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Iridal posterior pigment epithelial detachment induced by pilocarpine: a case report

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Case Report

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Abstract

Background

Pilocarpine is a commonly used miotic agent in clinical ophthalmology and a first-line medication for glaucoma treatment. In recent years, it has also been gradually applied in the field of presbyopia treatment. The drug has good clinical safety with rare adverse reactions. Known adverse reactions include anterior chamber flare, headache, decreased visual acuity, and rare drug-induced malignant glaucoma. This article reports a case of severe binocular anterior chamber flare accompanied by posterior iris pigment epithelium detachment and secondary glaucoma after miotic eye drops, aiming to provide a reference for clinical safe medication.

Case Presentation

A 39-year-old female patient presented to another hospital with "bilateral eye redness and photophobia for 3 days after staying up late and overworking". Ocular examinations showed normal visual acuity and intraocular pressure (IOP) in both eyes, conjunctival hyperemia, negative Tyndall sign in the anterior chamber, pupil diameter of approximately 4.5 mm, and absent light reflex. She was prescribed diclofenac sodium eye drops and tobramycin dexamethasone eye drops. Three days later, re-examination showed normal visual acuity and IOP, resolved conjunctival hyperemia, pupil diameter still around 4.5 mm, and absent light reflex. Since the patient's pupils were larger than normal, 1% pilocarpine eye drops were added to both eyes to relieve photophobia. After a single instillation of pilocarpine eye drops, the patient developed severe bilateral eye pain, increased IOP, and posterior iris pigment epithelial detachment. During this period, pilocarpine eye drops were continued, along with ocular IOP-lowering treatments, but IOP was not well controlled. Systemic IOP-lowering treatments and anterior chamber paracentesis were added, and IOP improved but was still not well controlled. Medication was adjusted: pilocarpine eye drops were discontinued, and local IOP-lowering treatments were continued. Subsequent re-examinations showed that bilateral IOP and anterior chamber flare gradually stabilized, and the pupil margin iris cyst significantly regressed before medication was stopped. The patient remained stable during a 2-year follow-up and is currently under continuous observation.

Conclusions

Pilocarpine eye drops are widely used in clinical practice with good medication safety, and reports of adverse reactions are rare. There are no previous reports of severe binocular anterior chamber flare accompanied by posterior iris pigment epithelium detachment and secondary glaucoma after pilocarpine eye drops. Therefore, we report this case to alert clinicians to pay attention to the adverse reactions of miotic drugs and provide a reference for clinical safe medication.

Background

Pilocarpine eye drops are a classic representative of anticholinergic drugs, widely used in the treatment of glaucoma, presbyopia, dry eye syndrome and other diseases. Pilocarpine is a cholinergic receptor agonist that acts on both the pupillary sphincter and ciliary muscle, causing rapid miosis. It can also promote lacrimal gland secretion and effectively relieve dry eye symptoms [1]. A study by Peyman et al. observed that instillation of 1% pilocarpine solution after monofocal intraocular lens (IOL) implantation can effectively improve patients' near vision without significantly affecting distant vision, with good safety [2]. In October 2021, the U.S. Food and Drug Administration approved a 1.25% pilocarpine hydrochloride eye drop for the treatment of presbyopia, which can improve near and intermediate vision without affecting distant vision. This drug has good safety and is widely used in clinical practice. Common adverse reactions include headache, blurred vision, eye pain, changes in pupil size, accommodative spasm, and posterior synechia of the pupil, etc. Most of these adverse reactions are mild and transient [3]. Some scholars have also reported rare ocular side effects, such as vitreomacular traction syndrome (VTS) [4, 5], rhegmatogenous retinal detachment [6], and vitreomacular traction that resolves after drug withdrawal [7]. This article introduces a rare adverse reaction of pilocarpine eye drops, manifested as anterior chamber flare, posterior iris pigment epithelial detachment, and secondary glaucoma.

Case Presentation

A 39-year-old female patient presented to another hospital on August 17, 2023, with "bilateral eye redness and photophobia for 3 days after staying up late and overworking". She had no special medical history, no history of ocular or systemic trauma or surgery. Ocular examinations showed visual acuity of 1.0 in both eyes, IOP of 8.9 mmHg in the right eye and 10.4 mmHg in the left eye, bilateral conjunctival hyperemia, negative Tyndall sign in the anterior chamber, pupil diameter of approximately 4.5 mm, and absent light reflex. She was prescribed diclofenac sodium eye drops and tobramycin dexamethasone eye drops. Three days later, re-examination showed resolved conjunctival hyperemia, negative Tyndall sign in the anterior chamber, pupil diameter still around 4.5 mm, and absent light reflex. Since the patient's pupils were larger than normal, 1% pilocarpine eye drops were added to both eyes to relieve photophobia. After a single instillation of pilocarpine eye drops, the patient developed severe bilateral eye pain and was referred to our ophthalmology department on August 22, 2023. At the time of referral, ocular examinations showed visual acuity of 0.8 in both eyes, IOP of 11.6 mmHg in the right eye and 13.9 mmHg in the left eye, no conjunctival hyperemia in both eyes, anterior chamber flare (+++), pupil diameter of approximately 5 mm, prominent iris cyst at the inferior pupil margin, transparent lens, clear vitreous cavity, clear optic disc margin with normal color, flat retina, normal vascular morphology, and clear foveal reflex. After frequent instillation of 1% pilocarpine eye drops (once every 5 minutes, 3 consecutive times), the patient developed bilateral blurred vision, eye pain accompanied by severe headache again. IOP was 42 mmHg in the right eye and 35 mmHg in the left eye. Systemic examinations showed normal blood routine, coagulation function, liver and kidney electrolytes, CRP, erythrocyte sedimentation rate, and infectious disease markers. Chest CT showed no obvious abnormalities. Auxiliary examinations: anterior segment photography showed obvious eversion of the pupil collar and

formation of iris cyst at the pupil margin in both eyes .24-hour IOP monitoring showed 27.4-38.6 mmHg in the right eye and 14.0-16.2 mmHg in the left eye. UBM examination showed posterior iris pigment epithelial detachment in both eyes.

Due to high IOP, brinzolamide eye drops, carteolol eye drops, oral acetazolamide tablets, and intravenous mannitol were immediately added for IOP-lowering treatment. Local treatment with pilocarpine, tobramycin dexamethasone eye drops, and diclofenac sodium eye drops was continued. Anterior chamber paracentesis was performed on the right eye due to poor IOP control. Ten days later, re-examination showed visual acuity of 0.5 in the right eye and 0.8 in the left eye, IOP of 31.2 mmHg in the right eye and 12.1 mmHg in the left eye, and anterior chamber flare in both eyes. Computerized visual field was normal in both eyes, and enhanced MRI of bilateral orbits showed no obvious abnormalities. Medication was adjusted: pilocarpine eye drops were discontinued, and tobramycin dexamethasone eye drops, brimonidine tartrate eye drops, carteolol eye drops, and brinzolamide eye drops were continued for both eyes. One week later, re-examination showed visual acuity of 0.8- in both eyes, IOP of 16.5 mmHg in the right eye and 15 mmHg in the left eye, anterior chamber flare in both eyes, Iris cysts at the pupillary margin showed significant regression (Figure 1).Subsequent follow-ups demonstrated gradual stabilization of intraocular pressure and anterior chamber flare in both eyes. UBM examination revealed gradual recovery of the detached posterior pigment epithelium of the iris in both eyes (Figure 2). Medications were discontinued after the iris cysts at the pupillary margin had significantly regressed.Follow-up examinations at 2 months, 6 months, 1 year, and 2 years later showed that the condition of both eyes remained stable with no ocular discomfort. The patient is currently under continuous observation and follow-up.

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

Discussion and Conclusion

Pilocarpine is an alkaloid extracted from pilocarpus shrubs, with amphipathic solubility and good corneal permeability. Pilocarpine eye drops of different concentrations (0.75%, 1.00%, 1.25%) are effective in improving ocular accommodation, and the higher the concentration, the greater the accommodation amplitude [8]. Both emmetropes and high myopes undergo morphological changes such as ciliary muscle contraction, trabecular meshwork and Schlemm's canal dilation during pilocarpine-induced accommodation. There is a correlation between ciliary muscle contraction and morphological changes of the trabecular meshwork and Schlemm's canal in emmetropes [9]. Systemic adverse reactions include dizziness, headache, pale face, chest tightness, dyspnea, unsteadiness, sweating, upper abdominal pain, nausea, etc. [10,11], but they are rare in clinical practice. Adverse reactions are more common in the eyes, including accommodative spasm, blurred vision, eye pain, ocular irritation, and iris anterior surface cyst [12]. Benozzi et al. [13] proposed that the combination of 1% pilocarpine and non-steroidal anti-inflammatory drugs such as 0.1% diclofenac sodium can reduce side effects.

We introduced a 39-year-old female patient who developed severe bilateral anterior chamber flare, posterior iris pigment epithelial detachment, and secondary glaucoma after instillation of pilocarpine eye drops. There are few reports of such adverse reactions of miotic drugs. This patient was initially diagnosed with slightly dilated pupils and conjunctival hyperemia due to eye redness and photophobia. After 3 days of local steroid and non-steroidal eye drop treatment, eye redness resolved but photophobia did not improve, and she was re-examined. 1% pilocarpine eye drops were added, and she developed headache after a single instillation and was referred to our hospital. Frequent instillation of pilocarpine eye drops worsened her condition, but the dosage of pilocarpine was within the normal range. Ocular symptoms recovered quickly and stabilized after discontinuing the drug. The patient developed severe bilateral eye pain and increased IOP about 15-20 minutes after each instillation of pilocarpine eye drops, so we inferred that pilocarpine eye drops may be the main cause of the patient's severe eye pain and rapid disease progression.

For primary open-angle glaucoma (POAG), the IOP-lowering mechanism of pilocarpine eye drops is mainly through exciting the longitudinal fibers of the ciliary muscle, causing ciliary muscle contraction, increasing the tension of the scleral spur, widening the trabecular meshwork gap, reducing aqueous humor outflow resistance, promoting aqueous humor outflow, and lowering IOP. For primary angle-closure glaucoma (PACG), it causes miosis by exciting the iris sphincter, making the peripheral iris leave the anterior chamber angle wall, reopening the anterior chamber angle, and allowing aqueous humor to flow out through the trabecular meshwork and Schlemm's canal, restoring normal aqueous humor circulation. However, sustained ciliary muscle contraction and spasm can cause pain in the forehead or periorbital area. In addition, ciliary muscle contraction leads to relaxation of the zonular fibers and anterior convexity of the lens, causing myopic shift. Headache usually occurs within 30-60 minutes after medication and lasts for 2-4 hours. The severe headache and bilateral blurred vision in this patient after frequent instillation of pilocarpine eye drops are considered to be related to this, also indicating that the patient is highly sensitive to this drug.

Anterior chamber flare can occur after a single local use of miotics such as pilocarpine [14], and long-term use can cause sustained mild anterior chamber flare which may worsen. Current studies show that pilocarpine does not increase the permeability of the ciliary body barrier [15] or significantly increase the permeability of iris blood vessels, that is, anterior chamber flare caused by miotics is not due to damage to the blood-aqueous barrier, and it may manifest as "physiological flare" without obvious symptoms, which is consistent with the severe anterior chamber flare in both eyes of this patient at the initial diagnosis in our department without obvious eye redness.

Under normal circumstances, plasma proteins infiltrate into the ciliary body stroma through fenestrated capillaries of the ciliary body and then diffuse into the anterior chamber through the iris root [16]. Since this diffusion channel is close to the aqueous humor outflow channel, it is likely that some proteins will be rapidly excreted from the eye through Schlemm's canal, and the remaining proteins will remain in the iris stroma [17]. Pilocarpine causes ciliary muscle contraction by stimulating M receptors, which may lead to anterior chamber flare and iris lesions through the following pathways: increased protein

exudation, sustained ciliary muscle contraction promoting the release of stored proteins in the iris stroma [14]; pilocarpine inhibits aqueous humor production, leading to increased protein concentration in aqueous humor; ciliary muscle contraction blocks the passage of protein substances from the anterior chamber to the suprachoroidal space and posterior uvea [18], redirecting these proteins to the anterior chamber; tight junctions between cells of the posterior iris pigment epithelium prevent these stored proteins from diffusing back into the posterior chamber [19], resulting in severe anterior chamber flare without obvious vitreous opacity in this patient.

Secondary iris cysts usually form after ocular surgery or trauma. Although rare, it has been reported that secondary iris cysts may also be caused by long-term medication, parasitic infections (such as ocular cysticercosis), inflammatory diseases (such as uveitis), ciliary body medulloepithelioma, iris melanoma, nevi, and metastatic tumors [20,21,22]. It has been reported that miotics and prostaglandin analogs can induce iris cysts, but long-term medication is required (average medication time of prostaglandin analogs is 5 weeks to 3 years) [23,24,25,26], while reports of iris cysts induced by miotics are rare [27]. In this case, the patient developed a pupil margin cyst after a single medication, which progressed to a 360° annular cyst within 24 hours and regressed after drug withdrawal. Combined with the severe anterior chamber flare in the patient, it suggests that the accumulation of exuded proteins in the iris stroma between the stroma and the posterior pigment epithelium may lead to posterior pigment epithelial detachment and cyst-like changes at the pupil margin. After discontinuing pilocarpine eye drops, the exuded proteins in the anterior chamber were eliminated and absorbed, and the posterior iris pigment epithelium reattached. However, further research is needed to determine whether pilocarpine can induce iris pigment epithelial detachment through other mechanisms. In addition, pigment dispersion glaucoma is caused by mechanical friction between the posterior iris surface and ciliary zonules due to factors such as posterior iris concavity, and the continuous release of pigment granules from the iris pigment epithelium blocks the trabecular meshwork. This patient had no developmental abnormalities of the anterior chamber angle such as posterior iris concavity, and friction between the posterior iris pigment epithelium and the lens fiber capsule may lead to pigment loss and deposition in the trabecular meshwork, resulting in secondary high IOP similar to pigment dispersion glaucoma [28].

We need to pay attention to the adverse reactions of pilocarpine. Miotics should be used with caution in patients with unexplained mydriasis. After medication, close monitoring of anterior chamber reaction and IOP is required. In case of decreased vision, worsened anterior chamber flare, etc., misdiagnosis and missed diagnosis should be avoided, and medication should be discontinued promptly for active treatment to improve prognosis.

Declarations

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Author contributions

Liang Z conceptualized the case report, collected the clinical data, and drafted the initial manuscript. Yanfang X contributed to data acquisition, image processing, and literature review,assisted with data interpretation, discussion of clinical implications, and critical revision of the manuscript. Xiusheng S supervised the clinical management, provided strategic guidance on the manuscript structure, and performed a thorough review for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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Data availability

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Ethics approval and consent to participate

Not applicable.

Consent for publication

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

Competing interests

The authors declare no competing interests.

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Figures

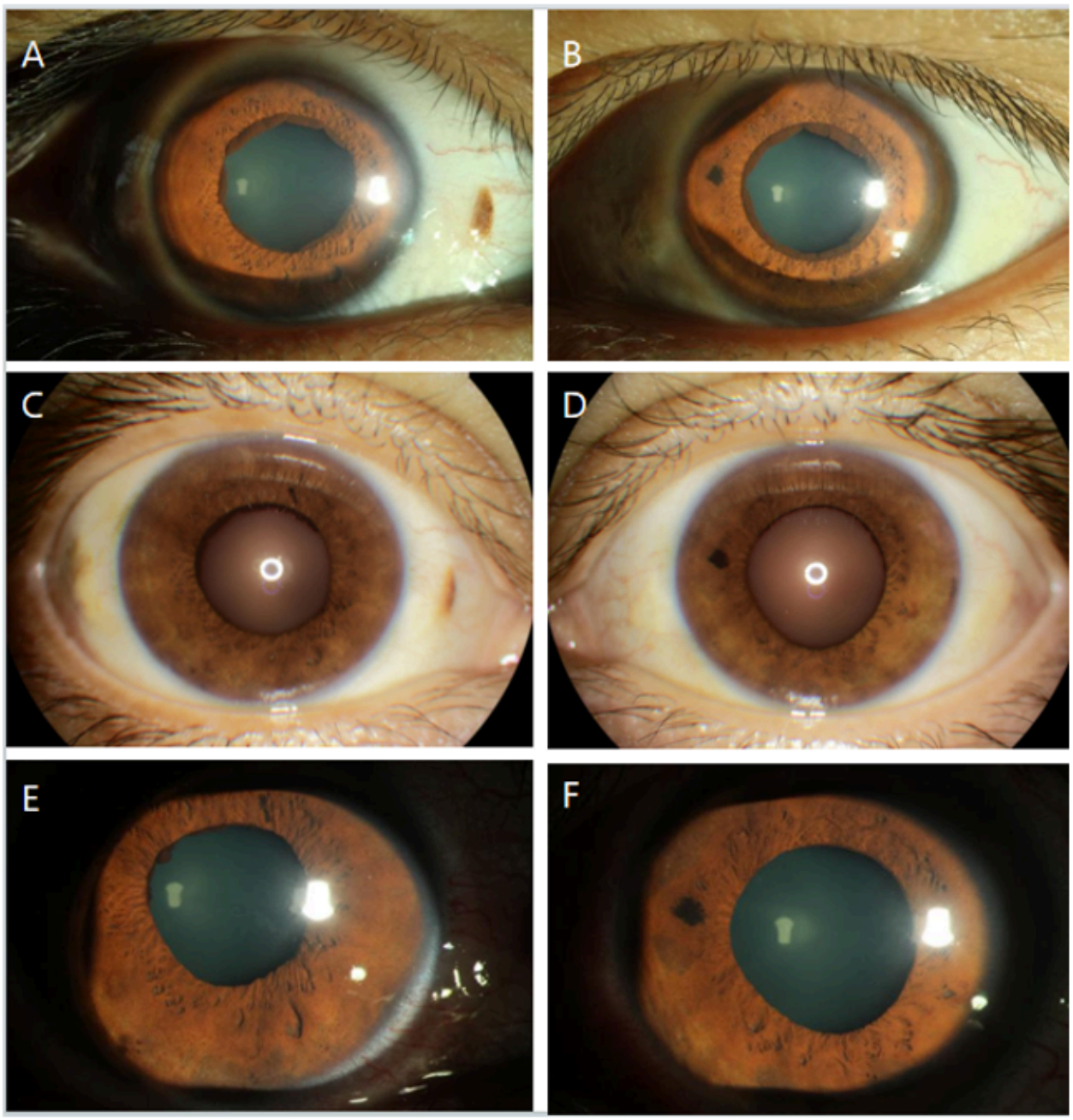


Figure 1

In **A** and **B**,Anterior segment images at 1 week after onset, showing a direct pupil diameter of approximately 4.5 mm and circular iris cysts at the pupillary margin (A: right eye; B: left eye).In **C** and **D**,Anterior segment images at 1 month after onset, showing a direct pupil diameter of approximately 4.5 mm with significant regression of the circular iris cysts at the pupillary margin (C: right eye; D: left eye).In E and F,Anterior segment images at 1 year after onset, showing further regression of the circular iris cysts at the pupillary margin (E: right eye; F: left eye).

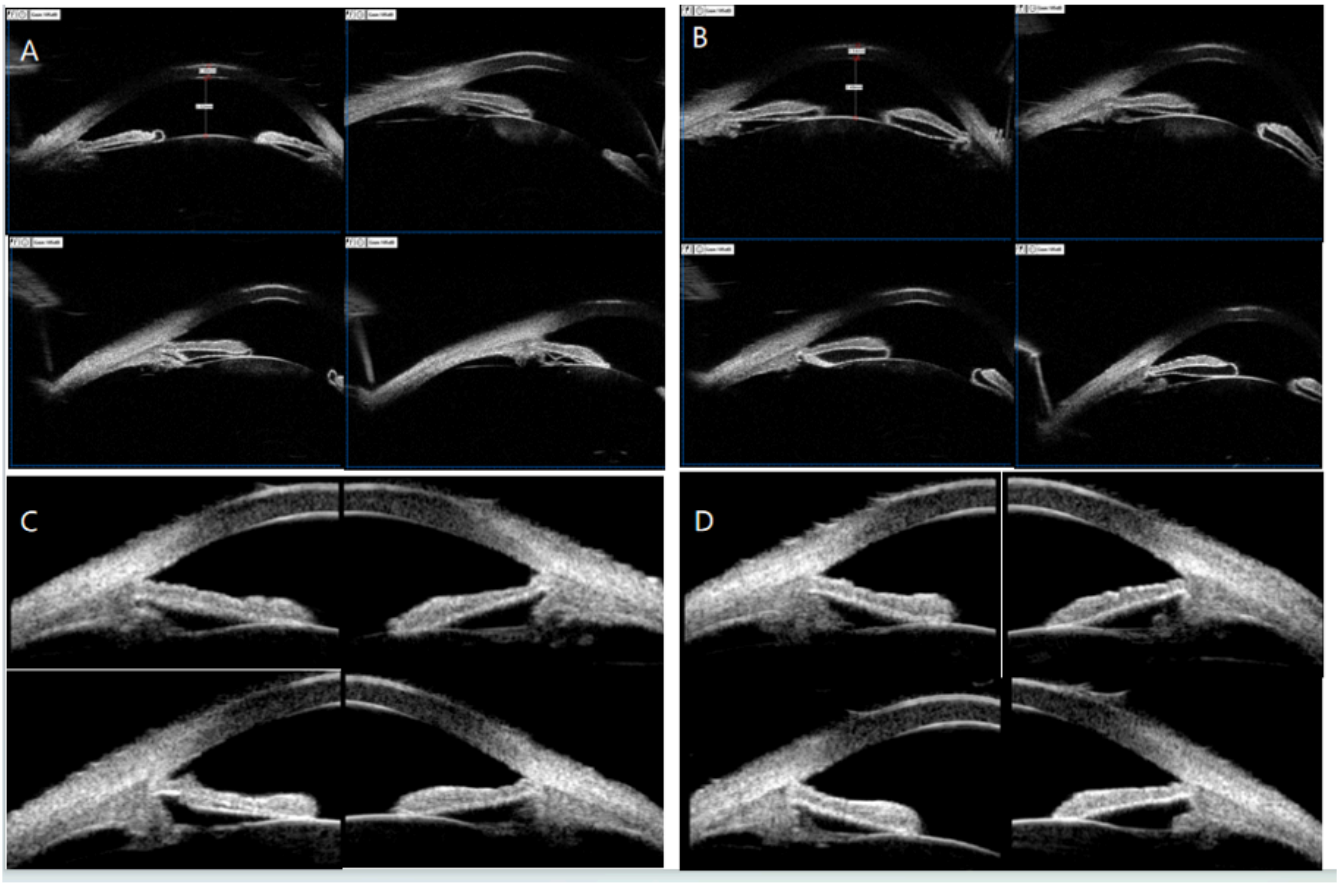


Figure 2

In **A** and **B**,UBM images of both eyes at 11 weeks after onset, showing formation of circular cysts behind the iris, with some protruding beyond the pupillary margin. The detached posterior pigment epithelium of the iris in the inferior and temporal regions is adjacent to the lens zonules (A: right eye; B: left eye).In **C** (Right eye), The echo of the iris root in the inferior region is irregular, and membranous echoes can be seen connecting behind the corresponding iris. A portion of the iris root is attached to the angle structures, obscuring the scleral spur. No significant differences in the distance between the lens equator and the ciliary processes are observed in all directions, and no abnormal echoes are detected in the ciliary body.In **D** (Left eye)A portion of the iris root is attached to the angle structures, obscuring the scleral spur. No significant differences in the distance between the lens equator and the ciliary processes are observed in all directions, and no abnormal echoes are detected in ciliary.