INTRODUCTION

Age-related macular degeneration (AMD) is a multifactorial disease and a major cause of blindness worldwide. Although choroidal neovascularization causes severe acute visual loss in AMD, around 20% of AMD patients who are legally blind have lost central vision due to geographic atrophy (GA). GA pathophysiology and natural history of lesion progression remain unclear. In previous studies, mean lesion progression rates vary widely between individuals. Moreover, different clinical characteristics, namely, history of smoking, hypertension, diabetes, the size of the lesion, its topography, fundus autofluorescence (FAF)-specific lesion AF pattern, and number of lesions have been associated with progression rate. ImageJ software is a straightforward open tool for the analysis of scientific images. Spectral-domain optical coherence tomography (SD-OCT) image processing with ImageJ has been extensively published in the literature. The primary objective of this study was to evaluate GA progression (GAP) rate in SD-OCT using ImageJ processing functions. The secondary objective is to evaluate the progression rate among different GA clinical characteristics.

METHODS: This was a retrospective observational study of patients with GA secondary to AMD. ImageJ v. 1.51 allowed planimetric measurements of areas in SD-OCT and evaluation of lesion progression. Stata software v. 13.1 was used to analyze data. The primary study end point was mean enlargement rate of the atrophic lesion. Secondary and additional end points included assessment of GA lesion size in different disease subgroups as determined by AF pattern (diffuse, banded, focal, and unspecific) and mean change from baseline best-corrected visual acuity (BCVA).

RESULTS: A total of 40 eyes from 23 patients (mean age 77.9 ± 7.8 years) were included in the study. The difference between BCVA at baseline and at the end of follow-up was statistically significant with \( P \leq 0.03 \) (mean difference −0.162 ± 0.052; 95% CI 0.057–0.268). Lesion progression rate was 0.558 mm\(^2\)/year (±0.944; minimum: 0.0134; maximum: 6.801). Progression rate according to FAF pattern was as follows: Diffuse 0.434 (±0.401; \( n = 17 \)), banded 1.254 (±2.008; \( n = 7 \)), focal 0.407 (±0.707; \( n = 6 \)), and unspecific 0.154 (±0.162; \( n = 5 \)).

CONCLUSIONS: FAF pattern could be a useful predictor of GAP. The banded pattern appears to be associated with a rapid progression. Our methodology using ImageJ is simple and appears to be effective in calculating GA lesion progression rates, and it could be used in different clinical settings and optimize scientific reading center approaches when testing future GA treatment strategies.

Key words: Age-related macular degeneration, geographic atrophy, image processing software, spectral-domain optical coherence tomography
GA is a progressive form of dry AMD characterized by permanent loss of retinal photoreceptors, retinal pigment epithelium (RPE), and choriocapillaris.[3]

GA pathophysiology and natural history of lesion progression remain unclear. In previous studies, mean lesion progression rates vary widely between individuals, ranging from 0.38 to 2.8 mm² per year.[4] Moreover, different clinical characteristics, namely, history of smoking, hypertension, diabetes, hyperlipidemia, family history, the size of the lesion, its topography, fundus autofluorescence (FAF)-specific lesion AF pattern, and number of lesions have been associated with progression rate.[5]

Recognition and monitoring of GA can be attained with different imaging modalities, including color fundus photography, fluorescein angiography (FA), FAF, near-infrared reflectance, spectral-domain optical coherence tomography (SD-OCT), and more recently optical coherence tomography angiography.[6,7]

Previous studies confirmed SD-OCT feasibility in monitoring GA and determining lesion size progression.[5]

ImageJ software is a straightforward open tool for the analysis of scientific images. SD-OCT image processing with ImageJ has been extensively published in the literature and applied by the authors in different clinical settings.[3,9]

The primary objective of this study is to evaluate GA progression (GAP) rate in SD-OCT using ImageJ processing functions. The secondary objective is to evaluate the progression rate among different GA clinical characteristics. We expect that results from this study provide insights into the natural history of GA and potential identification of relevant clinical features.

**METHODS**

This was a retrospective observational study of patients from one institution (Department of Ophthalmology, Egas Moniz Hospital, CHLO, Lisbon, Portugal).

The study protocol and procedures followed the tenets of the Declaration of Helsinki.

**Inclusion/exclusion criteria**

Patients with GA secondary to AMD were included in this study. Patients had to be at least 55 years old. Eyes had to have a GA lesion of at least 1.25 mm², evidenced in SD-OCT and FAF using Spectralis HRA+OCT™ (Heidelberg Engineering, Heidelberg, Germany). No signs of early or late CNV could be detectable by SD-OCT, neither signs or history of any other ocular diseases that might confound assessment of the retina.

**Parameters and measurements by SD-OCT using ImageJ**

ImageJ v. 1.51 (U. S. National Institutes of Health, Bethesda, Maryland, USA, https://imagej.nih.gov/ij/, 1997-2016) allowed planimetric measurements of areas in SD-OCT volume stacks and evaluation of lesion progression [Figure 1].

Lesion progression rate was calculated by dividing the difference between the baseline exam and the follow-up acquisition by the interval of time in months. This value was multiplied by 12 to achieve the annual lesion progression rate.

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\text{Lesion area} - \text{Lesion area at baseline} = \frac{\text{Lesion area}}{\text{Time span in months}} \times 12
\]

Lesion progression rates, as determined on SD-OCT images, were calculated and then stratified by lesion subtype according to specific lesion AF, according to the GAP study [Figure 2].[10]

**Statistical analysis**

The primary study end point was the mean enlargement rate of the atrophic lesion, from baseline as assessed by SD-OCT, using the previously described methodology.

Secondary and additional end points included assessment of GA lesion size in different disease subgroups as determined
by FAF and mean change from baseline best-corrected visual acuity (BCVA).

Stata software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) was used to analyze the data. Participant demographics and baseline characteristics, as well as lesion progression, were summarized with descriptive statistics (n, mean, standard deviation, median, minimum, and maximum).

RESULTS

A total of 48 eyes from 24 patients were analyzed. Eight eyes were excluded from the study, 4 due to the presence of signs indicative of neovascular AMD during the follow-up, 3 due to epiretinal membrane features on SD-OCT, and 1 eye with no evidence of GA.

Descriptive and clinical data for the eyes of the included subjects are summarized in Table 1.

The difference between BCVA at baseline and at the end of follow-up was statistically significant with $P \leq 0.03$ (mean difference $-0.162 \pm 0.052$; 95% CI 0.057–0.268). Of eyes with gradable imaging available, 97.9% had bilateral atrophic lesions.

Lesion progression rate was 0.558 mm$^2$/year ($\pm$0.944; minimum: 0.0134; maximum: 6.801). Table 2 displays the progression rate according to specific FAF characteristics.

DISCUSSION

Unlike active neovascular AMD, there is no effective treatment available for GA, other than visual aids and low vision rehabilitation.[11] Thus, a better understanding of the pathogenesis of GA is imperative.

Postmortem observations have shown that clinical visible areas of GA correspond to areas of RPE and photoreceptor loss and choriocapillaris closure.[12,13]

Consequently, the absence of RPE lipofuscin, containing the dominant fluorophores involved in the FAF signal, determines a markedly reduced AF signal at the site of atrophic lesions.[14]

A striking finding of FAF imaging in GA eyes is the common identification of high-intensity levels of AF at the junctional zone of atrophy.[15] This observation is in accordance with histological studies displaying enlarged lipofuscin-engorged RPE cells surrounding areas of atrophy.[16]

This was the rationale for targeting the detrimental accumulation of lipofuscin in the RPE using visual cycle modulators, namely fenretinide (N-[4-hydroxyphenyl] retinamide). A Phase II multicenter, randomized, double-masked, placebo-controlled study of the safety and efficacy of fenretinide in the treatment of GA displayed reduced lesion growth rates with both 100 mg and 300 mg daily oral fenretinide.[17]
In addition, genetic studies linked dysfunction of the alternative complement pathway to the pathogenesis of AMD.\textsuperscript{18,19} Accordingly, lampalizumab, a monoclonal antibody directed against complement factor D, was considered as a target therapy to GAP. However, a recent Phase III study (Spectri study) evaluating the safety and efficacy of lampalizumab failed to meet its primary end point of reducing the mean change in GA.\textsuperscript{20}

The fundus AF in AMD (FAM) study group highlighted the importance of abnormal AF intensities around GA lesions and introduced a morphological classification system for distinct patterns (unspecific, focal, banded, diffuse, and patchy).\textsuperscript{10} More recently, the GAP study was designed to identify GAP risk factors, adopting the same FAF patterns.\textsuperscript{5}

These AF distinct phenotypes appear to be of prognostic value for predicting the GAP rate and may reflect the heterogeneity of the underlying disease process.

In the present study, we found that the mean lesion progression, for the included population, was 0.558 mm\textsuperscript{2}/year. Our results were analogous to previous reports.\textsuperscript{10,21,22}

However, as previously reported, there is considerable variability in progression rate among patients. The mechanisms underlying the differences in progression rates among studies are not fully understood and may include variable lesion sizes and locations, different trial methods, imaging techniques, and varying genotype or exposure to environmental factors.

Although FAF is important for the accurate identification of GA lesions, monitoring with SD-OCT appears to be a valid option.\textsuperscript{23,24}

Although our small sample size limits conclusions, we also found asymmetric progression rate according to FAF pattern. Progression rate for banded FAF eyes was the highest, 1.254 (±2.008) mm\textsuperscript{2}/year. Although not statistically significant ($P = 0.163$), this tendency reproduces the impact of FAF phenotypic features on GAP described in the FAM study.

In conclusion, FAF pattern seems to be an important prognostic marker to predict progression on an individual basis.

Our methodology using ImageJ is simple and appears to be effective in calculating GA lesion progression rates, and it could be used in different clinical settings and optimize scientific reading center approaches when testing future GA treatment strategies. Our approach could be merged with software algorithms offering a breakthrough in understanding and managing GA.

Disclosures
The authors declare no relevant or material financial interests that relate to the research described in this paper.

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