The natural history of geographic atrophy, the advanced atrophic form of age-related macular degeneration

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Geographic atrophy is the advanced form of atrophic age-related macular degeneration. It is present in 3.5% of people age 75 and over in the United States. It progresses gradually over time, often sparing the fovea until late in the course of the disease. Forty to fifty percent of eyes with geographic atrophy and good visual acuity at baseline lose three or more lines of acuity by two years and 27% become worse than 20/200 by four years. This article discusses the information known about age-related geographic atrophy at the present time.

INTRODUCTION

Geographic atrophy (GA) of the retinal pigment epithelium is a form of advanced age-related macular degeneration (AMD) that, with choroidal neovascularization (CNV), is responsible for both severe and moderate central visual loss. GA is the natural endstage of the atrophic AMD process when CNV does not develop [1]. It will become increasingly prevalent as the population ages. Until recently, little attention has been focused on this relatively common disorder. Most of this symposium on age-related macular degeneration discusses CNV, because it is responsible for 80% of the legal blindness from AMD [2] and because there are treatments for some forms of choroidal neovascularization. At present, there is no treatment available for GA. As our knowledge of GA, factors that may be involved in retinal pigment epithelial cell death, genetics of AMD, new delivery systems of medications, and other aspects grows, it is hoped that interventions to prevent GA or slow its progression will be found.

CLINICAL AND HISTOPATHOLOGIC DESCRIPTION, AND PATHOGENESIS

Geographic atrophy is easily diagnosed clinically. It presents as a discrete area of loss of retinal pigment epithelium associated with loss of the overlying photoreceptors. This is seen clinically as an area of decreased retinal thickness which is lighter than the surrounding retina and through which the choroidal vessels may be seen more distinctly. On fluorescein angiography, GA appears as an area of discrete hyperfluorescence, representing a transmission defect and staining.

GA often develops first in the region near the fovea, but not involving the foveal center. It progresses gradually over time, sparing the fovea until late in the course of the disease [3-7]. It may develop following the fading of drusen, or in the context of an area of retinal pigment epithelial attenuation and pigmentary change. Several small areas may develop, and these tend to enlarge and coalesce over time. This may lead to a horseshoe of atrophy surrounding, but not involving the foveal center. The horseshoe may coalesce into a ring, still sparing the fovea. Finally, the fovea becomes atrophic. Not all cases of GA evolve in this way; it is difficult to know the evolution when one sees only a single solid area of GA, as was present in 39% of Sunness’ patients at baseline [8]. Areas of GA have a dense scotoma (blind spot) [9]. Thus, in GA, the measured visual acuity, by reading a letter chart for example, is often preserved until late in the course of the disease. However, the visual impairment due to the scotomas near and surrounding fixation is significant and is more severe than measured visual acuity may indicate [10]. A patient with GA and good acuity may not be able to read or recognize faces because the word or face does not ‘fit’ into the spared central island of vision. Statistics that measure only the incidence of legal blindness significantly underestimate the visual impairment and disability associated with GA. Also, GA is bilateral in more than half of patients [4,5,11], so the condition leads to significant difficulty with visual tasks. GA may also develop following the flattening of a retinal pigment epithelial detachment [12-17].

Histopathologic examination reveals an absence of RPE in the area of GA, with a secondary loss of overlying photoreceptors [4]. The choriocapillaris may be absent. There is experimental evidence that when the RPE is absent the choriocapillaris involutes secondarily [18,19]. There is controversy as to whether GA could develop on a basis of choroidal vascular insufficiency. Green and others have argued that choroidal vascular insufficiency should cause degeneration of all the outer retinal layers, which is not seen in GA [4]. Friedman suggests that choroidal vascular resistance may be related to the development of AMD and GA [20]. GA is associated with deposits in and thickening of Bruch’s membrane [1,21].
**The Incidence of Geographic Atrophy in Eyes with Drusen**

In the Beaver Dam Eye Study, eight percent of eyes with drusen larger than 250 µm developed GA over a five-year period. All eyes that developed GA had pigmentary abnormalities and at least 0.2 Macular Photocoagulation Study (MPS) disc areas of drusen at baseline [22]. Holz found a 7.7% three-year cumulative incidence of GA in patients with bilateral drusen over 65 years of age in a retinal referral center [23].

**The Prevalence of Geographic Atrophy**

GA is present in 3.5% of people over 75 years of age in the United States and other developed nations, based on two recent population-based studies [24, 25]. This is half the prevalence of CNV. GA is relatively uncommon in blacks [26-28], as is CNV. The prevalence of GA increases with age, to 22% in the population over 90 years of age [29, 30]. Forty-two percent of eyes with GA have acuity worse than 20/200 [31]. GA is responsible for 20% of the legal blindness from AMD [2].

**Natural History**

In a prospective natural history study of GA, 50% of eyes with GA that had visual acuity better than 20/50 at baseline lost three or more lines of acuity (doubling of the visual angle) by two years and 25% lost six or more lines of acuity (quadrupling of the visual angle) by two years [10]. Risk factors for more rapid loss of vision included GA within 250 µm of the foveal center and reduced visual function in dark-adapted testing [8, 10]. Twenty-seven percent of the eyes with 20/50 or better at baseline had visual acuity of 20/200 or worse at four years [8]. Of those eyes with baseline visual acuities between 20/50 and 20/200, 20% lost three or more lines of acuity over two years.

GA continues to enlarge over time. The mean rate of enlargement over a two year period was 2.2 MPS disc areas (equivalent to 5.6 mm² on the retina) [8]. GA resulting from flattening of a retinal pigment epithelial detachment also continues to enlarge over time [8]. The rate of enlargement increases with increasing baseline size of atrophy up to about five MPS disc areas, after which the rate plateaus. There is evidence that reading rate is inversely related to the size of the atrophy when the fovea is already involved [32], so that an intervention that could slow the rate of enlargement of atrophy could have a significant positive impact on visual function even when a central scotoma is present.

In patients with bilateral GA, the size of the GA is very symmetrical between eyes and often the configuration of the atrophy is symmetrical [8]. However, the acuities may often be disparate, because one eye has an area of foveal sparing with good acuity while the fellow eye has no sparing and poor acuity [8].

**The Relationship between Geographic Atrophy and Choroidal Neovascularization**

GA and CNV are both advanced stages of age-related macular degeneration. The GA discussed herein develops without evidence of the presence of CNV at any time during the course. But geographic atrophy can also develop following involu-
### Risk Factors for Developing Geographic Atrophy in Eyes with Drusen

As noted above, the presence of drusen larger than 250 μm and pigmentary abnormalities are risk factors for the development of GA. Within the group of patients with high risk drusen, other risk factors that have been identified include delayed chorioidal filling on fluorescein angiography [47,48] and diminished foveal dark-adapted sensitivity [49].

### Genetics

There is no doubt that there is a significant genetic component to AMD and to GA. GA has been found to be present in families with drusen and with CNV, and AMD has been found more commonly in monozygotic twins [50,51]. Dystrophies such as Zermatt’s macular dystrophy (associated with a dominant mutation of the RDS/peripherin gene) have been identified which resemble GA [52]. Mutations of the ABCR gene have been associated with atrophic AMD [53,54]; these studies are being replicated.

### Conditions Resembling Geographic Atrophy

There are a number of conditions resembling GA. These are presented at somewhat greater length elsewhere [55]. Within the spectrum of AMD, involved CNV, laser scars, and RPE rips can mimic GA. Patients with pattern dystrophy and vitelliform dystrophy may develop geographic atrophy [56]. Central areolar chorioidal sclerosis is a hereditary condition that causes areas of chorioretinal atrophy similar to GA but occurring at a younger age. Other causes of central and ring scotomas include Stargardt disease, cone dystrophy, North Carolina macular dystrophies, other macular and retinal dystrophies, and toxic maculopathies [57].

### Some Unanswered Questions Regarding Geographic Atrophy

There are a number of intriguing questions in terms of the pathogenesis and course of GA, including:

- What is the primary cause of GA?
- What is responsible for the death of the RPE cells?
- What is responsible for foveal sparing until late in the course of the disease?
- What is responsible for dark adaptation abnormalities of both rods and cones?
- Why is there a need for markedly increased illumination?

### Possible Treatments for Geographic Atrophy

While there is currently no treatment to prevent GA or to slow its progression, there are several avenues of interest regarding possible treatments for GA.

Within the general notion of treating AMD, vitamins and minerals are being studied. There is no clear evidence at present of benefit of nutritional supplementation for GA. The National Institutes of Health-funded Age-Related Eye Disease Study, for example, is looking at whether vitamins or minerals affect the development of AMD.

Retinal pigment epithelial transplantation for GA is being attempted [58,59]. The ultimate goal would be to replace the senescent RPE with new RPE thus preserving photoreceptor function, but this is not achievable at the present time. A more limited goal is to determine whether transplanted RPE can produce a factor necessary for RPE survival, or inhibit a toxic influence, and thereby slow down or stop the progression of GA. Attempts at transplantation have been complicated by rejection of the transplanted cells [59]. Peripheral RPE may be tried, but many patients with GA have peripheral reticular degeneration of the RPE [8,60], evidence that the noncentral RPE is also not healthy.

As more is learned about growth factors and proteins expressed by the RPE, there will be attempts to replace missing factors.

### Conclusion

GA is an important cause of visual loss from AMD. It is a degenerative process that progresses gradually over time. There is a large window of opportunity for introducing a potential treatment that could preserve a patient’s vision at a mild to moderate level of impairment even after the disease has already begun. It is hoped that over time, more will be learned about GA, its prevention, management (both medical and low vision), and treatment.

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### References

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