retinal vasculitis (usually near the focus of retinochoroiditis). Atypical features, which can present with retinochoroiditis, may be papillitis, neuroretinitis, retrobulbar neuritis, scleritis, retinal detachment, punctate outer retinitis, branch retinal artery occlusion, frosted branch angiitis, Coats'-type response, Fuchs-like anterior uveitis or multifocal diffuse necrotising retinitis.

Risk factors, which likely influenced new *Toxoplasma* infection and the development of atypical OT in our case, are his age and the route of infection (presumed oocyst ingestion in a salad of a potentially highly virulent parasitic genotype from South America). Older age is a known risk factor for the development of OT.<sup>14–16</sup> A recent study in the UK has shown that the majority of patients above the age of 60 with OT had a recent acquired infection with positive IgM rather than a reactivation from congenital infection.<sup>17</sup> Increased susceptibility to parasitic infections in the elderly may be due to the progressive dysfunction of innate and acquired immunity (ie, immunosenescence).<sup>18</sup> Cellular immunity, mediated by T lymphocytes and macrophages, plays a critical role in the normal host defences against intracellular pathogens like *T. gondii*. Ageing is associated with a progressive decline in immune function, primarily in T-cell-dependent, cell-mediated responses.

Atypical OT presentations following acquired new infection similar to this case have been reported in patients older than 60 years without any other systemic disease.<sup>19–25</sup> In atypical cases, with bilateral, extensive, multifocal disease and in the absence of a visible healed scar, the diagnosis can be difficult. Serology tests (anti-*Toxoplasma* titres of IgM and IgG) and the highly sensitive and specific diagnostic tool, PCR, of aqueous and vitreous samples are pivotal in these cases. The clinical picture in our patient was not easily recognised as OT. Endogenous infection could not be excluded; hence, he was treated with intravitreal and oral antibiotics while we waited for the results of our tests. He was responsive to antiparasitic drug therapy combined with oral prednisolone. Close monitoring was emphasised, given the risk of relapses.<sup>25</sup> Maintenance treatment is sometimes used in immunocompromised patients to prevent recurrence. This could also be considered in older adults, but there is limited evidence to suggest a preferred regimen.<sup>26</sup>

Available evidence in the literature suggests that parasite strain is a risk factor for severe illness particularly in the elderly. The higher incidence and severity of OT disease in tropical areas (eg, South America and Africa) and in some epidemics, compared with non-tropical areas (Europe and North America), are thought to be due to acquisition of the infection from oocysts rather than tissue cysts, and genetic differences in strain virulence.<sup>27–28</sup> Emerging evidence suggests that strain-dependent differences in cytokine expression are correlated with disease severity in OT, with South American strains associated with more severe ocular disease.<sup>29</sup>

Our patient had no history of contact with cats, litter or soil, and did not eat undercooked meat. His source of infection was most likely oocyst contamination of fresh salad while visiting Brazil. This route of infection is likely to be important in the UK, although currently available tests do not allow for determination of the route of transmission. A new method of detecting sporozoite-specific protein (T<sub>g</sub>ERP), which determines if infection with *T. gondii* was acquired from oocysts in the preceding 8 months, has been reported recently.<sup>30</sup> Using this method, one study in the USA reported that more than 70% of infections were related to unrecognised oocyst exposure.<sup>31</sup>

Awareness of risk factors for acquired OT is crucial to enable prevention of the initial infection. Methods that can distinguish sporozoites containing oocysts from bradyzoites containing tissue cysts as the source of infection would be greatly valuable for future epidemiological studies to assess the source of acute infection and the importance of foodborne burden in countries such as the UK.<sup>32</sup>

## Patient's perspective

I would like to thank all involved in treating my condition and their concerns for my well-being.

## Learning points

- ▶ Toxoplasmosis should be considered strongly in the differential diagnosis of elderly patients with bilateral necrotic retinochoroiditis.
- ▶ A thorough history focusing on known risks factors such as immunosuppression and potential routes of infection can be crucial in the design of ophthalmic differential diagnoses.
- ▶ PCR of intraocular fluids, serology of anti-*Toxoplasma* antibodies and response to adequate antiparasite treatment combined with prednisolone will confirm the definitive diagnosis.

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