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Vitreomacular Adhesion and the Risk of Neovascular Age-Related Macular Degeneration

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Purpose: To assess the prevalence of vitreomacular adhesion (VMA) in consecutive naïve eyes diagnosed with exudative age-related macular degeneration (AMD) in comparison with eyes with nonexudative AMD and age-matched controls, and to evaluate prospectively the incidence of vitreomacular interface changes over time and their influence on choroidal neovascularization (CNV) development.

Design: Retrospective cross-sectional analysis and longitudinal cohort study conducted at Sacrocuore Hospital, Negrar, Verona, Italy.

Participants: A total of 1067 eyes examined at Sacrocuore Hospital between August 2008 and June 2015 met the inclusion criteria and were evaluated in this study.

Methods: Eyes were classified into 3 groups: 403 eyes of 364 patients (mean [standard deviation; SD] age 77.8 [8.0] years) affected by exudative AMD; 350 eyes of 298 subjects (mean [SD] age 78.1 [8.2] years) with nonexudative AMD; and 314 eyes of 214 subjects (mean [SD] age 74.2 [8.2] years) with no signs of AMD enrolled as the control group. The vitreomacular interface status was evaluated by spectral-domain optical coherence tomography (OCT) and was graded according to the OCT-based International Classification System developed by the International Vitreomacular Traction Study Group by 2 independent masked observers.

Results: VMA was present in 101 (25.1%) eyes with exudative AMD, 84 (24.0%) eyes with nonexudative AMD, and 84 (26.8%) eyes with no signs of AMD (no statistical difference was found; $P = 0.3384$). Spontaneous release of VMA (RVMA) was found in 15 (15.3%) eyes with exudative AMD, 21 (28.0%) eyes with nonexudative AMD, and 10 (24.4%) eyes with no signs of AMD over a mean follow-up of 25.5, 25.9, and 24.1 months, respectively. The incidence of RVMA in exudative AMD eyes was significantly lower compared with nonexudative ($P = 0.0207$) and lower, but not statistically significant, with respect to eyes with no signs of AMD ($P = 0.1013$). In eyes with nonexudative AMD, de novo development of CNV occurred in 91 eyes (30.6%). There was no significant difference regarding the rate of CNV development in the presence or absence of VMA ($P = 0.0966$).

Conclusions: The present study found no significant difference in the prevalence of VMA in eyes affected by AMD compared with age-matched controls and no difference in the rate of de novo CNV development in eyes with or without VMA. Conversely, a lower incidence of RVMA over time was found in eyes affected by exudative AMD. The results of this study suggest that VMA might be a consequence rather than a causative factor in the development of CNV. *Ophthalmology 2017;■:1–10 © 2017 by the American Academy of Ophthalmology*

Age-related macular degeneration (AMD) is the leading cause of severe visual impairment in industrialized countries.[1–3] The pathogenesis is multifactorial and still not entirely understood. Several risk factors for the disease have been identified by large studies conducted on wide numbers of participants, such as age, cigarette smoking, heredity, and race.[4–7] Recently, vitreomacular adhesion (VMA) has also been hypothesized to be a further risk factor for AMD. This hypothesis has been derived from several studies that have reported a higher prevalence of VMA in eyes affected by exudative AMD compared with age-matched controls.[8–13] In addition, VMA was found to localize in the area of choroidal neovascularization (CNV).[9,11] However, the reported prevalence of VMA in eyes affected by exudative AMD differs substantially between the various articles, ranging from 12.2%[14] to 48.5%.[15] Moreover, several subsequent post hoc analyses have reported a much lower prevalence of VMA in eyes affected by exudative AMD than that reported in the previous literature. For example, in the large group of eyes enrolled in the Comparison of AMD Treatments Trials,[14] VMA was found remarkably infrequently. Similarly, the populations included in the EXCITE,[16] VINTREX,[17] and MONTBLANC[18] trials exhibited a much lower prevalence of VMA than that reported by previous studies. The reason for these differences remains unclear, and accordingly there is a lack of conclusive evidence on this matter.

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Furthermore, the association between VMA and CNV has raised speculation regarding the cause–effect relation. In fact, some authors have postulated that VMA might be a consequence, rather than a causative factor, in CNV development, because the exudative processes at the site of CNV could give rise to an abnormally strong adhesion between the posterior vitreous cortex and the area of CNV.

The aim of this study was to investigate the prevalence of VMA in a series of consecutive naïve eyes diagnosed with recent-onset exudative AMD, in comparison with eyes affected by nonexudative AMD and eyes with no signs of AMD. In addition, the incidence of spontaneous release of vitreomacular adhesion (RVMA) in the 3 groups over time, and the incidence of CNV development in the presence or absence of VMA in eyes affected by nonexudative AMD and with no signs of AMD, was evaluated.

Methods

Study Design

This study includes both a retrospective observational case series and cohort study conducted at a single Italian tertiary-referral center. The study was designed to evaluate the prevalence of VMA in all eyes affected by recent-onset, previously untreated exudative AMD diagnosed in the Sacrocuore Hospital, Negrar, Verona, Italy, from August 2008 to June 2015, in comparison with eyes affected by nonexudative AMD and eyes with no signs of AMD.

In addition, the following were evaluated longitudinally: the incidence of spontaneous RVMA in the 3 groups over time; and the incidence of CNV development in the presence or absence of VMA in eyes affected by nonexudative AMD and eyes with no signs of AMD.

Secondary endpoints were correlation between VMA and CNV location, correlation between VMA and CNV area size, and correlation between VMA and angiographic subtypes of CNV.

This research adhered to the tenets of the Declaration of Helsinki. Institutional review board approval from the Sacrocuore Hospital was obtained to review patient data.

Patient Enrollment

Three groups of eyes were enrolled: eyes affected by exudative AMD; eyes affected by nonexudative AMD; and eyes with no signs of AMD. When both eyes of a patient met the eligibility criteria, they were independently included within 1 of the 3 groups according to the clinical features.

Exudative Age-Related Macular Degeneration Group. The Hospital Clinical Database of the Data Center of Sacrocuore Hospital was used to obtain a complete list of all patients treated with intravitreal anti-vascular endothelial growth factor (VEGF) injections in the Department of Ophthalmology from August 2008 to June 2015. Spectral-domain optical coherence tomography (OCT; Heidelberg Engineering, Heidelberg, Germany) has been available at the department since August 2008, therefore, patients treated before this period were not included in the research. From this list, all patients treated for diseases other than AMD were excluded. Then, patients' medical charts were reviewed to identify only eyes presented with newly diagnosed, recent-onset, and previously untreated CNV. Thus, eyes that had received any kind of AMD treatment, such as photodynamic therapy or anti-VEGF injections, were excluded, as well as eyes with late-stage disease and/or cases of long disease duration.

Nonexudative Age-Related Macular Degeneration Group. This group comprised eyes of patients diagnosed with nonexudative AMD in the Department of Ophthalmology between August 2008 and June 2015. It also included the fellow eyes of patients with unilateral exudative AMD with the other eye having nonexudative AMD.

The diagnosis of nonexudative AMD was made by experienced retinal specialists, paying particular attention to exclude cases of pattern dystrophy, alterations of retinal pigment epithelium secondary to central serous retinopathy, and other conditions that share some features of AMD. The Age-Related Eye Disease Study (AREDS) classification system was taken into account to categorize eyes in this group, as explained further below.

Group with No Signs of Age-Related Macular Degeneration. The control group comprised eyes of patients with no signs of AMD who were attending the clinic during the same period for other reasons, such as cataract, glaucoma, or routine eye controls. It also included the normal fellow eyes of patients with unilateral diseases, such as retinal vein occlusion, as well as the normal fellow eyes of patients with unilateral exudative or nonexudative AMD with the other eye having no signs of AMD.

Exclusion criteria for the 3 groups of eyes were as follows: younger than 55 years of age; presence of concomitant diseases that would have influenced the vitreoretinal interface, such as diabetic retinopathy, high myopia (>6 diopters), uveitis history, vascular occlusion, and macular holes; history of vitreoretinal surgery; inadequate imaging with lack of sufficient quality (i.e., severe media opacities, asteroid hyalosis, and synchysis scintillans), or with lack of essential details to define the vitreoretinal interface status (i.e., absence of OCT lines passing through the edge of the optic disc, preventing the detection of the adhesion of vitreous cortex in that area).

Evaluation Procedures

All patients underwent a complete ophthalmologic examination, including medical history, best-corrected visual acuity (BCVA) assessed with Snellen visual charts, slit-lamp biomicroscopy, dilated fundus examination with a 90-diopter indirect lens, and OCT. The same OCT was used between 2008 and 2015. Patients with exudative AMD also underwent fluorescein angiography (FA) and indocyanine green angiography (ICG) with the Heidelberg Retina Angiograph (HRA), as a part of the routine practice for all patients diagnosed with exudative AMD, except those with a history of severe drug allergy or a known systemic problem. OCT was performed with the spectral-domain OCT-SLO (Heidelberg Engineering, Heidelberg, Germany). The routine scanning protocol at the Sacrocuore Hospital consisted of both an 8-mm cross-hair scan (with 2 sections perpendicular to each other) and a posterior pole series consisting of 128 horizontal B-scan images, each image composed of 512 axial scans, covering an 8×8 mm area of the posterior pole.

In addition to the routine protocol, further scans could be acquired at the physician's discretion.

As a routine practice for all patients diagnosed with exudative AMD at Sacrocuore Hospital, eyes with CNV were treated with 3 monthly intravitreal injections of anti-VEGF and then periodically underwent standardized examinations for subsequent pro re nata injections, including BCVA, fundus examination, OCT, and, at physician's discretion, FA/ICG.

Vitreomacular Interface Configuration Grading

All scans obtained from the eyes of each group were analyzed to define the vitreomacular interface status by 2 independent, masked observers (E.M., G.P.). OCT images were graded separately and then compared with regard to vitreomacular interface finding. In case of any discrepancy, agreement was reached upon subsequent re-examination of the OCT images by both investigators and a third observer (A.P.) and further discussion.

The vitreomacular interface configuration was graded taking into account the OCT-based International Classification System developed by the International Vitreomacular Traction Study Group.[19] Thus, it was graded into 1 of the following states: (1) VMA focal: persistent hyaloid adhesion at the macula with adhesion size ≤1500 μm; (2) VMA broad: persistent hyaloid adhesion at the macula with a size of the adhesion size >1500 μm; (3) VMT (vitreomacular traction): persistent hyaloid adhesion at the macula accompanied by anatomic distortion of the fovea, which may include intraretinal pseudocyst formation, macular schisis, elevation of the fovea from the retinal pigment epithelium, anatomic changes in the contour of the foveal surface, or a combination thereof; (4) VPA (vitreopapillary adhesion): persistent hyaloid adhesion at the optic disc's edge, without contact at the macula; (5) PVD (posterior vitreous detachment): no evidence of hyaloid adhesion at the macula and at the optic disc.

Eyes with VMA focal, VMA broad, and VMT were grouped as VMA+. Eyes with VPA and PVD were grouped as VMA−.

Figure 1 shows examples of the vitreomacular interface configurations from eyes of the studied population.

Cross-sectional Study

Prevalence of Vitreomacular Interface Configurations in the 3 Groups of Eyes. The prevalence of the above-mentioned patterns of adhesion was evaluated in the 3 groups of eyes.

Paired-Eye Analysis. In the study population, patients with unilateral exudative AMD with fellow eyes having nonexudative AMD or no signs of AMD were identified. The prevalence of VMA was compared between the 2 eyes. As seen in previous studies,[11,12] this analysis has the advantage to obviate the influence of confounding variables, such as demographic differences, age, gender, genetic factors, and environmental factors, including smoking, diet, and body mass index.

Additional Analysis in Exudative Age-Related Macular Degeneration Eyes. Eyes with exudative AMD were evaluated for further analysis, as reported.

Correlation between Vitreomacular Adhesion and Choroidal Neovascularization Location. The location of the CNV was classified as: subfoveal; juxtafoveal (CNV location not subfoveal, but within the central 3000 μm centered on the fovea); extrafoveal; or juxtapapillary (CNV location within 1500 μm to the edge of the

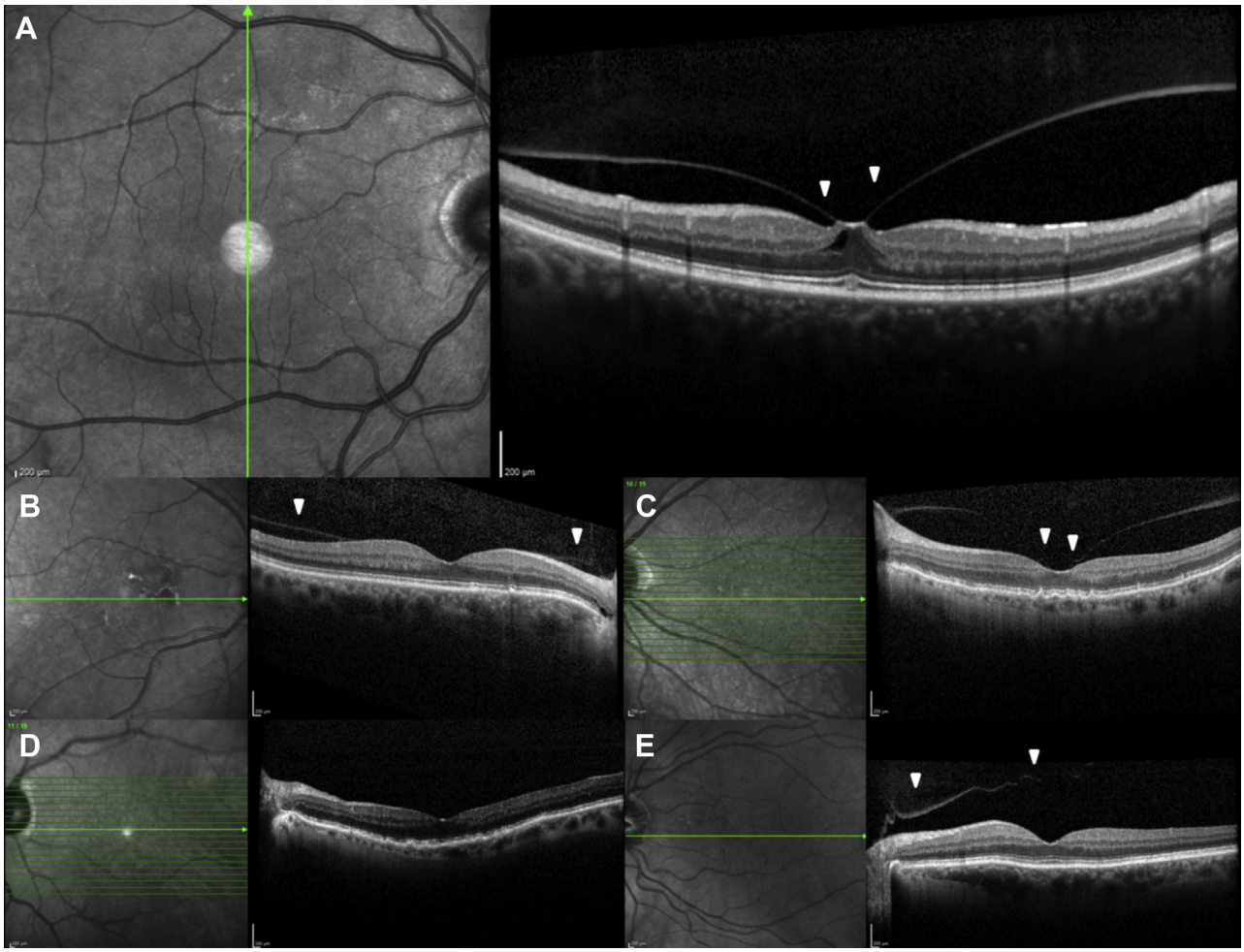

Figure 1. Examples of the vitreomacular interface configurations from eyes of the study population. **A**, Vitreomacular traction: persistent hyaloid adhesion at the macula accompanied by anatomic distortion of the fovea and intraretinal pseudocysts. **B**, Vitreomacular adhesion (VMA) broad: persistent hyaloid adhesion at the macula with size of adhesion >1500 μm. **C**, VMA focal: persistent hyaloid adhesion at the macula with size of adhesion ≤1500 μm. **D**, Posterior vitreous detachment: no evidence of hyaloid adhesion at the macula and at the optic disc. **E**, Vitreopapillary adhesion: persistent hyaloid adhesion at the optic disc edge, without contact at the macula. Arrowhead indicates the posterior vitreous cortex.

optic disc). Similarly, in eyes with VMA focal and VMT the location of the persistent hyaloid adhesion was classified as: foveal; juxtafoveal; or extrafoveal. The relation between CNV location and the site of the hyaloid adhesion was evaluated. The association between VPA and juxtapapillary CNV was also evaluated.

Correlation between Vitreomacular Adhesion and Choroidal Neovascularization Area Size. The size of CNV area was measured using late FA images with the system provided by the HRA software for drawing and measurement of area size. All the components of the CNV complex were considered: CNV, subretinal or/and intraretinal fluid, exudates, pigment epithelial detachment, blood. The corresponding OCT-SLO scans and the additional FA and/or ICG images contributed to the precise identification of the area (Fig 2). The relation between CNV area size and the presence of VMA was evaluated. The aim of this further analysis was to investigate if the exudative processes associated with CNV are more extensive in the presence of VMA.

Correlation between Vitreomacular Adhesion and Angiographic Subtypes of Choroidal Neovascularization. According to the FA/ICG features, lesions were classified into the following categories: classic (including pure classic and predominantly classic), occult (including pure occult and minimally classic), retinal angiomatous proliferation (RAP), and polypoidal choroidal vasculopathy (PCV).

The prevalence of the different patterns of adhesion was evaluated for each category.

Cohort Study

Longitudinal analyses were performed on the study population, as follows.

Evaluation of Vitreomacular Interface Changes over Time. Since the vitreomacular interface status is a dynamic condition, eyes with VMA may experience a spontaneous RVMA and conversion to PVD. Thus, in the study population eyes with a minimum follow-up (FU) of 3 months were identified and the incidence of RVMA evaluated in the 3 groups over time through examination of OCT scans obtained during the observation period. The aim of this further analysis was to investigate if the exudative processes in the site of CNV make PVD less likely to develop, as previously hypothesized.

Evaluation of Vitreomacular Adhesion Influence on the Development of Choroidal Neovascularization. In the groups with nonexudative AMD and with no signs of AMD, eyes with a minimum follow-up of 3 months were identified. OCT scans of these eyes obtained during the observation period were further investigated to evaluate the incidence of CNV development in the presence or absence of VMA. For this analysis, eyes affected by nonexudative AMD were classified into different categories according to the risk of developing exudative AMD, taking into account the AREDS classification system,[20,21] as follows: Category I, characterized by $\geq$5 but $\leq$15 small (<63 μm) drusen, no pigment abnormalities (increased pigmentation or depigmentation); Category II, characterized by >15 small drusen and/or at least 1 intermediate ($\geq$63, <125 μm) druse and/or pigment abnormalities; Category III, characterized by $\approx$65 intermediate drusen (about one-fifth disc area) and/or $\approx$20 intermediate soft indistinct drusen (about one-sixteenth disc area) and/or at least 1 large ($\geq$125 μm) druse; pigment abnormalities; Category IV, characterized by first eye same as category III with fellow eye having neovascular AMD or BCVA <20/32 owing to AMD; and Category V, characterized by geographic atrophy involving center of macula.

Statistics

Results are expressed as mean and standard deviation (SD) if variables are continuous and as a percentage if variables are categorical. For the continuous variables, Shapiro–Wilk test and the variance-comparison test were used to test the normality and the homoscedasticity, respectively.

The 2-sample test of proportion and the chi-square test were used, as appropriate, to compare categorial data while the 2-sample *t* test was used to compare the mean of 2 groups.

The κ-statistic was used to test the interobserver agreement.

A $P < 0.05$ was to be considered statistically significant. Analyses were performed using STATA (StataCorp, College Station, TX) version 14.0.

Results

A total of 1923 eyes were treated with intravitreal anti-VEGF injections between August 2008 and June 2015 in the Department of Ophthalmology at Sacrocuore Hospital. From these, 403 eyes of 364 patients met the inclusion criteria and were enrolled in the present study. The remaining eyes were excluded because they were not eligible, as listed in Table 1.

In addition, 350 eyes of 298 patients with nonexudative AMD and 314 eyes of 214 patients with no signs of AMD, who attended the clinic during the same period, met the inclusion criteria and were enrolled in the study.

The characteristics of the study populations are summarized in Table 2.

Cross-sectional Study

Prevalence of Vitreomacular Interface Configurations. VMA+ was present in 101 (25.1%) eyes with exudative AMD, 84 (24.0%)

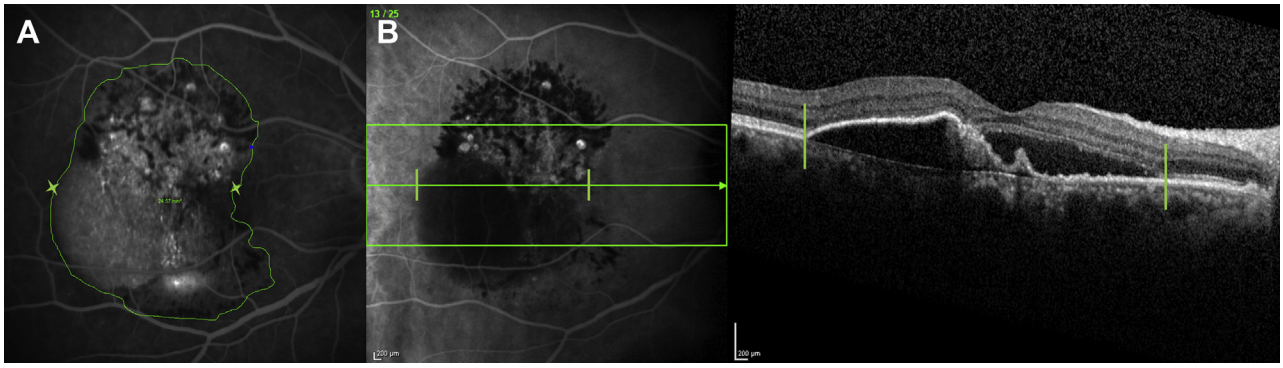

Figure 2. Example of measurement of choroidal neovascularization area size. **A**, The area was measured using fluorescein angiography late images. **B**, The corresponding OCT-SLO scans and images helped in the precise identification of the area.

eyes with nonexudative AMD, and 84 (26.8%) eyes with no signs of AMD (no statistical difference was found; $P = 0.3384$).

The prevalence of all the different patterns of adhesion is summarized in Table 2. No statistically significant differences were found between the 3 groups ($P = 0.929$).

Assessment of 16 cases originally differed between the 2 readers (7 eyes with exudative AMD, 3 eyes with nonexudative AMD, 6 eyes with no signs of AMD); agreement on these cases was reached upon subsequent re-examination of the OCT images by both investigators and a third reader and further discussion. The remaining gradings carried out by the first examiner were consistent with those by the second. Intergrader reliability (κ) was assessed with κ value 0.9707 (standard error = 0.0195) ($P < 0.00001$).

Paired-Eye Analysis. In many cases when both eyes of a patient met the eligibility criteria, they were both includable within the same group: 39 patients with both eyes in the Exudative AMD group; 52 patients with both eyes in the Nonexudative AMD group; 100 patients with both eyes in the Control group. Unfortunately, in many cases the fellow eyes were excluded because they did not meet the eligibility criteria specified in the methods section. A total of 259 patients presented with unilateral exudative AMD. The fellow eyes had nonexudative AMD in 208 cases and no signs of AMD in 51 cases. From these, VMA+ was present in both eyes of 44 patients, only in the exudative AMD eyes in 17, and only in the fellow eyes in 28. No statistically significant difference was found ($P = 0.0904$). Figure 3 shows examples of patients with unilateral exudative AMD, presenting with VMA− in the affected eye but VMA+ in the fellow eye.

Additional Analysis in Exudative Age-Related Macular Degeneration Eyes. The location of CNV in eyes affected by exudative AMD was foveal in 300 eyes, juxtafoveal in 69, extrafoveal in 21, and juxtapapillary in 13. The site of the adhesion in eyes with VMT and VMA focal was foveal in all 41 eyes (36 VMA focal + 5 VMT). In these eyes, CNV was foveal in 33 cases and extrafoveal/juxtafoveal in 8 cases, respectively. Therefore, in the majority of the cases there was a coincidence between the location of CNV and the site of the adhesion, both being foveal. On the contrary, in all 8 cases with extrafoveal or juxtafoveal CNV there was no coincidence (Fig 4).

In the group of eyes with juxtapapillary lesion (13 eyes), 3 eyes presented with VPA, while the remaining 10 eyes exhibited the following patterns of adhesion: 2 VMA focal, 6 PVD, and 2 VMA broad.

The size of lesion was measured on FA images in 396 eyes; 6 patients did not undergo FA/ICG because of severe allergy and 1 patient refused the examination because of advanced chronic renal disease. The mean size of CNV area was 7.98 (SD = 6.19) mm^2 (min = 0.45 / max = 29.50) in eyes with VMA− (PVD + VPA) and 9.51 (SD = 6.84) mm^2 (min = 0.17 / max = 40.44) in eyes with VMA+ (VMA focal + VMA broad + VMT). A statistically significant difference was found between the 2 groups ($P = 0.0251$).

The analysis of the angiographic features in the 396 patients who underwent FA/ICG evaluation revealed 268 occult lesions, 63 classic lesions, 43 RAP, and 22 PCV. The prevalence of the VMA+ in the angiographic subtypes was, respectively, 24.3%, 27.0%, 20.9%, and 36.4%. No statistically significant difference was found ($P = 0.551$).

Cohort Study

In the exudative AMD group, 384 eyes presented with a mean (SD) FU of 34.7 (21.29) months (min = 3, max = 82) and were included for the longitudinal evaluation. In the group of eyes included in the nonexudative group, 296 eyes presented with a mean (SD) FU of 35.65 (21.93) months (min = 3, max = 80); in the control group, 153 eyes presented with a mean (SD) FU of 31.59 (21.85) months (min = 3, max = 82).

Evaluation of Vitreomacular Interface Changes over Time. RVMA was found in 15 of 98 (15.3%) eyes with exudative AMD, 21 of 75 (28.0%) eyes with nonexudative AMD, and 10 of 41 (24.4%) eyes with no signs of AMD over a mean FU of 25.5, 25.9, and 24.1 months, respectively (Table 3). The incidence of RVMA in exudative AMD eyes was significantly lower with

Table 1. Criteria of Selection of Eyes Affected by Naïve-Treatment, Recent-Onset Exudative Age-Related Macular Degeneration

1923 eyes treated with intravitreal anti-VEGF injections between August 2008 and June 2015	915 excluded, because treated for diseases other than AMD	343 eyes with myopic CNV 317 diabetic ME 134 ME secondary to retinal vein occlusion 31 inflammatory CNV 26 CNV secondary to angioid streaks, 18 CNV complicating central serous chorioretinopathy 17 peripheral retinal neovascularization 16 neovascular glaucoma 7 CNV secondary to traumatic choroidal rupture 3 CNV complicating vitelliform macular dystrophy 3 CNV secondary to toxoplasmosis	
	1008 treated for exudative AMD	605 eyes excluded, because did not met the eligibility criteria	404 non-naïve 97 late-stage disease 65 no adequate imaging 24 previous vitreoretinal surgery 5 age less than 55 10 presence of concomitant diseases (8 myopia >6 D, 2 previous RVO)
		403 eyes included in the study	403 eyes affected by recent-onset, naïve exudative AMD included in the study

AMD = age-related macular degeneration; CNV = choroidal neovascularization; D = diopters; ME = macular edema; RVO = retinal vein occlusion.

Table 2. Baseline Characteristics of the Study Populations

	N Eyes (Pts)	Age	Gender	VMA+	VMA−	VMA Focal	VMA Broad	VMT	VPA	PVD
Exudative AMD	403 (364)	77.8 (8.0)	150 M (37.2%) 253 F	101 (25.1%)	302 (74.9%)	36 (8.93%)	60 (14.89%)	5 (1.24%)	50 (12.41%)	252 (62.53%)
Nonexudative AMD	350 (298)	78.1 (7.1)	130 M (37.1%) 220 F	84 (24.0%)	266 (76.0%)	29 (8.29%)	46 (13.14%)	9 (2.57%)	42 (12.0%)	224 (64.0%)
No signs of AMD	314 (214)	74.2 (8.2)	130 M (41,4) 184 F	84 (26.8%)	230 (73.2%)	28 (8.92%)	48 (15.29%)	8 (2.55%)	37 (11.78%)	193 (61.46%)

AMD = age-related macular degeneration; Pts = patients; PVD = posterior vitreous detachment; VMA = vitreomacular adhesion; VMT = vitreomacular traction; VPA = vitreopapilary adhesion.

respect to nonexudative ($P = 0.0207$) and lower, but not statistically significant, with respect to eyes with no signs of AMD ($P = 0.1013$).

Evaluation of Vitreomacular Adhesion Influence on the Development of Choroidal Neovascularization. In the group of eyes with no signs of AMD, 2 eyes out of 153 developed CNV over a mean period of 31.59 months; 1 eye presented PVD and 1 presented VPA. In the group of eyes affected by nonexudative AMD, 91 eyes out of 296 (30.7%) developed CNV over a mean period of 35.65 months; 19 eyes presented VMA+ and 72 presented VMA−. There was no significant difference regarding the rate of CNV development in the presence or absence of VMA ($P = 0.0966$). CNV incidence was more frequent in eyes at high risk for disease progression: category I, 25% (only 1/4); category II, 6.7% (3/45); category III, 12.6% (11/87); category IV, 56.8% (75/132); and category V, 3.6% (1/28).

Discussion

The results of this study show no significant difference in the prevalence of VMA in eyes affected by AMD compared with age-matched controls, and no influence of VMA on development of CNV in eyes with nonexudative AMD.

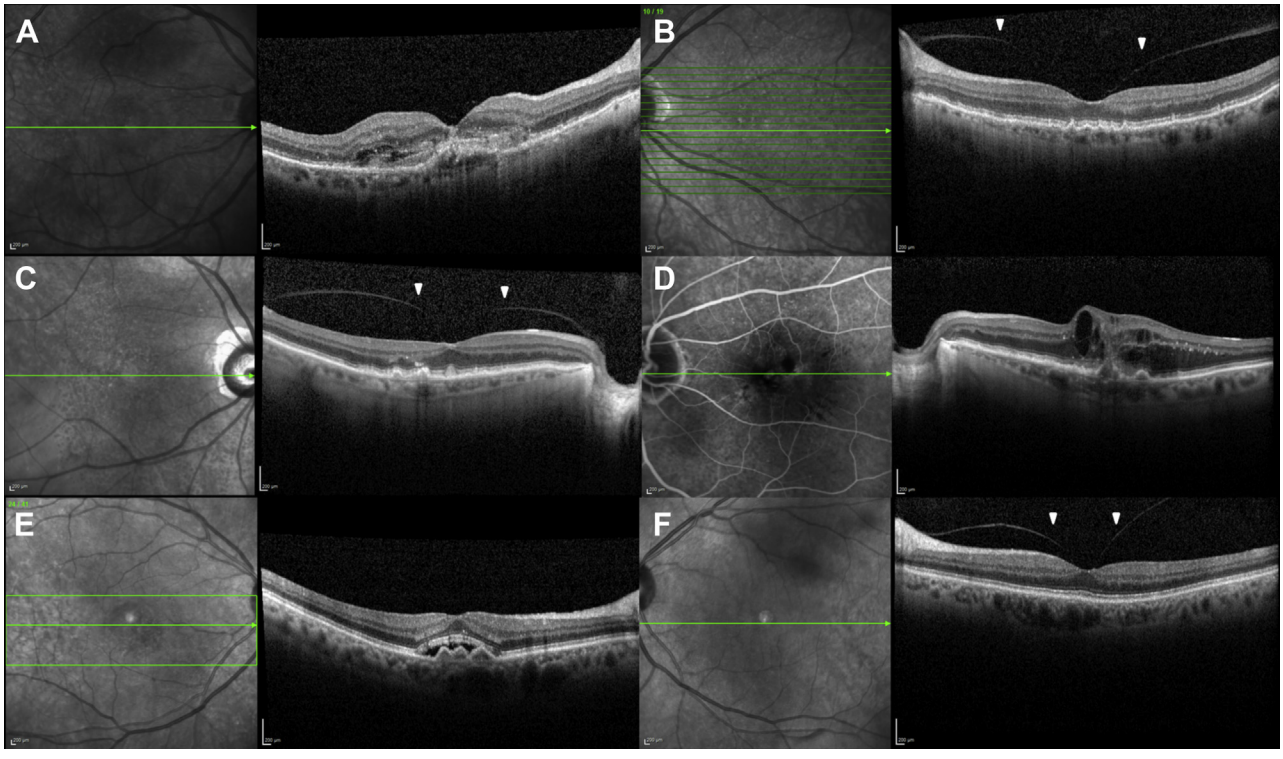

Figure 3. Examples of patients with unilateral exudative age-related macular degeneration (AMD), presenting with VMA− (defined as vitreopapillary adhesion + posterior vitreous detachment) in the affected eye but VMA+ (vitreomacular adhesion [VMA] focal + VMA broad + vitreomacular traction) in the fellow eye. **A**, **B**, Male patient, aged 74, presenting with choroidal neovascularization (CNV) in the right eye with VMA− and nonexudative AMD in the left eye with VMA focal; after 40 months of follow-up (FU) no CNV development and no release of VMA (RVMA) was found in the left eye. **C**, **D**, Female patient, aged 88, presenting with CNV in the left eye with VMA− and nonexudative AMD in the right eye with VMA focal; after 14 months of FU no CNV development and no RVMA was found in the right eye. **E**, **F**, Female patient, aged 73, presenting with CNV in the right eye with VMA− and nonexudative AMD in the left eye with VMA focal; after 48 months of FU no CNV development and no RVMA was found in the left eye. Arrowhead indicates the posterior vitreous cortex.

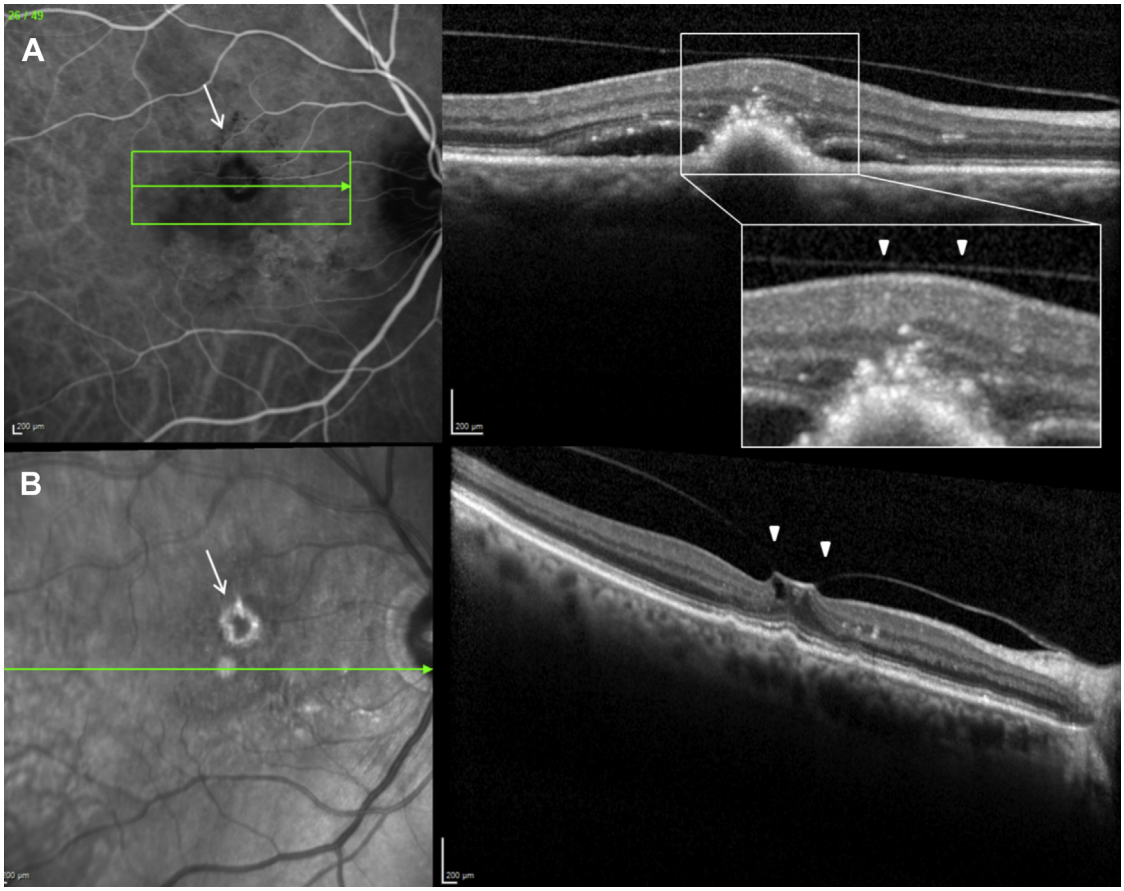

Figure 4. Example of discrepancy between the location of choroidal neovascularization (CNV) and the site of adhesion in a case of juxtafoveal CNV. *White arrows* indicate the site of CNV. **A**, Optical coherence tomography (OCT) scan across the CNV; the magnified area highlights the absence of interaction between the CNV and the hyaloid. **B**, OCT scan across the fovea showing vitreomacular traction. Arrowhead indicates the posterior vitreous cortex.

Conversely, a lower incidence of spontaneous PVD was found in eyes affected by exudative AMD.

Previous studies suggested a possible relationship between VMA and AMD. The prevalence of VMA was found to be higher in eyes affected by exudative AMD compared with eyes with nonexudative AMD, or with age-matched control population, and VMA was found to localize at the area of the CNV.[8–13] This increased prevalence of VMA was interpreted such that VMA might play a pathogenetic role in CNV development and some authors suggested that intervention to induce PVD might be a treatment option for exudative AMD. Nevertheless, this hypothesis was not confirmed in a prospective study by Waldstein et al[22] that included 49 eyes with AREDS category IV nonexudative AMD, who were prospectively examined over a period of 4 years to investigate the influence of VMA on the de novo development of CNV. The authors found no significant difference between eyes with and without VMA with regard to the rate of CNV development or time to disease progression. Therefore, they suggested that the higher prevalence of VMA reported in the previous literature might be interpreted as a consequence of CNV, rather than a causative factor. Inflammation, scarring, or chronic exudation at the site of CNV might cause an abnormally strong adhesion between the posterior vitreous and the macular region, thus

Table 3. Results of Cohort Study

	Number of Eyes	Mean FU Duration in the Whole Group, Months	Eyes with VMA+	Mean FU Duration in VMA+ Eyes, Months	Eyes Developing RVMA, N (%)	Eyes Developing CNV, N (%)
Exudative AMD	384	34.7	98	25.5	15 (15.3%)	
Nonexudative AMD	296	35.65	75	25.9	21 (28.0%)	91 (30.7%)
No signs of AMD	153	31.59	41	24.1	10 (24.4%)	2 (1.3%)

AMD = age-related macular degeneration; CNV = choroidal neovascularization; FU = follow-up; RVMA = release of vitreomacular adhesion; VMA = vitreomacular adhesion.

subsequently causing the VMA to be more frequent in eyes with CNV.

The previous studies evaluating the prevalence of VMA in AMD included heterogeneous populations, including eyes with late-stage disease, eyes with scarring, and eyes that had undergone treatments. This did not allow differentiation of VMA as a causative factor in CNV development or rather as a consequence of the lasting exudation in the macular region. To obviate this confounding factor, the present study included only eyes affected by recent-onset, naïve exudative AMD. The study did not find a significantly higher prevalence of VMA in this study population. These findings were confirmed by the paired-eye analysis. Similarly, several post hoc analyses reported a prevalence of VMA in eyes affected by exudative AMD lower when compared with the previous literature.[14–18] This discrepancy might be explained by the difference in the study populations: all post hoc analyses included only naïve eyes, which is more probable to also be more recent-onset disease than those who already received treatment. This allowed counteraction of the influence of a long-lasting exudation, inflammation, and scarring on the vitreomacular interface status, as seen in our study population.

Similarly to Waldstein et al,[22] in this study the longitudinal analysis showed no significant difference regarding the rate of CNV development in eyes affected by nonexudative AMD in the presence or absence of VMA. Actually, regardless of the vitreomacular interface status, the incidence of de novo CNV development was more frequent in eyes with high-risk categories.

A significantly lower incidence of RVMA over time was found in eyes affected by exudative AMD compared with eyes with nonexudative AMD. The incidence of RVMA was also lower compared with eyes with no signs of AMD, although this difference was not statistically significant. This result might have been affected by the limited number of eyes in the group with no signs of AMD. In fact, the evaluation of RVMA was only possible in 41 eyes of this group. The finding of a lower incidence of RVMA in eyes with exudative AMD seems to support the hypothesis that the exudative processes in the site of CNV might make the hyaloid more adherent, thus making PVD less likely to develop.

It is still not established whether the intravitreal injection procedure itself could favor the occurrence of PVD. The multicentric randomized phase III ocriplasmin study,[23] involving eyes with VMT and macular hole, found that 10.1% of the eyes in the control arm showed resolution of VMA after a placebo injection, suggesting that the effect of the injection procedure may be relevant. Similarly, a prospective study by Geck et al[24] evaluating the occurrence of PVD after intravitreal injections for different macular pathologies suggested that the procedure may promote the development of PVD. Nevertheless, this promoting effect was not observed in eyes affected by AMD included in a large prospective study by Veloso et al.[25] In fact, the injections rarely induced PVD in 396 eyes with CNV treated with anti-VEGF. Similarly, in our population a low incidence of PVD was found in eyes affected by exudative AMD. A possible hypothesis is that the promoting effect of injections in favoring PVD may be less evident in eyes with CNV because of the stronger adhesion of the hyaloid in the site of exudation.

In light of the above findings, our study seems to suggest that VMA might be a consequence rather than a causative factor in the development of CNV. The results indicate that VMA might not be a modifiable risk factor for exudative AMD, and that intervention to induce PVD, such as vitrectomy or pharmacological vitreolysis, would not be a treatment option for preventing exudative AMD.

Additional evaluation in the study population was performed to investigate the relationship between the pattern of adhesion and both the angiographic type of CNV and the lesion size. Results showed no correlation between the pattern of adhesion and the angiographic subtypes. On the contrary, a larger lesion size was associated with the presence of VMA. This finding seems to suggest that the exudative processes owing to CNV might be more extensive in the presence of VMA. Several previous studies have demonstrated an influence of vitreomacular interface status on treatment efficacy for exudative AMD. Patients with VMA were found to have significantly inferior visual and anatomic outcomes after treatment with intravitreal anti-VEGF and needed more intensive treatment in a pro re nata style of therapy.[14,16,17,26] A possible hypothesis might be that VMA, while not influencing the onset of CNV, could have an influence in maintaining the neovascular activity, making exudation more resistant to treatment and more extensive. The mechanism behind this phenomenon remains unclear, and cannot be explained by the current study. However, these findings suggest that VMA and CNV might have some mutual influence, setting up a vicious cycle; and therefore it is possible that induction of PVD, while not preventing exudative AMD, may have a positive therapeutic influence.

In the majority of the eyes, an association between the location of CNV and the site of adhesion was found. Nevertheless, in most cases they were both foveal; thus it is likely that this finding might be affected by the fact that the foveal region is one of the areas where vitreous cortex is more adherent. Notably, in all the cases where CNV was extrafoveal, no association was found (Fig 4).

Grading the vitreomacular interface status may be challenging. The present study has the advantage of being the first to use the OCT-based International Classification System developed by the International Vitreomacular Traction Study Group. This allowed a great concordance between the observers, which reduced the risk of mistakes and misinterpretations in the definition of the vitreomacular interface configurations. Moreover, this approach carries the advantage of making findings more comparable with any future study. Otherwise, different definitions of the adhesion patterns among the various articles could be an additional confounding factor that could increase the discrepancies between the various studies.

The present study has some limitations. The main limitation is its retrospective nature. Moreover, the study only included white patients and thus does not reflect the prevalence of VMA in a diversified population. The

analysis of angiographic subtypes included only few eyes with RAP and PCV. The definition of the vitreomacular interface status was based only on spectral-domain OCT findings. Additional diagnostic tools or novel imaging devices might be useful in cases in which the accurate definition of vitreomacular interface status is particularly challenging.

In conclusion, the results of this study seem to suggest that VMA might be a consequence rather than a causative factor in the development of CNV and, therefore, not a modifiable risk factor for preventing exudative AMD. This study does not enable a definitive conclusion about the role of VMA in the pathogenesis of AMD to be drawn. Nevertheless, it is beneficial to raise questions on this topic, with the possibility that VMA might not be an additional risk factor for AMD, and highlights the need for further investigations. Additional multicentric, prospective studies including larger populations are required to definitively clarify the role of VMA as a risk factor in AMD.

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **AREDS** = Age-Related Eye Disease Study; **BCVA** = best-corrected visual acuity; **CNV** = choroidal neovascularization; **FA** = fluorescein angiography; **FU** = follow-up; **HRA** = Heidelberg Retina Angiograph; **ICG** = indocyanine green angiography; **OCT** = optical coherence tomography; **PCV** = polypoidal choroidal vasculopathy; **PVD** = posterior vitreous detachment; **RAP** = retinal angiomatous proliferation; **RVMA** = release of vitreomacular adhesion; **SD** = standard deviation; **VMA** = vitreomacular adhesion; **VMT** = vitreomacular traction; **VPA** = vitreopapillary adhesion.

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