Bilateral intermediate uveitis with appearance of frosted branch angiitis and association with *Mycoplasma pneumoniae* infection: case report and review of the literature

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A 12-year-old girl presented with acute bilateral visual loss following a mild upper respiratory tract infection. Clinical examination revealed bilateral severe peripheral retinal vasculitis with an appearance of frosted branch angiitis and cystoid macular edema. All tests for etiological diagnosis were negative, apart from positive IgM and IgG antibodies for *Mycoplasma pneumoniae*. She was treated with broad-spectrum antibiotics and intravenous corticosteroids. She responded to treatment, with dramatic improvement of her visual acuity, remission of angiitis, and a residual macular star formation. This is the first reported case of bilateral intermediate uveitis possibly associated with *Mycoplasma pneumoniae* infection.

Frosted branch angiitis (FBA) is a rare condition characterized by acute bilateral uveitis with extensive retinal perivasculitis and severe sheathing of retinal vessels. Kleiner[1] classified FBA patients into three subgroups: (1) patients with leukemia or lymphoma who demonstrated a "frosted branch appearance" due to infiltration of retinal vessels by malignant cells, (2) patients with a "frosted branch response" to active infections or autoimmune diseases, and (3) otherwise healthy patients with an infectious precedent leading to "acute idiopathic frosted branch angiitis." The actual pathogenetic mechanism of FBA remains unclear. We describe a rare case of bilateral intermediate uveitis with acute idiopathic frosted branch angiitis, secondary to *Mycoplasma pneumoniae* infection.

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Case Report

A 12-year-old girl presented for emergent care at Papageorgiou General Hospital, Thessaloniki, with acute bilateral visual loss of 1 day's duration. One week prior to presentation she had recovered from an upper respiratory tract infection for which she received oral clarithromycin and antipyretics. She had no past medical history of note.

On ophthalmological examination, best-corrected visual acuity was counting fingers at 1 m in the right eye and 20/200 in the left eye. Intraocular pressure was normal in both eyes. Slit-lamp examination revealed bilateral anterior chamber inflammation (cells +2) and vitritis (cells +2). Dilated fundus examination revealed bilateral severe sheathing of the peripheral retinal vessels, with the appearance of frosted branch angiitis, and cystoid macular edema (CME; Figures 1A,B and 2A,B). No disk abnormalities or retinal hemorrhages were noted. She was otherwise systemically well. Spectral domain optical coherence tomography (SD-OCT) demonstrated a severely edematous macula; fluorescein angiography showed extensive dye leakage from all peripheral vessels. The patient was diagnosed with bilateral severe intermediate uveitis with acute FBA and secondary macular edema. She was started on topical corticosteroids (dexamethasone 0.1% eyedrops) and cycloplegics, broad-spectrum intravenous antibiotics (erythromycin, amoxicillin, acyclovir), and a 3-day course of high-dose intravenous corticosteroids (methylprednisolone 500 mg).

A thorough laboratory work-up was conducted, including the following: full blood count, renal and liver function tests, clotting, inflammatory markers (CRP, ESR), autoimmune profile (ANA, ANCA, RhF, HLA-B51), ACE levels, serological testing for infectious causes (HSV, VZV, EBV, CMV, toxoplasma, rubella, VDRL, FTA-ABS), antistreptolysin-O titer, atypical screen (mycoplasma, legionella), throat swabs, and blood and urine cultures. Mantoux and QuantiFERON assays were performed. Chest radiography and computed tomography (CT) of the thorax were also performed. The only abnormal results on the day of presentation were raised inflammatory markers (WCC, CRP). By the third day of treatment, after completion of the intravenous course of corticosteroids, the patient showed some improvement of best-corrected visual acuity (right eye, 20/400; left eye, 20/200) but still exhibited signs of vitritis and perivasculitis.

At this point she was switched to oral corticosteroids (prednisolone 4 mg/kg daily) and oral antibiotics (erythromycin, amoxicillin). Laboratory investigations disclosed no abnormal findings other than high titers of IgM and IgG antibodies for *M. pneumoniae* infection (IgM ≥ 1:16,

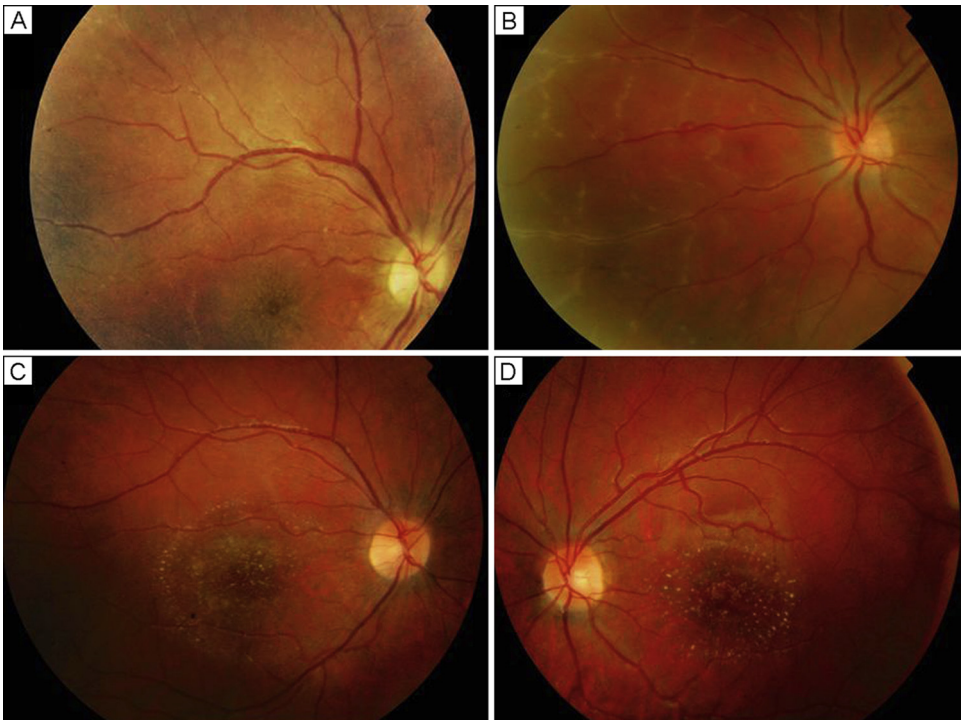

FIG 1. Fundus photographs of the right eye (A) and left eye (B) at presentation showing significant peripheral retinal vascular sheathing. The right eye (C) and left eye (D) at 2 months' follow-up showing complete resolution of active inflammatory signs and formation of macular star.

IgG ≥ 1:32), suggesting an active or more likely a recent mycoplasma infection. Consequently, her antibiotic treatment was tailored to the identified pathogen (erythromycin only), and she continued on reducing regime of oral corticosteroids. On day 7 of her admission she showed significant improvement, with her best-corrected visual acuity improving to 20/200 in the right eye and 20/100 in the left eye, while the perivasculitis had fully resolved. During the following weeks, repeat OCT and fundus examination confirmed resolution of the macular edema, which was followed by macular star formation (Figures 1C,D and 2C,D).

At 5-months' follow-up, best-corrected visual acuity had improved to 20/30 in the right eye and 20/25 in the left eye and retinal appearances had normalized. Meanwhile, she was completely weaned off prednisolone and had completed 3 separate 7-day courses of oral erythromycin for persistently raised *Mycoplasma* IgM antibody titers. The elevated IgM titers persisted for approximately 3 months, in agreement with previous reports,[2] where antibodies to *M. pneumoniae* (IgM and IgG) could persist for several months in serum after infection. Of note, the continued presence or absence of antibodies cannot be used to determine the success or failure of therapy.

Discussion

FBA is a rare retinal vascular reaction considered to result most frequently from exposure to an infectious agent; a neoplastic or idiopathic process may also be the cause.[3] Funduscopic findings are characteristic of this condition, which typically affects children and young adults. Systemic corticosteroids are the mainstay of treatment and often result in significant clinical improvement. The prognosis is generally good.

In our case there was presumably a link between the high titers of anti-*Mycoplasma* antibodies and the clinical syndrome of intermediate uveitis with acute idiopathic FBA, despite the lack of obvious lower respiratory tract infection, as confirmed by a normal CT chest scan. Although it cannot be directly demonstrated that the uveitis was secondary to *M. pneumoniae* infection, the fact that no other causative agent was identified and that uveitis is within *Mycoplasma*'s biological ability in terms of pathophysiology of extrapulmonary disease, together with the dramatic response to treatment (broad-spectrum antibiotics, systemic corticosteroids), support our assumption that *Mycoplasma* was the culprit in our case.

It is well known that *M. pneumoniae* causes atypical pneumonia often with extrapulmonary manifestations. Ocular manifestations mainly include conjunctivitis, papillitis, cranial nerve palsies, and, less frequently, uveitis.[4] Three possible pathophsyiological mechanisms have been suggested to explain the *M. Pneumoniae* extrapulmonary disease.[2,4] The first is direct, whereby the pathogen triggers local inflammation by cytokine induction at a distant site, where it is hematogenously