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Case report

Acute onset of fingolimod-associated macular edema

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ABSTRACT

Purpose: Fingolimod is among the first oral disease-modifying agents for the treatment of relapsing-remitting multiple sclerosis (MS). Despite its favorable safety profile, fingolimod may cause macular edema, a significant adverse event, which occurs within the first 4 months of therapy. Macular edema usually resolves upon discontinuation of fingolimod; however, the time required for resolution of this condition is unknown.

Observations: A 42-year-old white male with a history of relapsing-remitting MS presented with blurring of vision in his left eye 24 h after the first dose of fingolimod. Dilated fundus examination of the left eye revealed an increased retinal thickness and mild optic disc pallor. Spectral domain optical coherence tomography (SD-OCT) confirmed the diagnosis of cystoid macular edema. Topical nonsteroidal anti-inflammatory drug (NSAID) was initiated immediately after the diagnosis, and fingolimod therapy was discontinued shortly thereafter. Seven weeks after the initial presentation, intermediate uveitis was noted in the inferior periphery of the left eye, and SD-OCT revealed worsening of macular edema. Acetazolamide therapy was added to the topical NSAID to control the edema. Three weeks after initiation of acetazolamide, macular thickness reduced significantly. The patient then stopped all medications, and 3 weeks later macular edema rebounded. Systemic steroid was employed to control both the intermediate uveitis and macular edema.

Conclusions and importance: We report a case of acute and very rapid onset of fingolimod-associated macular edema (FAME). Acetazolamide may have a beneficial effect on macular edema secondary to fingolimod. It is unclear if intermediate uveitis is associated with the rapid development of FAME.

1. Introduction

Fingolimod is among the first oral disease-modifying therapeutic agents approved by the United States Food and Drug Administration for the treatment of the relapsing-remitting form of multiple sclerosis (MS).[1] It is a sphingosine-1-phosphate (S1P) receptor modulator that decreases the release of lymphocytes from peripheral lymphoid organs to systemic circulation, thereby reducing the immune-mediated infiltration of these lymphocytes into the central nervous system.[2] Macular edema is a significant ocular adverse event reported in randomized clinical trials of fingolimod therapy for multiple sclerosis. The overall incidence of fingolimod-associated macular edema (FAME) after a 0.5-mg dose in both the FREEDOMS and TRANSFORMS trials was 0.2%.[3] Several lines of evidence suggest that fingolimod increases vascular permeability via its effect on endothelial S1P receptor, which ultimately results in FAME.[4,5] Diabetes and prior history of uveitis were found to be associated with increased risk of developing FAME in initial clinical studies.[6–9] Most cases of FAME resolve spontaneously upon cessation of fingolimod therapy. However, given a relatively low incidence of this condition, the time period required for spontaneous resolution remains unknown. In this report, we describe a case of acute and very-rapid-onset FAME.

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2. Case report

Our patient was a 42-year-old white male with an 11-year history of relapsing-remitting MS involving the brainstem and spinal cord. The patient started to receive injectable interferon beta-1a (IFN-β1a) soon after the diagnosis and had not had major relapses or significant side effects from IFN-β1a since. The patient had no diabetes; his medical history was notable only for depression. The patient sought other treatment options after being weary of weekly intramuscular injections of IFN-β1a, severe flu-like symptoms, persistent fatigue, and worsened episodes of pre-existing depression. He was referred for baseline ophthalmological evaluation prior to switching from IFN-β1a to fingolimod. Neurological examination was unremarkable except for a mild left foot drop. Neuro-ophthalmological examination was normal except for residual left eye adduction saccade secondary to prior intranuclear ophthalmoplegia, mild relative afferent pupillary defect with mild optic nerve pallor secondary to previous episode of optic neuritis, and epipapillary vascular frond in the left eye (Fig. 1A). Best-corrected visual acuity (BCVA) on initial evaluation was 20/20 in both eyes. Funduscopic examination did not reveal any peripheral exudates, snowballs, or snow bank in both eyes. Humphrey visual fields and spectral domain optical coherence tomography (SD-OCT) macular thickness were within normal limits in both eyes. IFN-β1a was stopped on the day that fingolimod therapy was initiated. Twenty-four hours after the first 0.5-mg dose of fingolimod, the patient noticed painless blurring of vision in the left eye. The blurring initially affected the lower part of the visual field and gradually progressed to a ring/donut shape. Examination conducted 3 days after the initiation of fingolimod therapy revealed that the BCVA had declined to 20/30 in the left eye and remained unchanged in the right eye. Color vision was normal in both eyes, but contrast sensitivity was decreased in the left eye. Patient reported no pain with extraocular movements in either eye. Slit lamp examination was unremarkable in both eyes. Funduscopy revealed dull foveal reflex with retinal thickening and unremarkable periphery in the left eye. Diagnosis of macular edema was confirmed with SD-OCT, which demonstrated increased central macular thickness (CMT) of 501 μm, multiple intraretinal cystic spaces, and mild subretinal fluid (Fig. 2B) in the left eye. Immediately after the diagnosis, treatment with a topical nonsteroidal anti-inflammatory drug (NSAID) was started in the left eye. Fingolimod therapy was discontinued 3 days later by the neurologist after discussing other treatment options with the ophthalmologist and the patient. At the 2-week follow-up visit, after the diagnosis of FAME was made, the BCVA in the left eye remained stable; however, SD-OCT revealed worsening of macular edema with increased subretinal fluid and CMT to 613 μm (Fig. 2C). Four weeks after FAME was diagnosed, there remained subtle change in the macular edema with CMT of 590 μm; thus, topical dorzolamide was added. Three weeks later, fundus examination of the left eye revealed snowballs and snowbanks in the inferior periphery (Fig. 1B). Fluorescein angiography (FA) showed characteristic petaloid pattern of cystoid macular edema in the left eye along with perivascular leakage from the inferior peripheral vessels, hyperfluorescence of the dilated tortious epipapillary vascular frond, and staining of the optic nerve head (Fig. 1C and D). Macular edema was persistent with CMT of 550 μm. SD-OCT and FA of the right eye were unremarkable. A systemic carbonic anhydrase inhibitor, acetazolamide, in a dose of 500 mg twice daily was added to the current therapy. Three weeks after acetazolamide was added, the left eye showed significant reduction in the CMT to 331 μm with restoration of foveal contour, disappearance of intraretinal cysts, and resolution of the subretinal fluid (Fig. 2D). The BCVA in the left eye improved to 20/25 + 3. Following this improvement, the patient was instructed to continue treatment for 2 additional weeks and then taper acetazolamide to 250 mg twice daily. Despite these instructions, the patient stopped all medications. Three weeks later, SD-OCT detected recurrence of macular edema with a slight decline of BCVA to 20/25−2 in the left eye (Fig. 2E). In addition, fundus examination revealed persistent snowballs and snowbanks; similar to previous angiogram, FA continued to show macular leakage, periphlebitis, and staining of the optic disc in the left eye. Therapy with 40-mg/day oral prednisone was initiated to control both the periphlebitis and macular

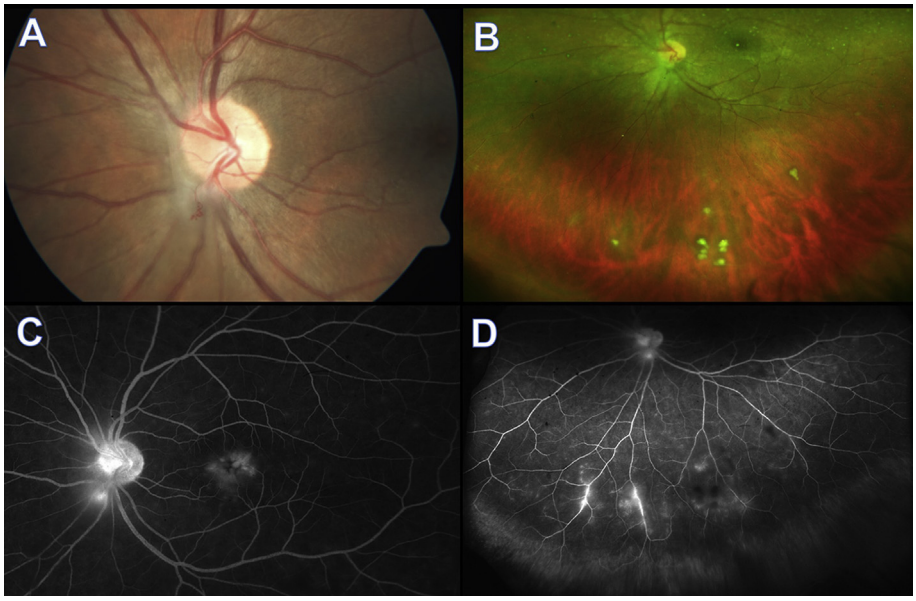

Fig. 1. Color fundus photograph of the left eye (A; initial fundus exam) and fluorescein angiograms (FA) of the left eye (B, C, and D; initial FA after diagnosis of fingolimod-associated macular edema). A: Dilated tortious vascular frond projecting into the vitreous and glial tissue inferonasal and nasal to the optic disc, respectively. B: Snowballs in the inferior periphery. C: Cystoid macular edema with hyperfluorescence inferonasal to the optic disc, corresponding to the dilated tortious vessel seen on the color photograph and staining of the nasal part of the optic disc. D: Perivascular leakage of retinal vessels in the inferior periphery.

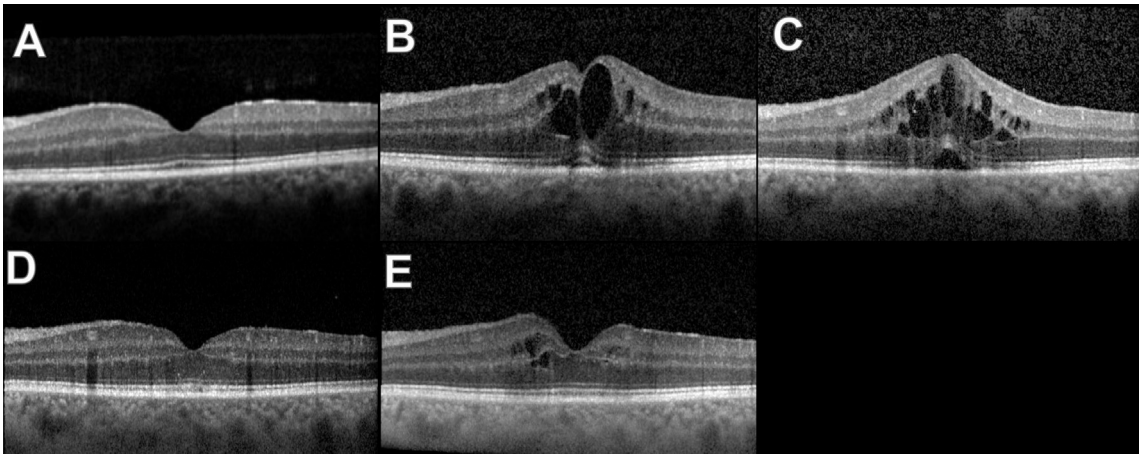

Fig. 2. Spectral domain optical coherence tomography images. A: Unremarkable macular appearance at baseline. B: Macular edema with minimal subretinal fluid right after fingolimod administration. C: Worsening of macular edema with increased subretinal fluid 2 weeks after stopping fingolimod. D: Resolution following acetazolamide supplementation. E: Rebound of macular edema 3 weeks after acetazolamide cessation.

edema. Prednisone was then tapered to 20 mg/day over 6 weeks. During the follow-up visit 8 weeks later, resolution of macular edema and decreased perivascular leakage were noted. Prednisone was continuously tapered to 5 mg/day, and the patient remained clinically stable without recurrence of uveitis or macular edema.

3. Discussion

To the best of our knowledge, this is the first report of the earliest case of FAME, occurring within 24 (based on symptoms) to 72 (based on SD-OCT) hours after initiation of fingolimod. The report also highlights the potential role of systemic carbonic anhydrase inhibitor in the management of FAME.

Apart from cessation of fingolimod therapy, there is no consensus about the optimal management of FAME. In the clinical trials of fingolimod for MS (TRANSFORMS and FREEDOMS), approximately 80% cases of FAME resolved spontaneously following cessation of the 0.5-mg fingolimod therapy.[10,11] In these trials, only 1 participant with FAME did not show improvement after fingolimod cessation, but detailed description and long-term follow-up of this case were lacking. Topical NSAIDs have been used to hasten the resolution of FAME with reports of edema resolution within 1 month of treatment. The potential benefit of NSAID therapy is edema resolution within 1 month as opposed to 4 months that may be needed for edema resolution after fingolimod cessation alone.[12] However, based on the currently available case reports, the natural course of FAME cannot be fully elaborated, and thus, it is unknown whether NSAID therapy is beneficial.

It is often challenging to demonstrate whether a certain treatment is effective or not, especially when macular edema can resolve spontaneously with discontinuation of fingolimod, leaving one to wonder whether time or therapy has led to edema resolution. In our case, worsening of macular edema occurred despite cessation of fingolimod and use of topical NSAIDs for more than 1 month. On the other hand, addition of acetazolamide resulted in significant decline in macular thickness and resolution of the intraretinal cysts within 3 weeks. Since acetazolamide for the treatment of FAME has shown benefits in a recent report,[13] we opted for such therapy after noting the failure of topical treatment and before proceeding with systemic steroid or invasive therapy such as intravitreal or sub-Tenon's steroid. Recurrence of macular edema after tapering acetazolamide treatment was previously described by Schröder et al.[13] In our case, premature discontinuation of acetazolamide and persistent intermediate uveitis may have contributed to this recurrence.

Development of intermediate uveitis after fingolimod administration is perplexing. IFN-β, previously used to treat relapsing MS in this patient, is known to be effective in controlling intermediate uveitis and CME associated with MS.[14,15] Thus, the abrupt discontinuation of IFN-β, rather than the commencement of fingolimod, might have led to recurrence of uveitis. In addition, it is possible that IFN-β cessation might have played a role in the rapid development of FAME in this patient. Also, subclinical or prior intermediate uveitis might have contributed to the acute onset of FAME. Several facts support this possibility. First, prior history of uveitis is associated with an increased risk of FAME, according to previous MS trials.[3] Second, it is possible that active intraocular inflammation existed but was insufficiently severe to be detected by clinical examination prior to fingolimod initiation. This existing inflammation could have precipitated the very rapid onset of macular edema following fingolimod initiation. Also, worsening of edema even after fingolimod discontinuation and recurrence of edema after acetazolamide cessation imply that an underlying inflammatory component, not just fingolimod, might have contributed to edema.

Currently, sufficient data on the use of fingolimod in the setting of active or prior intermediate uveitis are lacking; it is unknown if a pervious episode or active inflammation in the peripheral retina has any role in precipitating acute FAME as seen in this case.

In conclusion, FAME may occur very rapidly after initiation of fingolimod therapy. Acetazolamide may be considered as an option for the treatment of FAME before other, more invasive therapeutic options are explored. Careful examination of the peripheral retina to detect signs of intermediate uveitis is warranted before fingolimod initiation. IVFA to detect retinal periphlebitis may be considered as a baseline evaluation prior to fingolimod administration to exclude active uveitis, a potential risk factor for the acute development of FAME.

Patient consent

The patient consented in writing to participation in a study, in the course of which the images included in this report were taken. This report does not contain any identifying information.

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Conflict of interest

Dr. Nguyen is the Editor in Chief of American Journal of Ophthalmology Case Reports. Given his role as Editor in Chief, Dr. Nguyen had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Dr. Eric Suhler. Anna Boyum, the Managing Editor of American Journal of Ophthalmology Case Reports, helped to edit this report. As Managing Editor, Dr. Boyum is not authorized to make a decision to accept or reject articles submitted to the journal.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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