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Geographic atrophy: Mechanism of disease, pathophysiology, and role of the complement system

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Abstract

Geographic atrophy (GA) is an advanced form of age-related macular degeneration (AMD), characterized by atrophic lesions that first start in the outer retina and progressively expand to cover the macula and the fovea, the center of the macula, leading to irreversible loss of vision over time. GA is distinct from wet or neovascular AMD (nAMD), the other form of advanced AMD. Neovascular AMD is characterized by new invading leaky blood vessels in the macula that can lead to acute vision loss. GA and nAMD may coexist in the same eye.

The underlying pathophysiology of GA is complex and thought to involve chronic inflammation due to overactivation of the complement system that leads to the loss of photoreceptors, retinal pigment epithelium (RPE), and the underlying choriocapillaris. The disappearance of these structures appears as sharply demarcated atrophic lesions that are typical of GA.

Researchers have reported about 1 million reported cases of GA in the United States, and about 160,000 cases occur per year. The most important risk factors for GA are increasing age and family history.

Diagnosis of GA is usually made by using multimodal imaging techniques. Lesions associated with GA are highly heterogeneous, and the growth rate may differ from patient to patient. Despite the progressive nature of GA, the fovea may be spared until much later in the disease, thereby retaining central vision in patients. With time, atrophic lesions may progressively grow to involve the fovea, thereby severely impairing central vision. Vision loss can happen rapidly once lesions reach the fovea. However, even with out the involvement of the fovea, ongoing vision impairment impacting daily life may be present. Median time from GA not involving the center of the fovea (without subfoveal involvement) to GA with lesion boundary affecting the foveal center (subfoveal involvement) ranges from 1.4 to 2.5 years.

GA can greatly impact patients' functioning and quality of life and limit their independence by interfering with activities of daily living, including difficulties with reading, driving, watching television, recognizing faces, and being unable to do household chores.

No treatments have been available until intravitreal pegcetacoplan was recently approved by the US Food and Drug Administration for GA secondary to AMD.

Overview of GA

Age-related macular degeneration (AMD) has 3 distinct stages: early, intermediate, and advanced.[1] Within the advanced stage, there are 2 distinct forms: wet or neovascular AMD (nAMD) and dry AMD.[2,3] Geographic atrophy (GA) is the progressive, irreversible, advanced form of dry AMD.[4] Although the advanced form of wet AMD/nAMD is characterized by abnormal blood vessels leaking blood or other fluids into the macula, GA is characterized by atrophic lesions in the outer retina.[5,6] Although nAMD is characterized by acute vision loss, GA is a progressive disease that can lead to irreversible central blindness over time.[7] Median time to progression to legal blindness has been estimated to be 6.2 years (interquartile range [IQR] = 3.3–8.5 years).[8] Neovascular AMD can be treated with anti–vascular endothelial growth factor (VEGF) therapies to stop the leakage from blood vessels,[9] and only intravitreal pegcetacoplan, recently US Food and Drug Administration (FDA) approved, can be used to treat GA secondary to AMD.[9]

The prevalence of GA in the United States is estimated to be about 1 million people,[10] with 160,000 new cases occurring each year in the United States.[11] The average age of a patient with GA is 79 years.[12] From age 50 years, prevalence quadruples every 10 years, from 0.16% at 60 years to 2.91% at 80 years of age.[13] The incidence of GA is projected to increase in the coming decades because of an increase in the aging population.[14]

Several risk factors have been associated with GA, whereby age and family history have the strongest correlation. Smoking and genetic mutations in the complement system are additional risk factors.

Mechanism of Disease/Pathophysiology

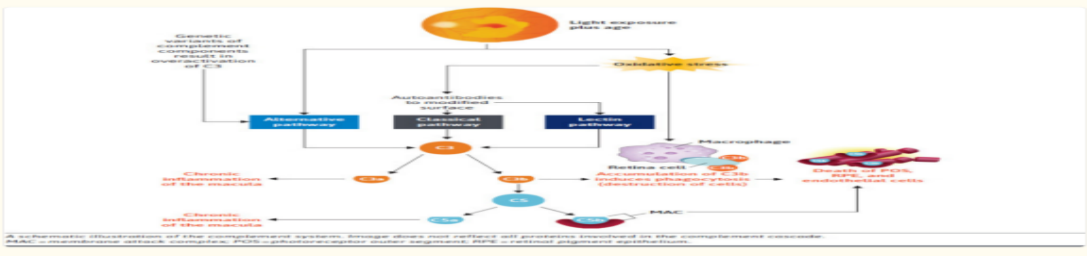
With aging, the retinal pigment epithelium (RPE) is exposed to intrinsic and extrinsic oxidative stressors as well as environmental stressors such as cigarette smoke. Oxidative damage accumulates, resulting in the formation of drusen, yellow deposits of lipids between the RPE and Bruch's membrane (early to intermediate AMD). The appearance and progression of drusen deposits are prognostic features of GA.[4] Excessive drusen accumulation and components of drusen, such as cellular debris, lipids, and lipoproteins, may trigger chronic inflammation via multiple pathways, including the complement cascade.[4] Chronic inflammation can eventually lead to photoreceptor, RPE, and choriocapillaris cell death, causing the appearance of sharply defined atrophic lesions, visually resembling geographic areas on a map, that are characteristic of GA and the appearance of choroidal vessels due to the missing RPE layer.

Role of Complement in GA

Genome-wide association studies have found genetic variants of factors of the complement pathway to be associated with increased risk of AMD. A genetic variant in the complement C3 gene was found to be associated with AMD, including GA.[4,15] Overactivation of the complement system is strongly associated with lesion development and progression in GA. In particular, it is associated with the loss of photoreceptors, RPE, and choriocapillaris.[4,16] Photoreceptors are specialized sensory cells that convert light into electrical impulse.[17] The outer segment of the photoreceptors is connected to the RPE, which is a single cell layer in the outer layers of the retina that plays a critical role in the maintenance and survival of the photoreceptor cells, in clearing cellular debris, and in regulating the integrity of the choroidal capillaries.[18,19] Choriocapillaris supplies blood to the outer layer of the retina and nourishes the retinal nerve cells.[18] When functioning normally, the complement system is an important part of the body's natural immune response. Under steady-state conditions, complement proteins are deployed to rapidly respond to microbes and stress signals. However, overactivation or loss of regulation of this host response can have detrimental consequences by perpetuating a vicious cycle of tissue injury and inflammation. Complement activity is found in both GA lesions and areas just outside the lesion. In areas outside the lesion, complement activation may accelerate cell damage, thereby increasing the risk of lesion growth.

In the complement system, the complement protein C3 plays a central role in driving the downstream damaging effects of complement overactivation and progression of GA for the following reasons[20] (Figure 1):

FIGURE 1.



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