

Hyperreflective Foci Number Correlates with Choroidal Neovascularization Activity in Angioid Streaks

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PURPOSE. To assess the changes in hyperreflective foci (HF) by means of spectral-domain optical coherence tomography (SD-OCT) in patients undergoing anti-VEGF treatment for subfoveal choroidal neovascularization (CNV) secondary to angioid streaks (AS).

METHODS. Fifteen eyes with diagnosis of AS-related CNV (8 males) and 15 control eyes with uncomplicated AS were consecutively recruited. Patients and controls underwent complete ophthalmologic examination and SD-OCT. Patients were subjected to a pro re nata treatment regimen, including monthly examinations and intravitreal aflibercept injection in case of fluid detection on SD-OCT. HF were measured on horizontal scans of the six-line radial SD-OCT, in the fovea and parafovea and the subdivided as retinal or choroidal. Specifically, HF were analyzed at the following time points: baseline, dry on SD-OCT, 1 month before its reactivation, and the time of CNV reactivation.

RESULTS. HF numbers resulted higher in all CNV phases with respect to controls, except during inactive phase. Moreover, foveal and parafoveal HF were found significantly increased in active, prereactive, and reactive phases when compared with inactive phase ($P < 0.05$). A similar trend was detected for choroidal HF. Interestingly, a subanalysis revealed that only foveal choroidal HF are significantly higher in a prereactive phase if compared with an inactive phase ($P = 0.03$). Our correlational analysis unveiled negative associations between intraretinal HF numbers and logMAR best-corrected visual acuity.

CONCLUSIONS. Our findings suggest that HF represent useful markers to monitor CNV activity. Choroidal HF appear already increased in the fovea 1 month before CNV reactivation. Validation of our results might lead to earlier anti-VEGF reinjection and possibly better visual outcomes.

Keywords: optical coherence tomography, angioid streaks, choroidal neovascularization, hyperreflective foci

Angioid streaks (AS) are defined as irregular linear breaks in a degenerated Bruch's membrane, radiating from the peripapillary area, and involving the posterior pole.¹ AS may present in isolation or in association with systemic diseases, including pseudoxanthoma elasticum, Paget disease, Ehlers-Danlos syndrome, and sickle cell disease.¹ While AS are normally asymptomatic, their most important vision-threatening complication is represented by the development of choroidal neovascularization (CNV), which can occur in at least one eye in 72% to 86% of cases,¹⁻⁴ and can also involve the fellow eye in up to 71% of cases.² The recent advent of treatment based on intravitreal anti-VEGF has completely revolutionized the management of AS-related CNV, both for subfoveal and nonsubfoveal forms, generally providing positive functional outcomes.³⁻¹² Nevertheless, all the clinical studies turned out to be largely uneven with regard to treatment duration of follow-up, treatment regimen, and lesion monitoring. For these reasons, the identification of a biomarker related to the activity of the CNV would certainly simplify the management of CNV treatment over a long-term follow-up. Increasing consideration has been recently dedicated to the assessment of hyperreflective foci (HF), a relatively new spectral-domain optical coherence tomographic (SD-OCT) sign

that has been clinically and histologically related to the accumulation of intraretinal fluid precursors and inflammatory cells in different macular disorders.¹³⁻²⁵ The aim of the present study was to analyze the changes in the number of HF detected by means of SD-OCT over the course of anti-VEGF treatment of subfoveal CNV secondary to AS.

METHODS

The study is designed as an interventional, prospective case series. All the procedures adhered to the tenets of the Declaration of Helsinki for research involving human subjects and the local institutional review board approved the protocol. Written informed consent was obtained from all the study subjects. A series of consecutive patients with recent diagnosis of AS-related CNV were enrolled from March 2015 to November 2016. The identification of CNV in AS was initially based on biomicroscopic fundus examination and confirmed by means of fundus fluorescein angiography (FFA). Patients with subfoveal CNV were included in the study. The control group consisted of a group of age- and sex-matched subjects affected by angioid streaks, but with no CNV. Both study cohorts underwent a



TABLE 1. Demographic and Clinical Characteristics of Patients Affected by Angioid Streaks With CNV, Including the Different Phases of Study, and Controls Carrying Angioid Streaks in the Absence of CNV

Groups	Eyes, <i>n</i>	Sex		Age (Range)	BCVA	
		Males (%)	Females (%)		logMAR	Snellen
Angioid streaks with CNV	15	8 (53)	7 (47)	54.5 ± 13.5 (28-78)		
Active phase					0.68 ± 0.41	20/100
Inactive phase					0.48 ± 0.39	20/63
Prereactive phase					0.52 ± 0.40	20/63
Reactive phase					0.74 ± 0.42	20/100
Angioid streaks without CNV	15	8 (53)	7 (47)	55.6 ± 15.6 (31-76)	0.01 ± 0.04	20/20

complete ophthalmologic examination, including measurement of best-corrected visual acuity (BCVA), using the Early Treatment Diabetic Retinopathy Study chart, fundoscopic biomicroscopy, and SD-OCT. In addition, FFA was performed when CNV was documented or suspected through the previous diagnostic tools. All the patients affected by AS-related CNV were given an injection of intravitreal aflibercept, in accordance with a pro re nata (PRN) treatment regimen that included monthly examinations and further reinjection when any sort of fluid was detected on SD-OCT.

FFA and structural SD-OCT were performed with Spectralis HRA+OCT (Heidelberg Eye Explorer, version 1.10.2.0; 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 to enhance the image resolution. Hyperreflective foci were defined as discrete, round lesions with greater reflectivity than RPE, and invisible on clinical examination,¹⁷ as measured by the horizontal line scan passing through the fovea. Patients were assessed monthly over the follow-up, with particular attention to HF analyses at the following time points: baseline (active CNV phase, characterized by SD-OCT-documented fluid); at least 1 month after anti-VEGF treatment, when CNV was dry on SD-OCT (inactive CNV phase); 1 month before CNV reactivation (prereactive CNV phase, when fluid was not detectable yet on SD-OCT); and the time of the CNV reactivation (reactive CNV phase, with SD-OCT-documented reappearance of fluid). The “follow-up” tool was enabled during the SD-OCT reacquisition protocol across the subsequent phases. HF distribution was classified as being in the foveal area (1500- μ m diameter) or parafoveal area (500- μ m external to the fovea, bilaterally), while, based on their location, HF were subsequently classified as being retinal or choroidal HF. In detail, in order to select the foveal and parafoveal regions, a vertical line was traced passing through the foveal center. From this line, two horizontal 750- μ m lines, respectively oriented on the left and the right, were selected to delimit the foveal region. Two further horizontal 500- μ m lines were outlined, external to the foveal area, to define the parafoveal regions.

Structural SD-OCT scan measurements were independently analyzed by two examiners (FR and AA) unaware of the purpose of the study and masked to the condition of the patients and controls. 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 for better HF visualization. The mean of the independent measurements of the same SD-OCT scans performed by the two graders was used for the analysis.

The primary outcome measure was to study the changes in HF number both in retina and choroid of eyes affected by subfoveal CNV secondary to AS. Secondary outcomes included the assessment of the HF number correlation with BCVA and with central retinal thickness (CRT).

Differences in the number of HF (retinal and choroidal; foveal and parafoveal) between patients and controls were analyzed by means of Student's *t*-test for continuous variables. ANOVA for repeated measures and Bonferroni's correction for post-hoc analysis were instead adopted to assess the differences between the different AS subgroups and controls. The relationship between variables was explored using nonparametric Kendall's Tau-b correlation tests. Results of descriptive analyses were expressed as mean \pm SD for quantitative variables and as frequency and percentages for categorical variables. Interobserver reproducibility for the measurement of HF was evaluated with intraclass correlation coefficients (95% confidence intervals); the Shapiro-Wilk test (W score) was employed to verify the Gaussian distribution for all the continuous variables. Statistical significance was set at $P < 0.05$, and all the analyses were performed using the SPSS Statistics Version 21.0 Software package (IBM, Armonk, NY, USA).

RESULTS

Overall, 15 treatment-naïve eyes of 15 patients with clinical diagnosis of CNV secondary to AS, eight being males (53.3%), were consecutively recruited for the study. Fifteen patients with uncomplicated AS served as age- and sex-matched controls. In detail, 10 patients with CNV (67%) and nine controls without CNV (60%) were affected by genetically confirmed pseudoxanthoma elasticum; no secondary causes of AS were detected in the remaining patients and controls (idiopathic). The mean age of patients and controls was 54.5 \pm 13.5 (range, 28-78), and 55.6 \pm 15.6 years (range, 31-76), respectively ($P = 0.93$). Mean BCVA in the treated eyes improved from 0.7, at the moment of CNV activity detection, to 0.5 logMAR, at the end of the follow-up (approximately corresponding to 20/100 and 20/63 Snellen acuity, respectively; $P < 0.0001$). All the patients regularly underwent aflibercept injections required by the PRN regimen over a mean follow-up of 6.1 \pm 1.8 months, requiring a mean of 2.9 \pm 1.1 injections. The full clinical/demographic data are set out in Table 1, whereas Figure 1 illustrates the acquisition scheme.

Overall, HF numbers were normally distributed and were found to differ significantly between the various phases ($P < 0.001$), being considerably higher in eyes affected by CNV compared with the controls at any time point ($P < 0.001$), except during the inactive CNV phase (Table 2). Foveal and parafoveal total HF turned out to be significantly elevated when the CNV was active, whether at baseline (12.7 \pm 5.4 and 11.7 \pm 3.7, respectively; $P < 0.001$), at reactivation (12.4 \pm 4.9 and 12.1 \pm 3.8, respectively; $P < 0.001$), or in the prereactive phase (9.7 \pm 4.0 and 9.9 \pm 4.5, respectively; $P = 0.008$ and 0.02), when compared with the inactive CNV phase (4.6 \pm 2.6 and 5.5 \pm 2.4). A similar trend was also observed for

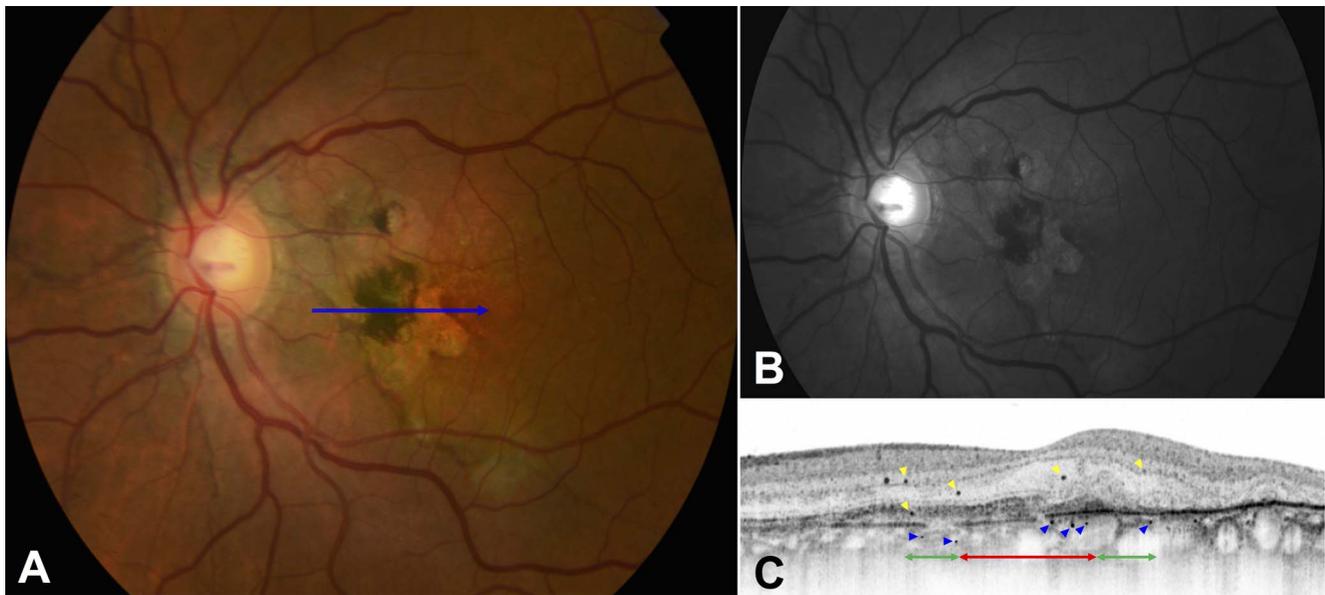


FIGURE 1. Fundus photo and SD-OCT of a patient with CNV secondary to angioid streaks. (A, B) Color and infrared photographs show the typical fundus aspect with irregular dark-red to gray lines, along with macular scarring and some pigment deposition; the *blue arrow* highlights the SD-OCT scan analyzed for the study. (C) Exemplifying SD-OCT scheme: *red and green double arrows* define the fovea and the parafovea, respectively; on the other hand, *yellow and blue arrowheads* point at retinal and choroidal HF, respectively.

choroidal HF, in the active CNV phase, and also in the prereactive CNV phase, featuring larger HF numbers. On the other hand, intraretinal HF appeared significantly increased exclusively in the presence of SD-OCT-documented fluid (9.5 ± 3.9 and 9.1 ± 3.1 for active and reactive CNV) as against inactive CNV (2.7 ± 2.1 ; $P = 0.005$ and 0.01 , respectively); although showing an incremental trend in intraretinal foci, the eyes in the prereactive phase did not achieve statistical significance ($P = 0.07$). Interestingly, a subanalysis conducted at the retinal and choroidal location revealed that only foveal choroidal HF differed significantly between the prereactive CNV phase and the inactive CNV phase (5.9 ± 2.6 vs. 2.1 ± 1.8 ; $P = 0.03$). Interobserver variability between the two investigators was good for all measurements (intraclass correlation coefficient = 0.901 [0.866 - 0.938]). No significant differences in HF numbers were found according to the location of the fluid exudation (subfoveal versus parafoveal; $P > 0.05$). HF changes occurring in an exemplifying case are shown in Figure 2. All HF values are shown in Figure 3.

With respect to nonparametric correlations, we found significant positive correlations regarding HF numbers, as well as significant positive correlations of BCVA values in consecutive phases ($P < 0.05$).

Moreover, we encountered noteworthy correlations when looking at the relationship between BCVA (as expressed in logMAR) and HF numbers. In particular, BCVA in logMAR in the active phase negatively correlated with intraretinal HF values of the prereactive ($\tau = -0.546$; $P = 0.007$) and reactive ($\tau = -0.490$; $P = 0.014$) phases. Comparable negative correlations were observed between BCVA in the dry phase and the intraretinal HF values of the prereactive ($\tau = -0.408$; $P = 0.04$) and reactive ($\tau = -0.606$; $P = 0.003$) phases. Likewise, the BCVA of the prereactive phase negatively correlated with the intraretinal HF of the reactive phase ($\tau = -0.551$; $P = 0.006$). No significant correlations were detected between the number of HF and CRT at any phase of our study ($P > 0.05$).

DISCUSSION

HF are described as discrete, dot-shaped, hyperreflective lesions that are identifiable solely on SD-OCT imaging. HF have been described in several retinal disorders, including diabetic retinopathy, retinal vein occlusions, central serous chorioretinopathy, AMD, and hereditary dystrophies.¹³⁻²⁵ In particular, retinal HF have been related to the activity of the CNV in patients affected by AMD.¹⁹⁻²¹ Our study focusing on

TABLE 2. Mean Numbers of HF in Different Phases of Angioid Streaks–Related CNV and Matched Controls (Angioid Streaks Without CNV)

HF Location	Active Phase		Dry Phase		Prereactive Phase		Reactive Phase		Controls	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Foveal total	12.7	5.4	4.6	2.6	9.7	4.0	12.4	4.9	2.1	1.9
Foveal intraretinal	4.5	2.0	2.5	1.9	3.9	2.3	4.3	1.3	1.0	1.0
Foveal choroidal	8.2	4.6	2.1	1.8	5.9	2.6	8.1	4.5	1.1	1.6
Parafoveal total	11.7	3.6	5.5	2.4	9.9	4.5	12.1	3.7	3.7	3.6
Parafoveal intraretinal	4.9	2.3	2.7	1.7	4.6	1.6	4.9	2.1	1.7	1.7
Parafoveal choroidal	6.8	2.7	2.8	1.5	5.3	3.5	7.2	2.6	1.9	2.5
Intraretinal total	9.5	3.8	5.2	3.3	8.5	3.4	9.1	3.1	2.7	2.1
Choroidal total	15	5.8	4.9	2.9	11.2	5.3	15.3	5.9	3.0	3.5

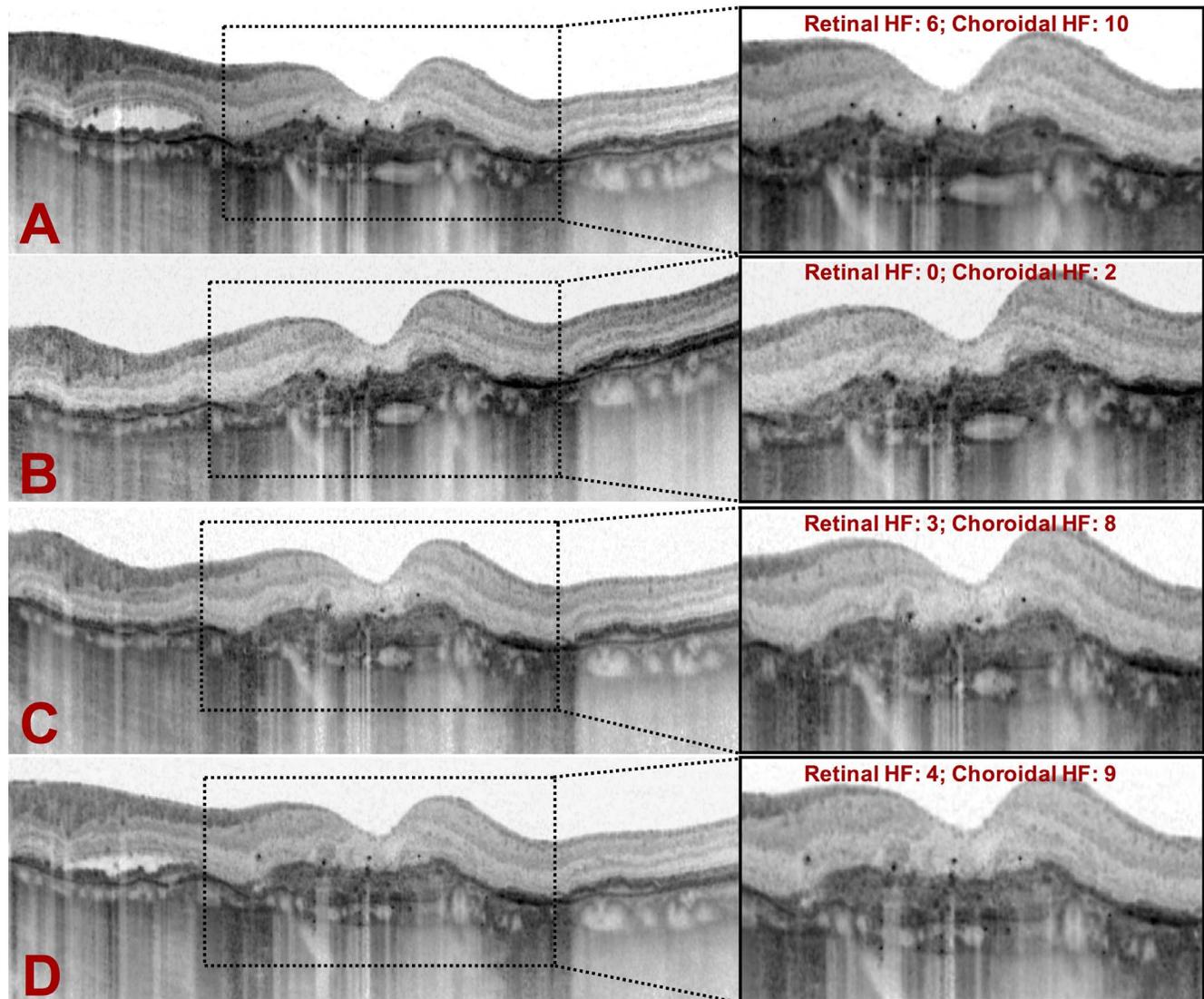


FIGURE 2. Variations in HF numbers across the different phases of choroidal neovascularization (CNV) activity. (A) Subretinal fluid is visible in the nasal retina of a patient with CNV in active phase. The *magnified box* on the *right* shows a large number of HF; the number of foci measured is stated in *red*. (B) A reduction in HF can be seen along with the disappearance of pathological fluid (inactive phase). (C) One month before reactivation (prereactive phase), HF start to increase in number despite the lack of any CNV activity on OCT. (D) With the reappearance of fluid on OCT, further HF expansion occurs, particularly in the choroid.

CNV secondary to AS reveals that HF correlate with CNV activity. Most interestingly, HF can be considered useful biomarkers of the activity of the CNV. Indeed, the number of foveal choroidal HF statistically increased in the prereactive CNV phase, corresponding to the examination performed 1 month before the SD-OCT-documented CNV reactivation. Thus, HF monitoring by means of SD-OCT can predict fluid formation consistent with the activation of the CNV, potentially enabling prompt retreatment to be performed before visual acuity deteriorates due to fluid accumulation. Moreover, the use of fixed landmarks, as those adopted in the present paper, helps to make HF quantification easily achievable and reproducible.

It is of interest how HF located within the choroid are particularly sensitive to these early modifications, whereas retinal HF tend to respond significantly by increasing in later stages. Although both HF locations assumed the same behavior in the different OCT-documented exudative phases, choroidal HF appear to be more suitable biomarkers for the CNV activity.

The explanation for these findings may be object of speculation. The histopathologic correlates behind these two types of foci might differ, with choroidal HF perhaps representing macrophage aggregates involved in the complex pathogenetic mechanisms of CNV development and growth.^{26,27} On the other hand, intraretinal HF have been more commonly related to focal exudative material and early signs of blood-retinal barrier breakdown or microglial cell activation,¹³ and might therefore lag behind the cellular response occurring in the choroid. In addition, we cannot exclude that the absence of a meaningful intraretinal HF increase represents a technology-related issue, with these developing exudative materials remaining under the resolution threshold of current SD-OCT power.

The similar HF numbers identified in the active and reactive phases are also an interesting finding. We speculate that this might be the result of a cyclic inflammatory response occurring during CNV activation, with comparable magnitude.

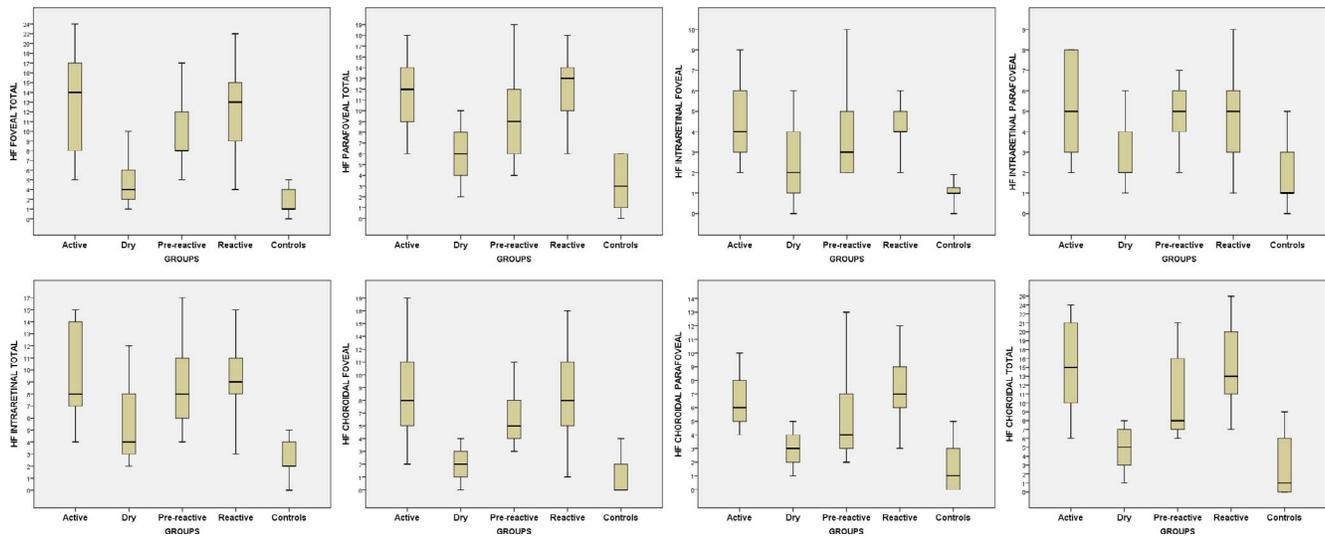


FIGURE 3. Differences in HF numbers between different angioid streaks-related CNV phases and controls. Foveal total: HF numbers are significantly higher in active, prereactive, and reactive phases when compared with inactive phase and controls ($P < 0.01$). No statistical difference is evident between inactive phase and controls ($P = 0.87$). Parafoveal total: HF numbers appear significantly increased in active, prereactive, and reactive phases when compared with inactive phase and controls ($P < 0.01$). Moreover, HF in the inactive phase result similar in numbers to controls ($P > 0.05$). Intraretinal (foveal, parafoveal, total): foci appear significantly higher in active, prereactive, and reactive phases when compared with inactive phase and controls ($P < 0.05$). HF do not statistically differ between inactive phase and controls ($P > 0.05$). Choroidal (foveal, parafoveal, total): HF are significantly increased in active, prereactive, and reactive phases when compared with inactive phase and controls ($P < 0.01$). Foci are not statistically different between inactive phase and controls ($P > 0.05$).

In this case, our hypothesis would further support HF evaluation as a stable and reliable marker to assess CNV activity.

As for the correlational analyses, the positive correlations between HF numbers in consecutive phases, as well as those related to BCVA, are as anticipated. More interestingly, logMAR BCVA in the active and inactive phases negatively correlated with the number of intraretinal HF in the prereactive and reactive phases. This means that a functionally healthier retina with higher visual acuity is also more reactive in terms of inflammation, expressed as a higher number of HF; this increase could be interpreted as an early sign of CNV reactivation. Augmented HF were clearly evident even in the prereactive phase. This finding bears important clinical implications as patients that are promptly diagnosed with AS-related CNV or are good responders might especially benefit from anti-VEGF reinjection in the prereactive phase, maintaining a favorable visual outcome over time. Moreover, the lack of correlation between HF number and CRT may further support the possible role of HF as biomarker for assessing the retinal functional status.

We are aware that our study is burdened with numerous limitations, the main ones being the relatively low number of patients and the inherent defects of OCT-based methodologies, which make the precise identification of HF difficult. In particular, the identification of both retinal and choroidal HF may be affected by the threshold resolution of SD-OCT, resulting in their underestimation. Moreover, to date, a standardized method to precisely quantify HF is still missing; however, we were more interested in the proof of concept rather than in making a precise calculation of HF. In addition, the lack of significant correlation between HF numbers and CRT across all phases might be related with the different patterns of fluid distribution, either subfoveal or parafoveal.

A further limitation is represented by the relatively short period of follow-up, with regard to the long and relapsing nature of AS-related CNV. Lastly, we specifically focused on patients with recent CNV onset, making it difficult to draw any inferences about long-term anatomic outcomes.

In conclusion, this study reveals that HF may be considered important biomarkers of CNV activity and responses to anti-VEGF treatment. HF numbers mirror the CNV activity as documented on SD-OCT, with foveal choroidal HF increment preceding fluid detection upon CNV reactivation. Further studies are warranted to confirm our preliminary data.

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