The Journey of "Geographic Atrophy" through Past, Present, and Future

Steffen Schmitz-Valckenberg

Department of Ophthalmology, University of Bonn, Bonn, Germany

Abstract

"Geographic atrophy" is a concise term that has been firmly established for the description of the end-stage manifestation of nonexudative age-related macular degeneration (AMD). "Geographic lesions" resembling sharply demarcated continents on a map have been originally described in the German literature in 1854 (*landkartenartiger/inselförmiger Zungenfratt*) for a manifestation later called "geographic tongue" in English. In 1970, Gass was the first to describe "geographic areas of atrophy" in "senile macular choroidal degeneration." Within a decade, the disease itself was named "geographic atrophy." Today, various meanings of the term are used in parallel both in research and in routine clinical care. Currently, we are on the verge of better understanding the different forms of atrophy development, manifestation, and progression in AMD, which will pave the way for a more rational approach to their nomenclature and classification.
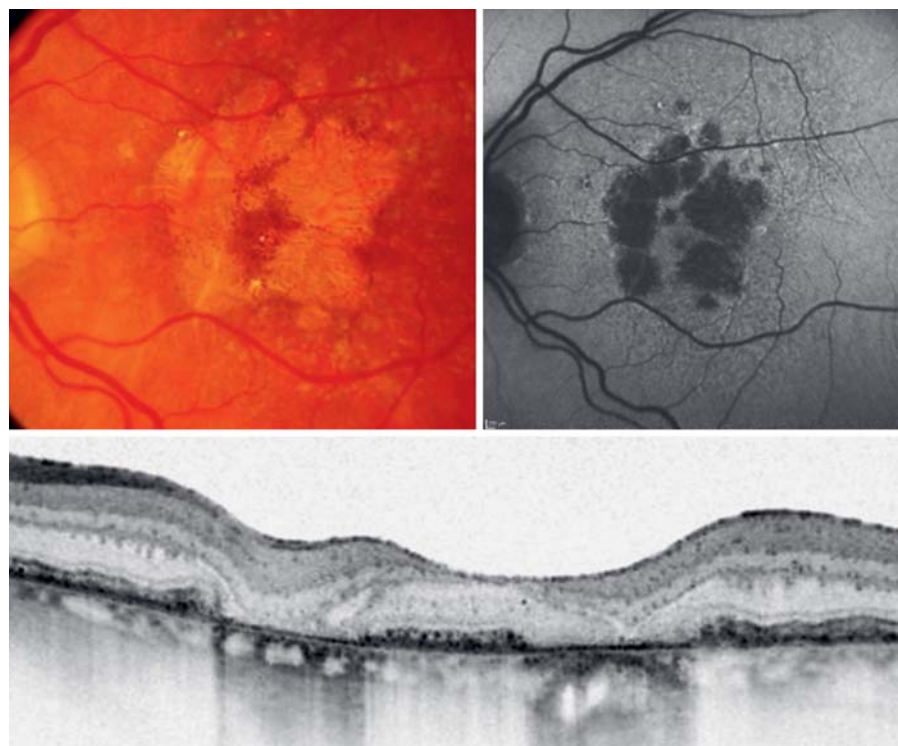
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Introduction

Advanced nonexudative age-related macular degeneration (AMD) represents a common cause of severe and irreversible visual loss (Fig. 1) [1, 2]. There is an unmet need for effective treatment, and substantial efforts in both basic and clinical research are being made [3].

The disease clinically manifests on ophthalmoscopy as 1 or more "atrophic" areas of complete or incomplete depigmentation, showing thinning of underlying tissue and, commonly, better visibility of large choroidal blood vessels as compared to the normal state [4–7]. Compared to histopathology, it should be noted that in the living eye the detection of the degree of tissue attenuation and degeneration – even when using high-resolution in vivo imaging – is limited. With the former method, loss of outer retinal layers including photoreceptors, substantial degeneration of the retinal pigment epithelium (RPE), and loss of the choriocapillaris have been reported in clinically visible areas of atrophy [4].

There is high variability in the location, number, and shape of individual lesions on clinical examination. At the same time, however, the occurrence and enlargement of atrophy appears not to be a totally random event. The phenomenon of "foveal sparing" is a very common observation, that is, involvement of the fovea by the atrophic process only during the later course of the disease and also the slower spread of atrophy towards the foveal cen-

Prof. Dr. med. Steffen Schmitz-Valckenberg, FEBO
Department of Ophthalmology, University of Bonn
Ernst-Abbe-Str. 2
DE–53127 Bonn (Germany)
E-Mail steffen.schmitz-valckenberg @ ukb.uni-bonn.de

Fig. 1. Manifestation of advanced nonexudative age-related macular degeneration on multimodal imaging. Top left: color fundus photograph; top right: confocal scanning laser ophthalmoscopy blue-light fundus autofluorescence image; bottom: spectral-domain optical coherence tomography B-scan at the fovea.

ter as compared to eccentric areas [7, 8]. Furthermore, atrophic areas do not appear to develop by chance at any extrafoveal location. Systematic analysis has revealed that initial atrophic areas occur predominantly in the parafovea (i.e., within the inner 4 fields of the Early Treatment of Diabetic Retinopathy Study [ETDRS] grid) [9].

Atrophic areas are commonly described as being "sharply demarcated" or having "clear-cut" edges (like being cut off with a sharp instrument [10]). However, areas may also appear more irregular, and it may be challenging to clearly define the borders of atrophic lesions, even using high-resolution imaging with systematic data acquisition (Fig. 2). In this context, it is important to remember that different pathways may lead to atrophy and that the exact evolution of an atrophic area is usually not delineable once it has been developed without prior information [11]. Further, a differentiation between the detection of regressed, subclinical, or successfully treated choroidal neovascularization (i.e., the [former] presence of exudative AMD) and a "pure," nonexudative lesion cannot be made with absolute certainty [12].

Finally, with regard to the clinical manifestation of atrophy in nonexudative AMD, 2 additional aspects need to be taken into consideration. First, one should remember that development of atrophy at the posterior pole is not an exclusive feature of AMD etiology [13]; there is a huge variety of different retinal and choroidal diseases that can turn into atrophy. Second, it would be different if the diagnosis of atrophy in advanced nonexudative AMD were made by clinical examination or – either alone or additionally – through findings made by multimodal retinal imaging.

The Semantics and Origin of the Term "Geographic"

A geographer is a scholar who makes maps by drawing features according to their location, configuration, and relationship to other structures, also including the borders of countries as well as continents (www.en.wikipedia.de). By the sheer "process of drawing," features may become sharply demarcated and may appear not to be specifically related to other structures.

According to medical dictionaries, a "geographic lesion" accordingly is a well-demarcated pattern resembling the outline of a land mass against water on a map [14, 15]. The first entity in medicine that was described as manifesting in this sense appears to be the "geographic tongue." This is a common and benign condition that was mentioned as early in 1831, albeit not using the term

Schmitz-Valckenberg
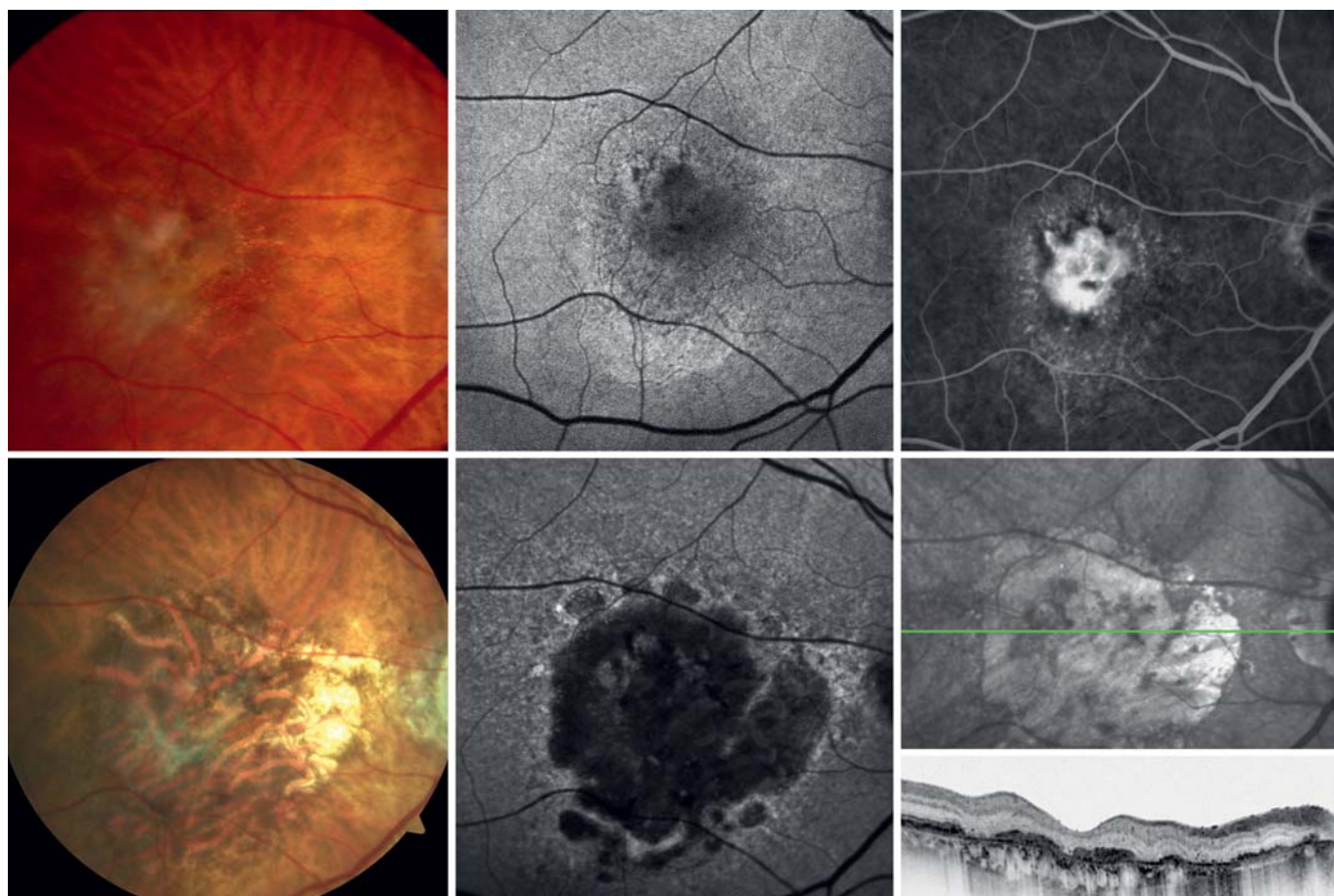
Fig. 2. Top row: baseline images of an active choroidal neovascular membrane in age-related macular degeneration (from left to right: color fundus photograph, confocal scanning laser ophthalmoscopy [cSLO] blue-light fundus autofluorescence image, and late-phase fluorescein angiography frame). Bottom row: development of a central atrophic lesion without any signs of an active neovascular membrane after 9 years of follow-up and multiple intravitreal injections of anti-vascular growth factor inhibitors (from left to right: color fundus photograph, cSLO blue-light fundus auto-fluorescence image, and cSLO near-infrared reflectance with corresponding optical coherence tomography [OCT] B-scan). Partly, the borders are not sharply demarcated, and hyperreflective material is noted by OCT at the level of the outer retina. There would be no consensus even among retinal specialists whether this not purely atrophic lesion should be called "geographic atrophy," also without the information about previous neovascularization, or whether the term should just be based on clinical examination or, additionally, on findings made by multimodal imaging.

"geographic" at this early time [16]. The first similar term in this context goes back to Santlus, a German doctor who lived in Hadamar and used the words *landkartenartig* (map-like) and *inselförmig* (island-shaped), which might later have been translated into Latin as "lingua geographica" and then further into English as "geographic tongue" [17–19]. In ophthalmology, geographic lesions were initially described in a variation of dendritic herpetic keratitis. In 1956, "geographic map" ulcers were reported to occur with the use of topical corticosteroids as epithelial lesions that extended through the basement membrane in the sense of a true ulcer [20]. At the same time, the use of this term was clearly explained: the outline of these lesions resembled the map of a continent. Interestingly, a similar terminology as later used in the context of AMD has also been applied until today in the context of herpetic corneal disease, probably best known as "disciform keratitis," which represents another herpetic variant but manifests as a deeper lesion than a geographic map ulcer.

Using the ophthalmoscope and visualizing alterations that are not visible otherwise, it is understandable that people particularly have tried to describe morphological changes by comparing them to the shape and appearance of well-known features. For example, in 1956 Kraffel [21]

Fig. 3. Left: fundus drawing of "landkarten-artige Choroidalatrophie" (map-like choroidal atrophy) in "chorioretinitis striata" by Kraffel (1956) [21, Abb. 1, p. 665; copyright with friendly permission by Thieme]. Right: fundus camera photograph of "eigentümliche Atrophie" (peculiar atrophy) by Dimmer and Pillat (1927) [36].
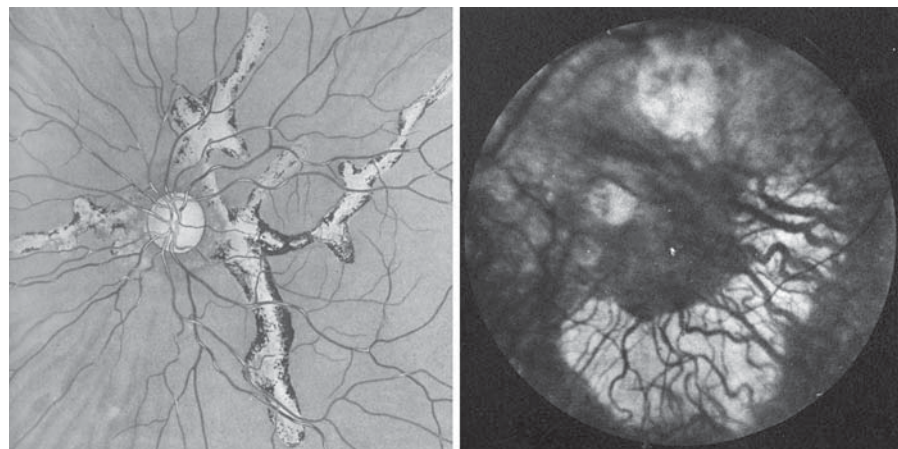
wrote of "chorioretinitis striata" as "landkartenartige [map-like] Choroidalatrophie" exhibiting the sharply demarcated borders of atrophy (Fig. 3). In the English literature, use of the term "geography" in the context of retinal lesions appears to have first been made in a presentation at the Wilmer 27th Residents Association Meeting in 1968 by Hyvärinen and Maumenee (cited by Schlaegel [22] as a meeting abstract with the title of "Geographic Choroiditis vs. Choroidal Vascular Abiatrophy"), which was followed by several peer-reviewed publications by different authors in the 1970s [22–24]. However, these reports were exclusively focused on "geographic choroiditis," which fits the current understanding of serpiginous choroiditis but not of atrophy in AMD.

"Geographic Atrophy" in the Context of "Senile Macular Degeneration"

It appears that it was Gass, in the first edition of his *Stereoscopic Atlas of Macular Diseases* of 1970, who extended the term "geographic areas of atrophy" to different diseases of the retina and choroid, including "senile macular choroidal degeneration," "central areolar choroidal sclerosis," and "serpiginous peripapillary choroiditis" (Fig. 3) [25]. According to his descriptions, these areas are sharply circumscribed, and, usually, large underlying choroidal vessels are exposed. It is interesting to note that Gass neither explained why he used this term nor referred to any of the previous authors and the previous use of the term in medicine – including in ophthalmology, as discussed above. It must be acknowledged that he clearly pointed out that different etiologies may lead to atrophy, an important observation that has not seldom

been neglected in different situations until today. Compared to the 1970s, it should be considered that with the advances in genetics and multimodal imaging, far more precise differential diagnoses are possible today [13]. For example, the term "areolar" should not be used anymore in the context of AMD. The literal meaning of this term denotes a small ring of color around a center portion like the surrounding area of the nipple of the breast. It is appropriate for the phenotype of central areolar choroidal dystrophy, a dominantly inherited macular dystrophy, which is different from the AMD phenotype and is caused by mutations in the PRPH2 gene (Fig. 4) [26]. This disease commonly manifests as a unifocal atrophic area with a ring of pigmentary changes or – better visible – speckled increased fundus autofluorescence (FAF) intensities around a large central patch of decreased FAF intensities. Therefore, the term does not describe the features of the central atrophic patch – as opposed to the term "geographic" – but the characteristic changes surrounding the atrophy. Further, the term would not appreciate the common multifocality of atrophic patches in AMD.

In 1972/1973, Gass published extensively on geographic atrophy of the RPE and the retina in elderly patients, also focusing on its evolution from drusen [27, 28]. Effectively, he not only described "geographic areas of atrophy," he named the disease itself "geographic atrophy of the retinal pigment epithelium." The first paper using this nomenclature in its title was written by Blair in 1975 [29]. One year later, Sarks published extensively on the histopathology of "geographical atrophy," later abandoning the British "geographical" in favor of the American "geographic" [4, 30]. In 1977, Green and Key [31] did not adopt the wording "geographic atrophy" in their landmark paper on the histopathology of "senile macular de-
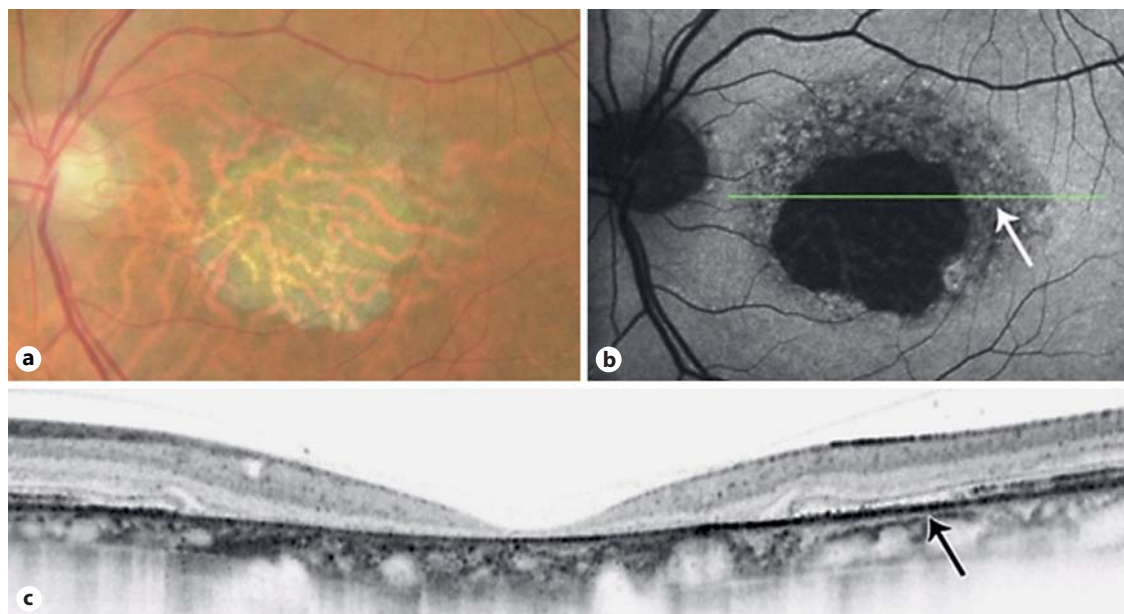
Fig. 4. Phenotype of central areolar choroidal dystrophy on color fundus photography (**a**), fundus autofluorescence (**b**), and optical coherence tomography imaging (**c**). The term "areolar" does not refer to the shape of the atrophic lesion, but particularly underscores the typical speckled ring (arrow) around the unifocal central lesion [reprinted from 26, Fig. 5, p. 8912; copyright with friendly permission by ARVO].

generation," still using the term "areolar atrophy." From 1980 onwards, the concise term "geographic atrophy" has appeared to have been firmly established [5, 6, 32].

The Origin of Atrophic AMD

In 1885, the Suisse ophthalmologist Otto Haab described "several new, previously unreported" – in addition to well-known – forms of macular diseases in German [33]. Specifically, he reported on one form in which the macular region sometimes spontaneously sickens in otherwise totally normal eyes of aged people, typically symmetrically in both eyes. The alterations were often minor but would cause strong visual impairment with a fairly poor prognosis. The disease was characterized by pale spots in the macular region that were due to atrophy of the pigment epithelium. Finally, for the time being, he suggested the term "senile." One year earlier, the English ophthalmologist Nettleship [34] had described the bilateral occurrence of large areas of atrophied choroid in the central region of the fundus in a 60-year-old woman. This publication is accompanied by a color plate that clearly shows a large area of atrophy with no drusen or any other surrounding changes. Further, Nettleship – as opposed

to Haab – did not associate the disease with spontaneous development in the elderly, but speculated on a family disease being inherited by one to the next generation [35].

The first atlas of fundus photography, written by Dimmer and Pillat in 1927 [36], includes several examples of atrophy. However, the plates are accompanied by descriptions such as "herdförmige Atrophie" (focal atrophy) and "eigentümliche Atrophie" (peculiar atrophy) (Fig. 3). Neither the expression "senile macular degeneration" nor the term "geographic" was used. Up to the 1960, fundus drawings (often in color) had been widespread – but not yet photographs. Three aspects appear to be particularly important with regard to the evolution of the terminology used with AMD/senile macular degeneration. First, the fact that both atrophic and exudative manifestations belong to the same disease entity – i.e., may develop from the same phenotype – was not well established [37]. For example, the first monograph on exudative AMD by Junius and Kuhnt [38] from 1926 did not even mention atrophic macular degeneration. Second, the atrophic form was often called "heredodegeneration," implying that the disease was passed on in families [39, 40]. In fact, depending on the age at manifestation, different forms of atrophy – including Stargardt disease and Best disease – were categorized into "juvenile" (e.g., Star-

gardt/Best), "adult," "pre-senile," and "senile." Third, there was a long-standing debate on which layers (the vitreous, different retinal, and different choroidal layers) were really affected and to which extent, both initially and later during the course of the disease.

Finally, it should be pointed out that the term "geographic areas of atrophy" – as discussed above – was introduced into ophthalmology for "senile macular degeneration," i.e., before the term "age-related macular degeneration" was introduced into the literature. In the ophthalmological literature, the latter term goes back to a paper by Ferris, Fine, and Hyman [41] from 1984, in which the authors substitute "senile" by "age-related" because "of the pejorative connotation of the word senile." In addition to senile macular degeneration, a parallel nomenclature had been used before including senile amblyopia, involutional macular degeneration, disciform macular degeneration, Kuhnt-Junius macular degeneration (the latter 2 rather focusing on exudative manifestations), and senile heredodegeneration (for the nonexudative manifestation) [35].

Definitions of "Geographic Atrophy" in Natural History Studies

From the 1980s onwards, several natural history studies have applied variable definitions for the systematic evaluation of the manifestation and progression of atrophy in nonexudative AMD under the term "geographic atrophy." It is not only that the minimal diameter or minimal lesion size of an individual atrophic spot has been defined differently, but also the single largest spot (either in diameter or lesion area) and/or the total size of atrophy (sum of all lesions) that has to be present in a given eye to meet the criteria for the disease manifestation of "geographic atrophy" has been variably specified [32, 42–45]. In addition, there has been no standard as to whether stereo or non-stereo images, or whether colors or fluorescein angiograms, should be used. Color differentiation between atrophic areas and choroidal vessels, areas of hypopigmentation, (confluent) drusen at the edge of atrophy, and overlying calcifications is challenging with color fundus photography, while atrophic areas may appear irregular or lesion boundary discrimination may be not accurately possible due to similar intensities of drusen as compared to atrophy by fluorescein angiography. These challenges obviously have an impact on intrasession and interreader variability in atrophic lesion detection, which is possibly also the reason why the Age-Related Eye Disease Study (AREDS) definition includes the grade "questionable" for atrophy [43].

To measure diameters and lesions, color and/or fluorescein angiography slides – as obtained with analog fundus cameras – were typically projected on a microfilm reader in order to then manually outline areas of atrophy using variable systems and individual analytical procedures. The scaling – converting lengths and lesion areas into the metric system – was typically based on measuring the size of the optic nerve head and assuming a standard disc area. Given the way of analysis and variability, it is evident that the ability to precisely and reliably measure lesion diameters and sizes was obviously limited. In effect, the definition and reported values in micrometers should therefore not be regarded as precise measurements but rather as estimations from the beginning. To make things even more complicated, it is noteworthy that the AREDS definition of atrophy doubles the minimal required lesion size of an individual atrophic spot from 1/8 (circle I_1) to 1/4 (circle I_2) of the standard optic disc and changes the diameter of the standard disc from 1,500 to 1,800 μm at the same time [46].

With the advent of new imaging modalities, the definition and analysis strategies for atrophy quantification progressed as well. FAF imaging, based on confocal scanning laser ophthalmoscopy (cSLO), was systematically applied for atrophy detection in the early 2000s [47, 48]. Due to the severely decreased FAF signal of atrophic areas (due to the loss of intrinsic fluorophores in degenerated RPE cells) as compared to nonatrophic areas, superior lesion border discrimination using a noninvasive imaging method became possible. In addition, the high contrast of atrophic areas also allowed for the introduction of semiautomated image analysis software using segmentation and region-growing algorithms (Fig. 5) [49, 50]. Together with a reduction of intra- and interreader variability, FAF imaging has become widely accepted for the detection of atrophy and its progression over time and is currently used in several large-scale, interventional clinical trials on geographic atrophy [51, 52]. For the assessment of foveal sparing – which is challenging with blue-light FAF imaging, due to only minor differences in intensity between the macular pigment and atrophy – the use of corresponding near-infrared reflectance images has been proposed [53].

Using simultaneous spectral-domain optical coherence tomography (SD-OCT) imaging, it was later confirmed that atrophic areas of severely reduced FAF intensities are spatially confined to loss of outer retinal layers with choroidal hypertransmission by SD-OCT [54]. Us-
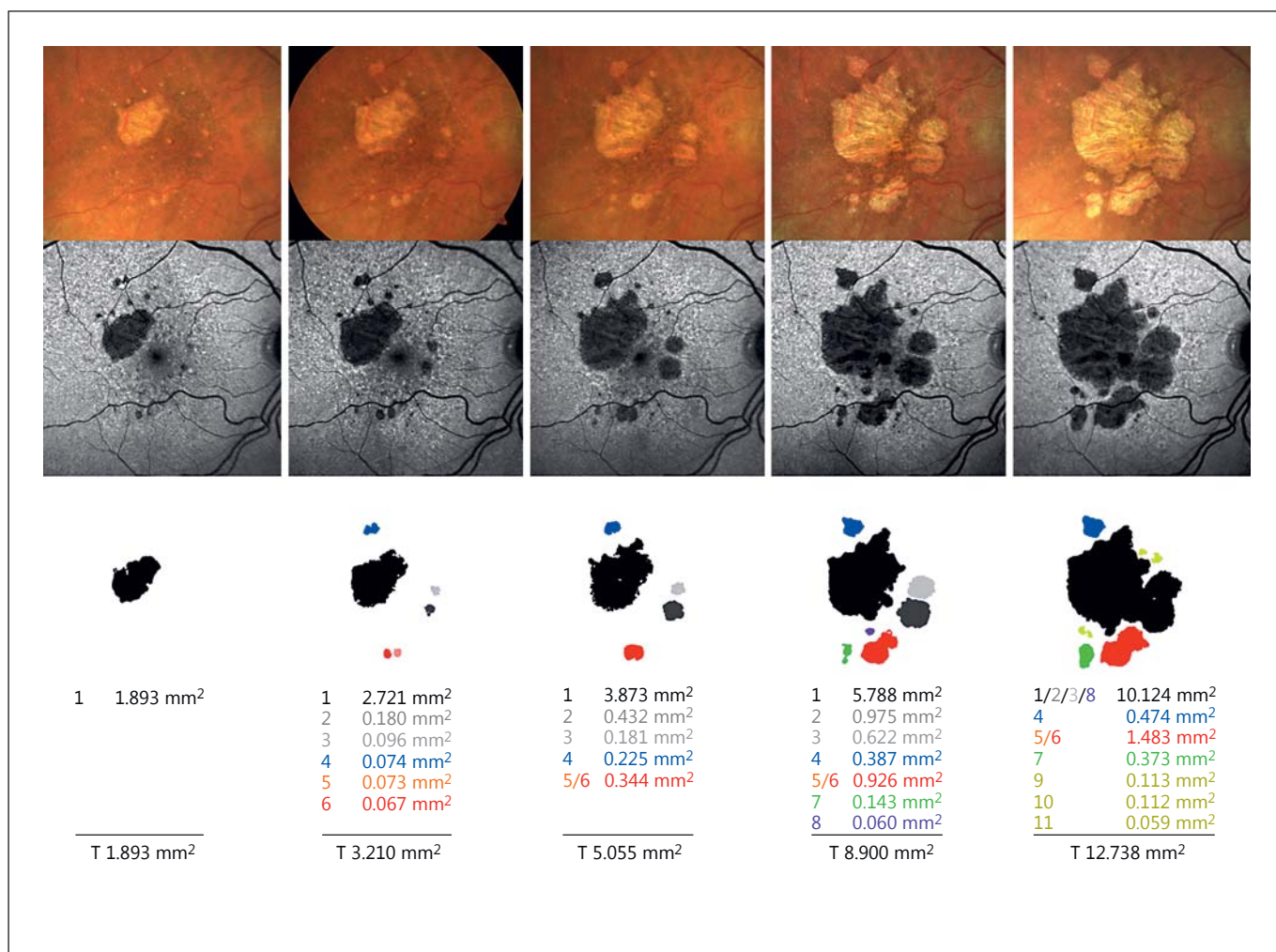
Fig. 5. Development and progression of atrophy in purely nonexudative age-related macular degeneration with annual retinal imaging during 4-year follow-up from baseline (first row: color fundus photographs; second row: confocal scanning laser ophthalmoscopy blue-light fundus autofluorescence images). Atrophic areas were semiautomatically detected and quantified with dedicated software (third row; also showing the size of the individual lesions [in different colors] and the total lesion size [T]). Note the superior detection of atrophy with fundus autofluorescence as compared to color fundus photography, which also allows for an accurate assessment of the enlargement of existing and the development of new individual spots as well as of the coalescence of spots over time. The minimum lesion size on fundus autofluorescence imaging is set at 0.05 mm². According to the definition of the AREDS, the minimal lesion size of an individual atrophic spot would be 0.145 mm² (1/8 of a disc diameter), which would lead to later detection of atrophic satellites and determination of a smaller overall size of atrophy at the different time points.

ing SD-OCT imaging for atrophy quantification obviously offers the advantage of using one device and one modality for the visualization of different retinal layers. The limitations of SD-OCT are (1) the limited size of the scan field, (2) the extensive acquisition time and increased amount of data when using dense raster scanning for accurate planimetric lesion detection (i.e., to limit interpolation between neighboring B-scans), and (3) its susceptibility to segmentation errors. While the latter 2 limitations may be largely overcome by hardware and software improvements in the future, one of the other major advantages of cSLO over SD-OCT imaging may more likely remain: while SD-OCT imaging has the key advantage of an outstanding vertical resolution (also permitting visualization of different retinal layers), its lateral anatomical resolution – and thus its ability to exactly allow for planimetric measurements such as atrophic lesion quantification – is inferior to that of cSLO. In addition, preliminary

data suggest that lesion boundary discrimination by SD-OCT imaging may be difficult in some subtypes of atrophy. Particularly in the so-called diffuse-tricking subtype, no sharply demarcated boundary of choroidal hypertransmission may be visible on SD-OCT imaging as compared to cSLO FAF imaging [unpubl. data]. This observation may indicate that FAF imaging allows for a more selective detection of atrophic areas by decreased signal intensities, as compared to the detection of probably more unspecific choroidal hypertransmission by SD-OCT imaging.

Geographic Atrophy Today

Up to the first half of the first decade of the 21st century, research on AMD and the clinical management of AMD were largely focused on neovascular AMD, while the pure, nonexudative form – "geographic atrophy" – was known but gained only little attention. This situation can be explained by several factors which have since changed dramatically and led to the increasing interest in "geographic atrophy" that is reflected in the steep rise in publications as well as in scientific sessions and discussions during the last 10 years [35]. While the slowly progressive disease of late-stage nonexudative AMD cannot really be appreciated with routine clinical assessment tools (i.e., central visual acuity remains stable for a long time, and changes in lesion size are not really detectable on ophthalmoscopy at different time points for years), neovascular AMD is characterized by a dramatic and rather rapid decline in visual function along with clear dynamic changes in fundus lesions that are visible within months. While therapeutic approaches with some evidence of efficacy (i.e., focal laser treatment and, later, photodynamic therapy) were available, patients with neovascular AMD remained the largest and most immediate burden for clinicians in their daily work. This situation turned with the advances in retinal imaging technology, allowing for better detection and documentation of geographic atrophy, and – probably far more importantly – with the introduction of anti-VEGF therapy for neovascular AMD. This therapy not only represented a major breakthrough in terms of successful treatment of the neovascular membrane, but also brought into focus the atrophic process that typically continues to evolve and becomes particularly evident in a successfully treated eye with nonexudative AMD as longitudinal management with multiple visits goes on. Along with these observations, the terminology for the

manifestation of atrophy in eyes with AMD has become even more complicated. Terms like "RPE atrophy," "outer retinal atrophy," "complete atrophy," "incomplete atrophy," and "macular atrophy" have been introduced. For example, the term "macular atrophy" – according to Abdelfattah et al. [55] – "generally refers to all cases of RPE atrophy whether caused by dry AMD (geographic atrophy) or by the fibrosis resulting from CNV [choroidal neovascularization] membrane maturation."

Currently, we are in the process of better understanding the different variants of atrophy development, manifestation, and progression in both exudative and purely nonexudative forms of AMD. Given the commonly rather slow progress in dynamic changes of atrophy – particularly in relation to CNV – we especially need well-defined, prospective clinical studies with longitudinal observations over several years to gain more insight into the disease process of atrophy. For this endeavor, the use of high-resolution multimodal imaging appears to be particularly important. For example, a recent report by the AREDS2 study group showed that "geographic atrophy" may be detected earlier by the use of FAF imaging as compared to color fundus photography [56]. Recent data suggest that the combination of SD-OCT with color fundus photography (as the historical gold standard) and cSLO FAF (as the gold standard for the assessment of atrophy manifestation and enlargement) allows for the detection of dynamic changes in atrophy development in eyes at high risk for conversion into late AMD [unpubl. data]. Different specific structural precursors such as confluent soft drusen, placoid lesions with hyperpigmentary changes, crystalline deposits, and serous RPE detachments appear to represent different local phenotypic variants leading to atrophy, while the pattern and the time course to development of manifest atrophy may vary substantially between these precursor lesions. These observations will allow for a more detailed description and classification of atrophy development and manifestation. With regard to the term "geographic atrophy," one approach might be to use this term only in a very general way for any atrophy as seen by clinical examination or color fundus photography, exhibiting more or less well-demarcated areas of loss of pigmentation with better visibility of underlying choroidal vessels. At the same time, the term should be used neither for presuming a clear etiology of AMD or the clear exclusion of any signs of active or past CNV nor for any lesions that have been detected by SD-OCT, FAF, or any modalities other than standard color fundus photography.

Conclusion

In conclusion, the term "geographic atrophy" without further description appears to be currently used all too frequently in ways other than to further classify the degeneration in question. The historical perspective of the introduction and development of the term is helpful in reviewing its current inconsistent usage. Further, it underscores the need for a more prudent application of the term "geographic atrophy" in today's world of ophthalmology, which is characterized by major advances in retinal imaging and in therapeutic approaches along with a better understanding of disease manifestations and classifications such as the identification of various genetic factors. The need for a more rational approach to the nomenclature and classification of atrophic AMD is clearly evident – not only for research and the development of further therapeutic strategies, but also for patient management in routine clinical care.

References

1 Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY: Age-related macular degeneration. Lancet 2012;379:1728–1738.

2 Holz FG, Schmitz-Valckenberg S, Fleckenstein M: Recent developments in the treatment of age-related macular degeneration. J Clin Invest 2014;124:1430–1438.

3 Holz FG, Strauss EC, Schmitz-Valckenberg S, van Lookeren Campagne M: Geographic atrophy: clinical features and potential therapeutic approaches. Ophthalmology 2014;121: 1079–1091.

4 Sarks SH: Ageing and degeneration in the macular region: a clinico-pathological study. Br J Ophthalmol 1976;60:324–341.

5 Maguire P, Vine AK: Geographic atrophy of the retinal pigment epithelium. Am J Ophthalmol 1986;102:621–625.

6 Schatz H, McDonald HR: Atrophic macular degeneration. Rate of spread of geographic atrophy and visual loss. Ophthalmology 1989; 96:1541–1551.

7 Sunness JS, Gonzalez-Baron J, Applegate CA, Bressler NM, Tian Y, Hawkins B, Barron Y, Bergman A: Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration. Ophthalmology 1999;106:1768–1779.

8 Schmitz-Valckenberg S, Fleckenstein M, Helb HM, Charbel Issa P, Scholl HP, Holz FG: In vivo imaging of foveal sparing in geographic atrophy secondary to age-related macular degeneration. Invest Ophthalmol Vis Sci 2009; 50:3915–3921.

9 Mauschitz MM, Fonseca S, Chang P, Göbel AP, Fleckenstein M, Jaffe GJ, Holz FG, Schmitz-Valckenberg S: Topography of geographic atrophy in age-related macular degeneration. Invest Ophthalmol Vis Sci 2012; 53:4932–4939.

10 Harms C: Anatomisches über die senile Makulaaffektion. Klin Monbl Augenheilkd 1904;42/I:448–461.

11 Klein ML, Ferris FL 3rd, Armstrong J, Hwang TS, Chew EY, Bressler SB, Chandra SR: Retinal precursors and the development of geographic atrophy in age-related macular degeneration. Ophthalmology 2008;115:1026–1031.

12 Steinberg JS, Göbel AP, Thiele S, Fleckenstein M, Holz FG, Schmitz-Valckenberg S: Development of intraretinal cystoid lesions in eyes with intermediate age-related macular degeneration. Retina 2015;36:1548–1556.

13 Saksens NT, Fleckenstein M, Schmitz-Valckenberg S, Holz FG, den Hollander AI, Keunen JE, Boon CJ, Hoyng CB: Macular dystrophies mimicking age-related macular degeneration. Prog Retin Eye Res 2014;39:23–57.

14 Dorland's Illustrated Medical Dictionary, ed 32. Philadelphia, Elsevier Saunders, 2011.

15 Anderson DM (ed): Mosby's Dictionary of Medicine, Nursing & Health Professions. St. Louis, Elsevier/Mosby, 2013.

16 Varoni E, Decani S: Images in clinical medicine. Geographic tongue. N Engl J Med 2016; 374:670.

17 Spehlmann O: Ein Beitrag zur Kenntnis der Lingua geographica. Dorpat, Schnakenburg's Buchdruckerei, 1892.

18 Santlus: Zur Lehre von der Zungenhäutung (Zungenfratt). J Kinderkrankheiten 1854;23: 161–167.

19 Prinz H: Wandering rash of the tongue (geographical tongue). Dent Cosmos 1927;69: 272–275.

20 Hogan MJ, Kimura SJ, Thygeson P: Observations on herpetic keratitis and keratoconjunctivitis. AMA Arch Ophthalmol 1956;56:375–388.

21 Kraffel G: Contribution on chorioretinitis striata (in English, German). Klin Monbl Augenheilkd Augenarztl Fortbild 1955;127:664–669.

22 Schlaegel TF: Essentials in Uveitis, ed 1. London, J & A Churchill Ltd, 1969.

23 Hamilton AM, Bird AC: Geographical choroidopathy. Br J Ophthalmol 1974;58:784–797.

24 Baarsma GS, Deutman AF: Serpiginous (geographic) choroiditis. Doc Ophthalmol 1976; 40:269–285.

25 Gass JD: Stereoscopic Atlas of Macular Diseases, ed 1. St Louis, CV Mosby, 1970.

26 Smailhodzic D, Fleckenstein M, Theelen T, Boon CJ, van Huet RA, van de Ven JP, den Hollander AI, Schmitz-Valckenberg S, Hoyng CB, Weber BH, Holz FG, Klevering BJ: Central areolar choroidal dystrophy (CACD) and age-related macular degeneration (AMD): differentiating characteristics in multimodal imaging. Invest Ophthalmol Vis Sci 2011;52:8908–8918.

27 Gass JD: Drusen and disciform macular detachment and degeneration. Trans Am Ophthalmol Soc 1972;70:409–436.

28 Gass JD: Drusen and disciform macular detachment and degeneration. Arch Ophthalmol 1973;90:206–217.

29 Blair CJ: Geographic atrophy of the retinal pigment epithelium. A manifestation of senile macular degeneration. Arch Ophthalmol 1975;93:19–25.

30 Sarks SH: Drusen patterns predisposing to geographic atrophy of the retinal pigment epithelium. Aust J Ophthalmol 1982;10:91–97.

31 Green WR, Key SN 3rd: Senile macular degeneration: a histopathologic study. Trans Am Ophthalmol Soc 1977;75:180–254.

32 Sarks JP, Sarks SH, Killingsworth MC: Evolution of geographic atrophy of the retinal pigment epithelium. Eye (Lond) 1988;2(pt 5): 552–577.

33 Haab O: Erkrankungen der Macula Lutea. Centralblat Augenheilkd 1885;9:384–391.

34 Nettleship E: Central senile areolar choroidal atrophy. Trans Ophthalmol Soc UK 1884;4: 165–167.

35 Schmitz-Valckenberg S, Sadda S, Staurenghi G, Chew EY, Fleckenstein M, Holz FG: Geographic atrophy: semantic considerations and literature review. Retina 2016;36:2250–2264.

36 Dimmer F, Pillat A: Atlas photographischer Bilder des menschlichen Augenhintergrundes. Leipzig/Wien, Franz Deuticke, 1927, Tafel 75, Abb 72.

37 François J, Deweer JP: Hereditary senile degenerescence of the macula (in French). Ann Ocul (Paris) 1952;185:136–154.

38 Junius P, Kuhnt H: Die scheibenförmige Entartung der Netzhautmitte (Degeneratio Maculae Luteae Disciformis). Berlin, Karger, 1926.

39 Behr C: Die Heredodegeneration der Makula. Klin Monbl Augenheilkd 1920;65:465–505.

40 Hollwich F: Erkrankungsformen der Netzhautmitte; in Velhagen K (ed): Der Augenarzt. Leipzig, Verlag für Kunst und Wissenschaft, 1963, V, pp 683–700.

41 Ferris FL 3rd, Fine SL, Hyman L: Age-related macular degeneration and blindness due to neovascular maculopathy. Arch Ophthalmol 1984;102:1640–1642.

42 Klein R, Davis MD, Magli YL, Segal P, Klein BE, Hubbard L: The Wisconsin age-related maculopathy grading system. Ophthalmology 1991;98:1128–1134.

43 Age-Related Eye Disease Study Research Group: The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6. Am J Ophthalmol 2001;132:668–681.

44 Klein R, Meuer SM, Knudtson MD, Klein BE: The epidemiology of progression of pure geographic atrophy: the Beaver Dam Eye Study. Am J Ophthalmol 2008;146:692–699.

45 Sunness JS, Bressler NM, Tian Y, Alexander J, Applegate CA: Measuring geographic atrophy in advanced age-related macular degeneration. Invest Ophthalmol Vis Sci 1999;40: 1761–1769.

46 Danis RP, Domalpally A, Chew EY, Clemons TE, Armstrong J, SanGiovanni JP, Ferris FL 3rd: Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2). Invest Ophthalmol Vis Sci 2013;54:4548–4554.

47 von Ruckmann A, Fitzke FW, Bird AC: Distribution of fundus autofluorescence with a scanning laser ophthalmoscope. Br J Ophthalmol 1995;79:407–412.

48 Schmitz-Valckenberg S, Jorzik J, Unnebrink K, Holz FG: Analysis of digital scanning laser ophthalmoscopy fundus autofluorescence images of geographic atrophy in advanced age-related macular degeneration. Graefes Arch Clin Exp Ophthalmol 2002;240:73–78.

49 Deckert A, Schmitz-Valckenberg S, Jorzik J, Bindewald A, Holz FG, Mansmann U: Automated analysis of digital fundus autofluorescence images of geographic atrophy in advanced age-related macular degeneration using confocal scanning laser ophthalmoscopy (cSLO). BMC Ophthalmol 2005;5:8.

50 Schmitz-Valckenberg S, Brinkmann CK, Alten F, Herrmann P, Stratmann NK, Göbel AP, Fleckenstein M, Diller M, Jaffe GJ, Holz FG: Semiautomated image processing method for identification and quantification of geographic atrophy in age-related macular degeneration. Invest Ophthalmol Vis Sci 2011; 52:7640–7646.

51 Jaffe GJ, Schmitz-Valckenberg S, Boyer D, Heier J, Wolf-Schnurrbusch U, Staurenghi G, Schmidt-Erfurth U, Holz FG: Randomized trial to evaluate tandospirone in geographic atrophy secondary to age-related macular degeneration: the GATE study. Am J Ophthalmol 2015;160:1226–1234.

52 Schmitz-Valckenberg S, Sahel JA, Danis R, Fleckenstein M, Jaffe GJ, Wolf S, Pruente C, Holz FG: Natural history of geographic atrophy progression secondary to age-related macular degeneration (Geographic Atrophy Progression study). Ophthalmology 2016; 123:361–368.

53 Lindner M, Böker A, Mauschitz MM, Göbel AP, Fimmers R, Brinkmann CK, Schmitz-Valckenberg S, Schmid M, Holz FG, Fleckenstein M: Directional kinetics of geographic atrophy progression in age-related macular degeneration with foveal sparing. Ophthalmology 2015;122:1356–1365.

54 Schmitz-Valckenberg S, Fleckenstein M, Göbel AP, Hohman TC, Holz FG: Optical coherence tomography and autofluorescence findings in areas with geographic atrophy due to age-related macular degeneration. Invest Ophthalmol Vis Sci 2011;52:1–6.

55 Abdelfattah NS, Al-Sheikh M, Pitetta S, Mousa A, Sadda SR, Wykoff CC: Macular atrophy in neovascular age-related macular degeneration with monthly versus treat-and-extend ranibizumab: findings from the TREX-AMD trial. Ophthalmology 2016, Epub ahead of print.

56 Domalpally A, Danis R, Agrón E, Blodi B, Clemons T, Chew E: Evaluation of geographic atrophy from color photographs and fundus autofluorescence images: Age-Related Eye Disease Study 2 Report Number 11. Ophthalmology 2016;123:2401–2407.