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Case Report

Atypical Presentation and Delayed Diagnosis of Gyrate Atrophy: Case Reports of Two Siblings

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Abstract

Gyrate atrophy (GA) is a hereditary condition characterized by ornithine aminotransferase deficiency-related large areas of retinal pigment epithelium and choriocapillaris lobular-shaped atrophy in the peripheral retina. In this report, we present a case of atypical presentation of GA. The aim of this report is to present two siblings, one of which was associated with a lamellar macular hole and with a history of previous diagnosis of retinitis pigmentosa. The delayed diagnosis of GA was made only after her brother, who was 5 years younger than her was diagnosed with GA. In addition, in this report, we evaluated GA in terms of multimodal imaging findings, differential diagnosis, and treatment of macular complications.

Keywords: Atypical presentation, gyrate atrophy, lamellar macular hole, multimodal imaging, retinitis pigmentosa

Introduction

Gyrate atrophy (GA) is a rare genetic ocular disease of autosomal recessive inheritance in which missense mutations occur on chromosome 10q26 encoding the enzyme ornithine aminotransferase (OAT) (1). Deficiency of the OAT causes hyperornithinemia (2). Ornithine plays an important role in the regulation of several metabolic processes. With an unknown mechanism, high levels of ornithine lead to progressive chorioretinal atrophy which gives the disease the name GA. The patients usually present with nyctalopia in the first decade of life, followed by visual field constriction, and finally central vision loss. Fundus examination is characterized by the large areas of retinal pigment epithelium (RPE) and choriocapillaris lobular-shaped atrophy in the peripheral retina. Furthermore, high myopia, posterior subcapsular cataract formation, and vitreous opacities are present with these patients (3). With the advent of optical coherence tomography (OCT), macular disorders such as foveoschisis and full-thickness macular hole have been described in patients with GA (4,5). The diagnosis is made by the presence of the characteristic clinical picture, the presence of hyperornithinemia in plasma, and the detection of mutations in the OAT gene. Arginine-restricted diet and vitamin B6 supplementation are the preferred treatment (6,7).

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In this report, we aimed to present two siblings, one of which was associated with a lamellar macular hole and with a history of previous diagnosis of RP. The delayed diagnosis of GA was made only after her brother, who was 5 years younger than her was diagnosed with GA. In addition, in this report, we evaluated GA in terms of multimodal imaging findings, differential diagnosis, and treatment of macular complications.

Case Report

An 18-year-old male patient presented with chief complaints of progressive diminution of vision on both eyes, especially at night (Case 1). After examining him, we asked her 23-year-old sister, who was diagnosed with RP, to come for the examination (Case 2). It was learned that their parents were relatives (consanguineous marriage). Both of these patients underwent detailed ophthalmic examination, which is discussed below.

Case 1 – The best-corrected visual acuity (BCVA) was 20/40 in the right eye and 20/60 in the left eye. Intraocular pressure was 13 mmHg bilaterally; anterior segment examination results were normal except bilateral pseudophakia. He reported having bilateral cataract surgery 5 years ago. Pupils were normal with no afferent pupillary defect. Examination of the posterior segment revealed multiple bilateral, sharply defined, and well-circumscribed chorioretinal atrophy areas in the posterior pole and peripheral retina. The posterior pole and peripheral retina were separated with a crescent-shaped island of the retina which seems to be clinically normal. In addition, the foveal region appeared to be protected bilaterally (Fig. 1). Fundus autofluorescence demonstrated hypo-autofluorescence areas of chorioretinal atrophy (Fig. 2a). There was no leakage in macular area on the late phase of fluorescein angiography (FA) (Fig. 2b). OCT showed thickening of the central fovea with multiple intraretinal cystic cavities and subfoveal fluid bilaterally. In addition, the retinal outer segment could not be detected except the foveal region in both eyes (Fig. 3).

The diagnosis of GA was made with the help of clinical evaluation and imaging methods. Elevated plasma ornithine (1063 nmol/mL, normal level <120 nmol/mL) and aspartic acid (71.9 nmol/mL, normal level <50 nmol/mL) levels confirmed the diagnosis. An arginine-restricted diet and B6 vitamin supplementation were prescribed by the department of endocrinology and metabolism. Oral acetazolamide 250 mg 3 times daily was given to treat the intraretinal cysts and subretinal fluid. After 2 months, subretinal fluid seems to be decreased bilaterally in OCT; however, there were no changes in BCVA (Fig. 4).

Case 2 – BCVA was 20/100 in the right eye and 20/200 in the left eye. Intraocular pressure was 14 mmHg bilaterally. Anterior segment findings were within normal limits except for bilateral pseudophakia and pseudophacodonesis. She reported that she had bilateral cataract surgery 5 years ago and was diagnosed with RP. Pupils were normal with no afferent pupillary defect. Fundus examination revealed multiple bone spicules in the retinal periphery with marked retinal and choroidal atrophy. The foveal region appeared to be protected bilaterally (Fig. 5). There was no leakage in the

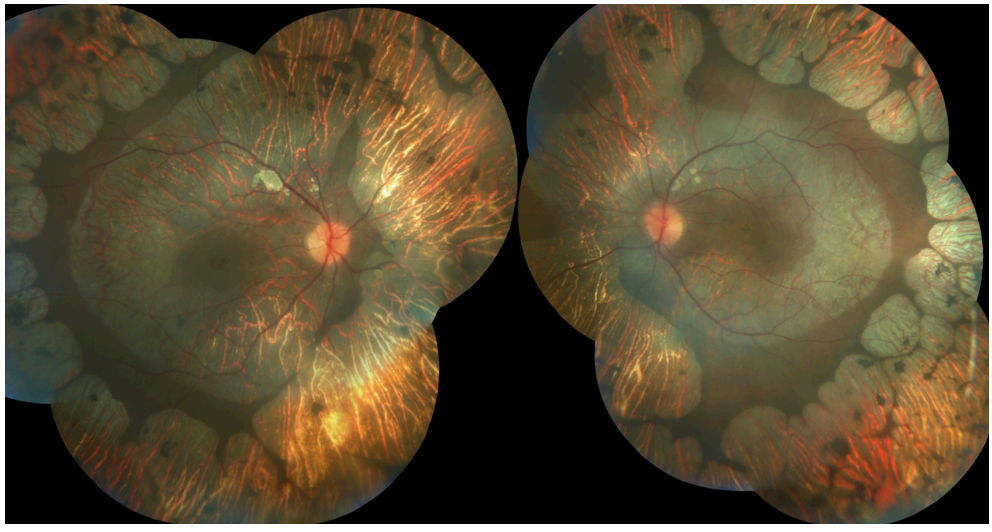

Figure 1. Colored fundus photographs of both eyes in Case 1. Wide-angle color fundus photographs show scalloped edges of the remaining posterior retina; foveal and peripapillary region appeared to be protected bilaterally. The patient has large, geographic, peripheral paving-stone – like areas of atrophy of the RPE and choriocapillaris, which gradually coalesce to form a characteristic scalloped border at the junction of normal and abnormal RPE.

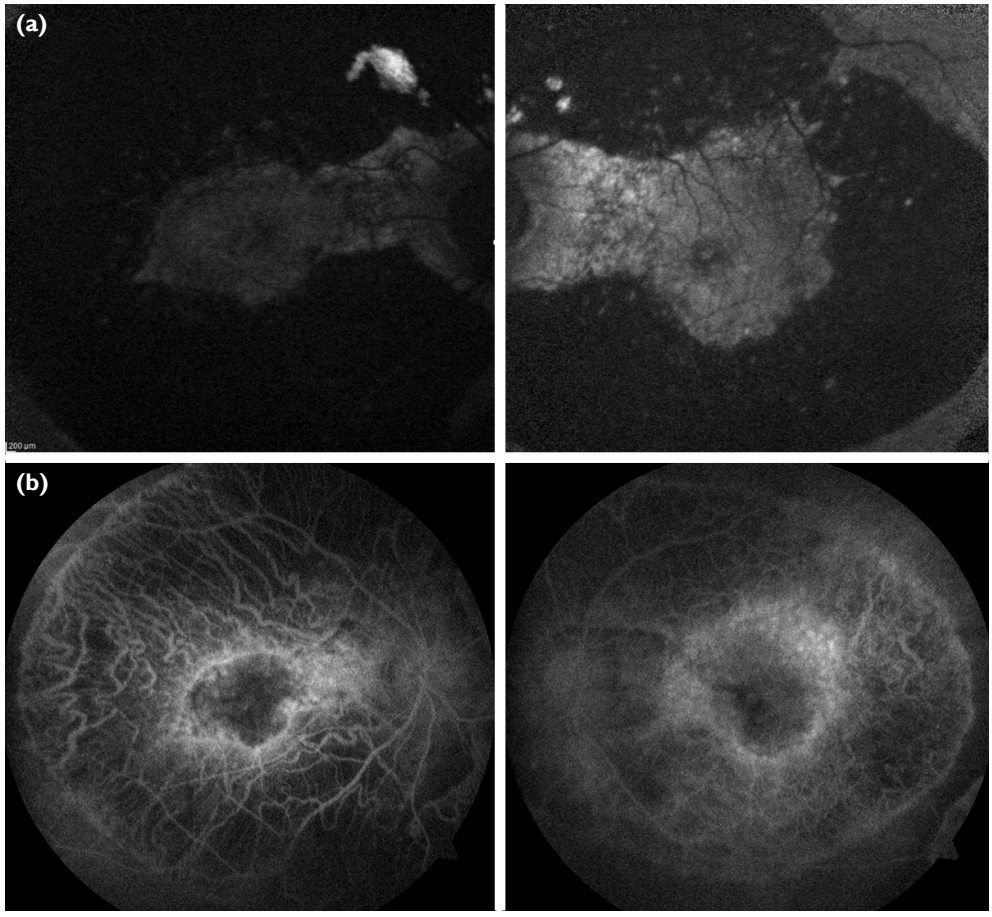

Figure 2. (a) Fundus autofluorescence of both eyes in Case 1. Fundus autofluorescences show decreased autofluorescence correlated with chorioretinal atrophy areas and foveal region appeared to be protected bilaterally. **(b)** Fluorescein angiographies of both eyes in Case 1. Fluorescein angiographies show no leakage in macular area on the late phase of fluorescein angiography. Large choroidal vessels can be seen easily in areas of atrophy of the RPE and choriocapillaris.

fovea on the late phase of FA (Fig. 6). OCT demonstrated a thickening of the central fovea with multiple intraretinal cystic spaces in the right eye and a lamellar macular hole in the left eye. In addition, the retinal outer segment could not be detected except for the foveal region in both eyes (Fig. 7).

In order to confirm the late diagnosis of GA, which comes to mind with the findings of previous cataract surgery, foveoschisis, and chorioretinal atrophy after the examination of the younger brother, serum amino acid levels were requested. Elevated plasma ornithine (926.8 nmol/mL, with the normal range being <120 nmol/mL) and aspartic acid (73.9 nmol/mL with the normal range being <50 nmol/mL) levels confirmed the diagnosis. An arginine-restricted diet and B6 vitamin supplementation were prescribed by the department of endocrinology and metabolism. Oral acetazolamide 250 mg 3 times daily was given to treat the intraretinal cysts and subretinal fluid. After 2 months, there were no changes in OCT findings and in BCVA.

Discussion

GA and RP are the most important retinal dystrophy subtypes with prevalent peripheral involvement. Night blindness, cataract, the presence of macular edema, and foveoschisis, which are the common findings of RP and GA, which are both genetically inherited, may cause misdiagnosis (8,9). Just like in the Case 2, the intact retinal islets, especially in the presence of advanced GA, can be confused with bone spicules. Careful examination of the entire retina, especially including the periphery, with multimodal imaging findings is very important in the differential diagnosis of GA.

Decreased vision in patients with GA may be due to the progression of retinal atrophy, cataract development, or macular involvement. Although the fovea seems to be the only preserved area macroscopically in patients with GA, OCT indicates macular involvement such as macular edema, subfoveal fluid, macular hole, or epiretinal membrane (5,10,11). The disruption of the outer blood–retinal barrier

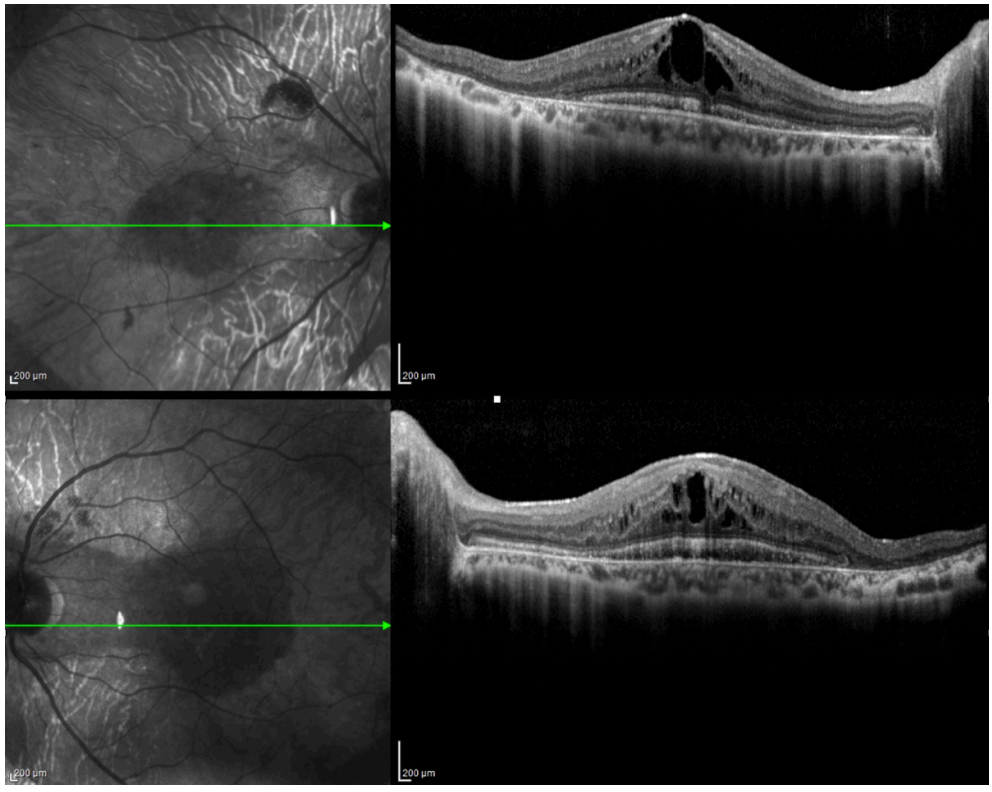

Figure 3. Baseline OCT images of both eyes in Case 1. OCTs demonstrate a thickening of the central fovea with intraretinal cystic spaces and flat subfoveal fluid bilaterally. Retinal outer segment cannot be seen in temporal to fovea in both eyes. The retinal outer segment is appeared to be protected in between optic disc and fovea in the left eye, but it cannot be seen nasal to fovea in the right eye.

due to RPE dysfunction is thought to be responsible for the diffusion of fluid into the intraretinal and subretinal spaces. However, many such cases show no petaloid leakage on FA suggesting foveoschisis (4). Tangential vitreous forces, disruption of the retinal cell-to-cell adhesion, and RPE pumping failure have also been considered potential causes of the macular edema and foveoschisis (11).

In the treatment, an arginine-free diet, if strictly obeyed, may decrease ornithine to normal levels. High-dose vitamin B6 is also recommended to prevent and treat macular complications (6,7). Oral carbonic anhydrase inhibitors and non-steroidal anti-inflammatory drops can be tried to reduce macular edema (12,13). In addition, ocular steroid and anti-VEGF injections may also be beneficial in treatment (14,15). Medical interventions in the early stages of the disease may be more effective. CAI normalizes the polarity of RPE cells followed by displacement of the fluid from the retina into the choroid (16). In Case 1, subretinal fluid was withdrawn after 2 months of oral CAI treatment, although there was no change in intraretinal cysts in both cases.

Epiretinal membrane and macular hole are very rare associations with GA (5,11). Macular hole in GA may be due to vitreomacular traction, posterior vitreous detachment, or un-roofing of foveal cysts. The recommended treatment is macular hole surgery with tight metabolic control (5). In Case 2, OCT showed a lamellar macular hole in the left eye. To the best of our knowledge, we report the 1st Case of a macular lamellar hole associated with GA. Subsequent follow-ups with OCT are important for the progression of the lamellar hole.

GA was diagnosed in patients with ornithine elevation. Some patients benefit from supplementation with the cofactor pyridoxine (vitamin B6), which contributes partially to the function of the OAT. The presence of high serum aspartic acid levels together with high serum ornithine levels suggested B6 dependency syndrome in patients. The fact that the siblings were not diagnosed when they had cataract surgery caused delay in treatment and progression of chorioretinal atrophy in both siblings. When the fundus examinations of the patients were compared, the delayed correct diagnosis and treatment caused the chorioretinal atrophy to be more severe because the older sibling was diagnosed with RP. As it is known, it is necessary to start an arginine-restricted diet for OAT deficiency. Considering the 5-year age difference between them, we would probably have seen more preserved retinal islets in the fundus of female patient 5 years ago.

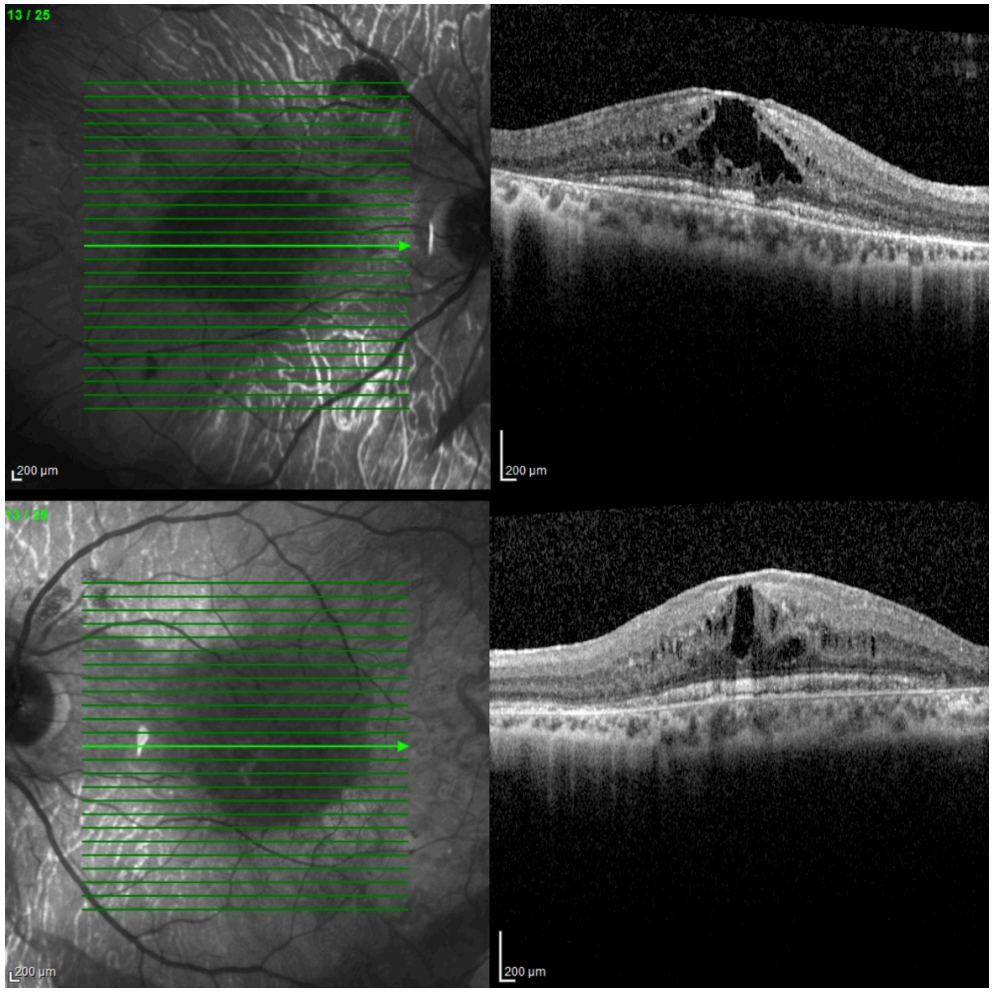

Figure 4. OCT images of both eyes after 2 months of lasting CAI therapy in Case 1. Bilaterally subretinal fluid seems to be decreased in OCT, but intraretinal cystic spaces change minimally.

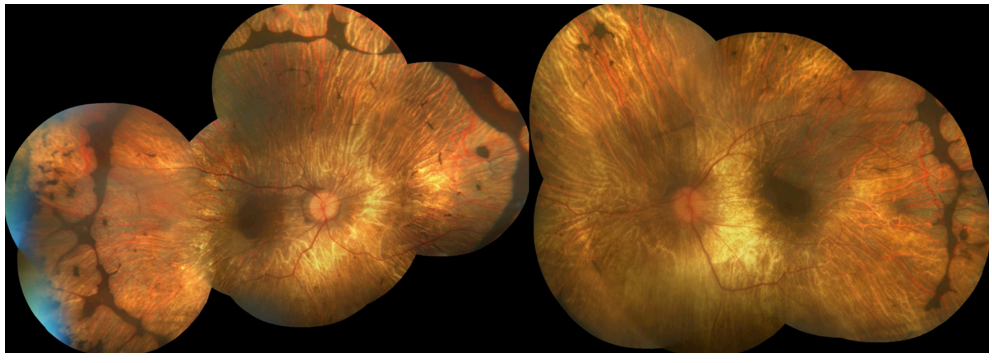

Figure 5. Colored fundus photographs of both eyes in Case 2. Colored fundus photographs show scalloped edges of the remaining posterior retina; foveal region appeared to be protected bilaterally. Clinically fundus examination of scalloped edges revealed multiple bone spicules in the retinal periphery with marked retinal and choroidal atrophy. Retinal and choroidal atrophies are severe when compared with Case 1.

Conclusion

Arginine-restricted diet and B6 vitamin replacement according to subtype of disease are important in preventing the progression of GA. Delayed treatment due to misdiagnosis causes the progression of irreversible chorioretinal atrophy in patients. Therefore, to make the correct differential diagnosis is crucial.

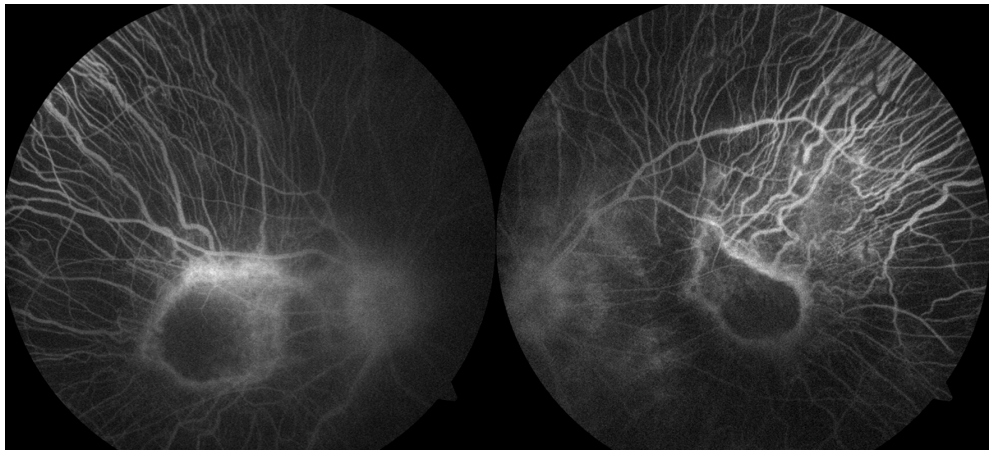

Figure 6. Fluorescein angiographies of both eyes in Case 2. There is no leakage in the fovea on the late phase of fluorescein angiographies.

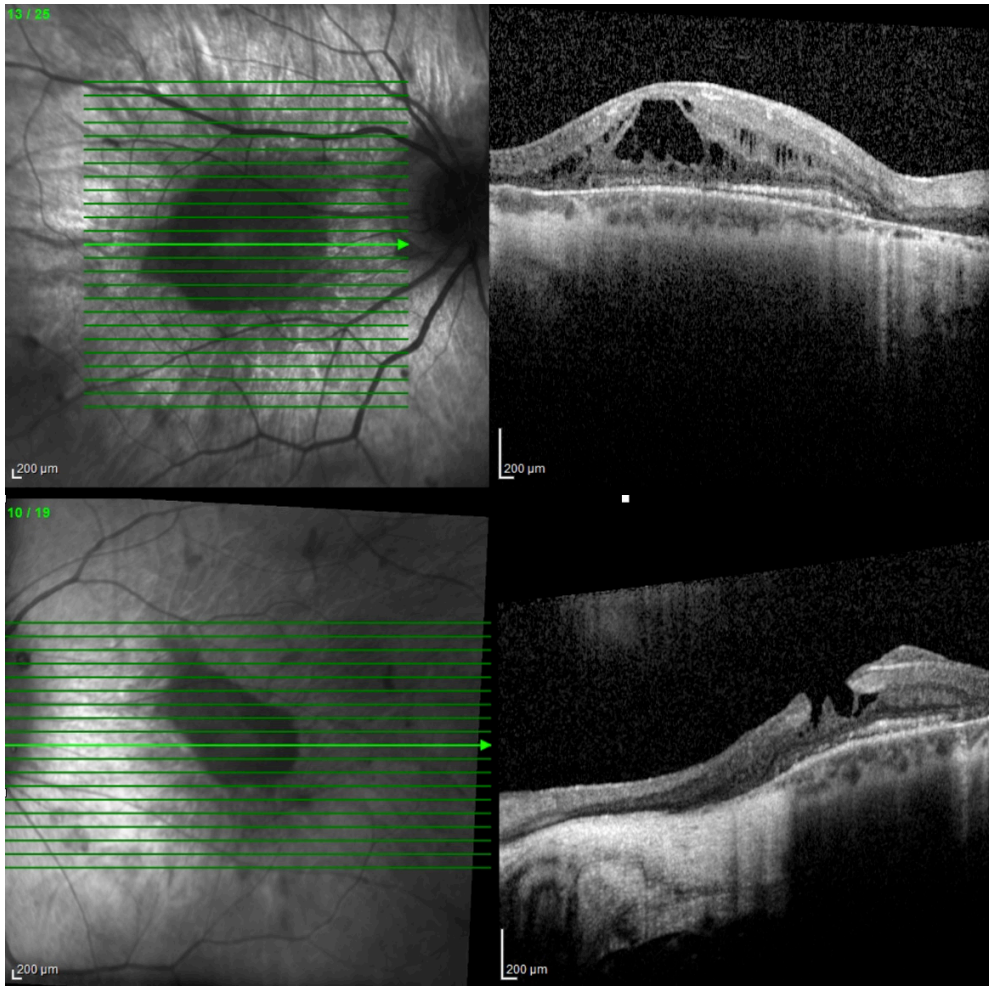

Figure 7. OCT images of both eyes in Case 2. OCT demonstrates a thickening of the central fovea with intraretinal cystic spaces in the right eye and lamellar macular hole in the left eye. Retinal outer segment cannot be detected except foveal region in both eyes.

Disclosures

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

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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