Neuromyelitis optica is an autoimmune disease of the central nervous system characterized by optic neuritis and longitudinally extensive transverse myelitis. Patients with neuromyelitis optica frequently have antibodies to aquaporin-4 (AQP4), a water channel expressed on astrocyte foot processes.1 Patients with AQP4 antibodies can also have isolated or recurrent episodes involving 1 or more combinations of optic neuritis, longitudinally extensive transverse myelitis, or cerebral or brainstem relapses that do not fulfill the revised Wingerchuk diagnostic criteria for neuromyelitis optica.2-4 Patients with AQP4 antibodies require long-term immunosuppression and urgent treatment of relapses, otherwise blindness, paraplegia, or even death may occur.2 We describe 2 patients with AQP4 antibodies who developed vision loss resulting from opportunistic retinal infections while receiving conventional doses of immunosuppressive therapy: one patient with cytomegalovirus retinitis as a result of treatment with azathioprine and low-dose corticosteroids and another patient with ocular toxoplasmosis as a consequence of therapy with low-dose corticosteroids and methotrexate sodium. Both patients provided written informed consent for publication of this report.

Case 1

A white woman in her 60s developed progressive ascending sensory loss, urinary retention, constipation, and paraparesis 2 weeks after herpes zoster infection in the T6 dermatome. Imaging revealed longitudinally extensive transverse myelitis (eFigure 1A and B in the Supplement) and laboratory testing detected serum AQP4 antibodies. The results of visual function and visual-evoked potential tests were normal. Intravenous methylprednisolone sodium succinate, 1 g/d for 3 days, was administered, followed by 5 days of plasma exchange. Long-term immunosuppressive treatment with azathioprine and oral prednisolone sodium phosphate was then commenced.

Fifteen months later, while receiving prednisolone, 10 mg once daily, and azathioprine, 2.5 mg/kg/d, she presented with painless vision loss in the right eye. Her best-corrected visual acuity was 20/80 OD and 20/20 OS. A right afferent pupillary defect was present and the results of undilated slitlamp biomicroscopy were unremarkable. A diagnosis of right retrobulbar optic neuritis was made and intravenous methylprednisolone, 1 g/d for 3 days, was administered. The

IMPORTANCE Patients with neuromyelitis optica who have aquaporin-4 antibodies are being identified and receiving immunosuppressant treatment earlier and more aggressively as a result of increasing awareness of the importance of preventing relapses responsible for the high morbidity and mortality associated with the disease. To our knowledge, opportunistic retinal infection in patients with aquaporin-4 antibodies who are receiving immunosuppressants has not been reported to date.

OBSERVATIONS We describe 2 patients with aquaporin-4 antibodies who were receiving conventional doses of first-line immunosuppressive therapy. Both patients presented with vision loss that was initially thought to be optic neuritis attacks. The subsequent diagnoses were ocular toxoplasmosis and cytomegalovirus retinitis.

CONCLUSIONS AND RELEVANCE Retinal opportunistic infections can occur in patients with aquaporin-4 antibodies who are receiving relatively low levels of immunosuppression, may mimic optic neuritis, and are a potentially reversible cause of vision loss when treated promptly.

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prednisolone and azathioprine doses were increased to 60 mg/d and 175 mg/d, respectively, for presumed right retrobulbar optic neuritis.

At a follow-up visit 3 months later, the patient reported an increase in “missing areas” in her right eye field of vision. On examination, her best-corrected visual acuity was noted to be reduced further to 20/100 OD and 20/30 OS, and she had evidence of bilateral retinitis, anterior uveitis, and vitritis, which were worse in the right eye (Figure 1). The white blood cell count was 3060/μL (neutrophils 2360/μL, lymphocytes 350/μL, monocytes 240/μL, and eosinophils 30/μL; to convert microliters to ×10⁹ per liter, multiply by 0.001). The total T lymphocyte count was reduced (640/μL; reference range, 700-2100/μL), and the CD8 count was at the lower limit of the reference range (200/μL); however, the CD19 B-cell subset was markedly reduced at 1/μL (lower reference range limit, 100/μL). Serum electrophoresis demonstrated a panhypogammaglobulinemia, with IgG level of 328 mg/dL (to convert to grams per liter, multiply by 0.01), IgA level of 20 mg/dL (to convert to milligrams per liter, multiply by 10), and IgM level of less than 4 mg/dL (to convert to milligrams per liter, multiply by 10) (reference ranges, 600-1600 mg/dL, 80-300 mg/dL, and 40-250 mg/dL, respectively) and a faint IgG κ paraprotein band that was too small to quantify. *Toxoplasma gondii* serologic factor (IgM and IgG) and serum human immunodeficiency virus antigen and antibody were negative. Cytomegalovirus IgG was detected in the serum (CMV IgM was negative) and high CMV DNA levels were detected in whole blood samples (1 696 918 copies/mL or 6.24 log copies/mL) by polymerase chain reaction. Polymerase chain reaction testing of a vitreous biopsy of a sample from the right eye confirmed the presence of CMV DNA. There was no evidence of systemic involvement as a consequence of CMV viremia. Intravenous antiviral therapy (acyclovir sodium, 10 mg/kg, 3 times daily for 3 days) was administered, followed by oral valacyclovir hydrochloride 1 g 3 times daily and valganciclovir hydrochloride 900 mg twice daily for 1 week. The valganciclovir dose was reduced after a further 2 weeks to a prophylactic dose of 900 mg/d thereafter. Azathioprine was withdrawn over 5 months (eFigure 2 in the Supplement).

At the time of writing, the patient had experienced no further relapses, with low AQP4 antibody titers, and was receiving only prednisolone, 15 mg/d. Cytomegalovirus retinitis was quiescent at the last follow-up visit, with best-corrected visual acuity of 20/200 OD and 20/40 OS.

Case 2

A white woman in her 60s with a history of recurrent inflammatory optic neuritis, positive for AQP4 antibodies, was admitted with painless visual loss evolving over 5 days. She had experienced 3 unilateral optic neuritis episodes from age 46 to 62 years, after which she had no light perception in the right eye but made a good recovery in the left eye. The dose of methotrexate, which she had been receiving for rheumatoid arthritis, was increased to 20 mg/wk (from 2.5 mg/wk) and low-dose prednisolone was commenced when serum AQP4 antibodies were identified after the third episode of optic neuritis.

At the present hospital admission, she presented with a 5-day history of “patchy” visual loss in the left eye. Visual acuity was unchanged from previous measurements, with no light perception OD, and 20/20 OS, which had a paracentral scotoma. The initial concern was recurrent left optic neuritis, but biomicroscopic examination of the left eye identified an isolated area of paler retinal infiltrate nasal to the foveola (Figure 2). The results of an initial Gram stain and culture of a vitreous biopsy on a sample from the left eye were negative. On day 4 of admission, empirical therapy for *T gondii* (oral pyrimethamine, 25 mg twice daily, and sulfadiazine sodium, 1 g 4 times daily) was added to broad-spectrum antibiotics and antifungal treatment (cefazidime sodium, vancomycin hydrochloride, and amphotericin B). An intravitreal injection of voriconazole and clindamycin hydrochloride was administered on day 6 because the woman’s left-eye retinal lesion was enlarging and her visual acuity in that eye had dropped from 20/20 to 20/120.
The white blood cell count and differential were within normal limits; however, the total T lymphocyte cell count (480/μL) as well as the CD4 (280/μL; reference range, 400-1000/μL) and CD8 (190/μL; reference range, 200-700/μL) counts were mildly reduced. Testing identified CMV IgG and Epstein-Barr virus nuclear antigen IgG in the serum, consistent with past infection. The results of human immunodeficiency virus antibody and antigen, CMV IgM, Treponema pallidum, and Toxocara canis serologic testing were negative. The cerebrospinal fluid was acellular, and cerebrospinal fluid polymerase chain reaction testing was negative for herpes simplex, varicella zoster, mumps, enterovirus, and parechovirus. The results of T gondii serologic (IgM and IgG positive) and vitreous polymerase chain reaction testing confirmed the diagnosis of ocular toxoplasmosis, and oral pyrimethamine and sulfadiazine were continued for 6 weeks. Methotrexate was discontinued in view of the risk of severe bone marrow suppression in combination with the antifolate agents pyrimethamine and sulfadiazine. The prednisolone dose was increased to 60 mg/d during this time. The left-eye visual acuity improved to 20/30 (from 20/120 at nadir) after 6 weeks of anti–T gondii treatment and the prednisolone dose was gradually reduced to 20 mg/d (eFigure 3 in the Supplement). The plan for longer-term therapy is to reinstitute methotrexate and continue low-dose prednisolone with the addition of T gondii prophylaxis.

Discussion

We have described retinal opportunistic infections mimicking optic neuritis in 2 patients with AQP4 antibody disease. Such infections are sight-threatening but treatable, and the cases discussed here demonstrate the importance of comprehensive assessment and investigation in patients with AQP4 antibodies presenting with new visual symptoms.

Ocular infections due to CMV and T gondii may be primary or the result of reactivated disease in immunocompromised individuals.5,6 Ocular toxoplasmosis may be acquired in utero (congenital) or postnatally and reactivation can occur with or without an immunocompromised state, whereas CMV retinitis rarely occurs in immunocompetent patients who are not receiving immunosuppressants.7,8 In both of our patients, there was evidence for newly acquired infection: in case 1, baseline CMV serologic testing was negative, but became positive 15 months later when CMV retinitis was diagnosed; in case 2, recent infection was suggested by detection of serum IgM for T gondii.

The cases described in the present report highlight the difficulty in differentiating AQP4-associated optic neuritis from opportunistic retinal infections and the importance of careful ophthalmologic evaluation.

Figure 2. Case 2 Images

Images of the patient’s left eye at presentation. A, A wide-field red-green composite image (Optomap; Optos) demonstrates a fovea-threatening infiltrate. B, A fluorescein angiogram demonstrates late-phase contrast leakage with a central area of nonperfusion. C, The horizontal green arrow through the infrared en face fundus image shows the axial section scanned on optical coherence tomography (OCT). D, The OCT demonstrates focal retinal edema with distortion of the internal limiting membrane.
including slitlamp biomicroscopy and dilated fundus examination. With the earlier diagnosis and use of immuno-suppression in AQP4 antibody disease, a low index of suspi-

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