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LETTER TO THE EDITOR

Lamellar macular hole following intravitreal aflibercept injection in a patient with neovascular age-related macular degeneration

Neovasküler yaşa bağlı makula dejenerasyonu bulunan bir hastada intravitreal aflibercept enjeksiyonu sonrası lamellar makula deliği gelişimi

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To the Editor,

Lamellar macular hole (LMH) is described as an irregular foveal contour and a partial thickness defect of the central macula with intact underlying retinal pigment epithelium (RPE) and photoreceptor layers[1]. In the literature, LMH is divided into two main subgroups: degenerative and tractional[2]. To better understand the pathophysiology of both types of LMH formation, many studies tried to explain the intertwined relationships between tractional forces at retinal surface induced by many factors such as contraction of epiretinal membrane, presence of vitreomacular traction, treatment with intravitreal drugs and predisposing retinal diseases, which have degenerative process leading to loss of retinal tissue. In fact, many of those eventually interact with each other by aging[2,3]. Being one of the degenerative diseases, age-related macular degeneration (AMD) is regarded as the main reason of irreversible blindness among aged population in advanced countries. The pathogenesis of macular degeneration, as put by Schulze et al. (2008), was previously based merely on a retinal, pigment- epithelial disease, with many questions remaining unclear. Recently, however, a greater attention is being paid to the vitreoretinal interface, the role of the vitreous and its adherence to the retina[1]. Thus, physiological as well as pathological vitreous changes appear to affect retinal and, particularly, foveal structures, as shown in many diseases.

The exudative type of AMD has been treated mainly by anti-vascular endothelial growth factor (anti-VEGF) agents. Among anti-VEGF agents, aflibercept is a new, fully human, recombinant fusion protein, which binds all isoforms of VEGF-A and placental growth factor (PGF). In so doing, it prevents the binding and activation of VEGF receptors. Aflibercept is used intravitreally to treat choroidal neovascularization secondary to AMD.Herein, we report a case where a LMH developed following intravitreal injection of aflibercept due to nAMD, even with an accompanying whole posterior vitreous detachment (PVD) at fovea. To our knowledge, this type of LMH formation after intravitreal aflibercept injection has not been reported yet.

In this connection, a 70-year-old man came in with his left eye's vision blurry for the past week. The initial visual acuity was hand-moving in the right eye and 0.2 in the left eye. Intraocular pressure was 13 mmHg OD and 17 mmHg OS. Slit lamp examination of anterior segment was unremarkable in both eyes. On funduscopic examination, optic atrophy and drusen in the right eye and a choroidal neovascular membrane in the left eye were observed. Fundus autofluorescence image showed hypoautofluorescent area in fovea. As shown in Figure 1, OCT demonstrated subretinal fluid, detachment of posterior hyaloid and hyperreflective line on retinal surface in the left eye, but only drusen in the right eye. Fundus fluorescein angiography demonstrated leakage of dye from neovascular membrane in the left eye.

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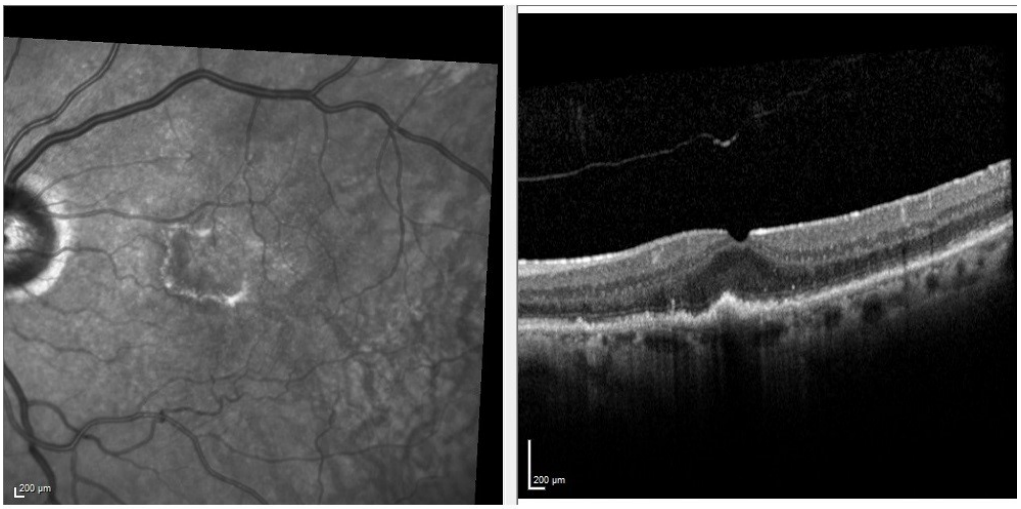

Figure 1. Optical coherence tomography, showing subretinal fluid, pigment epithelium detachment, and retinal pigment epithelium changes, as well as disruption in ellipsoid zone.

After receiving a written informed consent to publish the findings and images obtained from him, and at Dışkapı Training and Research Hospital has ruled that approval of ethics committee was not required for the study. The patient underwent intravitreal aflibercept injections in the left eye for three months. Later, resolution of the subretinal fluid was revealed by OCT and best corrected visual acuity (BCVA) improved to 0.6 (from 0.2) and remained stable for 3 months (Figure 2). One month later, visual impairment occurred (BCVA: 0.4) in respect to activation of neovascular membrane (Figure 3). Therefore, intravitreal injection of aflibercept was performed again. After one month following the last injection, LMH developed, as demonstrated by OCT, in addition to resolution of subretinal fluid and partial visual improvement (BCVA: 0.5) (Figure 4).

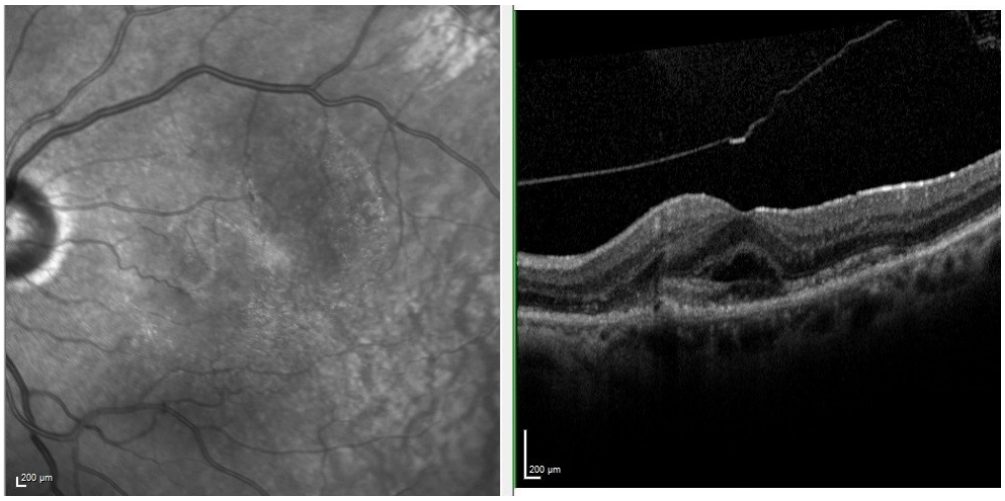

Figure 2. Optical coherence tomography, showing resolution of subretinal fluid with some intraretinal fluid.

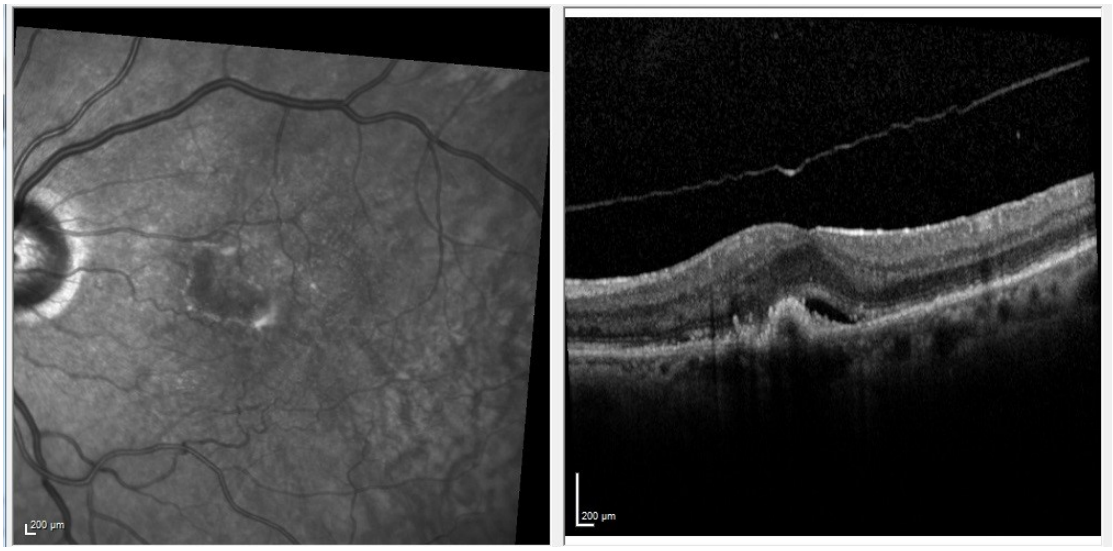

Figure 3. Optical coherence tomography, showing subretinal fluid due to activation of CNV.

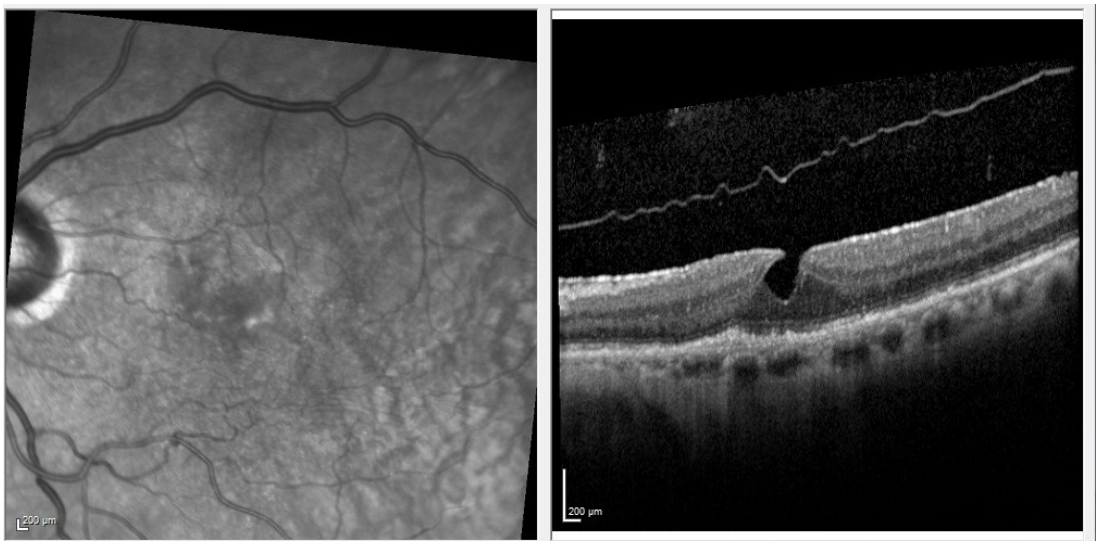

Figure 4. Lamellar macular hole formation following intravitreal injection.

Degenerative and tractional LMH constitutes the two forms of disease depending on structural differences detected with OCT[2]. While the predominant factor in tractional subtype of lamellar hole development is mechanical forces; in degenerative form, with a distinct pathway, it is the damage of the retinal tissue and the disruption of the ellipsoid layer induced by a slow, chronic, degenerative process.

To better understand the pathophysiology of lamellar hole formation, it is necessary to consider the interactions between anatomically contiguous structures such as retina (affected by many diseases, especially fovea), vitreous, vitreoretinal interface as a whole. Moreover, it is also critical to take into account the effect of intravitreal administration of drugs on those structures.

In terms of its impact on the pathophysiology of LMH, AMD was the focus of most studies in explaining the LMH formation, which leads to apoptosis of RPE cells and loss of the outer retina. This could further engender disruption of cell-to-cell adhesions and foveal destabilization, thus increasing the likelihood of LMH formation in the fovea[4]. Recently, Francona et al. (2019) reported a greater rate of the degenerative LMH compared to the tractional LMH in patients with AMD.

The pathogenesis of macular degeneration was previously relied merely on a retinal, pigment-epithelial disease, but many issues remained unclarified. As indicated earlier, there is also greater attention today on the vitreoretinal interface and associated implications. Abnormal vitreomacular interface (VMA, VMT) in AMD has been reportedly implicated among the potential risk factors for the increased incidence of exudative AMD[1]. Additionally, abnormal vitreomacular interface may have originated focal sites of tractional forces on the retinal surface, thereby causing an LMH.

In the literature, there exists only a few case reports on the formation of lamellar hole following intravitreal agents. In those reports, alternative mechanisms are provided in explaining the formation of LMH. These include (i) increased anteroposterior mechanical forces at target fovea due to vitreous incarceration at injection site, (ii) accelerated formation of macular hole as a part of natural history of vitreomacular interface diseases, (iii) the exacerbation of tangential traction by sudden subretinal fluid resolution (as a response to anti-VEGF) with changes in central foveal thickness[5], and contraction of neovascular membrane, (iv) impacts of anti-VEGF agents on fibrotic process[6].

We came across with four case studies in the literature reporting LMH formation following intravitreal injection in patients with nAMD or diabetic cystoid macular edema[6,7]. However, the agent used in these case studies was not aflibercept. One of them presented a case with complete separation of the posterior hyaloid membrane (PHM) and the absence of an epiretinal membrane (ERM) in pre-injection OCT[6].

In our case, full separation of the PHM was observed, but together with hyperreflective line on retinal surface, which can be interpreted as either remnant of detached posterior hyaloid or epiretinal membrane. ERM formation is primarily linked to an abnormal PVD, where glial cells migrate through microscopic defects of inner limiting membrane (ILM) and then proliferate on the surface of the retina after PVD. The presence of ERM may aid the formation of LMH through increasing tangential tractional forces. Previous research revealed that eyes with ERM can have up to four eccentric retinal contraction centres.

Additionally, it is important to identify the existence of vitreo-papillar adhesion (VPA) to determine the existence of complete PVD (the total separation of the fibrils from ILM, at both optic disk and macula). Moreover, potential impact of VPA on the amplification of tangential traction nasally could also play a role in the formation of LMH, especially in tractional type of LMH. In this context, a former study had found a 37% prevalence of VPA in LMH. Accordingly, ERM and VPA are said to exist in the vast majority of tractional but not degenerative LMH[8].

There are a number of studies suggesting potential contribution of anti-VEGF agents to fibrotic process leading to increased tractional forces[9]. It was also reported that bevacizumab can exert pro-fibrotic effects by upregulating the expressions of fibrosis-related cytokines (CTGF, bFGF, TGF-β2, and MMP-2) in human umbilical vein endothelial cells in-vitro.

The presence of a vital balance between the connective tissue growth factor (CTGF) and the VEGF was suggested in another study in patients with PDR, which found low levels of VEGF and high vitreal levels of CTGF after intravitreal therapy. This increased CTGF, as one of the fibrosis-related cytokines, led to consider it as an angiofibrotic switch leading vitreoretinal traction and fibrosis[10].

In our case, LMH was formed following aflibercept injection; yet, the presence of any inhibition of PGF, as a distinctive feature of aflibercept among other anti-VEGF agents, on fibrotic process remains unclear.

A limitation of our case study is the inability to determine whether VPA and peripheral vitreoretinal release exist and accompanied to the detachment of posterior hyaloid at target fovea. This was needed to thoroughly evaluate possible mechanical forces that contribute the formation of LMH.

In conclusion, the prevalence of nAMD and thereby intravitreal administration of anti-VEGF agents has

been increasing worldwide in the course of time. Prior to initiation of intravitreal anti-VEGF agents in patients with nAMD, it is important to ensure that any factor inducing tractional forces on retinal surface such as VMA, VMT, ERM does exist. However, whole detachment of posterior hyaloid at fovea may indicate that retina was exposed to former tractional forces, which may cause initiation of LMH formation.

Consequently, retinal fluid may mask the damage on retinal microstructure caused by tractional forces during the detachment of posterior hyaloid at fovea. Then, repetitive reduction of subretinal fluid following anti-VEGF treatment may disclose the presence of LMH and/or may contribute the progression of LMH formation, which initially started to develop by the action of tractional forces.

Thus, LMH formation following anti-VEGF injection was considered to be closely related with reduction of subretinal fluid on damaged retinal tissue rather than being an adverse effect of injection itself. Moreover, in order to improve our existing knowledge on the potential impacts of anti-VEGF injections on tractional forces, the effects of other anti-VEGF agents and aflibercept on fibrotic process (PGF inhibition in addition to VEGF) need to be further investigated.

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