DOI: 10.14744/eer.2023.94695
Eur Eye Res 2023;3(2):94-100

EUROPEAN EYE RESEARCH

CASE REPORT

Should all macular edema be treated with intravitreal injection? Importance of fundus fluorescein angiography in macular edema

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Abstract

Macular edema (ME) is a common entity that can accompany a wide range of diseases. Diagnosing the underlying cause of ME is therefore of great importance. We present two cases of persistent ME. The first patient was a 43-year-old female and the other was a 31-year-old male. Both patients were diagnosed with ME before applying to our clinic and were treated with intravitreal anti-VEGF injections. Detailed examination revealed vitritis and fundus fluorescein angiography showed vasculitic leakage in both patients. The patients were diagnosed as uveitic ME and treated accordingly. Moreover, the second patient was diagnosed with Behçet's disease in a very short time. Multimodal imaging and detailed examination are crucial in handling of patients with ME. Especially in young patients, uveitis and vasculitis should be suspected.

Keywords: Fundus fluorescein angiography; macular edema; multimodal imaging; uveitis.

Macular edema (ME) is defined as intra or subretinal collection of fluid in the macular area. It is a common manifestation of a wide range of various clinical entities including diabetes, retinal vein occlusion, central serous retinopathy, age-related macular degeneration, and posterior uveitis.[1,2] Fortunately, although ME stands as a major cause of visual morbidity, it is also one of the most treatable causes of visual impairment with the options of antiangiogenic and glucocorticoid agents. However, if the underlying cause is not correctly diagnosed and treated, ME often recurs or becomes persistent. This adversely affects the patients' vision. Therefore, it is of great importance to diagnose the underlying cause and treat these patients accordingly. In this article, we aimed to present the diagnosis and treatment process of two patients with ME whose etiology was not investigated, and appropriate diagnostic tests were not performed.

Case Report

Case 1 – A 43-year-old female patient applied to the rheumatology outpatient clinic with the complaint of back pain and was consulted to our clinic as she had a complaint of blurred vision. She had been given five intravitreal bevacizumab injections with the diagnosis of ME in a different

Cite this article as: Sarigul Sezenoz A, Gur Gungor S, Gunay SE. Should all macular edema be treated with intravitreal injection? Importance of fundus fluorescein angiography in macular edema. Eur Eye Res 2023;3:94-100.

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Submitted Date: 04.05.2023 **Accepted Date:** 13.07.2023

center. The best-corrected visual acuity (BCVA) was 0.8 in the right eye and 1.0 in the left eye in decimals. The biomicroscopic anterior segment evaluation was within normal limits; however, a +2 vitritis was observed in the right eye. The intraocular pressure (IOP) was 19 mmHg with Goldmann applanation tonometry. Fundus examination revealed bilateral hyperemic optic discs (Fig. 1a). Color vision, tested with Ishihara, was normal in both eyes.

The spectral domain macular optical coherence tomography (OCT) revealed cystoid ME and subretinal fluid in the right eye (Fig. 1b). Fundus fluorescein angiography (FFA) was performed, and significant bilateral peripheral vas-

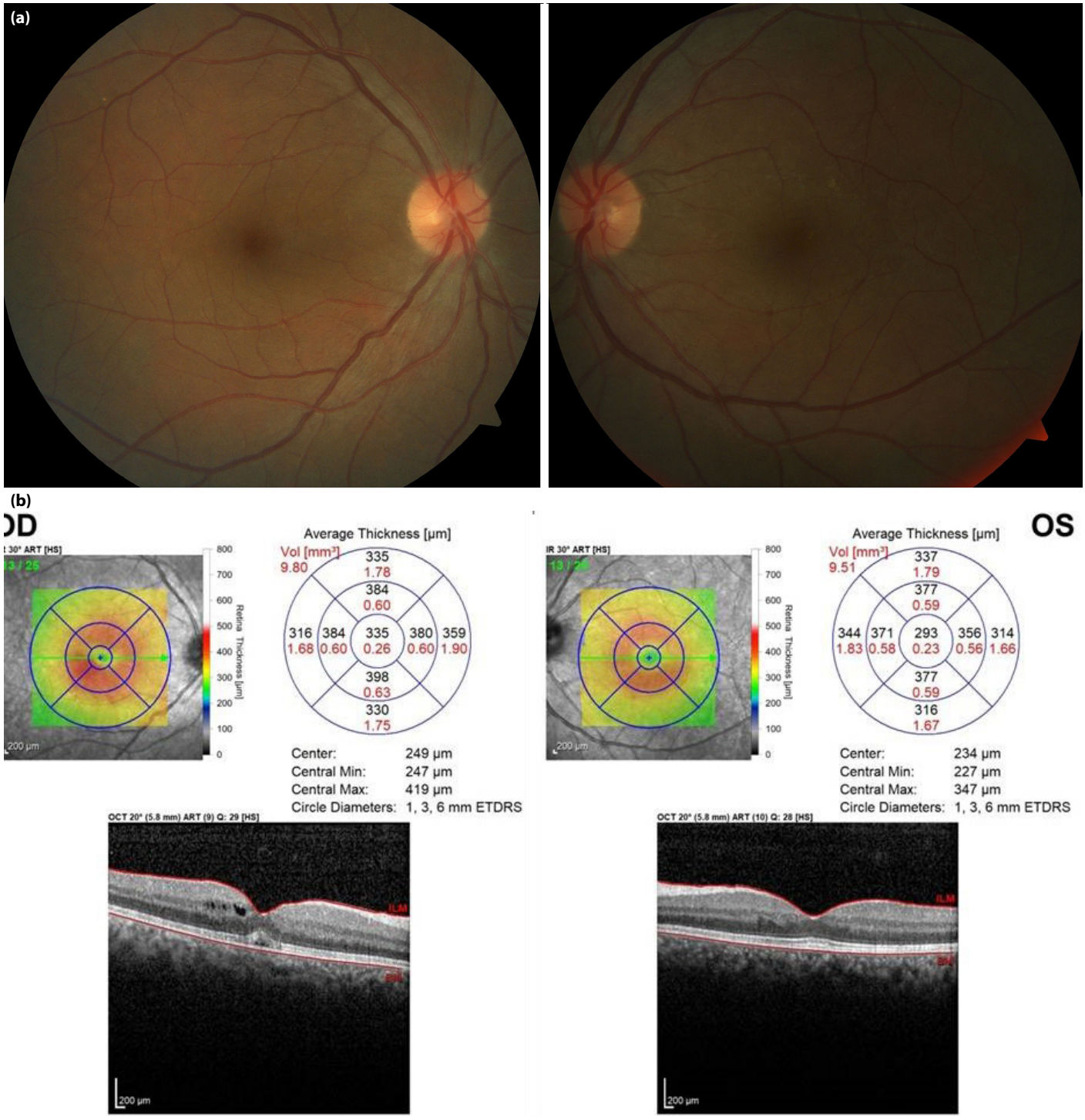

Fig. 1. **(a)** The fundus photograph of case 1 showing of bilateral optic disc hyperemia, **(b)** The spectral domain macular optical coherence tomography image showing cystoid macular edema and subretinal fluid in the right eye.

culitic leakage and optic disc hyperfluoresence were observed (Fig. 2).

The patient was screened for the possible infectious uveitic and rheumatologic causes. The complete blood count (CBC) and erythrocyte sedimentation rate (ESR) were within normal limits. C-reactive protein level (CRP) was slightly elevated. Tuberculin skin test, chest radiography, Treponema pallidum hemagglutination test-VDRL, serum angiotensin converting enzyme level, serum lysozyme, and Borrelia serology were all negative. HLA tissue typing did not reveal any specific diagnosis. The patient was diagnosed as undifferentiated seronegative spondyloarthropathy-related sacroiliitis and bilateral ischial enthesopathy. The patient was given a subtenon triamcinolone injection and started on azathioprine 150 mg/day. In her last visit 3 months after, the BCVA was 1.0 in both eyes, anterior segment was normal and the vitreous was clear. No obvious ME was present in macula OCT (Fig. 3). No IOP raise was observed during the follow-up period.

Case 2 – A 31-year-old male patient had a complaint of reduced vision in his right eye for 6 months. He was given three doses of intravitreal ranizumab injections for ME with a diagnose of central serous chorioretinopathy. He had a history of anisometropic amblyopia. His BCVA in decimals was 0.3 in the right eye and 0.4 in the left eye. The spherical equivalent obtained after cycloplegin was +0.50 D in the right eye and +2.00 in the left eye. The IOP measured with Goldmann applanation tonometry was 17 mmHg in the right eye and 19 mmHg in the left eye. Biomicroscopic anterior segment evaluation and fundus examinations were within normal limits except +2 vitritis in the right eye. Color vision tested with Ishihara was normal for both eyes.

A FFA was performed which revealed optic disc hyperfluoresence with diffuse capillary leakage in the right eye and vasculitic leakage in temporal area in the left eye (Fig. 4). Cystoid ME in the right eye was observed with macula OCT (Fig. 5a).

His detailed anamnesis revealed that he also had a story of recurrent oral ulcers. The CBC, CRP, and ESR were with-

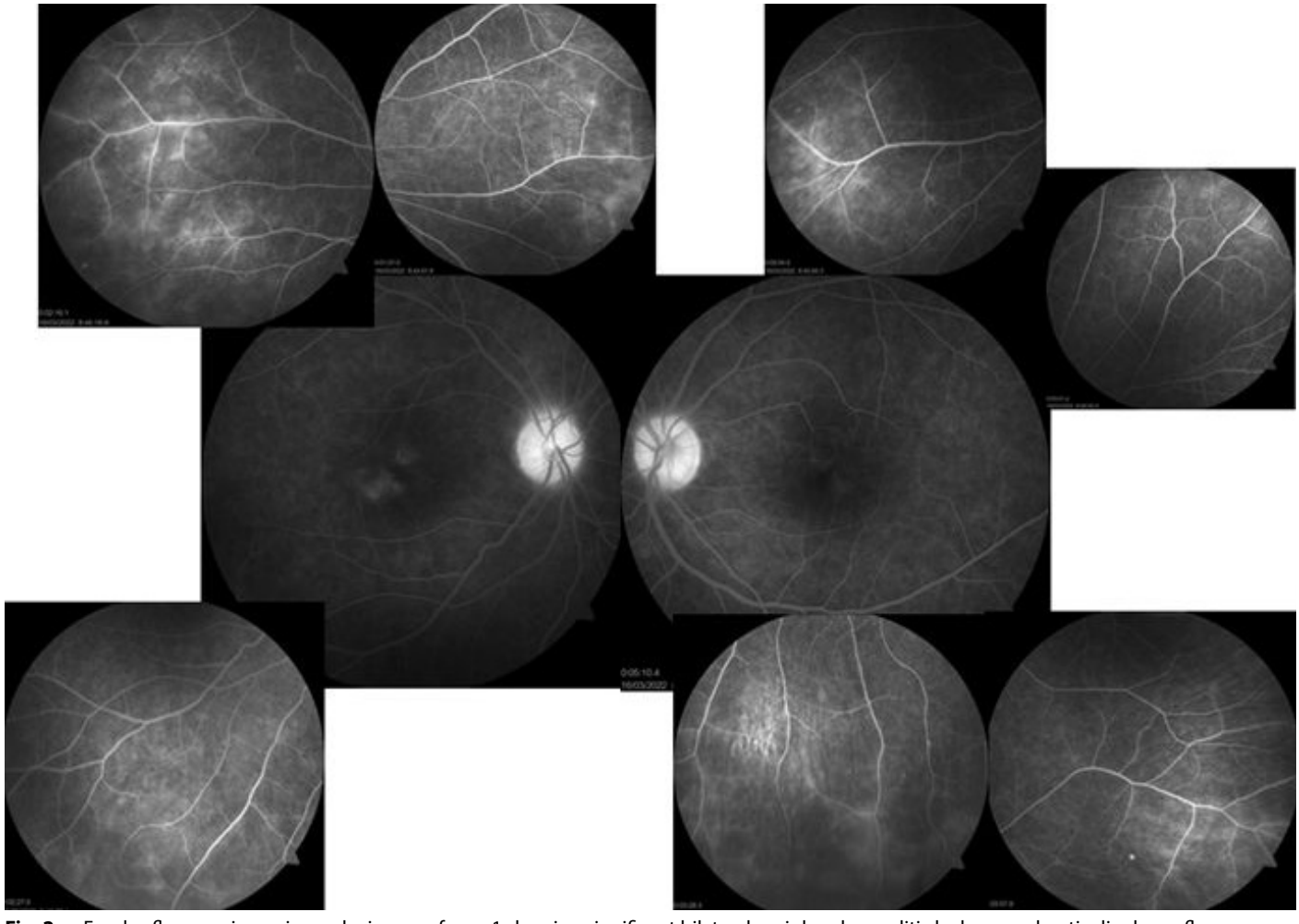

Fig. 2. Fundus fluorescein angiography image of case 1 showing significant bilateral peripheral vasculitic leakage and optic disc hyperfluoresence.

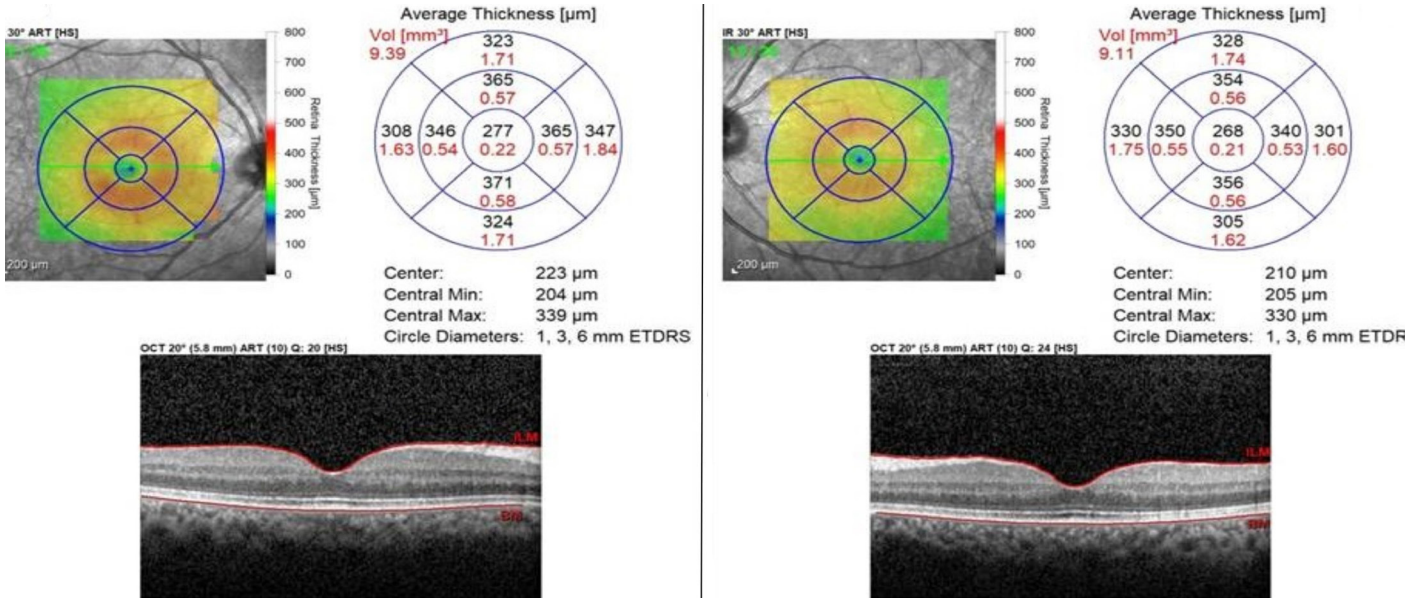

Fig. 3. The macular optical coherence tomography image of case 1 after treatment.

in normal limits. Tuberculin skin test, chest radiography, Treponema pallidum hemagglutination test-VDRL, serum angiotensin-converting enzyme level, serum lysozyme, and Borrelia serology were all negative. The patient was consulted to the rheumatology department, and he was tested positive for pathergy. He was diagnosed as Behçet's disease and was immediately started on azathioprine 100 mg/day and prednisolone 32 mg/day. In the follow-up, he developed a deep vein thrombosis in his left leg and therefore the azathioprine dose was increased to 150 mg/day. Systemic anticoagulant therapy was also started. 3 months later, the cystoid ME of the right eye regressed but not totally recovered, so cyclosporine 150 mg/day was added. Interferon alfa 6 mIU/day was started at the

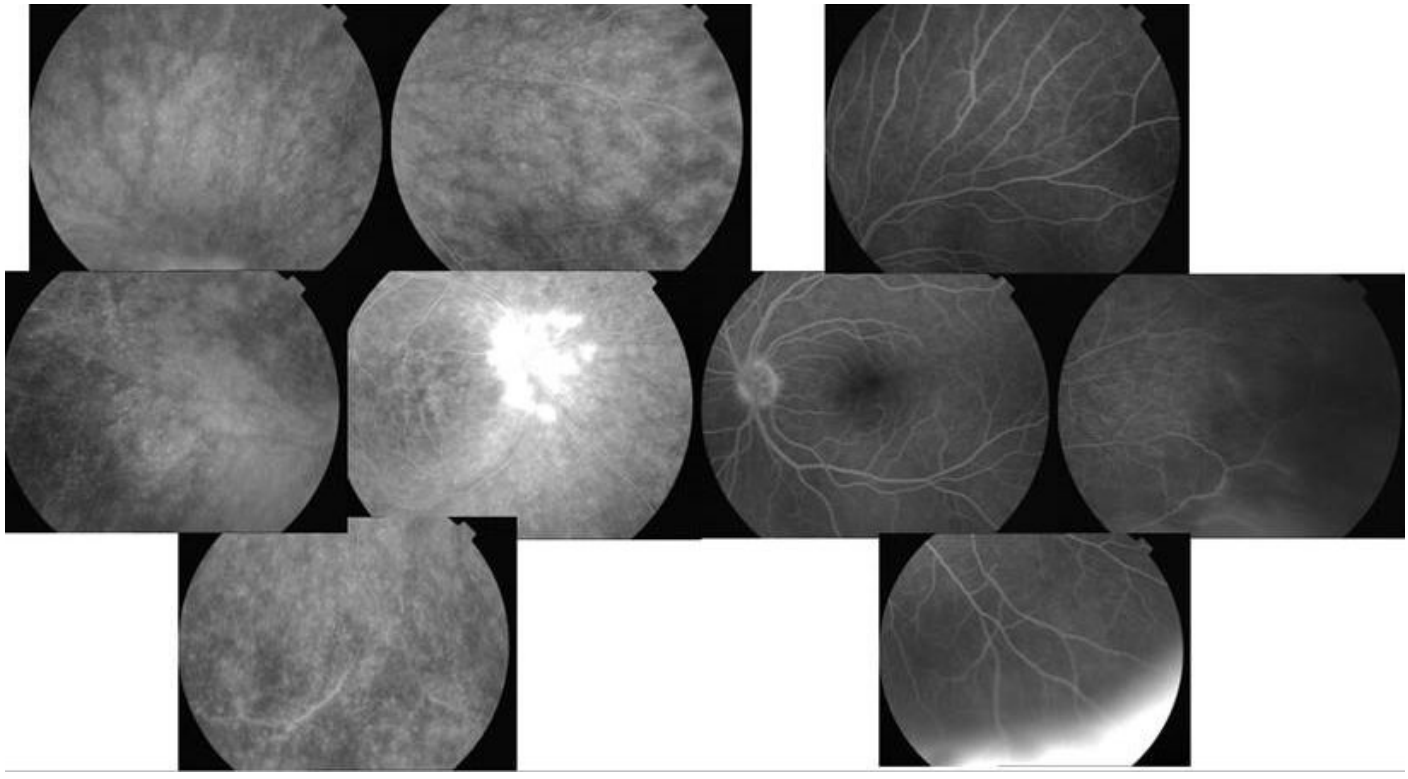

Fig. 4. The fundus fluorescein angiography images of case 2 showing optic disc hyperfluoresence with diffuse capillary leakage in the right eye, vasculitic leakage in temporal area in the left eye.

6th month of treatment because of the persistence of vascular leakage in FFA and recurrence of ME. The patient's ME responded well to this treatment and completely recovered (Fig. 5b). Afterward, the patient moved to another city due to his profession and was excluded from our follow-up.

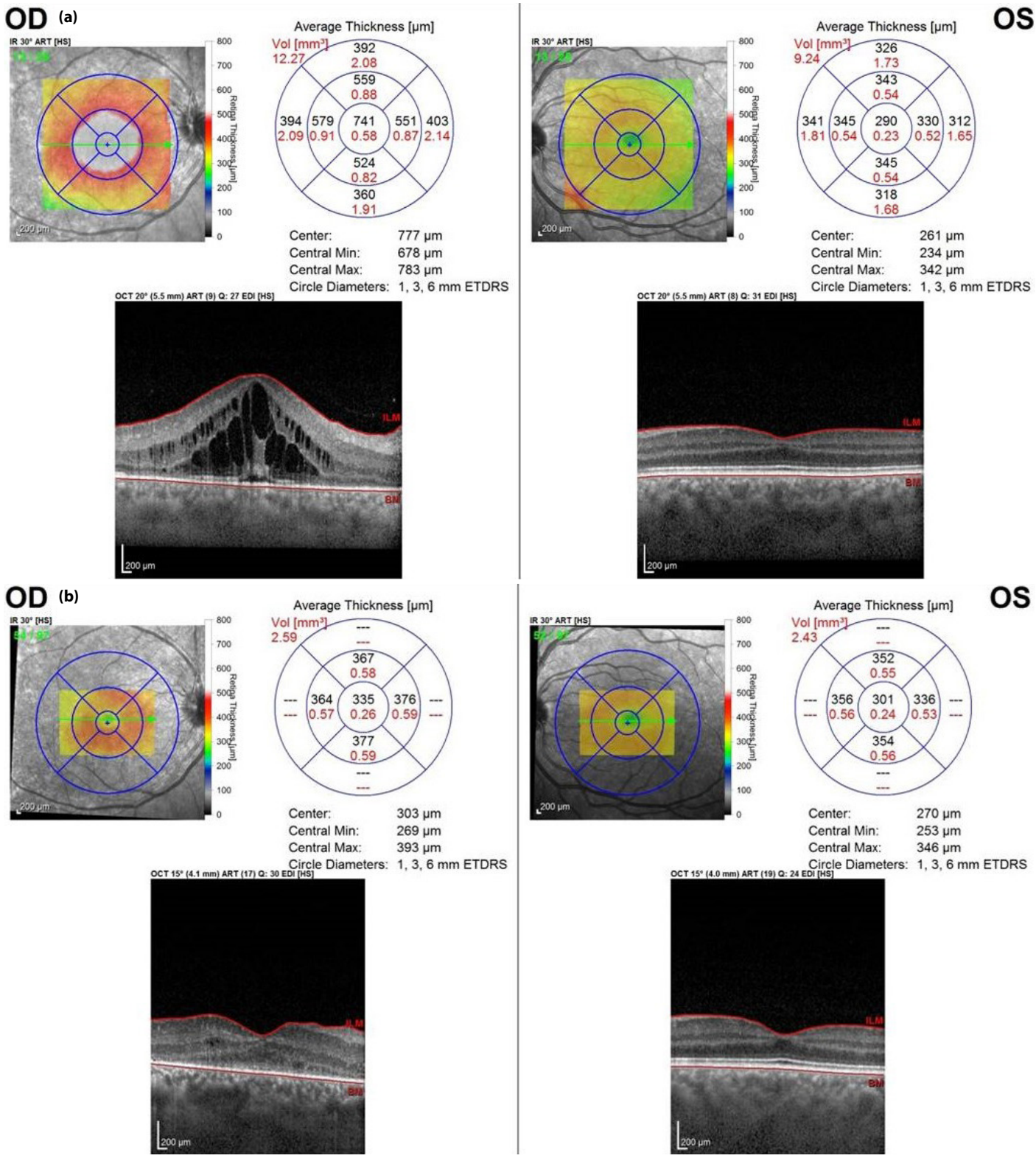

Fig. 5. **(a)** The spectral domain macular optical coherence tomography (OCT) image of Case 2 showing cystoid macular edema in the right eye, **(b)** The macular OCT image after treatment.

Discussion

Uveitic cystoid ME is a common cause of visual morbidity and can lead to substantial sight-threatening visual loss in more than 30% of uveitis patients.[3-5] It is thought to be caused by fluid leakage over the blood-retinal barrier and build-up in the macular area, with a distinctive distribution in the outer plexiform layer and subretinal area. This results in macular thickening and central visual disturbance.[2] Chronic and persistent uveitic ME can result in permanent visual impairment by causing photoreceptor and retina pigment epithelial cell damage and macular ischemia.[3,5,6]

ME can be detected easily by macular OCT imaging. However, OCT alone is not enough to determine the underlying cause. Multimodal imaging methods need to be used for accurate differential diagnosis of ME. OCT and FFA are sensitive methods to present ME and they complement each other.[7] OCT has advantages to evaluate the vitreomacular interphase, while FFA has the advantage to evaluate the macular perfusion and involvement of central and peripheral retinal vasculature and optic disc.[5]

In both of our cases we present, the misdiagnosis was caused by the lack of proper use of appropriate multimodal imaging techniques as both patients had no FFA images taken before administration to our clinic. ME is an entity that can occur as a result of a wide range of uveitic and non-uveitic diseases leading to breakdown of the blood–retinal barrier, increased inflammatory mediators, vascular compromise/hyperpermeability, or dysfunction of the retinal pigment epithelial pump mechanism.[5] Uveitic ME is most commonly associated with noninfectious causes of posterior, intermediate, and panuveitis including HLA B27-positive anterior uveitis, juvenile idiopathic arthritis, sarcoidosis, multiple sclerosis, and pars-planitis, Behcet's disease, HLA-A29 positive Birdshot retinochoroidopathy, sympathic ophthalmia, and also infectious retinitis.[8] In uveitic ME, the main mechanism is the breakdown of blood–retina barrier due to inflammatory cytokines. Second, another mechanism is the altered function of Muller cells. Finally, traction of vitreous and epiretinal membrane also contribute to the ME.

Real-life based research shows that properly treated uveitic ME has favorable long-term prognosis.[9] However, ME persisting for more than 6 months can cause retinal structural changes such as the formation of cyst, macular hole, fibrosis, and scarring.[10] To avoid unnecessary patient morbidity and burden to health-care systems, it is important to identify the underlying cause of the presence of ME in time. In differential diagnosis of uveitic ME, OCT and FFA should be performed. OCT is the gold standard for the diagnosis of uveitic ME and is helpful in the monitoring of response to treatment. Furthermore, OCT is useful in detecting any underlying choroiditis or chorioretinitis that can be helpful in differential diagnosis. In addition, OCT can also show the traction of epiretinal membrane or vitreous.[11] FFA can document the cystoid ME and also can reveal diffuse leakage of choriocapillaris, enlargement of foveal avascular zone, and dye leakage from the optic disc head, vasculitis, chorioretinits, and neovascularization areas in uveitic patients.[12]

Recent reviews in the literature show that uveitic ME patients can have a transient benefit from intravitreal injections of anti-VEGF agents such as our cases, however, the underlying cause of inflammation need to be controlled with appropriate choose of steroids, immunosuppressive or biologic agents.[3,13,14]

Conclusion

Detailed patient anamnesis in addition to a careful anterior segment and fundus examination is of great importance. FFA should be performed as it is an important diagnostic test in detecting the etiology of ME. Especially when ME is detected in young patients, uveitis should be considered an etiological factor and its treatment should be applied accordingly.

Informed Consent: Written informed consent was obtained from the patients for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: A.S.S., S.G.G., S.E.G.; Design: A.S.S., S.G.G.; Supervision: S.G.G.; Resource: S.G.G.; Materials: S.G.G.; Data collection and/or processing: A.S.S., S.G.G., S.E.G.; Analysis and/or interpretation: A.S.S., S.G.G., S.E.G.; Literature search: A.S.S., S.E.G.; Writing: A.S.S., S.G.G., S.E.G.; Critical review: S.G.G.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

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