Pseudophakic macular edema involving epiretinal proliferation associated with macular hole

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This case report describes an unusual course of an impending macular hole (MH) throughout a 72-month follow-up period. A 53-year-old female presented with impending MH associated with epiretinal proliferation (EP) which showed unusual progress including full thickness MH, spontaneous closure, reopening as lamellar MH, and full anatomical closure with EP tissue. After cataract surgery, cystoid spaces occurred involving both EP tissue and neuroretina. Due to full recovery following a single dose of aflibercept, the source of the cystoid spaces was thought to be associated with postoperative inflammation leading to pseudophakic macular edema involving not only but also EP tissue.

Key words: Epiretinal proliferation, macular hole, pseudophakic macular edema

Epiretinal proliferation is a newly defined clinical entity that is classically associated with lamellar macular holes (LMH) but occasionally with full-thickness macular holes (FTMH).[1,2] It is firstly described as a thick epiretinal membrane (ERM) at the margin of an inner defect of a lamellar macular hole which had different characteristics from typical contractile ERM imaged with ultrahigh-resolution optical coherence tomography (OCT).[3] Pang et al. offered the term of “lamellar hole associated epiretinal proliferation (LHEP)” for this thick epiretinal material.[2]

The aim of this report is to demonstrate cystoid changes involving both neuroretina and epiretinal proliferation tissue after an uneventful cataract surgery and to describe the unusual course of an impending macular hole throughout follow-up period.

Case Report
A 53-year-old female presented with decrease of vision in both eyes for the past 1 year. The best-corrected visual acuity (BCVA) was 20/40 and 20/80 in her right and left eyes, respectively.

![Figure 1: Multimodal fundus images of the patient at presentation. Color fundus photography showing a yellowish spot on the macula of the right eye (a) and an apparent macular hole in the left eye (b). Optical coherence tomography revealed an impending macular hole associated with epiretinal proliferation in her right eye (c), and a full thickness macular hole in her left eye (d). Fundus autofluorescence images demonstrated a faint hyperautofluorescence (e) in the fovea of the right eye and a prominent circular hyperautofluorescence in the left eye (f).](https://example.com/figure1.jpg)

Fundus examination showed a yellowish spot on the macula of the right eye and an apparent macular hole with ERM in the left eye [Fig. 1]. The spectral-domain OCT showed an impending macular hole and epiretinal proliferation in the right eye and an FTMH in her left eye. The patient underwent a successful macular hole surgery for her left eye [Fig. 2]. During the postoperative follow-up period, an FTMH with epiretinal proliferation occurred in her right eye [Fig. 3a]. The base diameter of MH was 593 µm and the minimum diameter was 120 µm. Cysts were observed on both edges. Six months later, the inner borders of the hole were spontaneously closed resembling stage 1B impending hole again [Fig. 3b]. After 12 months, surprisingly, the lesion was turned into a LMH with partial recovery of ellipsoid zone (EZ) and external limiting membrane (ELM) [Fig. 3c]. Then, LMH closed with epiretinal proliferation covering the whole roof of the LMH.
Figure 4: Multimodal fundus images of the patient at the final visit. Color fundus photography showing a thin, translucent, and cellophane-like membrane (a). A faint hyperautofluorescence which is especially visible at the inferior part of fovea centralis (b). Optical coherence tomography showing the spontaneously closed hole cavity with epiretinal proliferation tissue invaginating into the outer nuclear layer (c)

causing an empty cystic space in the fovea center [Fig. 3d]. After a total of 67-month follow up, epiretinal proliferation appeared to fill in the space completely [Fig. 3e]. The patient underwent an uneventful cataract surgery with intraocular lens implantation. Two months later, pseudophakic macular edema occurred affecting both epiretinal proliferation tissue and neuroretina [Fig. 3f]. A single intravitreal injection of 2.0 mg/0.05 ml aflibercept was performed. After the injection, all cysts disappeared. At the end of the 72-month follow-up period, BCVA was 20/80 and the previous macular hole cavity was filled fully with epiretinal proliferation tissue invaginating into the outer nuclear layer [Fig. 4].

Discussion

Cystic spaces within LHEP tissue were firstly described in both eyes of a 94-year-old man with lamellar macular hole in the right eye and a long-standing FTMH in the left eye after cataract surgery.\(^4\) The authors proposed that expression of VEGF resulted in the leakage of fluid from fibrovascular tissue that composed the ERMs and that the vascular component of this tissue was derived from the retina. Then Pang et al. defined two cases, an 83-year-old man with a history of traumatic eye injury and a 64-year-old woman with retinopathy related to radiation therapy, suggesting this finding as a feature of chronicity.\(^5\) In our case, we described the development of cystoid edema immediately after the cataract surgery involving both epiretinal proliferation and neuroretina.

After the cataract surgery, in response to anterior chamber manipulation, inflammatory mediators, released from uveal tissue, diffuse posteriorly into the vitreous and disrupt the blood–retinal barrier.\(^5\) This disruption leads to increased permeability of the perifoveal capillaries and fluid accumulation within the macula. Then transudate accumulates in the outer plexiform and inner nuclear layers of the retina and cysts are formed.\(^6\) ERM is one of the many defined risk factors for pseudophakic macular edema (PME) with a relative risk of 5.6 which is the highest risk for development of PME in patients who did not have diabetes.\(^7\) Epiretinal proliferation may also be a risk factor for PME with a possible similar mechanism.

Figure 2: Multimodal fundus images of the left eye of the patient after a successful hole surgery. Color fundus photography showing a fairly visible annular yellowish spot on the fovea centralis (a). Recovery of physiological hypoautofluorescence of the fovea (b). Optical coherence tomography demonstrated successful closure of the macular hole with partial disruption of ellipsoid zone and external limiting membrane (c)

Figure 3: Optical coherence tomography and infrared reflectance (insets) images of the right eye throughout the follow-up period. A full thickness macular hole with epiretinal proliferation (EP) with cysts on both edges (a). Spontaneous closure of the inner borders of the hole resembling impending hole again (b). Occurrence of the lamellar hole (c). Full closure of the lamellar hole with EP causing an empty cystoid space in the fovea center (d). EP appeared to fill in the space completely (e). Occurrence of pseudophakic macular edema involving both EP and neuroretina after the cataract surgery (f)
Inflammatory changes may lead gliotic Muller cells to lose their potassium (Kir 2.1 and 4.1) and water channels (AQP4-5) causing retinal edema.\(^8\) Muller cells have been speculated to be the source of the epiretinal proliferation tissue, because they are the only cell type in the neural retina that have the potential to hypertrophy and proliferate to form such a thickened material.\(^9\) Additionally, a glia specific protein, anti-glia fibrillary acidic protein, was demonstrated in this tissue proving the role of the glial proliferation in LHEP formation.\(^9\) This data help us to explain why cystoid spaces occurred in both epiretinal proliferation tissue and inner retinal layers.

Spontaneous closure of idiopathic FTMH has been associated with various factors including smaller hole diameter, sharp edge and bridging-like structures, cystic spaces, and presence of vitreomacular traction. However, late reopening as a LMH is an extremely rare situation.\(^10\) Previously, Garcia Fernandez et al. defined a case with a stage IV full-thickness idiopathic macular hole and a small epiretinal membrane. Three months after the presentation, they observed that the hole spontaneously closed, however two years later it reopened as a lamellar macular hole.\(^10\) To the best of our knowledge, our case is the first report describing the epiretinal proliferation tissue associated with macular hole which spontaneously closed and reopened as a LMH, and spontaneous full anatomical closure of the whole hole cavity with EP tissue.

**Conclusion**

In conclusion, postoperative inflammation and the release of inflammatory mediators may be responsible for the formation of cystoid spaces in both epiretinal proliferation tissue and neuroretina by not only increasing vascular permeability but also disturbing the homeostatic function of Muller cells.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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