



# Identification of hyperreflective foci in angioid streaks

Francesco Romano <sup>1,2</sup> · Stefano Mercuri<sup>1</sup> · Alessandro Arrigo<sup>1</sup> · Alessandro Marchese<sup>1</sup> · Maria Vittoria Cicinelli<sup>1</sup> · Giorgia Carlotta Albertini<sup>1</sup> · Francesco Bandello<sup>1</sup> · Maurizio Battaglia Parodi<sup>1</sup>

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## Abstract

**Aims** To assess hyperreflective foci (HF) number in angioid streaks (AS) by means of spectral-domain optical coherence tomography (SD-OCT).

**Methods** Observational and cross-sectional study. Sixty-two eyes with AS and 62 controls underwent best-corrected visual acuity (BCVA), funduscopy, and SD-OCT. HF were assessed on the horizontal scan of a six-line radial OCT, in the fovea (1500- $\mu$ m diameter) and parafovea (500  $\mu$ m external to the fovea), and sub-classified as retinal or choroidal, small or large. Eyes were distributed in one of four groups, as carrying foveal AS without choroidal neovascularization (CNV) (14 eyes), extra-foveal AS without CNV (14), active CNV (20), and inactive CNV (14). Primary outcome was HF assessment in AS. Secondary outcomes included their correlations with BCVA.

**Results** AS-affected eyes had higher HF numbers. Our sub-analysis revealed that patients with active CNV had a larger number of retinal and choroidal HF than all the other groups, whereas retinal and choroidal foci were significantly increased in inactive CNV only with respect to controls. Interestingly, patients with foveal AS showed HF number increase in the choroid and fovea. BCVA deterioration positively correlated with the total HF number found in the fovea and the choroid.

**Conclusion** HF are significantly increased in patients with AS. Despite being especially evident in active CNV, the increasing number in eyes without CNV might suggest new pathogenetic aspects of the disease.

## Introduction

Angioid streaks (AS) appear as irregular, dark red to gray lines under the retina resulting from breaks in the Bruch's membrane [1], and can be idiopathic in origin or associated with systemic diseases (e.g., pseudoxanthoma elasticum, Ehlers–Danlos syndrome, Paget disease, and sickle cell anemia) [2–5]. The development of classic choroidal neovascularization (CNV) in the correspondence of the streaks represents the most common complication, occurring in 42–86% of the cases and frequently leading to severe visual

loss [6–8]. Hyperreflective foci (HF) are a relatively new spectral domain-optical coherence tomographic (SD-OCT) finding, and have been documented in several retinal and choroidal diseases as biomarkers of disease activity or pathogenesis [9–17]. SD-OCT has indeed proved a valuable imaging tool in the past to assess and follow-up these patients [18, 19].

The aim of our study is to analyze the number and the location of HF in patients with AS by means of SD-OCT, and to investigate the functional correlates with the different AS presentations.

## Methods

The study was designed as an observational and cross-sectional case series in patients affected by AS. All the procedures adhered to the tenets of the Declaration of Helsinki for research involving human subjects and the protocol was approved by the local institutional review board. A series of consecutive patients with recent diagnosis of AS and a group of sex- and age-matched healthy controls were enrolled in the Retinal Heredodystrophies Unit of our

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✉ Francesco Romano  
f.romano@studenti.univr.it

<sup>1</sup> Department of Ophthalmology, University Vita-Salute, Scientific Institute San Raffaele, Milan, Italy

<sup>2</sup> Eye Clinic, Department of Biomedical and Clinical Science, Luigi Sacco University Hospital, Milan, Italy

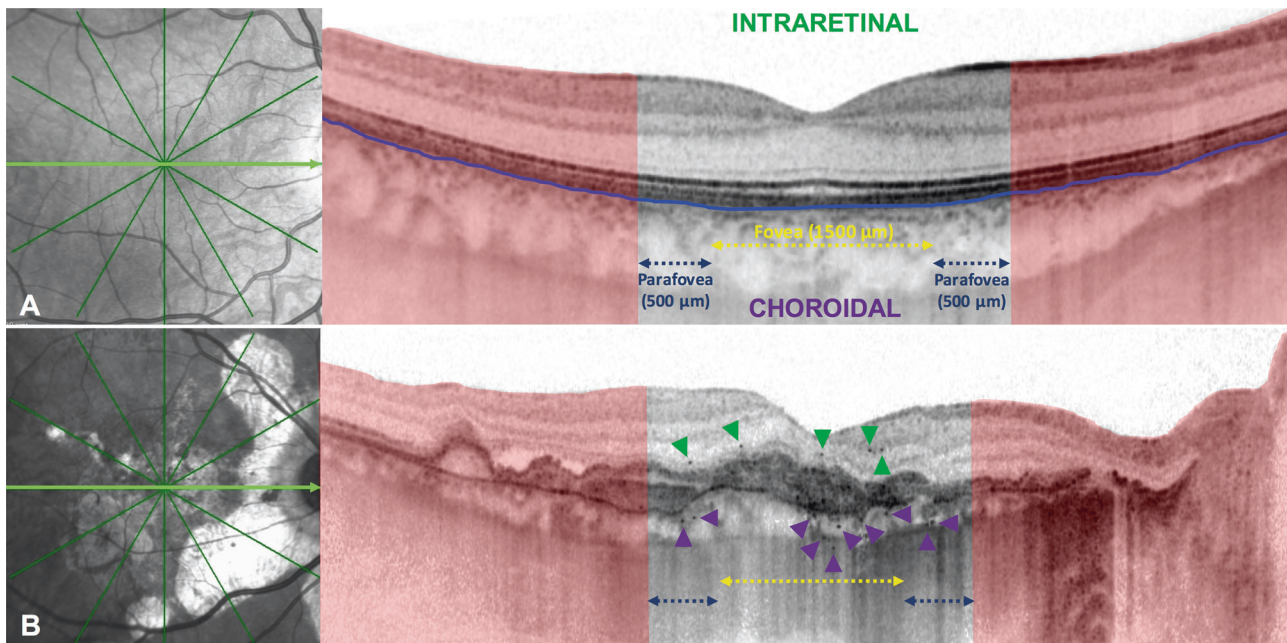
Department of Ophthalmology (Scientific Institute San Raffaele—Milan, Italy) from March 2015 to April 2018. Exclusion criteria included the presence of significant media opacities and of unstable fixation, precluding the acquisition of high-quality images. Written informed consent was obtained from all the study subjects.

Both groups (patients with AS and control subjects) underwent a complete ophthalmologic examination, including measurement of best-corrected visual acuity (BCVA) using Early Treatment Diabetic Retinopathy Study chart, slit-lamp biomicroscopy, fundoscopy following pupil dilation with Tropicamide 1%, and SD-OCT examination. The identification of AS was based on the clinical biomicroscopic fundus examination, and subsequently confirmed by fundus fluorescein angiography. Patients were further subdivided as carrying AS crossing the fovea without CNV (foveal AS), AS not crossing the fovea without CNV (extra-foveal AS), AS with SD-OCT-documented active sub-foveal choroidal neovascularization (CNV) (showing subretinal and/or intraretinal fluid on SD-OCT scans), and SD-OCT-documented inactive sub-foveal CNV (no evidence of fluid on SD-OCT scans). SD-OCT examination was acquired using the Spectralis HRA + OCT (Heidelberg Engineering; Heidelberg, Germany). The acquisition protocol included a six-line radial SD-OCT pattern (1024 A-scans per B-line scan), centered on the fovea, at 30° distance. Eye tracking was enabled during image

acquisition. Hyperreflective foci were defined as discrete, round lesions with greater reflectivity than retinal pigment epithelium, and as invisible on clinical examination [20]. They were arbitrarily subdivided according to their greatest linear dimension in two subgroups: small (if < 15 μm) or large (if > 15 μm). HF were evaluated on the horizontal scan of the six-line radial pattern, and measured in the fovea (1500-μm diameter centered on umbo) and in the parafoveal area (500 μm external to the fovea) by two independent graders (S.M. and F.R.); foci were subsequently classified according to their location as retinal or choroidal. The two examiners were unaware of the purpose of the study, and the SD-OCT scans were assessed on a high-magnification section, after being converted from “white-on-black” to “black-on-white” with contrast adjustment to enhance their visualization. The mean of the two independent measurements of the same SD-OCT scans was used for the analysis. Figure 1 thoroughly depicts the scheme employed for the assessment of HF.

The primary outcome measure was the assessment of HF in the retina and the choroid of patients affected by AS. Secondary outcomes included their correlations with BCVA and the evaluation in the different subgroups of AS patients.

Differences in the number of HF (retinal and choroidal; foveal and para-foveal) between patients and controls were analyzed by means of Student’s *t* test for continuous variables. Analysis of variance (ANOVA) for repeated



**Fig. 1** Explanatory acquisition schemes in a control subject and a patient with active choroidal neovascularization secondary to angioid streaks. **a** Infrared fundus photograph with the corresponding optical coherence tomographic (OCT) six-line radial scheme of a normal subject; hyperreflective foci were divided as retinal or choroidal, and assessed in the fovea (yellow dashed line, 1500 μm) and parafovea

(500 μm external to the fovea, bilaterally). Red shaded areas were excluded from the analysis. **b** shows the infrared photograph and structural OCT of a patient with AS and active sub-foveal CNV. Green and purple arrowheads point to the retinal and choroidal foci, respectively

measures and Bonferroni's test for post hoc analysis were adopted to assess the differences among the different AS subgroups and controls. The relationship between variables was explored using Kendall's Tau-b (non-parametric) correlation tests. The results of descriptive analyses are expressed as mean  $\pm$  SD for quantitative variables, and as frequency and percentages for categorical variables. Inter-observer reproducibility for the measurement of HF was evaluated with intra-class correlation coefficients (95% confidence intervals); Shapiro–Wilk test (W score) was employed to verify the Gaussian distribution for all the continuous variables. Statistical significance was set to  $p < 0.05$ , and all the analyses were performed using SPSS Statistics Version 21.0 Software package (IBM; Armonk, NY).

## Results

Overall, 31 patients (62 affected eyes), with 16 males, and 31 control subjects (62 healthy eyes) were recruited for this study. Mean age was  $54.2 \pm 16.2$  years for the patients (range: 18–83), with a BCVA of  $0.36 \pm 0.41$  LogMAR

(~20/50 Snellen equivalents) and  $54.4 \pm 16.9$  years for healthy controls (range: 18–82), with no significant differences in age and sex between the two cohorts ( $p = 0.96$  and  $0.99$ , respectively). In the patients group, 14 eyes (22.6%) revealed foveal AS, 14 (22.6%) had extra-foveal AS, 20 (32.3%) showed signs of OCT-documented active CNV, while 14 (22.6%) had SD-OCT established inactive sub-foveal CNV. Twenty patients (64.5%) had histologic or genetic diagnosis of pseudoxanthoma elasticum, whereas the remaining eyes carried idiopathic AS. Complete clinical data and demographic features of both groups are listed in Table 1.

Altogether, affected eyes did show a significantly higher number of retinal and choroidal HF, both in the fovea and parafovea, when compared with control eyes ( $p < 0.001$ ). Table 2 and Fig. 2 thoroughly show the HF figures and the statistical comparison among AS subgroups and the control subjects. Of notice, retinal and choroidal HF were statistically increased in eyes with OCT-documented active CNV, with respect to all the other subgroups ( $p < 0.001$ ). In addition, patients with inactive sub-foveal CNV showed a higher number of foci than control eyes ( $p$ : from  $< 0.001$  to  $0.02$ ), but not when compared with AS patients without

**Table 1** Demographic and clinical characteristics of patient affected by angioid streaks, including their subgroups, and healthy controls

Groups	Eyes (%)	Sex		Age	BCVA	
		Males (%)	Females (%)		LogMAR	Snellen
Angioid streaks	62	32 (52%)	30 (48%)	$54.2 \pm 16.2$	$0.36 \pm 0.41$	20/50
Foveal AS	14 (22.6%)			$47.1 \pm 21.2$	$0.03 \pm 0.05$	20/20
Extra-foveal AS	14 (22.6%)			$45.2 \pm 15.8$	$0.01 \pm 0.03$	20/20
Active CNV	20 (32.3%)			$57.7 \pm 14.5$	$0.64 \pm 0.42$	20/100
Inactive CNV	14 (22.6%)			$60.4 \pm 14.4$	$0.57 \pm 0.34$	20/80
Healthy controls	62	32 (52%)	30 (48%)	$54.4 \pm 16.9$	$-0.03 \pm 0.03$	20/20

BCVA best-corrected visual acuity, LogMAR logarithm of the minimum angle of resolution, AS angioid streaks, CNV choroidal neovascularization

**Table 2** Mean number of hyperreflective foci in patients with different angioid streaks phenotypes and healthy controls

Groups	Eyes (n)	Foveal			Para-foveal			Total	
		Total	Retinal	Choroidal	Total	Retinal	Choroidal	Retinal	Choroidal
Angioid Streaks	62	$7.2 \pm 5.3^a$	$2.5 \pm 2.2^a$	$4.7 \pm 3.8^a$	$7.9 \pm 4.8^a$	$3.3 \pm 2.4^a$	$4.6 \pm 2.9^a$	$5.8 \pm 4.3^a$	$9.3 \pm 6.1^a$
Foveal AS	14	$4.5 \pm 1.9^a$	$1.1 \pm 1.4$	$3.4 \pm 1.3$	$4.3 \pm 1.5$	$1.8 \pm 1.7$	$2.5 \pm 1.1$	$2.9 \pm 2.4$	$5.9 \pm 2.4^a$
Extra-foveal AS	14	$2.0 \pm 1.9$	$0.3 \pm 0.6$	$1.7 \pm 1.5$	$4.1 \pm 2.6$	$1.7 \pm 1.6$	$2.4 \pm 1.3$	$2.0 \pm 1.6$	$4.1 \pm 2.2$
Active CNV	20	$12.5 \pm 5.1^{a,b,c,d}$	$4.8 \pm 1.8^{a,b,c,d}$	$7.7 \pm 4.4^{a,b,c,d}$	$11.9 \pm 3.3^{a,b,c,d}$	$4.9 \pm 2.3^{a,b,c}$	$7.0 \pm 2.6^{a,b,c,d}$	$9.7 \pm 3.5^{a,b,c,d}$	$14.7 \pm 5.6^{a,b,c,d}$
Inactive CNV	14	$5.4 \pm 3.1^a$	$2.0 \pm 1.0$	$3.4 \pm 2.5$	$7.2 \pm 4.8^a$	$3.2 \pm 2.5^a$	$4.0 \pm 2.8^a$	$5.2 \pm 3.0^a$	$7.4 \pm 4.9^a$
Healthy controls	62	$1.1 \pm 0.8$	$0.4 \pm 0.6$	$0.7 \pm 0.8$	$0.9 \pm 0.7$	$0.5 \pm 0.5$	$0.4 \pm 0.4$	$0.9 \pm 0.8$	$1.1 \pm 1.0$

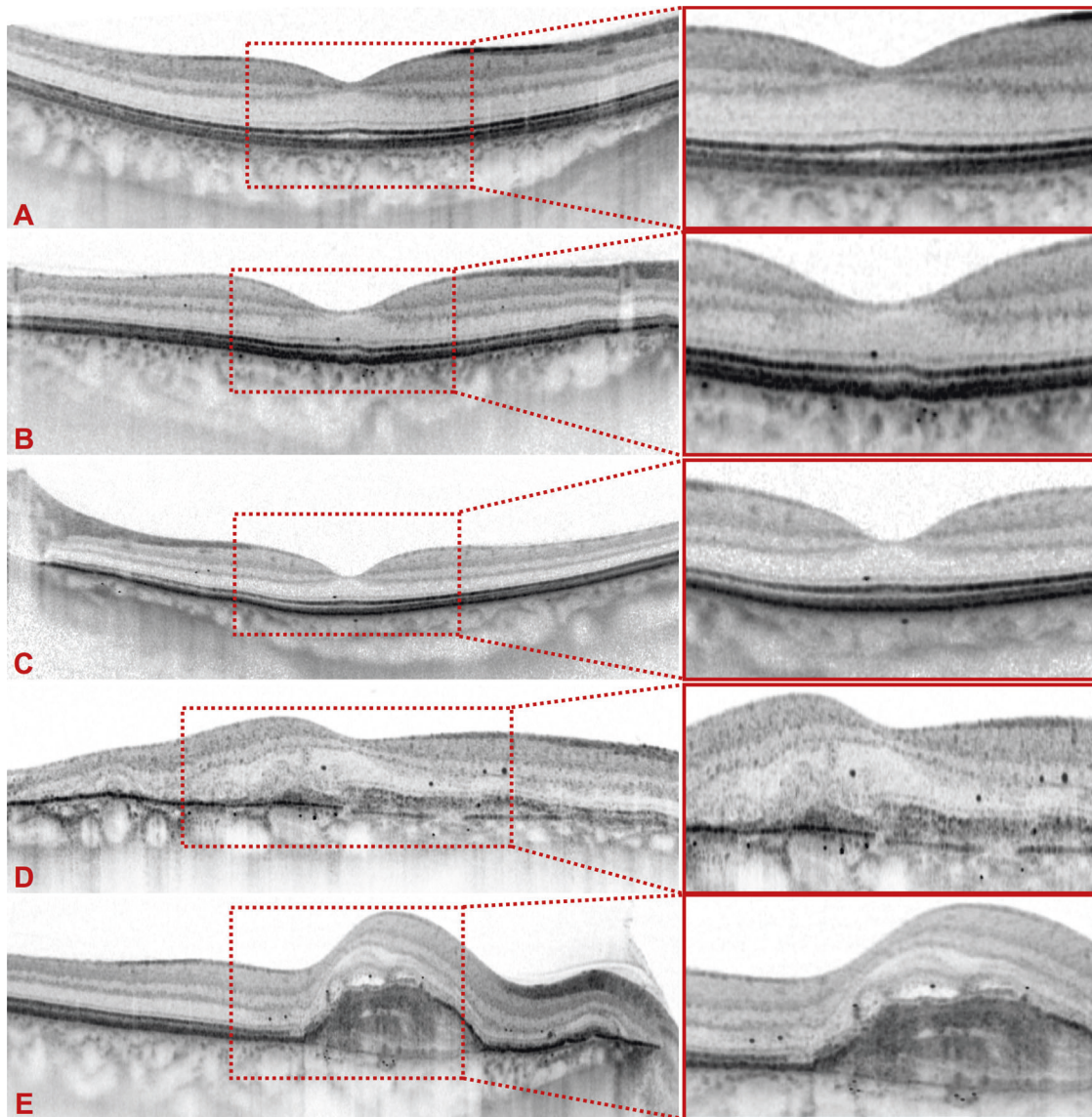
N number, AS angioid streaks, CNV choroidal neovascularization

<sup>a</sup>statistically significant ( $p < 0.05$ ) when compared with controls

<sup>b</sup>statistically significant ( $p < 0.05$ ) when compared with extra-foveal AS

<sup>c</sup>statistically significant ( $p < 0.05$ ) when compared with foveal AS

<sup>d</sup>statistically significant ( $p < 0.05$ ) when compared with inactive CNV

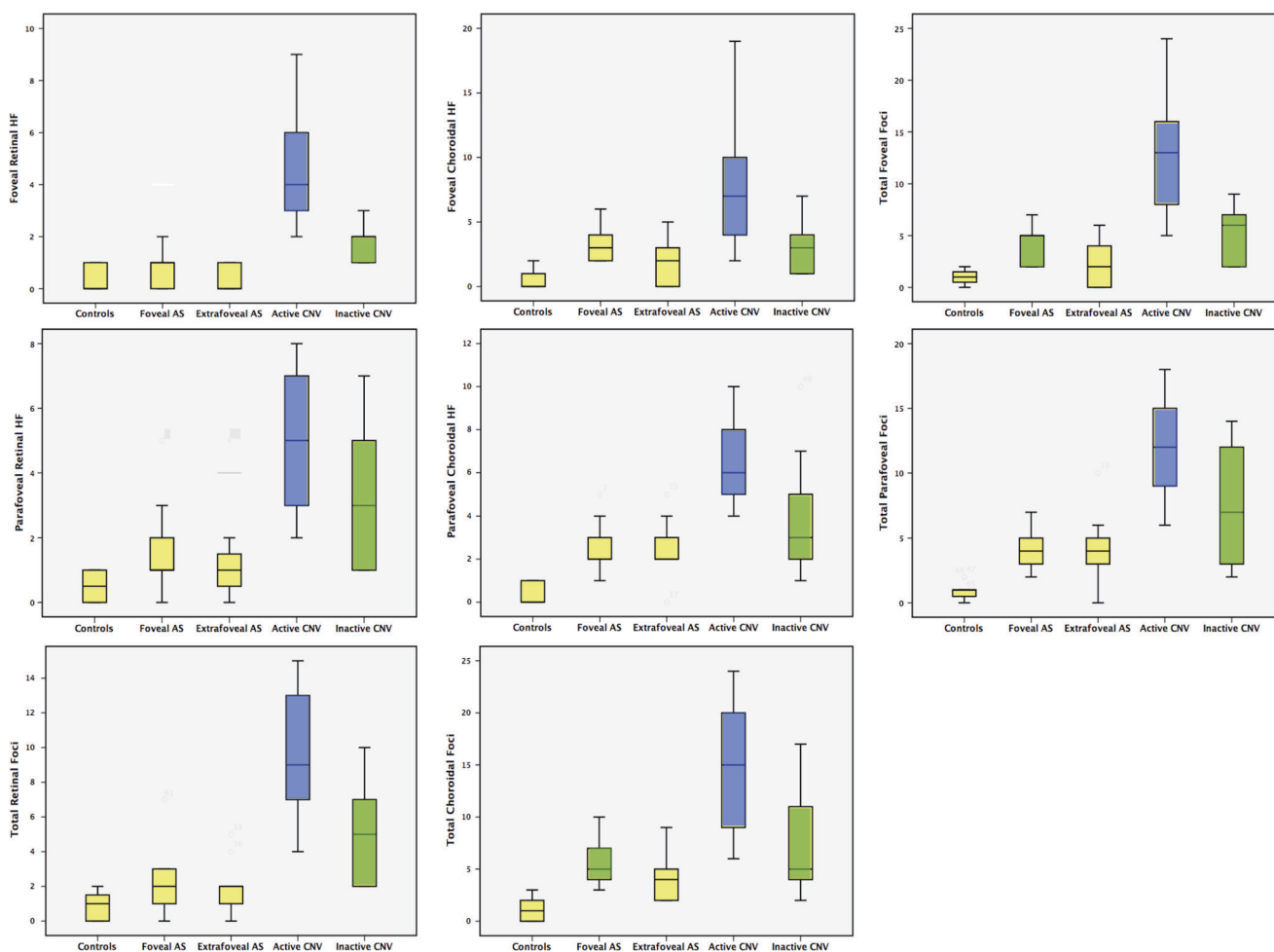


**Fig. 2** Differences in hyperreflective foci (HF) between different phenotypes of angioid streaks (AS) and controls. First row: box-and-whisker plots showing the mean number of HF in the fovea (retinal, choroidal, and total). Larger figures are noticed in patients with active choroidal neovascularization (CNV), when compared with all other groups and controls (blue boxes). Eyes with inactive CNV showed an increased number of HF compared with controls, whereas those carrying foveal AS had more total foveal foci than controls (green boxes). Second row: box-and-whisker plots showing the mean number of HF

in the parafovea (retinal, choroidal, and total). An increased number is noticed in patients with active CNV, when compared with all other groups and controls (blue boxes). Eyes with inactive CNV showed an increased number of HF compared with controls (green boxes). Third row: box-and-whisker plots showing the mean number of total HF in the retina and the choroid. HF resulted significantly increased in patients with active CNV (blue boxes). Eyes with inactive CNV had an increased number of HF compared with controls, with total choroidal HF being increased in patients with foveal AS (green boxes)

CNV ( $p$ : from 0.26 to 0.99 and from 0.09 to 0.99 for foveal and extra-foveal AS, respectively). No meaningful differences were noticed between controls and eyes without CNV, with the exception of foveal and total choroidal HF appearing significantly increased in the eyes carrying foveal AS with respect to controls ( $p = 0.001$ ). With regard to the size of HF, they were mostly small, with large HF being especially found in foveal AS complicated by CNV. In particular, large retinal HF were detected in 85% of eyes

with OCT-documented active CNV, 57% of those with inactive CNV and 7% with foveal AS; on the other hand, 80% with active CNV and 43% with inactive CNV and with foveal AS presented large choroidal HF. No patient with extra-foveal AS had any large HF, either retinal or choroidal. Inter-observer variability between the two investigators was acceptable for all the measurements (ICC = 0.919 [0.899–0.940]). Figure 3 shows HF in patients and controls.



**Fig. 3** Black-on-white optical coherence tomographic (OCT) horizontal scans of a control subject (**a**) and patients with different phenotypes of angioid streaks (AS; **b–e**). While hyperreflective foci are not visible in controls (**a**), their number slightly increases in patients

with foveal and extra-foveal AS (**b, c**, respectively). Accordingly, their figures result even larger in the presence of inactive or active sub-foveal choroidal neovascularization (**d, e**)

With regard to the visual outcomes, the patients group showed worse BCVA when compared with controls ( $0.36 \pm 0.41$  LogMAR vs.  $-0.03 \pm 0.03$  LogMAR;  $p < 0.001$ ). In particular, the subgroups of patients with active CNV and with inactive sub-foveal CNV had a significantly worse visual function ( $0.65 \pm 0.41$  LogMAR and  $0.55 \pm 0.32$  LogMAR, respectively;  $p < 0.001$ ). Interestingly, a decline in BCVA positively correlated with the total number of HF detected in the fovea (Kendall's  $\tau = 0.486$ ;  $p < 0.001$ ) and in the choroid (Kendall's  $\tau = 0.490$ ;  $p < 0.001$ ) (Supplementary Fig. 1).

## Discussion

Angioid streaks have been histologically described as breaks within an abnormally thickened and calcified Bruch's membrane, radially spreading from the optic nerve

[21, 22]. They are generally observed in patients affected by PXE [2], but can be found in other systemic diseases or can be idiopathic, as well [3, 4]. While AS onset occurs between the second and the fifth decade [23], their progression is believed to arise from the reduced resistance of BM to mechanical stress [24]. Although AS does not directly affect visual function [21], the break in BM often leads to the development of Type 2 CNV and eventually to fibrotic scars, invariably damaging the photoreceptors and causing a severe deterioration of visual acuity [25]. Hyperreflective foci are, instead, discrete and dot-shaped, clinically invisible, hyperreflective lesions that have been detected by means of SD-OCT in several retinal disorders, including age-related macular degeneration, diabetic retinopathy, as well as hereditary dystrophies [9–17]. In particular, HF frequency has already been shown to correlate with the degree of activity in retinal vascular diseases and macular diseases complicated by choroidal neovascularization

[11, 26–28]. HF can be found both in retina and the choroid [11], but the most attention was addressed to retinal HF. Despite the scant histological evidence pointing toward an RPE origin of these OCT-documented lesions [29], numerous etiologies have been proposed regarding their nature, including predictive signs of intraretinal fluid [8], activated microglia cells [12, 30], and RPE cells undergoing trans-differentiation [16, 31–33]. Our survey represents the first study to describe the presence of HF in patients with AS, and to analyze their distribution and functional correlates in different AS phenotypes. Our data suggest that HF are more frequently represented in the choroid of AS patients. In particular, choroidal HF turned out to be more numerous when the streaks pass through the fovea, and particularly when CNV is present. AS are typically characterized by a multifaceted degenerative process at the level of the Bruch's membrane [8, 34–36], involving various mechanical and biochemical factors [35, 36]. A critical role seems to be played by macrophages, which can significantly contribute to the integrity and functionality of the Bruch's membrane [35–39]. In this regard, we hypothesize that HF located within the retina may derive from RPE cells undergoing intraretinal migration [33], whereas choroidal HF may represent a sign of the macrophage activation. In correspondence of the AS, as measured in the foveal area, choroidal HF are more common, resulting even more numerous when CNV develops. Bearing in mind that the Bruch's membrane typically appears irregular and fragmented in patients affected by AS, we cannot rule out that RPE cells may get through the Bruch's membrane following a trans-differentiation process by means of epithelial-to-mesenchymal transition, thus becoming indistinguishable from the abovementioned choroidal resident macrophages [40–42].

Identification of HF related to CNV activity in AMD patients has been previously described [11, 43]; likewise, the higher number of HF in our AS cohort with sub-foveal CNV might be explained by a progressive recruitment of inflammatory cells (e.g., monocytes), or activated microglia cells from the interaction with Muller cells. The expansion of choroidal foci in patients without CNV might, in this sense, reflect a sub-clinical inflammatory process; moreover, the presence of large choroidal HF in a sub-group of AS patients might be another sign of this process. Therefore, we speculate that HF pathogenesis may be related to the progression of the disease, and foci might represent important biomarkers to predict CNV development in patients affected by AS.

We acknowledge that our study carries several limitations, including the limited size of our cohorts and the lack of a longitudinal follow-up in time to assess the changes in the number of HF. In addition, the foci were manually measured by two masked examiners as no

automated software to count them is currently available, and our statistical analyses included both eyes of the same patients, variably introducing a source of bias [44]. However, AS is a rare retinal condition, making a profuse recruitment of patients challenging to achieve. We also acknowledge that the interpretation of HF origin may be simply matter of speculation in the absence of specific histopathologic studies.

In conclusion, HF seem to be a valuable sign of neovascular exudation in angioid streaks; moreover, foci appear increased in the fovea and the choroid of eyes with foveal AS, even in the absence of CNV. Their number correlates with the visual function of these patients and might help identifying eyes that are at greater risk of developing choroidal neovascularization, anticipating the appearance of clinically evident exudation. Further studies are warranted to investigate the changes of HF distribution in time, possibly enrolling a larger number of subjects in the study, and thus validate our hypotheses.

## Summary

### What was known before

- Different angioid streaks phenotypes disclose an increased number of hyperreflective foci on SD-OCT, especially in the presence of CNV.
- These foci might help unveiling new pathogenetic aspects and be predictive of angioid streaks evolution.

### What this study adds

- New insights in angioid streaks pathogenesis.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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