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Siponimod-associated cystoid macular edema without known risk factors

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ABSTRACT

Purpose: This case report highlights the importance of monitoring ocular health for patients starting on siponimod treatment, a sphingosine-1-phosphate receptor modulator, for relapsing-remitting multiple sclerosis. By showing how medication adverse events present in patients, we can revisit the current guidelines on ophthalmic evaluation recommendations.

Observations: We report a 60-year-old patient who presented with unilateral blurry vision upon initiating siponimod therapy for the treatment of relapsing-remitting multiple sclerosis. Her exam findings did not show visual field defects but were significant for cystoid macular edema distorting the foveal contour. Upon stopping siponimod therapy, the patient's macular edema and symptoms resolved significantly within 7 days and completely resolved 1 month later.

Conclusions and importance: This case showcases siponimod-associated cystoid macular edema in a patient without known risk factors, such as diabetes mellitus and uveitis. The patient also had the earliest reported symptom onset to date following the initiation of siponimod therapy. Current recommendations from the American Academy of Ophthalmology and FDA stress the importance of ophthalmic evaluation three to four months after treatment initiation for patients with a history of risk factors. Given our current case and its comparison with four previously reported cases, we recommend that physicians inform patients of possible ocular adverse events with siponimod therapy regardless of their past medical history and duration of treatment.

1. Introduction

Cystoid macular edema (CME) is an accumulation of fluid within the macular retinal layers due to multifactorial etiologies, such as uveitis, retinitis pigmentosa, medication adverse events, and age-related macular degeneration.[1,2] Symptoms of CME include visual distortion and blurred vision. Siponimod is a sphingosine-1-phosphate receptor (S1PR) modulator used to treat relapsing forms of multiple sclerosis, such as relapsing-remitting multiple sclerosis (RRMS).[3] While Siponimod has proven efficacious in decreasing the relapse rates of multiple sclerosis episodes, it is associated with CME.[4,5]

CME was identified during clinical trials of siponimod. In the BOLD study, a double-blind, randomized phase 2 trial, one patient with a history of uveitis developed CME at the highest dose of siponimod.[6] In the Phase 3 EXPAND study, an increased incidence of CME was reported with siponimod therapy compared to the placebo group, affecting 2 % and <1 % of participants respectively.[7] According to the FDA label for siponimod, patients with uveitis and diabetes mellitus are at an increased risk for developing CME as an adverse event and are recommended for ophthalmic evaluation before and after starting treatment.[8]

Currently, there is a limited number of reported siponimod-associated CME cases.[9–12] Here, we present a case of a patient with no known risk factors who rapidly developed CME after initiating siponimod therapy, highlighting the importance of ophthalmic evaluation.

2. Case report

A 60-year-old female with a history of RRMS presented with blurry vision in the right eye. Her symptoms started 4 weeks before her annual comprehensive eye exam. Her exam was significant for mild bilateral nuclear sclerotic cataracts, with the best corrected visual acuity of 20/40 in the right eye and 20/20 in the left eye. She was referred to neuro-ophthalmology for further evaluation due to a lack of improvement.

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Abbreviations

CME	Cystoid macular edema
RRMS	Relapsing-remitting multiple sclerosis
OCT	optical coherence tomography
S1PR	Sphingosine-1-Phosphate receptor
AAO	American Academy of Ophthalmology
OS	Left eye
OU	Both eyes
OD	Right eye
T2DM	Type 2 Diabetes Mellitus
PDR	Proliferative diabetic retinopathy
BCVA	best corrected visual acuity
CF	Counting fingers

In addition to her diagnosis of RRMS, the patient's past medical history was significant for ulcerative colitis in remission for 40 years, basal cell carcinoma, and migraines. Her list of medications on the day of presentation included siponimod (daily dose of 2 mg after 5 days of titration process) as RRMS therapy, amitriptyline and rizatriptan for her migraine control, and fluorouracil cream for basal cell carcinoma treatment.

The patient was initially diagnosed with RRMS following recurring tingling and numbness and started on a disease-modifying therapy with siponimod. She noticed sudden worsening vision about a week after initiating siponimod. All other diagnoses have been well-controlled and followed up with their corresponding medical specialists without complications. She does not have any known risk factors for siponimod-associated CME.

2.1. Investigation

Our examination revealed a visual acuity of 20/30 in the right eye and 20/20 in the left eye, with no relative pupillary defect bilaterally. Her intraocular pressures measured 14 mmHg in the right eye and 12 mmHg in the left eye, and neuro-ophthalmology evaluation did not reveal evidence of current or prior optic neuritis or uveitis. The optical coherence tomography (OCT) of the optic disc analyzing the average retinal nerve fiber layer (RNFL) thickness (Fig. 1) showed normal values of 114 μm and 116 μ m in the right and the left eye, respectively, and the Humphrey Visual Field 24–2 was unremarkable.

The macular OCT (Fig. 2) of the right eye showed multiple cystic spaces and macular edema affecting the inner and outer nuclear layers with a small pocket of subretinal fluid. The foveal contour was distorted. The examination and OCT of the left eye were within normal limits.

Based on the presentation and lack of other unifying diagnoses, including uveitis, diabetic macular edema, and post-surgical CME, we suspected that the patient's CME was due to siponimod. The patient was advised to stop siponimod therapy and referred to a retina specialist for CME monitoring.

2.2. Outcome & follow-up

The patient stopped taking siponimod and switched to ofatumumab. Within one week of stopping siponimod, the patient's CME improved significantly, and vision clarity returned to normal. At the one-month follow-up examination, the patient's CME resolved completely and the patient had 20/20 visual acuity with normal OCT imaging bilaterally (Fig. 3).

3. Discussion

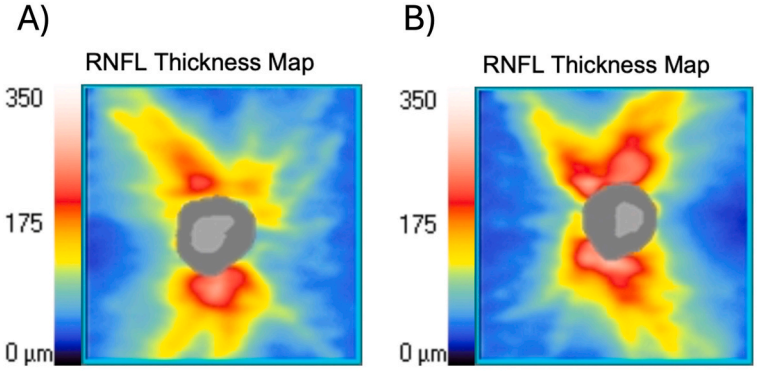
We report a patient without known risk factors who developed CME one week after starting siponimod therapy, which spontaneously resolved a week after stopping siponimod. Siponimod is a new-generation FDA-approved oral drug that works as an S1PR modulator specific to subtypes S1P1 and S1P5 used to treat multiple sclerosis.[13] Multiple sclerosis is a chronic inflammatory neurodegenerative disease, and S1PR modulators work by internalizing the receptor and ultimately preventing lymphocytes from being released from the lymph nodes to be recruited to inflammation sites of the central nervous system.[3] Siponimod has been widely used for its efficacy in stabilizing both clinical and radiological outcomes.[14]

However, as in all medications, siponimod has associated adverse events. Similar to fingolimod, an S1PR modulator that has been on the market for a longer period, patients receiving siponimod are more likely to experience bradycardia, hypertension, lymphopenia, CME, and convulsions compared to placebo.[4,7,15] Although the exact mechanism of S1PR modulation causing CME is unknown, it is postulated that inhibiting S1PR's role in controlling vascular endothelial-cadherin at endothelial junctions and regulating vascular permeability may compromise the blood-retina barrier to cause CME.[3]

Since the EXPAND phase 3 trial on siponimod, only four other cases of siponimod-associated CME have been reported (Table 1). Only two of these cases report patients with known risk factors. This case report presents the earliest symptom onset to date.

The American Academy of Ophthalmology (AAO) recommends that patients with uveitis, diabetic retinopathy, recent intraocular surgery, or optic nerve pallor undergo an initial and a repeat evaluation approximately three to four months after starting fingolimod since most fingolimod-associated CME cases are reported in this timeframe. Six months and annual surveillance are recommended thereafter.[16,17] Currently, there is no AAO recommendation for patients receiving siponimod.

The FDA label for siponimod indicates that diabetes mellitus and uveitis increase the risk of siponimod-associated CME.[8] Based on the



C)

	OD	OS
Average RNFL Thickness	114 µm	116 µm
RNFL Symmetry	82%	
Rim Area	1.74 mm²	1.77 mm²
Disc Area	2.37 mm²	2.15 mm²
Average C/D Ratio	0.50	0.42
Vertical C/D Ratio	0.47	0.43
Cup Volume	0.058 mm³	0.064 mm³

Fig. 1. OCT imaging shows RNFL thickness map of the right eye (OD) (A) and the left eye (OS) (B). The distribution of RNFL by quadrant is shown (C).

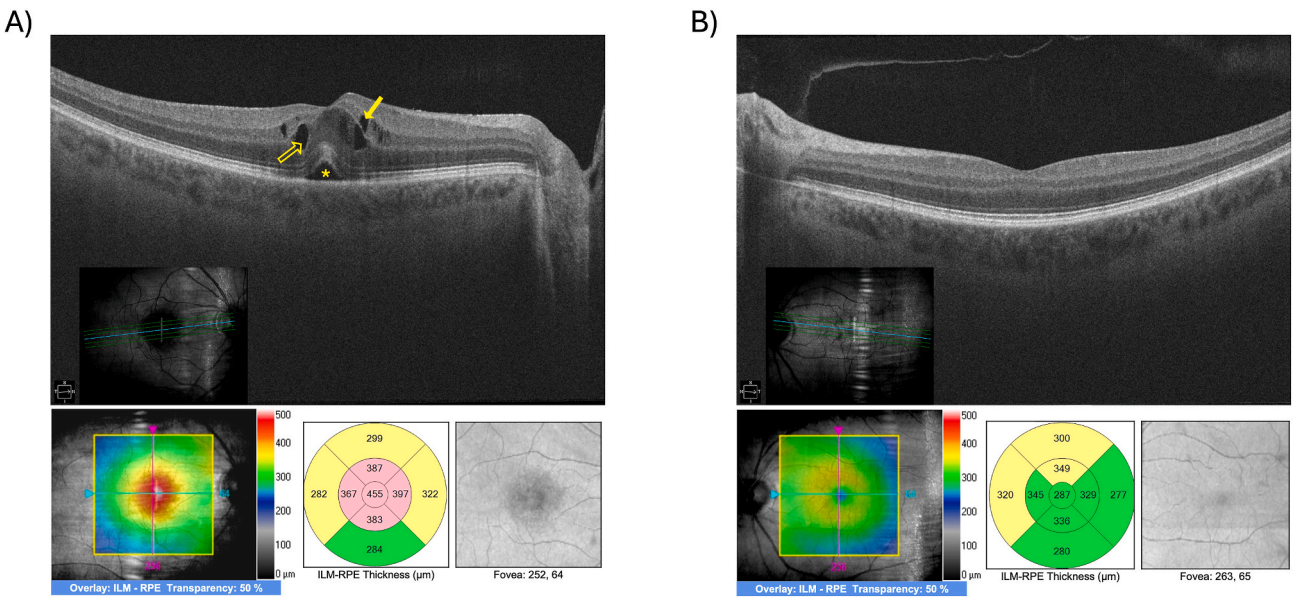


Fig. 2. OCT OD (A) shows cystic spaces in the inner (solid arrow) and the outer (outlined arrow) nuclear layers along with trace subretinal fluid (asterisk). Internal limiting membrane to the retinal pigment epithelium (ILM-RPE) thickness increased due to the underlying cystic spaces. OCT OS (B) shows intact retinal layers with no changes in ILM-RPE thickness.

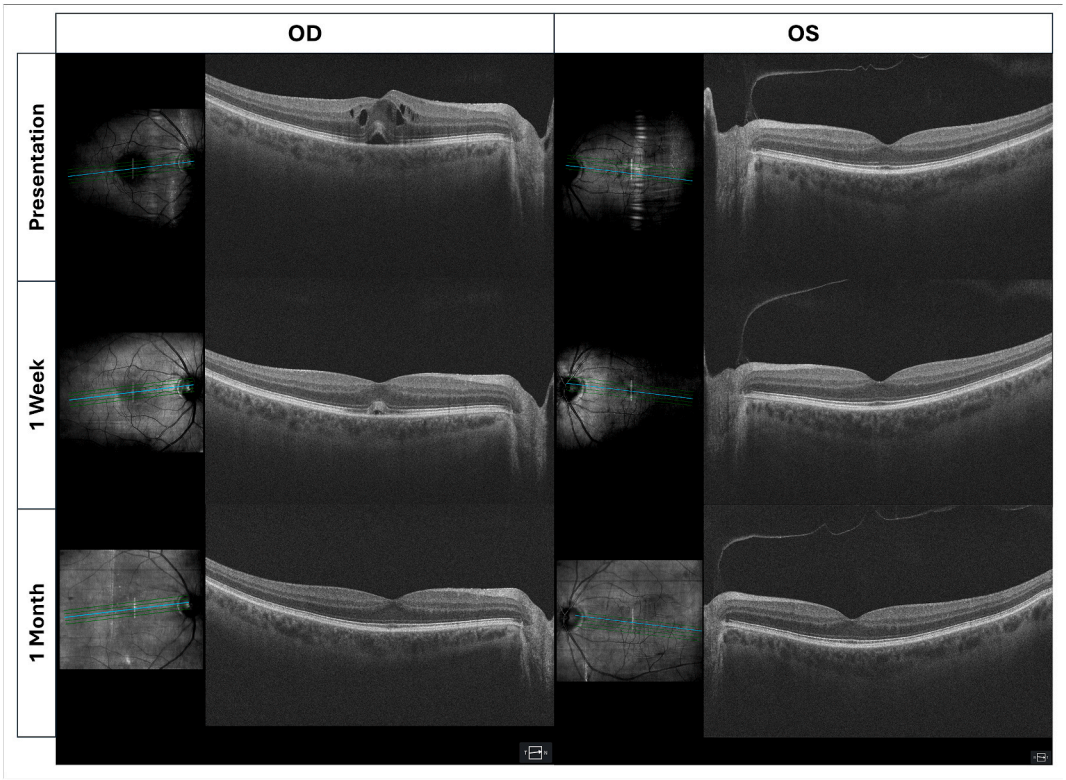


Fig. 3. OCT images at baseline presentation, one week after stopping siponimod, and one-month follow-up. OCT OD shows resolution of cystic spaces in the inner and outer nuclear layers after a week of stopping siponimod with complete resolution at one-month follow-up. OCT OS shows no clinically significant cystic spaces with no noticeable changes throughout.

case presented herein and the cases we reviewed in the literature, we propose that ophthalmic evaluation should be considered for all patients on siponimod regardless of the presence of risk factors.

4. Conclusions

This case highlights the importance of screening and early continuous monitoring for patients starting siponimod therapy. While siponimod-associated CME is a relatively rare adverse event, the increased use of siponimod as a disease-modifying therapy for RRMS

Table 1
Reported cases of siponimod-associated cystoid macular edema in the literature.

Authors	Sex (Age in years)	Presentation	Known Risk Factors	Ocular History	Siponimod (prior to Symptoms)	BCVA (OD, OS)	MS diagnosis	Treatment	Follow-up[#]
Rettler and Gratton (2021)	F (54)	Blurry vision (OS)	Iritis	Iritis	3 months	n/a, 20/25	Unknown	Stopped Siponimod Topical bromfenac & difuprednate	2W: Improved OCT 1M: Complete OCT resolution
Foos et al. (2022)	F (~50)	Blurry vision (OS)	T2DM (A1c: 10.2)	Optic neuritis (OU) PDR w/o ME (OU)	5 months	CF'2, 20/60	RRMS 6 months before presentation	Stopped Siponimod Topical ketorolac & prednisolone	3W: Subjective and OCT improvement 2M: Improved acuity and complete OCT resolution
Li et al. (2023)	F (23)	Incidental ME (OU)	None	None	4–5 months	20/20 OU	RRMS 6 years before presentation	Stopped Siponimod	1M: Improved OCT, Restarted Siponimod 1Y: No changes
Miscioscia et al. (2024)	F (50)	Blurry vision (OU)	None	None	3 weeks	20/50, 20/70	RRMS 12 years before presentation	Stopped Siponimod	13D: Recovered visual acuity and complete OCT resolution
Our case	F (60)	Blurry vision (OD)	None	None	1 week	20/30, 20/20	RRMS 3 months before presentation	Stopped Siponimod	7D: Improved acuity and OCT 1M: Complete OCT resolution

Cases were found based on a PubMed search using the keywords [(siponimod) AND (macular edema)] and Google Scholar search with the keywords (siponimod, "macular edema", "case report").
Abbreviations: OU: Both eyes, T2DM: Type 2 diabetes mellitus, PDR: Proliferative diabetic retinopathy, BCVA: Best corrected visual acuity, CF: Counting fingers.
[#] Units of time given as W: week, M: month, Y: year time points since initial treatment for CME.

may result in increased incidence and warrants consideration for increased ophthalmic screening of these patients. Understanding how adverse events present in clinical settings is crucial in fostering future investigation on mechanisms of adverse outcomes and formulating comprehensive guidelines for therapeutic use.

Patient consent

The patient consented to publication of the case in writing.

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Authorship

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

CRediT authorship contribution statement

Min Young Kim: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Anas Alkhabaz:** Writing – review & editing, Visualization, Methodology, Investigation, Data curation. **Stephen J. Smith:** Writing – review & editing, Validation, Supervision, Resources, Investigation. **Yaping Joyce Liao:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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