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ORIGINAL RESEARCH

Geographic Atrophy Secondary to Subclinical Angioid Streaks in Age-Related Macular Degeneration: Progression of the Disease at 2-Year Follow-Up

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ABSTRACT

Introduction: The purpose of the study is to characterize the rate of progression of geographic atrophy (GA) areas in patients with age-related macular degeneration (AMD) with subclinical angioid streaks (AS), compared to patients with AMD without subclinical AS.

Methods: This is a retrospective, longitudinal, case–control study. Among a cohort of patients with AMD, we selected patients with GA with subclinical AS and followed them for a 2-year follow-up. An age- and sex-matched control group with GA secondary to AMD without subclinical AS was selected. Demographics and differences in the GA progression between the two groups were analyzed.

Results: Among 60 eyes of 60 patients affected by GA secondary to AMD, 20 eyes of 20 patients (mean age 82 ± 5 years old) were included in the subclinical AS group, whereas 40 eyes of 40 patients (mean age 79 ± 6 years old, $p = 0.077$) were in the control group.

All 20 eyes of subclinical AS group showed reticular pseudodrusen at the baseline compared to 73% of patients without AS ($p = 0.002$). In the subclinical AS group, 90% of eyes showed peripapillary atrophy in comparison to 63% in the control group ($p = 0.026$). Subclinical AS eyes showed a significantly lower subfoveal choroidal thickness in comparison to the control group (124 ± 60 µm vs. 161 ± 84 µm, respectively, $p = 0.043$). At 2-year follow-up, the rate of progression was higher in the patients with subclinical AS; the yearly growth rate was 0.41 ± 0.17 mm/year after the square root transformation in the subclinical AS group, in comparison to 0.32 ± 0.14 mm/year in the control group ($p = 0.017$).

Conclusions: Patients with subclinical AS showed a more aggressive phenotype of GA in comparison to AMD patients without subclinical AS, characterized by a higher rate of progression of GA areas during a 2-year follow-up.

Keywords: Age-related macular degeneration; Angioid streaks; Biomarker; Geographic atrophy; Multimodal imaging; OCT; Reticular pseudodrusen; Subclinical angioid streaks

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Key Summary Points

Why carry out this study?

Subclinical age-related angioid streaks (AS) is an aggressive phenotype of age-related macular degeneration (AMD).

This study aimed to describe the progression of geographic atrophy secondary to AMD with subclinical AS during a 2-year follow-up.

What was learned from the study?

Geographic atrophy secondary to AMD with subclinical AS showed a higher rate of progression of atrophic areas during 2 years of treatment in comparison to geographic atrophy secondary to AMD without subclinical AS.

Our results suggest that age-related subclinical AS etiology is a negative predictor of atrophy progression in patients with geographic atrophy.

INTRODUCTION

Age-related macular degeneration (AMD) is the most frequent macular disease associated with severe visual acuity impairment in developed countries [1]. AMD is classified into three stages (early, intermediate, and late) based on the presence of different landmarks [2]. Geographic atrophy (GA) is one of the two forms of the late AMD stage. GA is characterized by a progressive loss of photoreceptors, retinal pigment epithelium (RPE) cells, and the underlying choriocapillaris, leading to a progressive visual impairment [3]. In the last years, thanks to the introduction of different imaging modalities (such as fundus autofluorescence (FAF), structural high-resolution optical coherence tomography (OCT), and OCT-angiography (OCT-A)), several features have been associated with different rates of progression of GA lesions [4–12]. Fragiotta et al. [13] have recently reported that the phenotype of intermediate AMD could influence the development and progression of GA, especially the presence of basal laminar deposits (BLamD) and the presence of reticular pseudodrusen (RPD).

Recently, our group reported a new frequent phenotype of AMD, namely subclinical angioid streaks (AS) [14]. Eyes affected by subclinical AS showed the structural OCT findings typical of AS (Bruch's membrane (BM) undulations, BM breaks, and BM large dehiscences) concomitant with landmarks of AMD (i.e., drusen and RPD) [14]. However, no visible AS were visible at fundus examination (for this reason "subclinical"). Patients with subclinical AS are characterized by a greater involvement of the BM and high prevalence of RPD. Furthermore, patients with macular neovascularization (MNV) with subclinical AS phenotype showed worse functional and anatomical outcomes after 2-year anti-vascular endothelial growth factor (VEGF) treatment in comparison to MNV secondary to AMD without subclinical AS [15]. However, to date, no data were available about the prognosis of patients affected by GA secondary to subclinical AS phenotype.

This study aimed to analyze the progression of GA in AMD patients with subclinical AS over a 2-year follow-up, and to compare it with patients with GA secondary to AMD but without subclinical AS.

METHODS

Study Population

This is a retrospective, longitudinal, observational, case–control study. We reviewed charts of patients with a diagnosis of GA secondary to AMD presented to the Medical Retina and Imaging Unit, IRCCS San Raffaele Hospital, University Vita-Salute San Raffaele in Milan, Italy, between June 2021 and June 2022. Patients were followed for 2-year follow-up (until June 2024). All included patients signed a written informed consent for the retrospective study that was previously approved by San Raffaele Ethics Committee. However, due to the retrospective and observational nature of the study, the study does not require a specific Ethics Committee Approval in line with Italian laws. The study followed the

tenets outlined in the Declaration of Helsinki for research involving human subjects.

We included patients with (1) age greater than 50 years old; (2) diagnosis of GA secondary to AMD; (3) presence of subclinical AS; (4) 2-year follow-up (range ± 1 month). The diagnosis of subclinical AS was based on the presence on structural OCT of BM breaks, and/or BM large dehiscences with absence of AS employing fundus examination [14]. The presence of subclinical AS was confirmed independently from two retinal experts (RS and SM); in case of disagreement, a senior author (GQ) was involved. The presence of GA was defined as a complete RPE and outer retinal atrophy (cRORA) on structural OCT [3].

We excluded patients with (1) previous macular treatment before the baseline; (2) presence of macular neovascularization (MNV) at the baseline [16]; (3) development of MNV during the follow-up; (4) presence of any other macular disease; (5) optical opacities reducing the quality of imaging; (6) myopia greater than 6D and/or axial length > 25.5 mm; (7) presence visible AS at fundus examination; (8) presence of systemic diseases related to AS (pseudoxanthoma elasticum, Paget's disease, hemoglobinopathies.

We included a control group with age- and gender-matched subjects affected by GA secondary to AMD but without subclinical AS. In detail, controls were selected using a cohort of AMD patients with GA in the same age range as the study population and in the same sex distribution. The control group sample was chosen with a 1:2 ratio due to the higher prevalence of GA secondary to AMD without subclinical AS. Indeed, subclinical AS is a relatively infrequent disease in comparison to AMD without subclinical AS, and thus we used this ratio in order to increase the statistical power [17, 18]. Inclusion criteria of patients of control group were: (1) age greater than 50 years old and in the same range of age of the study group; (2) diagnosis of GA secondary to AMD; (3) 2-year follow-up (range ± 1 month). The exclusion criteria were the same as the study group. Furthermore, we excluded patients with evidence of subclinical AS.

If both eyes of a patient matched inclusion and exclusion criteria, only one eye for a patient was chosen flipping an actual coin and included in the study.

All patients of both groups were evaluated at the baseline and at the end of the 2-year follow-up with best-corrected visual acuity (BCVA) using Snellen charts and converted to LogMAR for statistical evaluation, fundus examination, infrared reflectance (IR), FAF, and structural OCT. At the baseline or during the follow-up, also fluorescein (FA) and indocyanine green angiographies (ICGA) and/or OCT-A were performed in case of suspect of MNV presence (i.e., presence of exudation or presence of double layer signs using structural OCT). Infrared reflectance, structural OCT, FA, and ICGA were acquired using HRA2 + OCT Spectralis (Heidelberg Engineering, Heidelberg, Germany), whereas OCT-A using PLEXElite 9000 (Car Zeiss, Meditec Inc. Dublin, CA, USA). For our clinical practice, structural OCT minimum protocol of acquisition included: 19 horizontal raster linear B-scans, each composed of nine averaged OCT B-scans (1024 A-scans per line) at 240-µm intervals (area of 20° × 15°); six radial linear B-scans, each composed by 25 averaged OCT B-scans (768 A-scans per line) at 30 degrees centered on the fovea; 49 horizontal raster dense linear B-scans, each composed by 16 averaged OCT B-scans (384 A-scans per line) at 30-µm intervals (area of 15° × 5°).

Several clinical features were evaluated: BCVA, central macular thickness (CMT), subfoveal choroidal thickness (ChT), and mean ChT at the baseline and at 2-year follow-up; presence of drusen, RPD, or both; fellow-eye status (intermediate AMD, neovascular AMD, or GA); area of GA, presence of foveal involvement of GA, and presence of peripapillary involvement of GA at the baseline and at 2-year follow-up. In detail, the area of GA was measured on FAF by two trained graders masked (RS and SM) to each other and to patients, who independently outlined the GA area using the polygon selection tool of the Spectralis inbuilt software. We included atrophic areas of the macular in the GA measurement, excluding the peripapillary atrophy or peripheral atrophy. The mean measurement of GA between the two readers was considered for the statistical analysis. The rate of progression was determined by subtracting the area of atrophy (in mm^2) at the 2-year follow-up

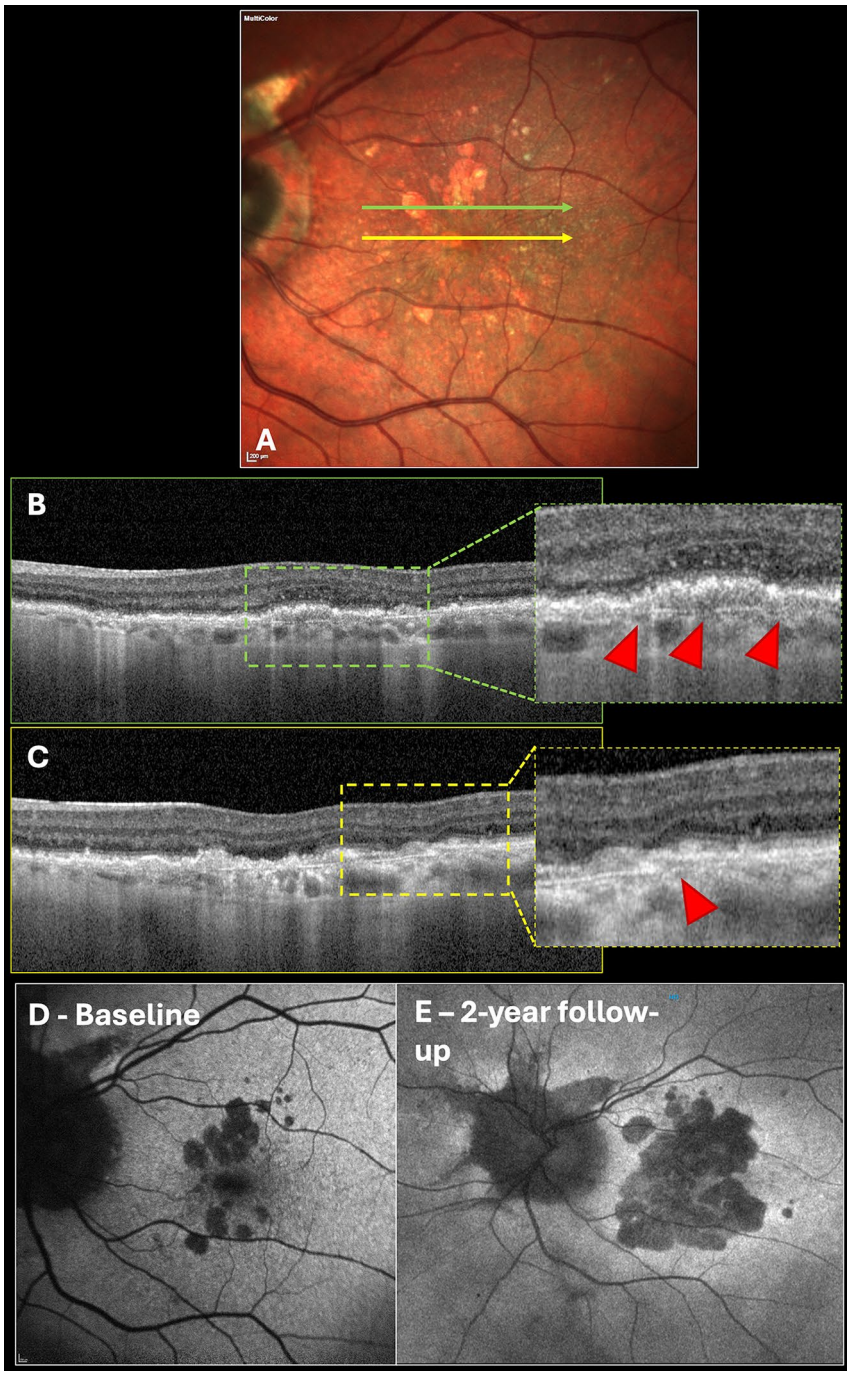

Fig. 1 A representative case of a patient affected by geographic atrophy (GA) secondary to age-related macular degeneration (AMD) with subclinical age-related angioid streaks in the left eye. **A–C** Baseline (i.e., diagnosis of GA secondary to AMD). MultiColor imaging (**A**) and combined infrared reflectance (IR) with structural optical coherence tomography (OCT) B-scan passing through the macula (**B**, **C**) showing the presence of complete retinal pigment epithelium and outer retina atrophy (cRORA), Bruch's membrane undulations and breaks (*red triangles*) in the macular area. Furthermore, the patient was affected by both drusen and reticular pseudodrusen. **D–E** Two-year follow-up. Fundus autofluorescence at baseline (**D**) showing the presence of GA areas in the macular area and peripapillary atrophy with petaloid aspect. Fundus autofluorescence at 2-year follow-up (**E**) showing the great enlargement of atrophic areas

from the area of atrophy at baseline divided by 2 (number of years). The GA areas were converted using the square root transformation in order to eliminate the influence of different baseline dimensions of the GA among different patients [19]. After that, the yearly growth rate of GA was calculated as (√"GA area at 2-year follow-up" − √"GA area at the baseline")/2.

CMT was automatically assessed within a 1-mm ETDRS circle centered on the fovea by using the inbuild Spectralis OCT software. Subfoveal ChT was measured in structural EDI OCT with the inbuilt caliper in the foveal location. Mean ChT was calculated as the mean ChT among five measurements: subfoveal ChT and ChT measured 500 and 1000 µm nasally and temporally to the fovea [20]. Similar methodologies have been presented previously [15].

Statistical Analyses

Statistical calculations were carried out using Statistical Package for the Social Sciences (SPSS) software (ver. 28.0.1.0; SPSS, Inc., Chicago, IL, USA). Counts and percentages were reported for categorical variables, whereas means ± standard deviation for continuous variables. The difference between the proportions of independent categorical variables has been analyzed with Pearson's chi-square test. Continuous variables were tested for normal distributions using the Kolmogorov–Smirnov test. The intraclass correlation coefficient (ICC; 95% CI) was used to estimate the agreement between individual measurements from both readers. Measurement values between subclinical AS and control groups were compared using Student's *t* test for independent samples. The *p* value cut-off point for statistical significance has been set to 0.05.

RESULTS

Patients' Demographics and Main Clinical Findings at Baseline

Sixty eyes of 60 patients affected by GA secondary to late AMD were enrolled. All patients were white. Among 60 eyes, 20 eyes of 20 patients (14 women and six men; mean age 82 ± 5 years old) were included in the subclinical AS group (Fig. 1), whereas 40 eyes of 40 patients (33 women and seven men; mean age 79 ± 6 years old) were enrolled in the control AMD group (Fig. 2). No statistically significant difference in age and sex was disclosed between patients with subclinical AS and patients with other phenotypes of AMD (i.e., control group) ($p = 0.077$ and $p = 0.326$, respectively). All 20 eyes of the subclinical AS subgroup showed the presence of BM breaks, whereas the presence of BM dehiscences was disclosed in five out of 20 cases (25%) (Fig. 1). Fellow eyes of patients affected by subclinical AS were usually characterized by a more advanced stage of AMD (70% were affected by neovascular AMD and 25% by GA) in comparison to the fellow eyes of patients in the control group (30% were affected by neovascular AMD and 53% by GA) ($p = 0.012$) (Table 1).

At the baseline, mean BCVA was lower in the subclinical AS group in comparison to controls (about 20/50 Snellen equivalent, 0.39 ± 0.40 LogMAR, in the subclinical AS group, and less than 20/40 Snellen equivalent, 0.32 ± 0.21 LogMAR, in the control group, respectively) even if the difference was not statistically significant ($p = 0.173$). No significant difference was disclosed analyzing the CMT ($p = 0.205$), but subclinical AS eyes showed a significantly lower subfoveal ChT and mean ChT in comparison to the control group (subfoveal ChT: 124 ± 60 µm vs. 161 ± 84 µm, respectively, $p = 0.043$; mean ChT: 122 ± 59 µm vs. 159 ± 83 µm, respectively, $p = 0.027$) (Table 1).

Analyzing the landmarks of AMD (presence of drusen, RPD, or both), all 20 eyes with subclinical AS presented RPD, in combination with drusen (ten out of 20 cases, 50%) or without (ten out of ten cases, 50%). No cases showed only drusen without RPD. This distribution was significantly different ($p = 0.003$) in comparison to the control group (i.e., eyes with AMD but without subclinical AS) (Table 1). Indeed, in the control group, RPD were presented in 73% of cases (29 out of 40 cases), in combination with drusen (23 out of 40 cases) or without (6 out of 40 cases). Eleven out of 40 cases (27%) presented only drusen.

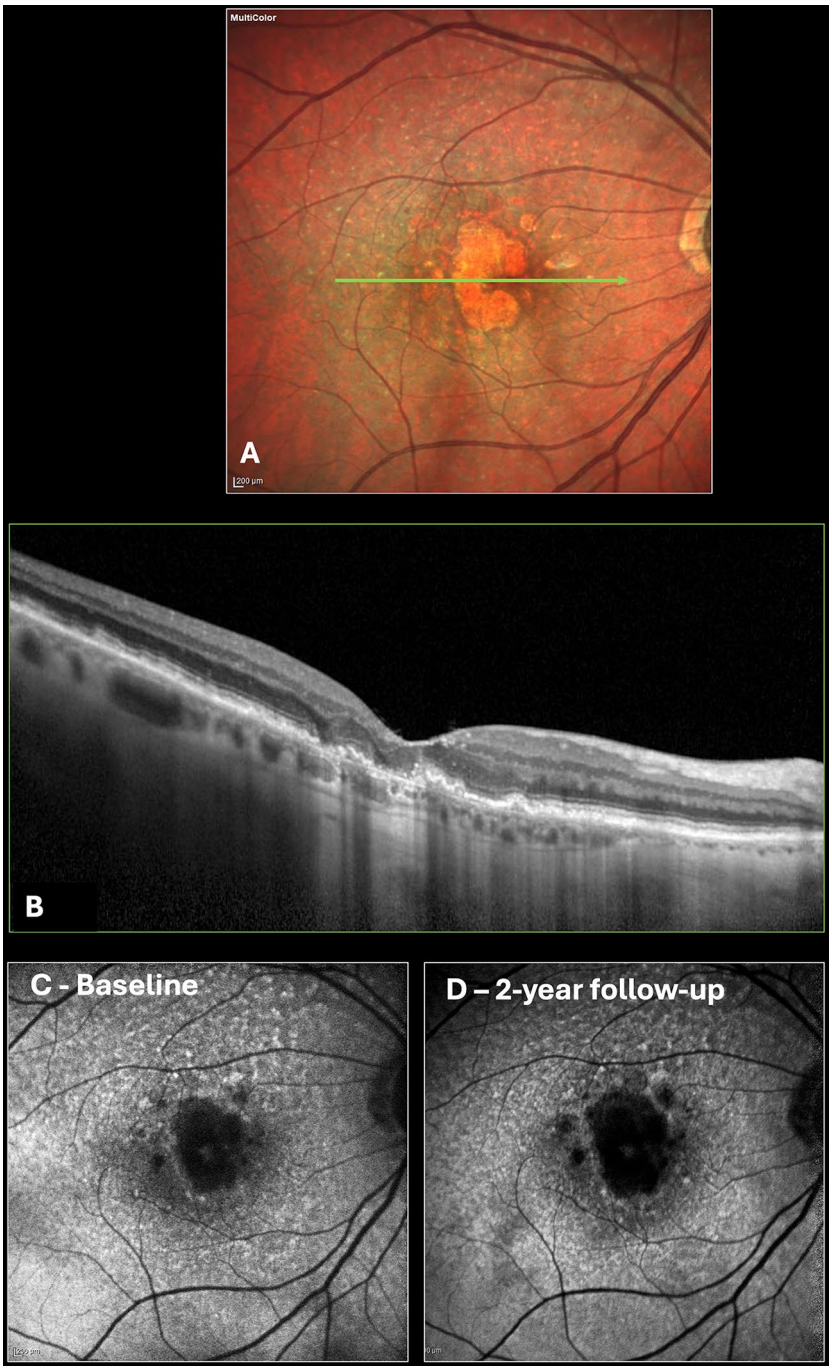

Fig. 2 A representative case of a patient affected by geographic atrophy (GA) secondary to age-related macular degeneration (AMD) without subclinical age-related angioid streaks in the right eye. **A**–**C** Baseline (i.e., diagnosis of GA secondary to AMD). MultiColor imaging (**A**) and combined infrared reflectance (IR) with structural optical coherence tomography (OCT) B-scan passing through the macula (**B**) showing the presence of complete retinal pigment epithelium and outer retina atrophy (cRORA), without Bruch's membrane undulations and/or breaks. Furthermore, the patient was affected by both drusen and reticular pseudodrusen. **C** and **D** Two-year follow-up. Fundus autofluorescence at baseline (**C**) showing the presence of GA areas in the macular area and their slow enlargement during the 2-year follow-up (**D**)

Analyzing the GA lesions at the baseline, no differences were disclosed between the two groups in terms of GA area (7.74 ± 6.94 mm^2 vs. 5.99 ± 4.80 mm^2 for subclinical AS group and controls, respectively, $p = 0.129$) and of GA foveal involvement (60% vs. 67% for subclinical AS group and controls, respectively, $p = 0.566$) (Table 1). Interestingly, in the subclinical AS group 90% of eyes (18 out of 20 cases) showed peripapillary atrophy in comparison to 63% (25 out of 40 cases) in the control group ($p = 0.026$). Peripapillary atrophy in subclinical AS group was usually characterized by a "petaloid" aspect (Fig. 1).

Main Clinical Findings at 2-Year Follow-Up

By means of FAF, the mean GA area significantly increased in both groups. In detail, mean GA increased from 7.74 ± 6.94 mm^2 at the baseline to 12.44 ± 9.09 mm^2 at the end of 2-year follow-up ($p < 0.001$) in the subclinical AS subgroup (Fig. 1), whereas mean GA increased from 5.99 ± 4.80 mm^2 at the baseline to 9.39 ± 6.37 mm^2 at the end of 2-year follow-up ($p < 0.001$) in the control group (Fig. 2). This accounts for a mean yearly growth rate of 0.41 ± 0.17 mm/year after the square root transformation in the subclinical AS group, and a mean yearly growth rate of 0.32 ± 0.14 mm/year after the square root transformation in the control group ($p = 0.017$). Furthermore, eyes affected by subclinical AS showed a greater GA area in comparison to eyes with AMD without subclinical AS at the end of 2-year follow-up (12.44 ± 9.09 mm^2 and 9.39 ± 6.37 mm^2, respectively, $p = 0.068$), starting from similar GA area at the baseline 7.74 ± 6.94 mm^2 vs. 5.99 ± 4.80 mm^2 for subclinical AS group and controls, respectively, $p = 0.129$). Analyzing GA foveal involvement, no differences were disclosed at the end of the 2-year follow-up between AMD eyes with and without subclinical AS (80% vs. 87%, respectively, $p = 0.443$).

Regarding BCVA outcomes, both groups (AMD eyes affected by subclinical AS and controls) showed no significant worsening in BCVA during the 2-year follow-up. In detail, BCVA was 0.39 ± 0.40 LogMAR at the baseline and 0.35 ± 0.30 at 2-year follow-up ($p = 0.547$) in the subclinical AS group, whereas BCVA was 0.32 ± 0.21 LogMAR at the baseline and 0.38 ± 0.18 at 2-year follow-up ($p = 0.067$) in the subclinical AS group (Table 2).

From an anatomical point of view, CMT showed no significant changes during the 2-year follow-up in both groups ($p = 0.204$ and $p = 0.543$ in the AMD with AS and AMD without AS groups, respectively). However, subfoveal ChT showed a significant decrease during the 2-year follow-up in the subclinical AS group (from 124 ± 60 µm at the baseline to 104 ± 55 µm at 2-year follow-up, $p = 0.002$) and a borderline decrease in the control group (from 161 ± 84 µm at the baseline to 153 ± 85 µm at 2-year follow-up, $p = 0.054$). The same trend was confirmed by analyzing the mean ChT (subclinical AS group: from 122 ± 59 µm at the baseline to 102 ± 54 µm at 2-year follow-up, $p < 0.001$; control group: from 159 ± 83 µm at the baseline to 151 ± 83 µm at 2-year follow-up, $p = 0.032$) (Table 2).

DISCUSSION

In this study, we reported that eyes with GA secondary to subclinical AS are characterized by a higher rate of progression of GA areas during a 2-year follow-up in comparison to eyes with GA secondary to AMD without subclinical AS.

Recently, our group reported a new AMD phenotype, namely subclinical AS [14]. Subclinical AS are characterized by structural OCT findings typical of AS (BM undulations, BM breaks, and large dehiscence of BM) but with the absence of AS employing fundus examination (for this reason "subclinical") in patients with landmarks of AMD (i.e., drusen and RPD) [14]. The involvement of BM with its conversion from an elastic structure to a calcified and brittle one is a well-known feature predisposing to developing AS. Due to the similar BM alterations and peripapillary involvement of subclinical AS in AMD, we suggested the predominant involvement of Bruch's membrane as a driving factor of this phenotype [14]. The BM involvement might also play a role in the high prevalence of RPD in this phenotype (100% of cases in the current series).

Table 1 Demographics and main clinical features of the study population at the baseline

	AMD with subclinical AS	AMD without subclinical AS	*p* value
Patients, *n*	20	40	–
Eyes, *n*	20	40	–
Age, years (mean ± SD)	82 ± 5	79 ± 6	0.077
Sex, *n* (%)			
Men	6 (30)	7 (18)	0.326
Women	14 (70)	33 (82)	
AMD phenotype (eyes), *n* (%)			
Only drusen	0 (0)	11 (27)	0.003
Only RPD	10 (50)	6 (15)	
Drusen + RPD	10 (50)	23 (58)	
Fellow eye status, *n* (%)			
Intermediate AMD	1 (5)	7 (17)	0.012
Neovascular AMD	14 (70)	12 (30)	
Geographic atrophy	5 (25)	21 (53)	
BCVA, LogMAR (mean ± SD)	0.39 ± 0.40	0.32 ± 0.21	0.173
CMT, μm (mean ± SD)	263 ± 44	253 ± 43	0.205
Subfoveal ChT, μm (mean ± SD)	124 ± 60	161 ± 84	0.043
Mean ChT, μm (mean ± SD)	122 ± 59	159 ± 83	0.027
GA area, mm^2 (mean ± SD)	7.74 ± 6.94	5.99 ± 4.80	0.129
GA foveal involvement, *n* (%)			
Yes	12 (60)	27 (67)	0.566
No	8 (40)	13 (33)	
Peripapillary atrophy, *n* (%)			
Yes	18 (90)	25 (63)	0.026
No	2 (10)	15 (37)	

AMD age-related macular degeneration, *AS* angioid streaks, *n* number, *SD* standard deviation, *RPD* reticular pseudodrusen, *BCVA* best-corrected visual acuity, *CMT* central macular thickness, *ChT* choroidal thickness, *GA* geographic atrophy

Indeed, it is well known that BM plays a role in the pathogenesis of RPD [21–23]. A recent study suggested the aggressive profile of subclinical AS phenotype in AMD patients with MNV. Indeed, it was shown that MNV secondary to AMD with subclinical AS showed a higher percentage of macular atrophy development and worse visual outcomes after 2 years of treatment, despite the greater number of injections needed [15]. These results suggest that age-related subclinical AS etiology plays a negative predictor of functional outcomes in patients with neovascular AMD [14]. The aggressive pattern and high prevalence of MNV in this peculiar population were also

Table 2 Main clinical features of the study population at the baseline and at the end of 2-year follow-up

	AMD with subclinical AS ($n=20$)			AMD without subclinical AS ($n=40$)		
	Baseline	2-year follow-up		Baseline	2-year follow-up	
	Mean ± SD	Mean ± SD	*p* value	Mean ± SD	Mean ± SD	*p* value
BCVA, LogMAR	0.39 ± 0.40	0.35 ± 0.30	0.547	0.32 ± 0.21	0.38 ± 0.18	0.067
CMT, μm	263 ± 44	271 ± 49	0.204	253 ± 43	256 ± 41	0.543
Subfoveal ChT, μm	124 ± 60	104 ± 55	0.002	161 ± 84	153 ± 85	0.054
Mean ChT, μm	122 ± 59	102 ± 54	< 0.001	159 ± 83	151 ± 83	0.032
GA area, mm^2	7.74 ± 6.94	12.44 ± 9.09	< 0.001	5.99 ± 4.80	9.39 ± 6.37	< 0.001

Statistical analysis: student paired *t* test

AMD age-related macular degeneration, *AS* angioid streaks, *n* number, *SD* standard deviation, *BCVA* best-corrected visual acuity, *CMT* central macular thickness, *ChT* choroidal thickness, *GA* geographic atrophy

confirmed in the current study; analyzing the fellow eye, patients with subclinical AS showed 70% of eyes affected by MNV in comparison to 30% of control eyes (Table 1). However, to date, no data were available about the GA features in patients affected by subclinical AS secondary to AMD.

Currently, GA is defined as the presence of cRORA on structural OCT [3]. GA is marked by distinct atrophic lesions involving photoreceptors, RPE cells, and the underlying choriocapillaris. These lesions could progressively enlarge over time, but the visual impairment is different based on their localization. In detail, the involvement of the subfoveal area leads to significant visual impairment in terms of visual acuity reduction [24]. Thanks to a multimodal imaging approach, several features were associated with different rates of progression of GA lesions. In detail, different phenotypes using FAF were described to be associated with different rates of progression of GA lesions [5]. Using structural OCT, several biomarkers were identified to be associated with greater GA progression, such as a greater impairment of choroidal vascularity index (CVI) and of choroidal patterns, a greater elevation of the RPE from the Bruch's membrane in the area around GA lesions, and the presence of hypertransmission defects [6–8, 25]. Furthermore, using OCT-A several groups reported that the impairment of the choriocapillaris flow is strictly related to the expansion of the GA itself [9–12, 26]. Finally, our group has recently reported that the phenotype of intermediate AMD could influence the development and progression of GA, especially the presence of BLamD and the presence of RPD [13].

The results of our study showed that the rate of progression of GA areas in patients with this new phenotype of AMD (i.e., subclinical AS) was greater than in controls. Eyes affected by subclinical AS showed a greater GA area in comparison to eyes with AMD without subclinical AS at the end of 2-year follow-up (12.44 ± 9.09 mm^2 and 9.39 ± 6.37 mm^2, respectively, $p=0.068$), despite the similar GA area at the baseline. Furthermore, of greater interest is that the yearly rate of GA expansion, after square root transformation, was significantly higher in patients affected by GA secondary to subclinical AS in comparison to controls (mean yearly growth rate of 0.41 ± 0.17 mm/year vs. 0.32 ± 0.14 mm/year after the square root transformation, respectively, $p=0.017$). Analyzing GA foveal involvement, no differences were disclosed at the end of the 2-year follow-up between AMD eyes with and without subclinical AS (80% vs. 87%, respectively, $p=0.443$). Furthermore, subfoveal ChT was significantly reduced in patients with subclinical AS at baseline compared to controls (124 ± 60 μm vs. 161 ± 84 μm, respectively, $p=0.043$) and showed a further significant reduction during the 2-year follow-up (from 124 ± 60 μm to 104 ± 55 μm, $p=0.002$). This

characteristic is also known to lead to a more atrophic phenotype and is at greater risk of progression of areas of atrophy. Another atrophic feature characterizing the subclinical AS eyes is the greater involvement of the peripapillary area (90% of patients) in comparison to the control group (63%). Furthermore, in previous studies, it was found that 36% of patients presented with a typical "petaloid-like" pattern of atrophy that is described in the literature to be a typical pattern of AS secondary to PXE [27]. Finally, subclinical AS were characterized by a close relationship with RPD (present in 100% of subclinical AS cases vs. 73% of control cases) and thus we are not completely able to say if subclinical AS or RPD influenced more the GA progression. All these data confirm that GA secondary to subclinical AS shows a more aggressive pattern, characterized by a faster progression and expansion of GA, a greater peripapillary involvement, and a greater atrophic background (i.e., greater reduction of the ChT).

The characterization of this more aggressive pattern of GA is of paramount relevance for the prognosis of the patients, but also for a better characterization of the different phenotypes of AMD. We are, in fact, entering a new era in which it is hoped to have at our disposal innovative and effective pharmacological strategies to be able to treat patients with an atrophic form of AMD. In order to achieve this goal, it is imperative to categorize patients in the best way possible so that they can be directed to the right drug trial and the potential of the new therapies can be fully exploited [22]. Age-related macular degeneration is a multifactorial and complex disease, and the main driver for GA development and expansion could be different between different patterns and phenotypes of GA. In this way, different drugs could have different results based on the phenotypes of GA.

Limitations of the present study are mainly related to the relatively small sample size and the study's retrospective design. Furthermore, all included patients were white, and genetic testing was not performed to determine the underlying cause of GA. New prospective studies with greater sample sizes are warranted to support our conclusions. Furthermore, we did not consider the possible different distribution of FAF phenotype between the two groups.

CONCLUSIONS

We characterize a new aggressive phenotype of GA secondary to subclinical AS in AMD. We reported that GA secondary to subclinical AS is characterized by greater expansion of GA areas during 2-year follow-up, greater peripapillary involvement, and greater choroidal thinning in comparison to GA secondary to AMD without subclinical AS.

Characterizing this phenotype in clinical practice is useful for the prognosis of the patients and for personalized new treatments that are incoming in patients with GA.

Author Contributions. Riccardo Sacconi, Francesco Bandello, Giuseppe Querques: concept and design. Riccardo Sacconi, Simone Marra, Elena Spada, Federico Beretta, Matteo Menna, Stefano Menecozzi: drafting the manuscript. Riccardo Sacconi: statistical analysis. Simone Marra, Elena Spada, Federico Beretta, Matteo Menna, Stefano Menecozzi: collecting data.

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Data Availability. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Riccardo Sacconi is a consultant for Allergan Inc (Irvine, CA, USA), Bayer Schering-Pharma (Berlin, Germany), Carl Zeiss Meditec (Dublin, CA, USA), Novartis (Basel, Switzerland), Roche (Basel, Switzerland). Francesco Bandello is a consultant for Alcon (Fort Worth, TX, USA), Alimera Sciences (Alpharetta, GA, USA), Allergan Inc (Irvine, CA, USA), Farmila-Thea (Clermont-Ferrand, France), Bayer

Schering-Pharma (Berlin, Germany), Bausch And Lomb (Rochester, NY, USA), Genentech (San Francisco, CA, USA), Hoffmann-La-Roche (Basel, Switzerland), Novagali Pharma (Évry, France), Novartis (Basel, Switzerland), Sanofi-Aventis (Paris, France), Thrombogenics (Heverlee, Belgium), Zeiss (Dublin, CA, USA). Giuseppe Querques is a consultant for Alimera Sciences (Alpharetta, GA, USA), Allergan Inc (Irvine, CA, USA), Amgen (Thousand Oaks, CA, USA), Heidelberg (Germany), KBH (Chengdu, China), LEH Pharma (London, UK), LumiThera (Poulsbo, WA, USA), Novartis (Basel, Switzerland), Bayer Schering-Pharma (Berlin, Germany), Sandoz (Berlin, Germany), Sifi (Catania, Italy), Soof-Fidia (Albano, Italy), Zeiss (Dublin, CA, USA). Giuseppe Querques is an Editorial Board member of Ophthalmology and Therapy. Giuseppe Querques was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Simone Marra, Elena Spada, Federico Beretta, Matteo Menna, and Stefano Menecozzi have nothing to disclose.

Ethical Approval. All included patients signed a written informed consent for the retrospective study that was previously approved by San Raffaele Ethics Committee. However, due to the retrospective and observational nature of the study, the study does not require a specific Ethics Committee Approval in line with Italian laws. The study followed the tenets outlined in the Declaration of Helsinki for research involving human subjects.

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