

Case series

Transient Macular Edema after Uncomplicated Cataract Surgery: Below the Surface

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Abstract

Purpose: To present analysis of 17 case reports of 17 patients who had an acute transient macular edema appeared after uneventful cataract surgery.

Observations: In literature about 12 case series of toxic macular edema development after cataract surgery are described and all of them were accompanied by the cefuroxime intracameral usage. Also, there are reports of macular edema development after several weeks after uncomplicated phacoemulsification due to pseudophakic cystoid macular edema (Irvine-Gass syndrome) or due to vitreomacular traction syndrome. We observed a series of transient acute macular edema with 3,8% incidence occurring on the first days after uncomplicated phacoemulsification with IOL implantation that had no signs of vitreomacular traction or acute inflammation. Optical coherence tomography (OCT) was performed on patients complaining on blur vision and who had signs of macular edema by ophthalmoscopy. By OCT high and often extensive neuroepithelium and local pigment epithelium detachments were observed on the first day after surgery in 17 patients with quiet postoperative condition of the eye. The edema resolved on the 3-6-th day by standard phaco accompanying pharmacological treatment. In most cases posterior vitreous cortex was adjacent to the retina except 3 patients with posterior vitreous detachment in macular area. We found a paper by Costen M.T.J. et al. (2007) about the same striking appearance of maculopathy called by authors "A-sign" maculopathy because of A-shaped pattern on OCT images in 3 patients after routine cataract surgery. Yaman A (2008) and Panagiotidis D (2010) also reported same findings after uncomplicated cataract surgery. We compared our findings with 3 papers mentioned above, as well as with typical pseudophakic cystoid macular edema (CME) and vitreomacular traction syndrome.

Conclusion: It's obvious that observed case series are cefuroxime induced. But its comparison with CME in terms of morphology of the macula could improve our understanding of mechanisms of the interstitial fluid flow in the eye tissues.

Keywords: macula; pseudophakic cystoid macular edema; phacoemulsification; Irvine-Gass syndrome.

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1. Introduction

In 2014-2015 we observed unusual cases of transient macular oedema in 17 patients after a routine cataract surgery with peri-operative topical usage of non-steroid, steroid anti-inflammatory drugs and antibiotics including standard dose of intracameral cefuroxime (1 mg/0,1 mL). An anterior segment of the eye was clear and calm but patients complain on blur vision. On the OCT there were neuroepithelium detachment with local pigment epithelium detachment that resolved in 3-6 days on standard anti-inflammatory treatment. Patients stayed in the hospital until full recovery. We had not found similar cases at that time [1]. But recently we have discovered in the «Nature» similar cases described by Costen M.T.J. with colleagues in 2007 for the first time, and this paper suggests us the necessity of publication of our cases.

2. Material and methods:

literature overview, retrospective analysis of medical documentations of 17 cases including the age, sex, presence of associating diseases and drug treatment, length of the eye, keratometry, intraocular pressure (IOP) and OCT image of the macular region made by RTVue-100 (Optovue®, USA).

3. Results

The average age of patients was $68,24 \pm 9,71$ years old (50-82). The men women ratio was 14:3. The phacoemulsification with IOL implantation (Acrysof IQ, Alcon®, USA) was performed under a combination of topical and subtenon anesthesia through a 2,4 mm incision. A cataract density mostly was about 2-3 degree but patient №13 was with soft posterior subcapsular cataract and patient №3 with mature hard 4-degree cataract. All operations were carried out by the same trained surgeon on the «Millenium» machine (Baush&Lomb®, USA) by the “cross” method on the Burst mode with a maximum ultrasound power of 40%, vacuum 250 mm Hg and with the velocity of passive irrigation of balanced salt solution about $90 \text{ sm}^3/\text{min}$. All IOLs were implanted in the capsule bag. During the period from the beginning of 2014 until the end of 2015 there were 449 phacoemulsifications performed by the mentioned surgeon. Thus, the incidence of occurred acute transient macular edema (ATMO) was 3,8%.

Three patients had bilateral compensated primary open angle glaucoma at the different stages (patients № 2, 12 and 15), and one of them underwent the trabeculectomy a year ago (№15). There were three patients with a mild and high myopia (№ 1, 7 and 14).

The most common associated disease was systemic arterial hypertension – 15 from 17 cases. Also, the permanent form of atrial fibrillation was mentioned (patients № 2 and 4). Implanted sinus pacemakers were observed in 3 patients (№ 2, 10 and 16). Patients № 10 and 16 suffered from the coronary heart disease and underwent vessel's stenting. Beside the cardiovascular diseases there were a nephrolithiasis and hydronephrosis (cases № 10,14, 17), a cirrhosis of the liver (case № 7) and a rheumatoid arthritis (cases № 4 and 16).

Three patients suffered from the diabetes mellitus: two of them were insulin-dependent (patients № 6 and 7) and one (patient №11) took hypoglycemic drugs orally. None of them had signs of diabetic retinopathy. Among constantly taking antihypertensive medications there were a diuretic (patients № 1,11) and β -blockers (patients № 8,11 and 12). Antiplatelet drugs (“Cardiomagnil”) was taken by two patients (№8 and №16).

Patient №3 with mature cataract was in the interval between chemotherapy courses for breast cancer with metastases.



The second eye was pseudophakic in 5 patients.

The mean uncorrected visual acuity before surgery was $0,11 \pm 0,11$, and corrected $0,21 \pm 0,18$. In spite of presence of macular edema the mean corrected visual acuity on the first day after surgery was $0,31 \pm 0,20$. When the macular edema resolved the mean uncorrected visual acuity was $0,48 \pm 0,28$ and the best corrected visual acuity was $0,82 \pm 0,16$.

IOP before surgery was $21,18 \pm 2,38$ mm Hg. On the first days after the surgery the IOP was within the normal values and was $19,5 \pm 3,2$ mm Hg at patients' discharge.

The mean length of the eye was $23,93 \pm 1,23$ mm ($22,45$ - $26,2$ mm), the mean keratometry along two main meridians was $43,41 \pm 1,41$ D ($40,1$ - $45,5$ D).

Postoperative inflammatory reaction was minimal: one male patient (№1) had +1 cell reaction in the anterior chamber's aqueous humor on the first day after surgery. All patients receive medical treatment: instillations of non-steroidal anti-inflammatory drugs (Indocollyre 0,1%), dexamethasone 0,1% and ciprofloxacin 0,4% 4 times a day, and subconjunctival injections of the dexamethasone 0,3 ml 0,4% № 2-5.

A high detachment of the neuroepithelium in the macular region was observed on OCT in the majority of cases on the first day after surgery due to liquid accumulation in the outer nuclear layer and under the photoreceptors layer. Local pigment epithelium detachment also was detected. This typical swelling resolved in 3-6 days. The OCT image of patient №9 on the first day after surgery with high (772 mkm) detachment of the neuroepithelium is presented on Figure 1. On the third day after surgery the detachment of the neuroepithelium has almost resorbed, with only a tiny detachment of the photoreceptor's layer left which disappeared on the fourth day.

Changes that were observed on the OCT between the second and fifth day in case №3 are represented on the Figure 2.

"A-pattern" of the retinoschisis described by Costen M.T.J. et al. was mentioned only in case №5 which also had a posterior vitreous detachment (PVD) (Figure 3).

There is an interstitial swelling of the outer retina layers resulting in partial or total neuroepithelium detachment in the majority of cases. On the OCT images in the fovea region above the detached bodies of the photoreceptors there are low-differentiated shapeless structures that in some cases had radial direction and could represent Henle fibers or swelled Muller cells' bodies and processes locating in the radial direction on the frontal plane [2].

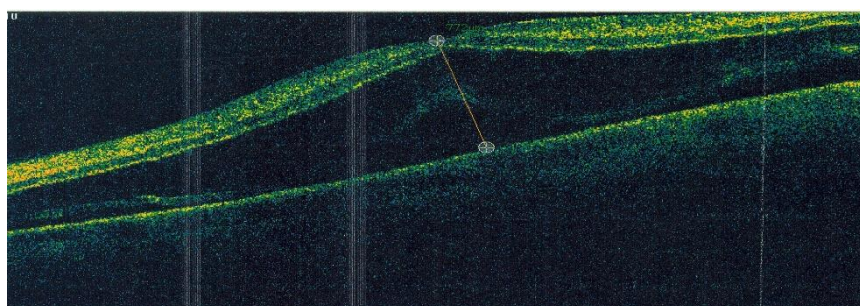


Figure 1. OCT image OD of case 9 on the 1st day after surgery. 772 mkm neuroepithelium detachment



Patient №6 had hard drusen and dyspigmentation in the macula region observed ophthalmoscopically but on the OCT there are only pigment movement in the complex pigment epithelium – Bruch's membrane – chorocapillaries (Figure 4). Interesting to note that none of the patients had structures with high optical density such as large drusen or neovascular membranes.

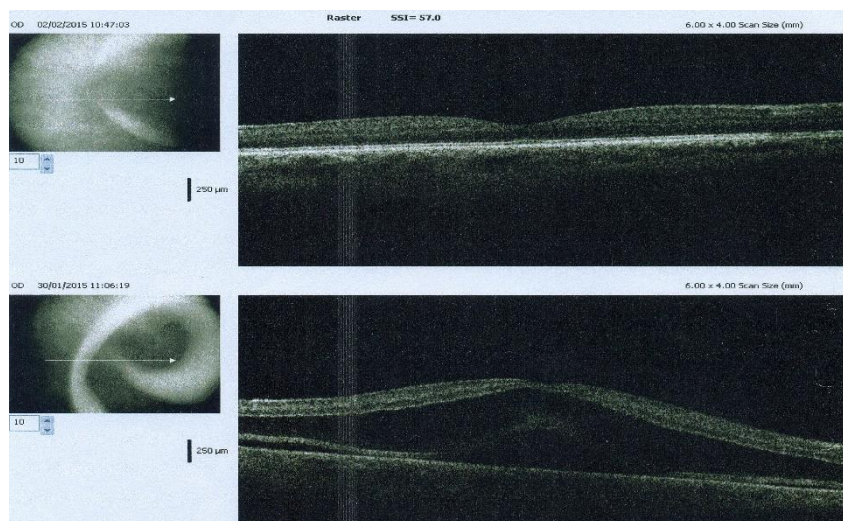


Figure 2. OCT OD of case 3 on the 2nd (below) – 5th (top) days

OCT images of the patients №7 and №14 are similar to those that are observed in pseudophakic cystoid macular edema with cysts in the outer plexiform and nuclear layers (Irvine-Gass syndrome) (Figure 5 and 7).

The lowest detachment of the neuroepithelium on the first day was observed in patient №8 (Figure 6). Nevertheless, the enlargement of the outer nuclear layer, appearance of optical voids in the outer plexiform layers and detachment of the photoreceptors with or without the pigment epithelium in some cases local and in some cases throughout the whole macula region.



Figure 3. Dynamic on OCT OD of case 5: 3^d day (below) and 6th day (top), «A-sign», PVD

The OCT image of the patient №14 with a high myopia on the second day after surgery is represented on the Figure 7. Worthy to note the small size of the cysts in the outer nuclear layer. Complete resorption of edema was observed on the third day after surgery.



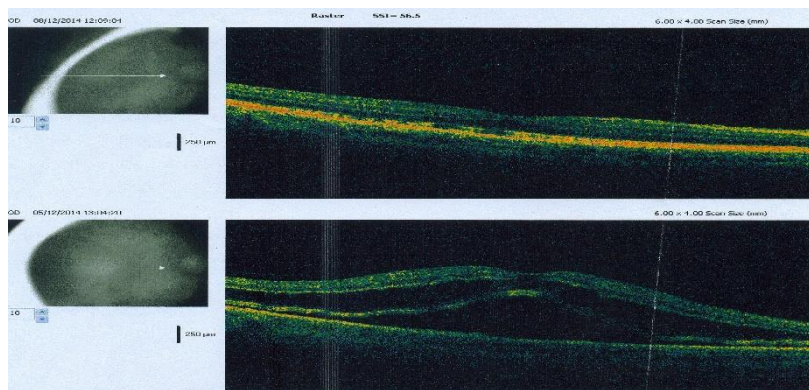


Figure 4. OCT OD dynamics of case 6 on the 2nd (below) - 5th (top) days

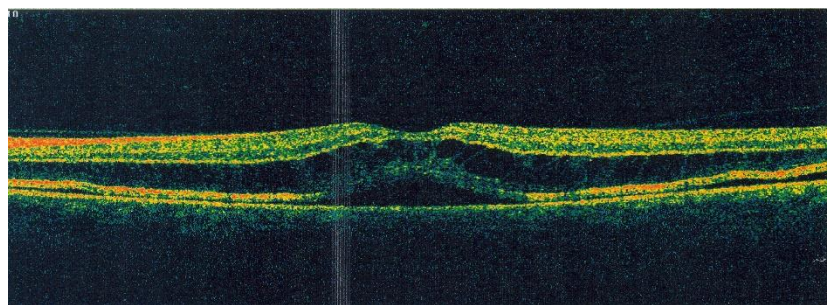


Figure 5. OCT OS dynamics of case 7 on the 3^d day, no PVD

In patient №15 with surgically treated stage III and IOP normalized glaucoma the resolution of the edema was detected on the sixth day (Figure 8).

On the OCT images of the patient № 16 (Figure 9) and patient № 17 (Figure 10) beside the neuroepithelium detachment the epiretinal fibrosis was detected which has not changed after resorption of the edema. Patient № 17 had complete resolution on the 4 – 5th day.

There was no PVD in the macula region in 9 cases. Sometimes the posterior hyaloid was elevated on the sides of the detached neuroepithelium but lay down again after the resorption of the oedema. In spite of high neuroepithelium detachment the foveal pit remained in all cases which means that the structure of the inner retina layers that normally may suffer from a vitreous traction was saved during observed condition.

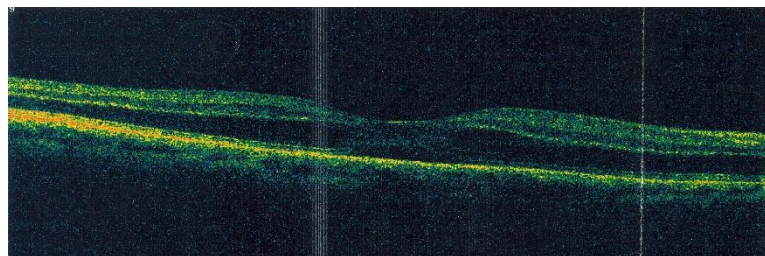


Figure 6. OCT image OS of case 8 on the 1st day



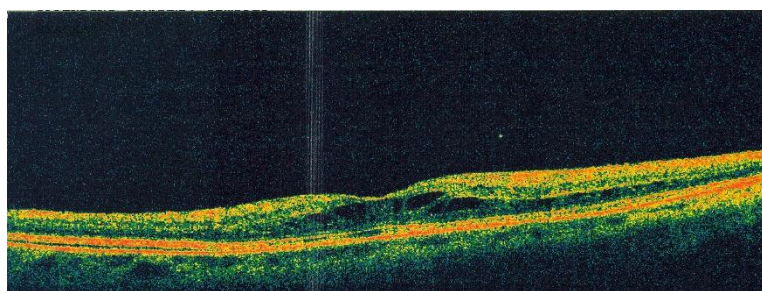


Figure 7. OCT image OD of case 14 with high myopia on the 2nd day

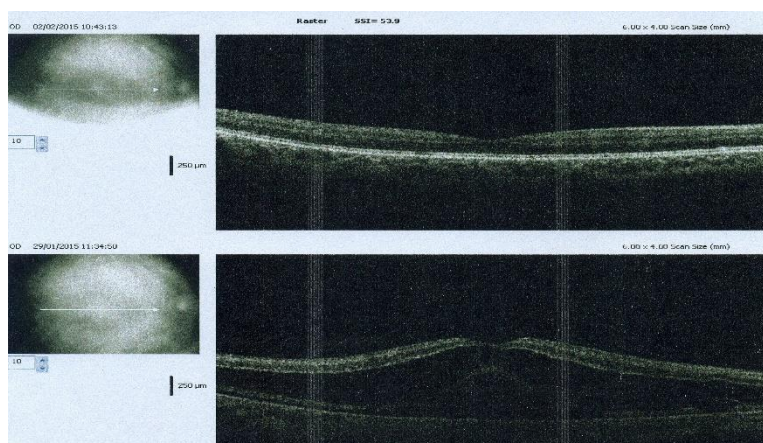


Figure 8. OCT OD dynamics of case 15 on the 2^d (below) - 6th (top) days, POAG

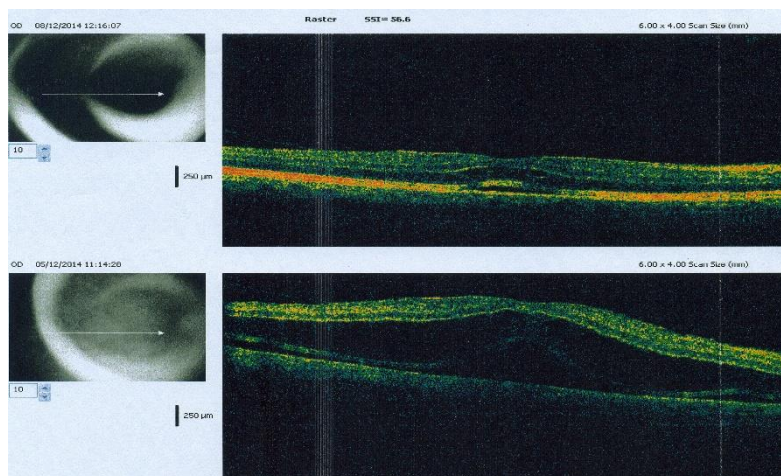


Figure 9. OCT OD dynamics of case 16 on the 2nd (below) and 5th (top) days, ERM



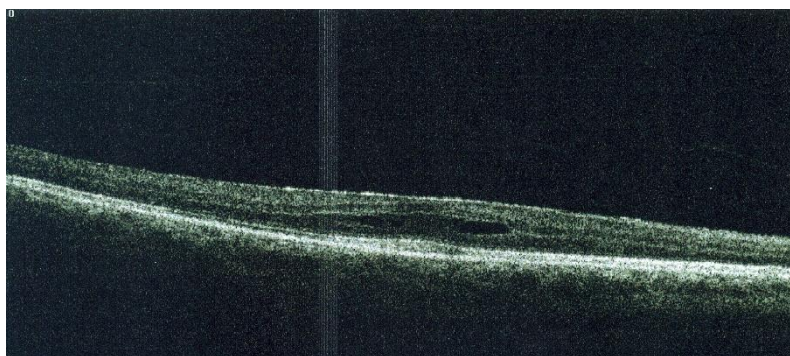


Figure 10. OCT image OD of case 17 on the 2nd day, SRD and ERM

Thus, on the majority of the images there are cavities in the outer nuclear layer which merge and split inner and outer nuclear layers. Also, there is detachment of the photoreceptors and the pigment epithelium but the order of this processes is unknown. Complete anatomical recovery of the macular region on the OCT usually occurs on the fourth day (3-6 days) after the surgery. Associated glaucoma, diabetes mellitus, treatment with diuretics influenced little on the area and height of the edema.

4. Discussion

Costen MTJ et al. in 2007 described similar cases. The incidence of them was not mentioned. Patients were two women and a man at age 72, 59 and 66 years old respectively. In the paper authors mentioned that all three patients had no signs of PVD but on the OCT image of the second patient there is almost a total PVD indicated except the foveal region where a contact with the internal limiting membrane is observed (<http://nature.com/articles/6702587>). British colleagues confused to determine the cause of the oedema but supposed that vitreomacular traction could be the reason of the described cases [1].

“A-sign” OCT image pattern described by Costen MTJ et al. may be explained by the structure of Muller cells that form a carcass in the macula region. The horizontal bar of the A sign probably is the part of this carcass as a part of the outer limiting membrane. A side bars sometimes wavy, sometimes compact and straight, which were noted on the OCT images, go up from the detached photoreceptors in the fovea, form an inverted trapezoid, and highly likely represent Henle fibers layer [2-4], which is located in tight connection with the Muller cells in the parafovea region. Matet A et al. in 2015 by the immunohistochemistry and the OCT detected a Z-like location of the Muller cells’ processes in the sagittal plane: oblique path in the outer plexiform layer together with Henle fibers and vertical path in the inner retinal layers forming bonds with axons of the cones [5].

In 2008 Aylin Yaman et al perform a prospective study with 59 patients (59 eyes) who underwent cataract surgery. Macular swelling on the first day after the surgery was detected in 2 patients (3,3%) and its resorption has been occurred during a week. Patients had a total PVD after resorption and no sign of leakage on the fluorescent angiography. Authors considered that the cause of the described two cases was a vitreo-macular traction [6].

In 2010 Panagiotidis D et al. retrospectively described five cases of the acute macular swelling on the first day after the routine cataract surgery which are also resolved spontaneously in ten days due to PVD as authors supposed [7]. Traction genesis of the swelling also was suggested,



but the authors noted the common pathogenesis with a pseudophakic cystoid macular edema. “A-sign” pattern was mentioned in 2 cases. The incidence of those cases was 1:600 but authors mentioned that it should be higher in fact. One patient with a structural change in the pigment epithelium complained on metamorphopsia even after edema resorption as well as the two patients described by Costen MTJ et al.

Idiopathic traction macular syndrome which was described in 1967 by Jaffe NS [8] and in 1970 by Reese AB [9] is characterized by a partial detachment of the posterior hyaloid in case of its tight adhesion to the inner limiting membrane and results in changed foveal contour. This condition may spontaneously resolve in 10% of cases without a macular hole formation but only on condition of complete PVD [10-12]. There are rare cases of the macular holes occurring on the first day after uncomplicated cataract surgery in the literature [13,14]. Also, there are conditions documented when after a routine cataract surgery vitreo-macular adhesion and traction resulted in CME development refractive to anti-inflammatory drug treatment and resolved only after the vitrectomy [15,16].

The involvement of the vitreomacular adhesion in the pathogenesis of the observed cases is doubtful considering the intact foveal pit amid the high neuroepithelium detachment and the absence of the PVD after the resorption in most cases. The volume of the extracted lens is several times lower of the IOL, so there should be changes in the structure of the vitreous body under the action of anterior-posterior forces which could be involved in the pathogenesis of the macular holes [14]. But only in 3,8% of our cases and 3,3% of Yaman A. cases transient changes of the macular region were observed. Moreover, several prospective researches measuring by the OCT thickness of the macular region before and after the phacoemulsification, have found only minimal enlargement in the macula in early and late terms after surgery [17-19] and in 3,2% of cases CME [19].

We noted that the OCT images at the certain stages are similar to that in cystoid macular edema with still unknown etiology. But Irvine-Gass syndrome occurs on the 4-6 week after the cataract surgery. It is characterized by the leakage of the dye on the fundus angiography through the parafoveal capillaries at the late stages of the investigation and by the cysts in the outer plexiform and nuclear layers on the OCT. The risk factors of its appearance are: age, male gender, uveitis, diabetes mellitus, duration of the surgery, rupture of the anterior hyaloid, loss of the vitreous body [20,21]. In the era of small incision surgery, the incidence of this condition decreased and is about 1,17%. The additional risk factors are: epiretinal fibrosis, history of vitreoretinal surgery and branch retinal thrombosis. It was noted that high myopia, dry age related maculodystrophy and the usage of the prostaglandin analogues do not increase the incidence of the pseudophakic cystoid macular edema [22].

Gulkilik G. et al found that CME after uneventful phacoemulsification with IOL implantation is observed on the tenth week more frequently if there were signs of postoperative inflammation on the first days after the surgery as cell reaction 2+ in the aqueous humor - 43,2% versus 11,5% in case of absence of the cell reaction. The presence of the total PVD had a protective effect against CME development [23]. Many authors consider that the real incidence of the CME after routine cataract surgery is not 0,1 - 2,5% [24,25], but 10 times higher and may reach 25,5% which is confirmed by the investigations with the usage of fundus angiography [23,26]. Mentis J. et al detected that the incidence of CME found on the angiography after the phacoemulsification



is about 9,1% that is comparable with its incidence after the extracapsular methods of the cataract extraction [27].

Unlike our cases in CME there is a cystoid pattern on the OCT images and subretinal fluid with the detachment of the neurosensory retina is rarely observed [25].

Systemic cardiovascular and autoimmune diseases undoubtedly affect the level of microcirculation in all structures of the eye. A fluctuation of the IOP during the operation and release of inflammatory mediators due to tissue injury leads to changed permeability of the capillaries. There are cases of occlusion of the retinal microcirculation in the parafoveal region on the first day after cataract surgery in case of so-called paracentral middle maculopathy which is characterized by permanent paracentral visual field defects and ischemic hyper reflexivity in the projection of the deep capillary layer of the retina on the OCT images [28].

Ioshin I.E. considers that pseudophakic CME is developed when the velocity of the capillary filtration exceeds the outflow rate of the interstitial fluid from the retina through the perivascular pathways despite the auto regulation mechanisms, and probably some autoimmune reactions to the IOL play a role in this process [29].

The intracameral usage of cefuroxime is considered to be the cause of such conditions as we observed with serous retinal and pigment epithelium detachment [30,31]. The toxic effect of cefuroxime is thought to be the reason of structural changes of the macular region. Although the underlying mechanism of such individual reaction is unknown. But the goal of this paper is to pay attention to the similarity of the OCT images of ATMO and CME at the certain stages of the process. Avascularity of the foveal region makes it susceptible to any changes in the molecular or chemical compound of the intraocular and interstitial fluids. The fact that pseudophakic CME usually occurs 4 weeks after surgery and has an OCT image that resembles the resorption stage in ATMO suggests a late breakdown of some compensatory mechanisms normally providing the homeostasis in this region.

The resorption of the intra- and subretinal fluid took place simultaneously in the outer retinal layers and along an entire zone under detached photoreceptors mainly due to the reactivation of the retinal pigment epithelium ion channels and pumps. All patients had a native vitreous body. Structure features of the vitreous body described by Worst J. (1975), i.e., connection between the retrolental bursa and premacular bursa through the central channel, probably has an impact to the pathogenesis of the ATMO, and even subconjunctival injection of cefuroxime also causes macular edema [32].

5. Conclusions

Thus, the incidence of macular edema induced by the standard dose of cefuroxime is from 0,35% [30] to 3,8%. Men are more likely to develop this condition rather than women. These two features together with fluid accumulation in the outer nuclear layer are similar to CME and central serous chorioretinopathy but in contrast, there is no dye leakage on the fundus angiography [6,7,31]. The individual intolerance of the standard dose of cefuroxime revealed us a part of the mechanisms of resorption of the interstitial fluid that normally occurs in the posterior segment of the eye. It is known that one of the functions of the retinal pigment epithelium is ion-dependent water transport due to transepithelial potential difference [33]. Muller cells also play a huge role in the maintaining of water-metabolic balance of the retina. A new point of view on the development of macular diseases arose from the analysis of these case series [34].



The disadvantages of this study: it is retrospective, so OCT images were available only in the paper format. OCT scans were performed in linear regimes not in 3D which reduces the morphology details and its connection to the optic disc.

We hope that this study may help investigators to understand the mechanisms underlying the interstitial fluid circulation in the posterior segment of the eye and in the retina particularly. Further research is needed to reveal the fluid-tissue exchange in the retina.

Declarations:

Ethics approval and consent to participate

Not applicable.

Consent for publication

We obtained written consent from patients to publish this report.

Availability of data and materials

All data and materials in this article are available.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JB was a major contributor to the drafting of the manuscript and acquired all the data. AIS and SAK reviewed and edited the manuscript. All named authors take responsibility for the integrity of the manuscript as a whole and gave their approval for publication.

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