Autologous Transplantation of the Choroid and Retinal Pigment Epithelium Patch Graft in Massive Submacular Hemorrhage Secondarty to Armd

YBMD'ye Sekonder Masif Submakuler Hemoraji Olgularında Otolog RPE ve Koroidal Yama Greft Transplantasyonu Cerrahi Sonuçları

Mehmet Özgür ÇUBUK[1]
Şengül ÖZDEK[2]

1- Uz. Dr., Bingöl Devlet Hastanesi
2- Prof. Dr., Gazi Üniversitesi Tıp Fakültesi Göz Hastalıkları Anabilim Dalı

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Yazışma Adresi / Correspondence Adress:
E-mail: www.sengulozdek.com

Phone: 0530 966 2142

ABSTRACT

Purpose: To present the results of autologous transplantation of the choroid and retinal pigment epithelium patch graft in massive submacular hemorrhage secondary to age-related macular degeneration (ARMD).

Methods: Patients who had massive submacular hemorrhage, hemorrhagic detachment and vitreous hemorrhage in the last 5 years, treated with pars plana vitrectomy, 360-degree retinotomy, extraction of the subretinal membrane and autologous transplantation of the choroid and retinal pigment epithelium patch graft with at least 6 months follow-up were involved in this study. Mean best-corrected visual acuity (BCVA) post-treatment results and complications of patients were presented.

Results: A total of 5 eyes of 5 patients were involved in this study. The mean duration of hemorrhage was 11, 0±8, 9 days. The mean duration of follow-up was 17, 6±9, 4 months. Visual acuity increased in all of the cases postoperatively. One patient had PVR related inferior localized retinal detachment and two patients had limited subretinal hemorrhage at the donor site. There was subretinal fibrosis at the temporal edge of the graft in one case.

Conclusion: The treatment of submacular hemorrhage with autologous transplantation of the choroid and retinal pigment epithelium patch graft is an encouraging procedure leading to improved visual acuity in these eyes with naturally poor prognosis.

Keywords: Submacular hemorrhage, age-related macular degeneration, choroid, and retinal pigment epithelium patch graft surgery.

ÖZ

Amaç: Yaşa bağlı maküla dejenerasyonuna (YBMD) sekonder masif submaküler hemoraji olgularında otolog RPE ve koroidal yama greft transplantasyonu cerrahisi ile yapılan submaküler cerrahi sonuçlarının değerlendirilmesi.

Gereç ve Yöntem: Son 5 yılda YBMD ye sekonder masif submaküler hemoraji, hemorajik dekolman ve vitreus hemorajisi olan vakalardan, pars plana vitrektomi, 360 derece retinotomi, subretinal membran ekstraksiyonu, otolog RPE ve koroidal yama

greft transplantasyonu, cerrahisi uygulanmış olan ve en az 6 ay düzenli takibi olan olgular çalışmaya dahil edildi. Olgular görsel ve anatomik sonuçlar ile cerrahi komplikasyonlar açısından değerlendirildi.

Bulgular: Bu cerrahinin uygulandığı 5 hastanın 5 gözü çalışmaya dahil edildi. Submaküler hemorajinin ortalama süresi 11, ±8, 9 gün idi. Ortalama takip süresi 17, 6±9, 4 ay idi. Olguların tamamında cerrahi sonrası görme keskinliği düzeyinde artış olduğu görüldü. Komplikasyon olarak 1 olguda inferiorda sınırlı retina dekolmanı, 2 olguda donor alanından sınırlı postop subretinal hemoraji ve bir olguda ise graft temporalinde sınırlı subretinal fibrosis izlendi.

Sonuç: Bu çalışmada YBMD ye sekonder masif subretinal hemoraji tedavisinde 360 derece retinotomi, subretinal membran ektraksiyonunu takiben otolog RPE ve koroidal yama greft transplantasyonu cerrahisinin, prognozu çok olumsuz olan bu hastalarda ümit verici bir yöntem olduğu gözlenmiştir.

Anahtar kelimeler: Submaküler hemoraji, Yaşa bağlı maküla dejenerasyonu, otolog RPE ve koroidal yama greft cerrahisi.

INTRODUCTION

Age-related macular degeneration (ARMD) is a crucial cause of untreatable blindness in the developed world. Approximately 20% of people older than 50 suffer from ARMD.[1, 2] Choroidal neovascularization (CNV) is a destructive complication of ARMD that can impair the function of the overlying neurosensory retina.[3, 4] Although CNV can be treated with intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents, treatment of massive submacular hemorrhage, RPE tear or geographic atrophy (GA) remains controversial. Especially submacular hemorrhages secondary to CNV concludes poor vision due to the retinal toxicity of iron release from hemoglobin and it also acts as a mechanical barrier which inhibits diffusion of nutrients and metabolites.[5] Subretinal surgery may be an important option to restore submacular anatomy for this patients.[6] Surgical techniques aim to restore contact between the macula and healthy subretinal tissue (RPE and choroid). Previous studies have shown that removal of CNV alone although technically available does not improve or preserve visual acuity over 24 months.[7, 8] Machemer et al introduced macular translocation surgery with the restoration of foveal contact to healthy RPE and this surgical concept was refined to reduce complications.[9-11] A relatively new surgical procedure was autologous transplantation of the retinal pigment epithelium and choroid which avoids image cyclotorsion caused by macular translocation surgery.[12, 15, 17] Equatorial RPE is used for this procedure as it is relatively unaffected by ARMD and therefore is a good donor site.[12] Van Meurs was the first author to describe this surgery and it was adopted by others later.[15-18] Although these procedures are the only suitable surgeries for massive submacular hemorrhage secondary to ARMD, there is no randomized controlled study for these procedures.

In the present study, we aimed to present the results of subretinal surgery with autologous transplantation of the choroid-retinal pigment epithelium patch graft for the treatment of submacular massive hemorrhage secondary to ARMD in our clinic.

METHOD

The medical charts of patients with massive subretinal hemorrhage were reviewed retrospectively. Patients who underwent pars plana vitrectomy, 360-degree retinotomy, subretinal membrane and hematoma extraction and autologous transplantation of the choroid-retinal pigment epithelium patch graft with silicone tamponade surgery with a minimum follow-up of 6 months were involved in this study.

Ophthalmologic records of patients were examined for anticoagulant/antiaggregant use history, anti-VEGF treatment history, fellow eye findings, duration of hemorrhage, preoperative and postoperative best-corrected visual acuity (BCVA) (Snellen line), anterior segment examination findings, IOP and fundus findings. Postoperative fundus fluorescein angiography (FFA), indocyanine green angiography (ICG), optic coherence tomography (OCT), fundus autofluorescence (FAF) images were rechecked. Postoperative position and vascularization of graft, silicone oil retention time, complications and

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follow-up time were evaluated. RPE survival was checked with serial postoperative FAF images.

RESULTS

A total of 5 eyes of 5 patients with a mean age of 72, 4 ±5, 1 years, with subretinal massive hemorrhage, were involved in this study. The mean period of hemorrhage was 11, 0±8, 9 days. All patients had a visual acuity of less than 20/200 in their fellow eye because of ARMD related scarring previously. All of them had hemorrhagic retinal detachment and some vitreous hemorrhage. They underwent pars plana vitrectomy, 360-degree retinotomy, subretinal hemorrhage and membrane extraction, autologous transplantation of the choroid and retinal pigment epithelium patch graft with silicone oil tamponade. The graft was harvested from a healthy looking part of the equatorial area, mostly from the superior part.

The mean duration of follow-up was 17, 6±9, 4 months (6-30). There was only one patient with the history of antiaggregant/anticoagulant use. The mean number of preoperative anti-VEGF injection received to the surgical eye was 5, 0±2, 0 (Table 1).

Visual acuity increased in all of the cases postoperatively. The postoperative improvement of BCVA was statistically significant (p=0.04 Wilcoxon paired samples t-test) (Table 1). There was no recurrence of CNV and no patient needed anti-VEGF treatment postoperatively. Graft vascularization as detected with postoperative ICG and RPE survival as detected with fundus autofluorescence could be presented in all of the cases postoperatively (figure 1-2, 4, 5). Silicone oil was removed within 3 months in all of the cases except one (case 4) who preferred to be operated in another center. The characteristics of patients have been shown in Table 1.

An inferior limited PVR related retinal detachment was detected during the post op 1st month in one eye (case 4), which was reattached with 2nd surgery in another clinic. Postoperative limited subretinal hemorrhage from donor site was detected in 2 of the cases (case 2 and 3) both of which resolved spontaneously. There was subretinal fibrosis at the temporal edge of the graft in one case (case 5).

Here we present Case 1 in detail as a demonstrative case:

Case 1: A 64 years old male patient, who was having a series of anti-VEGF injections for ARMD in the better seeing left eye, referred to our clinic with sudden vision loss occurring 2 days ago in his left eye. His visual acuity was 0.05 (Snellen) in the right eye and hand motion (HM) in the left eye. There was a disciform macular scar in the right eye and vitreous hemorrhage associated with massive subretinal hemorrhage causing hemorrhagic retinal detachment in the left eye (Figure 1a-b). Pars plana vitrectomy, subretinal membrane, and hematoma extraction and autologous transplantation of the choroid-retinal pigment epithelium patch graft with silicone oil tamponade surgery was performed (figure 3). Postop 1st-month visual acuity was 0.1 with central fixation (figure 1c-d). Retina was attached, the graft was central and vascularized

Table 1: The demographic and clinical characteristics of patients

Patient	Age (y)	Period of hem. (d)	Preop BCVA	Postop BCVA	Follow up(m)	Complications	Extra treatment	Anti-VEGF	Anticoagulant history	Fellow eye BCVA	Silicone retention	Graft vascularisation (ICG)
1 (M)	66	2	HM	0.4	30	-	-	6	-	0.05/F.scar	3m	+
2 (M)	70	25	HM	0.03	24	Hemorrhage	-	4	-	P(-)/F.scar	3m	+
3 (F)	74	7	HM	CF 1mt	15	Hemorrhage	-	7	+	CF/GA	3m	+
4 (F)	80	7	CF	CF1mt	13	PVR-RD	-	6	-	CF/F. scar	Still (+)	+
5 (M)	72	14	HM	0.3	6	Fibrosis	-	2	-	CF/F. scar	3m	+

S: Sex, M: Male, F: Female, Y: Year, d: day, BCVA: Best corrected visual acuity (Snellen), Hem: Hemorrhage HM: Hand motions, m: month, RD: Retinal detachment CF: counting finger fibrosis: Fibrosis around graft GA: Geographical atrophy mt:meter Anti-VEGF: preoperative anti-vascular endothelial growth factor treatment history p: perception

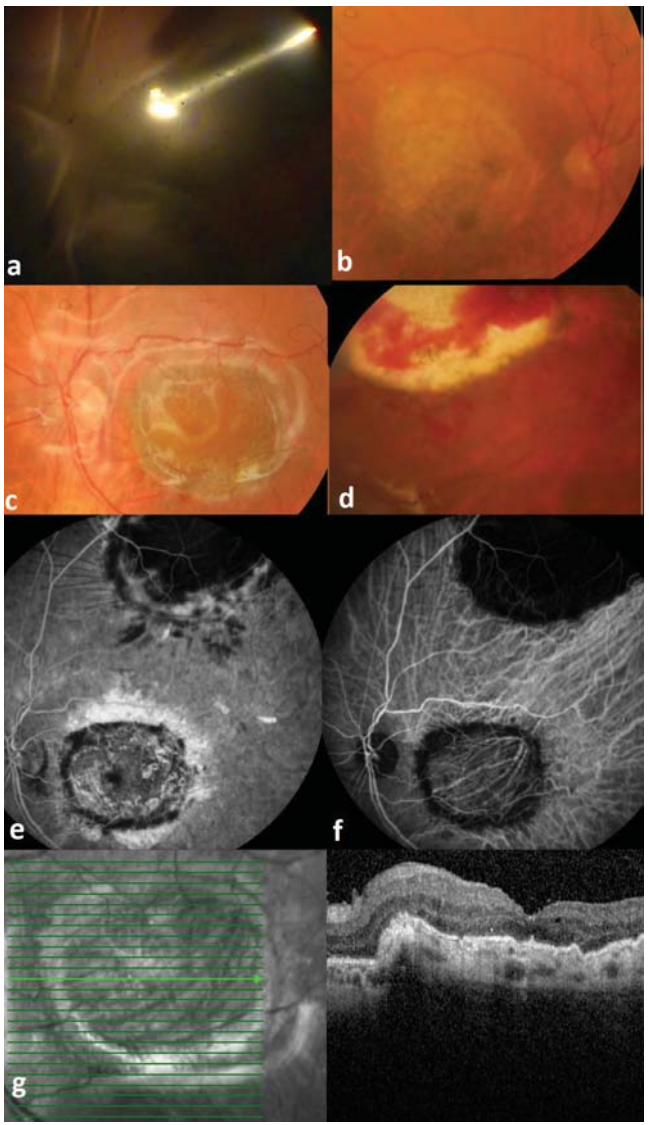

***Figure 1 a**. Peroperative fundus picture of case 1 showing vitreous hemorrhage associated with massive subretinal hemorrhage causing hemorrhagic retinal detachment (left eye) **b**. The right eye of the same patient demonstrating we ARMD related macular scarring. **c**. Postop 1st -month fundus picture of the same case. Note that, the graft is central and visual acuity was 0.1 with central fixation. **d** Postop 1st month donor site **e**. The graft was central and vascularized as seen in FFA and **f**. ICG. **g.** There was double layered choroid with a good foveal contour without edema in OCT*

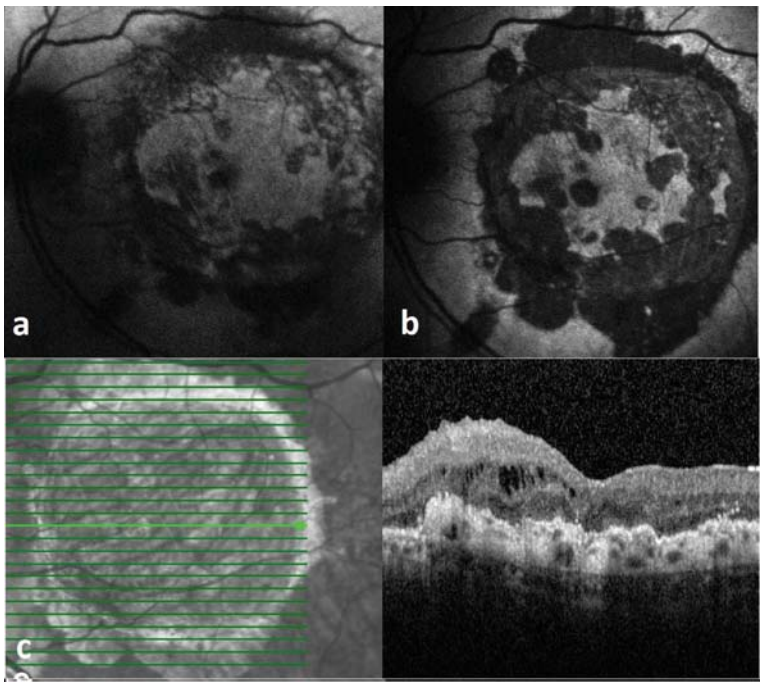

***Figure 2 a.** Postop 1st month RPE looked healthy in FAF image of case 1. **b.** There was RPE atrophy progressing during follow-up at the end of 13th month. **c.** OCT shows well preserved foveal contour at one year. Visual acuity improved to 0.4 at the end of the 13th month without recurrence of CNV.*

as seen in ICG (Figure 1e-f). RPE looked healthy in FAF image (Figure 2a) and there was double layered choroid with a good foveal contour without edema in OCT (figure 1g). Silicon oil was removed within 3 months and his visual acuity improved to 0.4 at the end of the 13th month (Figure 2b-c). He could read the small newspaper prints with +4.00 glasses. There was no recurrent CNV and need for anti-VEGF treatment during 2-year follow-up period. However, there was RPE atrophy over the graft which was progressing during the follow-up period (Figure 2b).

DISCUSSION

Submacular hemorrhage is a serious complication of ARMD, which leads immediate loss of vision. If the appropriate treat-

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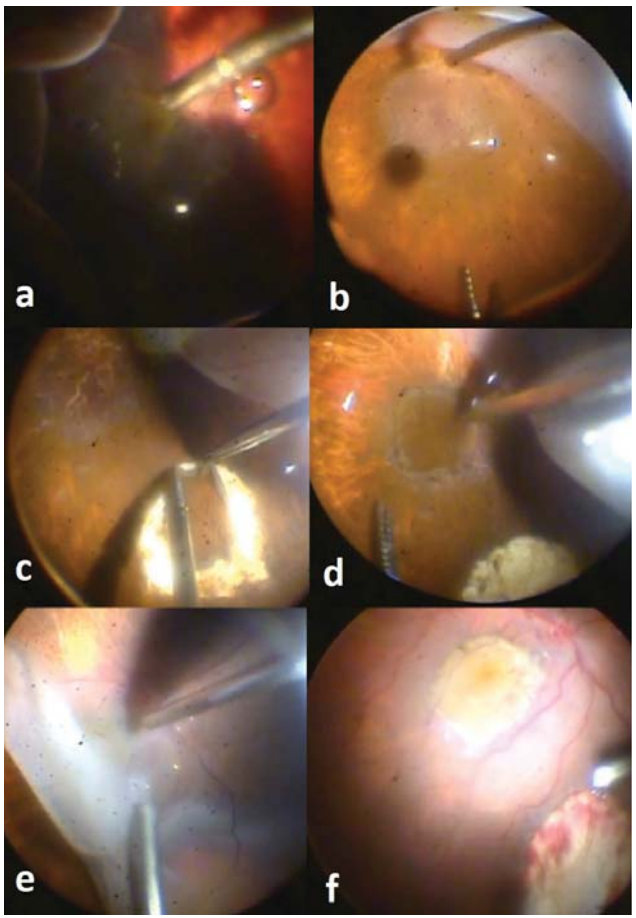

Figure 3 a. *Peroperative appearance of massive submacular hemorrhage of case 1.* ***b.*** *Note the naked macular area lacking RPE following removal of subretinal membrane and hematoma after 360 retinotomy. Temporal retina was folded over the nasal retina.* ***c-d.*** *A patch of RPE-choroid graft was prepared from a healthy superior equatorial area and carried over the fovea with minimal manipulation under PFCL with bimanual technique.* ***e.*** *Temporal retina was unfolded over the graft and retina was reattached with the help of PFCL* ***f.*** *Surgery ends up with 360 peripheral laser and PFCL-silicon oil exchange.*

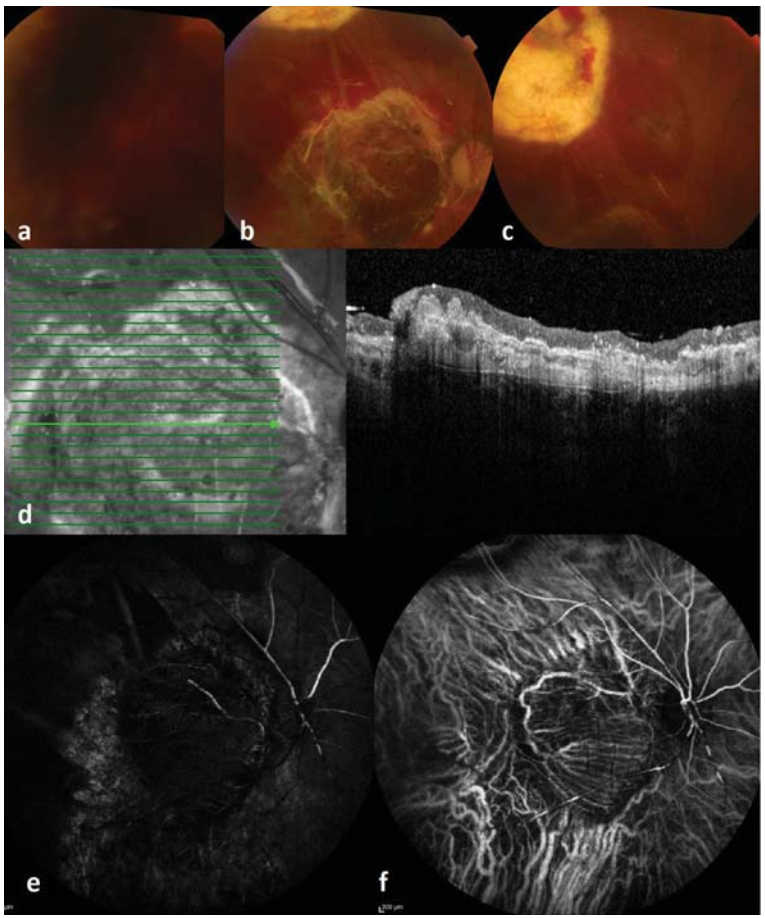

Figure 4 a. *Preop fundus picture of case 2. Note subretinal and vitreous hemorrhage* ***b****. Fundus picture of the case at postoperative 1st month visit. Note the well-centered graft.* ***c****. Superior donor site.* ***d****. Postoperative 1st month OCT of the case: Note there was no edema in fovea* ***e-f.*** *Total vascularization of the graft in FFA-ICG in the postop 1st month.*

ment is not performed, hemorrhage usually ends up with large thick fibrotic scarring causing irreversible vision loss due to the destruction of retinal pigment epithelium cells and photoreceptors.[13] Although limited subretinal hemorrhage can be treated with pneumatic displacement with expansive gas and anti-VEGF injections,[14] the treatment of massive subretinal hemorrhage is formidable and necessitates more aggressive vitreoretinal surgical procedures. The decision of surgical treatment was depended on the conditions of the patient. Age and expectations of the patient, compliance of prone position,

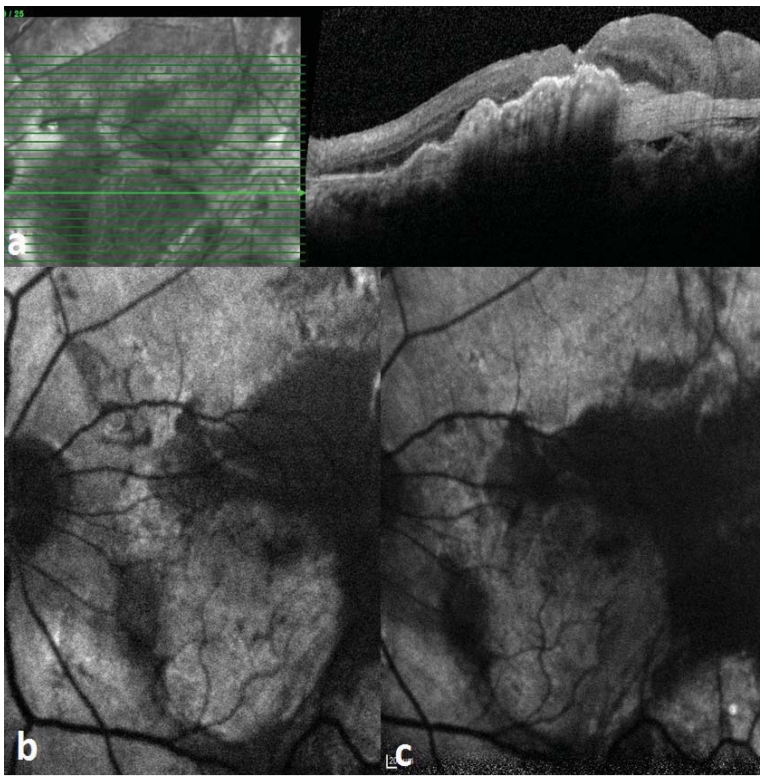

Figure 5. a. *Postoperative 1st month OCT of the case 5. Note there was no edema in the fovea. RPE looks healthy in FAF image at the postop 1st month* ***(b)*** *and the 6th month* ***(c).***

social life, visual acuity of the fellow eye, amount and period of the hemorrhage and involvement of the fovea could affect the decision of surgical treatment.

Pneumatic displacement (IV anti-VEGF + IV gas ± tPA) can be used to manage sub-macular hemorrhage and can be performed in office conditions with a low rate of complications but it works better in eyes with the limited amount of sub-macular hemorrhage.[5, 14]

On the other hand, the treatment of massive subretinal hemorrhage is formidable and necessitates more aggressive vitreoretinal surgical procedures including macular translocation surgery or autologous transplantation of the retinal pigment epithelium and choroid. Subretinal membrane and hematoma extraction can be performed through retinotomy and detachment of retina in both procedure.[9-12, 15, 17] Restoration of foveal contact to healthy RPE can be achieved with macular translocation surgery.[9-11] The disadvantages of macular translocation are postoperative cyclotorsion, the necessity of extraocular muscle surgery in patients with binocular vision and the need of healthy RPE in close vicinity of macular area.[9-12, 15, 17] Autologous transplantation of the retinal pigment epithelium and choroid, on the other hand, avoids image cyclotorsion and healthy RPE does not have to be in close vicinity of macula as opposed to macular translocation surgery.[12, 15, 17] Equatorial RPE is used for this procedure as it is relatively unaffected by ARMD and therefore is a good donor site.[12] The disadvantages of autologous transplantation of the retinal pigment epithelium and choroid are the hemorrhage of the donor area, vascularization problems of graft, graft fibrosis, RPE atrophy and proliferative vitreoretinopathy.[9-12, 15, 17]

In previous studies, angiographic observations showed that a small patch of RPE-choroid can become revascularized when transplanted as a free graft into the subretinal space.[15, 16] In addition to that, visual improvement could be achieved in most of the cases.[16] Furthermore, MacLaren et al presented an improvement of visual acuity in 3 of 12 ARMD patients which were sustained at least 1 year. They suggested that patients with neovascular ARMD who are nonresponsive to anti-VEGF therapy and with a mechanical disruption of the RPE, such as a rip, or geographic atrophy could be treated with autologous RPE-choroid transplantation.[15] It was suggested that patients with higher mean initial BCVA had better final BCVA.[16] In our study, BCVA improved in all of the cases postoperatively and was sustained during the follow-up time similarly.

Recurrence of CNV is another potential problem after surgery. Even though Joussen et al reported no recurrent CNV, a mean recurrence rate of CNV presented by other studies was between 10 to 14%,[17, 19-21] Similar to Joussen et al, in the present study, there was no recurrent CNV and need for anti-VEGF treatment in any of our cases.

Fibrosis around the graft is another potential postoperative complication [17]. Joussen et al reported this problem in 24 of

45 eyes.[17] Parolini has suggested that larger graft had a lesser risk of fibrosis[16]. In the present study, one patient had subretinal fibrosis at the temporal edge of the graft.

Early postoperative subretinal hemorrhage on donor sites was seen in 2 of our cases. As the hemorrhage was limited, it did not threaten the graft survival. However, if it was a massive hemorrhage, this might cause avascular necrosis of our graft[15]. High risk of complications that limited the final visual improvement, were also mentioned in the previous studies.[15,17,18] Robert E et al reported high rate (5/11 case) of retinal detachment postoperatively. They suggested that high rate of proliferative vitreoretinopathy (PVR) may contribute to the high incidence of retinal detachment[15]. However, it was not so common in other series. The rate of PVR was between 5% to %31 in other literatures.[17, 19-21] There was only one retinal detachment (20%) in our series which was related to a bad head positioning of the patient. We feel that PVR rate is not higher than standard rhegmatogenous retinal detachment.

Although the number of patients is limited in this study, autologous RPE-choroid transplantation seems to be a good treatment option for patients with massive submacular hemorrhage causing hemorrhagic retinal detachments secondary to CNV. These cases would have a permanent visual loss if treated only with anti-VEGFs. Similar studies with a large group of patients comparing different treatment modalities must be designed for more reliable results.

REFERENCES/KAYNAKLAR

1. Chopdar A, Chakravarthy U, Verma D. Age-related macular degeneration. BMJ 2003;326:485– 8.
2. Gibson JM, Rosenthal AR, Lavery J. A study of the prevalence of eye disease in the elderly in an English community. Trans Ophthalmol Soc UK 1985;104:196 –203.
3. Hageman GS, Luthert PJ, Victor Chong NH, et al. An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. Prog Retinal Eye Res 2001;20:705–32.
4. Ambati J, Ambati BK, Yoo SH, et al. Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. Surv Ophthalmol 2003;48:257–93.
5. Chan WM, Liu DT, Lai TY, et al. Extensive submacular hemorrhage in polypoidal choroidal vasculopathy managed by sequential gas displacement and photodynamic therapy: A pilot study of one-year follow-up. Clin Experiment Ophthalmol 2005;33:611-618.
6. Del Priore LV, Tezel TH, Kaplan HJ. Maculoplasty for age-related macular degeneration: reengineering Bruch's membrane and the human macula. *Prog Retin Eye Res.* 2006;25:539–562.
7. Submacular Surgery Trial Research Group. Surgery for subfoveal choroidal neovascularization in age-related macular degeneration: ophthalmic findings. SST report No. 11. Ophthalmology 2004;111:1967–1980.
8. Thomas MA, Dickinson JD, Melberg NS, et al. Visual results after surgical removal of subfoveal choroidal neovascular membranes. Ophthalmology 1994;101:1384 –96.
9. Machemer R, Steinhorst UH. Retinal separation, retinotomy, and macular relocation: II. A surgical approach for age-related macular degeneration? Graefes Arch Clin Exp Ophthalmol 1993;231:635– 41.
10. Eckardt C, Eckardt U, Conrad HG. Macular rotation with and without counter-rotation of the globe in patients with age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 1999;237:313–25.
11. Mruthyunjaya P, Stinnett SS, Toth CA. Change in visual function after macular translocation with 360 degrees retinectomy for neovascular age-related macular degeneration. Ophthalmology 2004;111:1715–24.
12. van Meurs JC, Van den Biesen PR. Autologous retinal pigment epithelium and choroid translocation in patients with exudative age-related macular degeneration: short-term follow-up. Am J Ophthalmol 2003;136:688–95.
13. Benner JD, Hay A, Landers MB, III, Hjelmeland LM, Morse LS: Fibrinolytic-assisted removal of experimental subretinal hemorrhage within seven days reduces outer retinal degeneration. Ophthalmology 1994; 101: 672–681.
14. Cubuk MO, Ozdek S, Hasanreisoglu B. Comparison of Pneumatic Displacement Method Anti-VEGF and tPA with Intravitreal Anti VEGF-Therapy Alone in Fresh Limited Submacular Hemorrhage Cases. Retina-Vitreous 2015; 23(2):154-158

15. MacLaren RE, Uppal GS, Balaggan KS et al. Autologous Transplantation of the Retinal Pigment Epithelium and Choroid in the Treatment of Neovascular Age-Related Macular Degeneration. Ophthalmology, 2007;114(3):561-70

16. Parolini B. Choroidal Patch Graft Surgery for AMD Retina-Vitreous 2013;21:77-81

17. Joussen AM, Heussen FM, Joeres S, et al. Autologous translocation of the choroid and retinal pigment epithelium in age-related macular degeneration. Am J Ophthalmol 2006;142:17–30.

18. Joussen AM, Joeres S, Fawzy N, et al. Autologous translocation of the choroid and retinal pigment epithelium in patients with geographic atrophy. Ophthalmology. 2007 Mar;114(3):551-60.

19. Treumer F, Bunse A, Klatt C, et al. Autologous retinal pigment epithelium choroid sheet transplantation in age related macular degeneration: morphological and functional results. Br J Ophthalmol 2007;91:349–53.

20. Maaijwee K, Heimann H, Missotten T, et al. Retinal pigment epithelium and choroid translocation in patients with exudative age-related macular degeneration: long-term results. Graefes Arch Clin Exp Ophthalmol 2007;245:1681–9. 11/84

21. van Zeeburg EJT, Maaijwee K, Missotten TOAR, et al. A free retinal pigment epithelium-choroid graft in patients with exudative macular degeneration; results up to seven years. Am J Ophthalmol 2012;153:120–7.