Pattern Dystrophy

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Abbreviations

AMD	Age-related macular degeneration
AOVPD	Adult onset vitelliform pattern dystrophy
BPD	Butterfly-shaped pattern dystrophy
CNV	Choroidal neovascularization
EOG	Electrooculography
ERG	Electroretinogram
FA	Fluorescein angiogram
FAF	Fundus autofluorescence
OCT	Optical coherence tomography
ONL	Outer nuclear layer
PD	Pattern dystrophy
RPE	Retinal pigment epithelium
SD-OCT	Spectral domain optical coherence tomography

Introduction

Pattern dystrophy (PD) refers to a group of inherited retinal dystrophies with changes primarily at the level of the retinal pigment epithelium (RPE). The typical features include deposits of yellow, orange, or gray pigment in the macula, associated with mild to moderate visual disturbance. Depending on the pattern of pigment disposition, five subtypes have been described by Gass:

1. Butterfly-shaped pigment dystrophy (Deutman et al. 1970)
2. Adult onset vitelliform pattern dystrophy (peculiar foveomacular dystrophy) (Gass 1974; Epstein and Rabb 1980)
3. Sjogren reticular dystrophy of the RPE (Sjogren 1950)
4. Fundus pulverulentus (Slezak and Hommer 1969)
5. Multifocal pattern dystrophy simulating Stargardt disease

Etiopathogenesis

PDs are most commonly inherited in an autosomal dominant manner. Mutations in peripherin/*RDS* gene (now known as *PRPH2)* have been found to be the most common (Pajic et al. 2006). *PRPH2* encodes for peripherin, a protein with four transmembrane domains that is important for photoreceptor outer receptor function. *PRPH2* assembles into homotetramers and locates in the rim regions of the rhodopsin-containing disk/lamellae of the photoreceptor outer segments, where its putative function is to maintain stability. *PHRP2* also forms heterotetramers with another tetraspanin known as the highly homologous rod outer segment 1 (ROM1) protein (Khan et al. 2016). In disease states, the outer segments become disorganized or fail to form entirely, and the photoreceptors subsequently degenerate (Stuck et al. 2016).

In PDs, the primary defect is presumed to be present in photoreceptor cells, with subsequent damage to RPE and choriocapillaris.

Dominant *PRPH2* mutations have been associated with a variety of retinal phenotypes typically of adult onset and often affect the macula. Phenotypes other than PD include cone-rod dystrophy, retinitis punctata albescens, central areolar choroidal dystrophy, retinitis pigmentosa, fundus

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flavimaculatus, age-related macular degeneration-like late onset maculopathy, and other unspecified autosomal dominant macular dystrophies.

Variable expressivity is also common in *PHRP2* mutations. If one or more of the abovementioned phenotype is present in a family, heterozygous mutations should be suspected.

Clinical Features

Patients commonly present in middle age with disturbance in central vision and may experience macular photostress. The fundus may show a variety of yellow, orange, or gray deposit in the macula. When patients present in advanced age, atrophy of the RPE-photoreceptor complex may develop and result in more severe visual loss. In such cases, pattern dystrophy can be confused with age-related macular degeneration (AMD). Some important differentiating factors include the lack of drusen and high level of symmetry in PD. Rarely, choroidal neovascularization (CNV) can complicate pattern dystrophy (Battaglia Parodi et al. 2003; Marano et al. 1996).

Butterfly-Shaped Pattern Dystrophy (BPD)

The butterfly-shaped pigmentation can be yellow, white, or black. The accumulation of pigment resembles the wings of a butterfly. Generally, the onset of visual symptoms is in the 20s or 30s (Figs. 5.1 and 5.2).

Adult Onset Vitelliform Pattern Dystrophy (AOVPD)

In AOVPD, there are typically symmetric yellowish subretinal lesions at the fovea, or presence of flecks. The vitelliform lesion may be confused with the later stages of Best disease. The yellow foveal lesions may develop a central gray or orange clump of pigment. Later, the foveal lesions may fade, leaving an area of RPE depigmentation (Fig. 5.3).

Sjogren Reticular Dystrophy of the RPE

In reticular dystrophy of the RPE, a network of pigmented lines can be seen in the macula which resembles fishnet with knots or chicken wire. With increasing age, most lesions fade and become replaced by atrophic changes in the RPE. In advanced disease, the network becomes bleached and irregular and small white dots appear in the RPE (Fig. 5.4).

Fundus Pulverulentus

This is the rarest form of PD. Patients typically have mild visual loss associated with prominent, coarse, punctiform mottling of the RPE in the central macula. Some cases are associated with pseudoxanthoma elasticum.

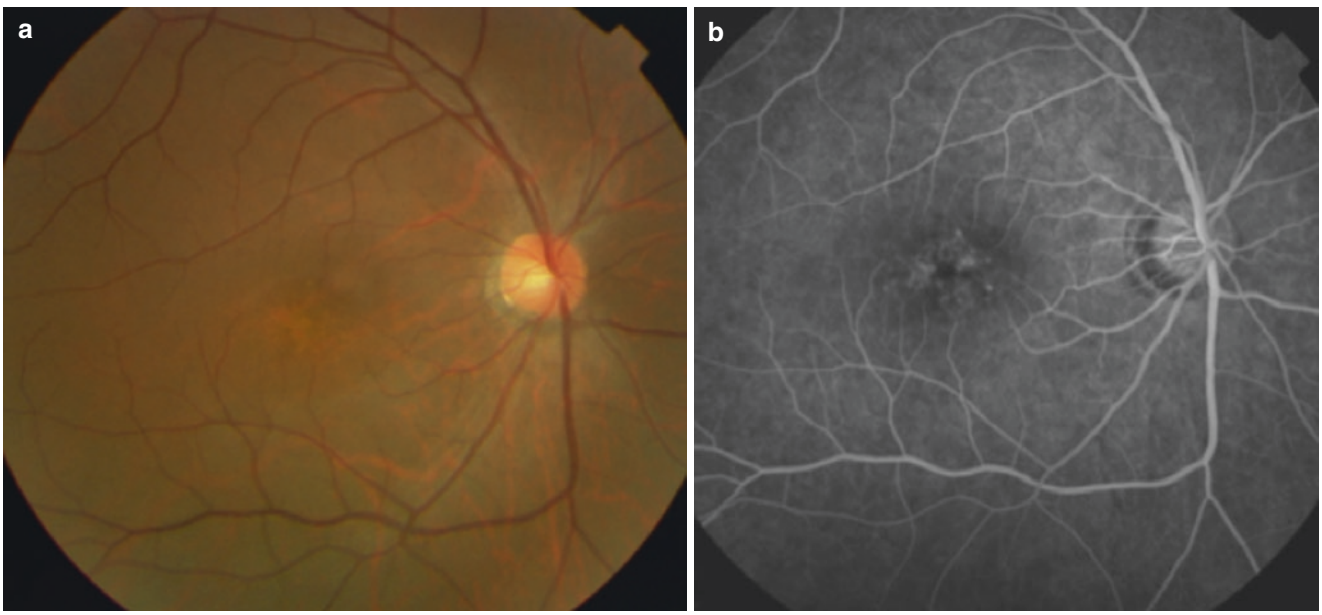


Fig. 5.1 A 40-year-old male with right decreased vision for 3 months. Visual acuity (VA) 6/24 OD (**a**) Color fundus photograph showing yellowish pigment deposition in a shape resembling wings of a butterfly. (**b**) Fluorescein angiogram (FA) showing areas of blocked fluorescence corresponding to the "wings"

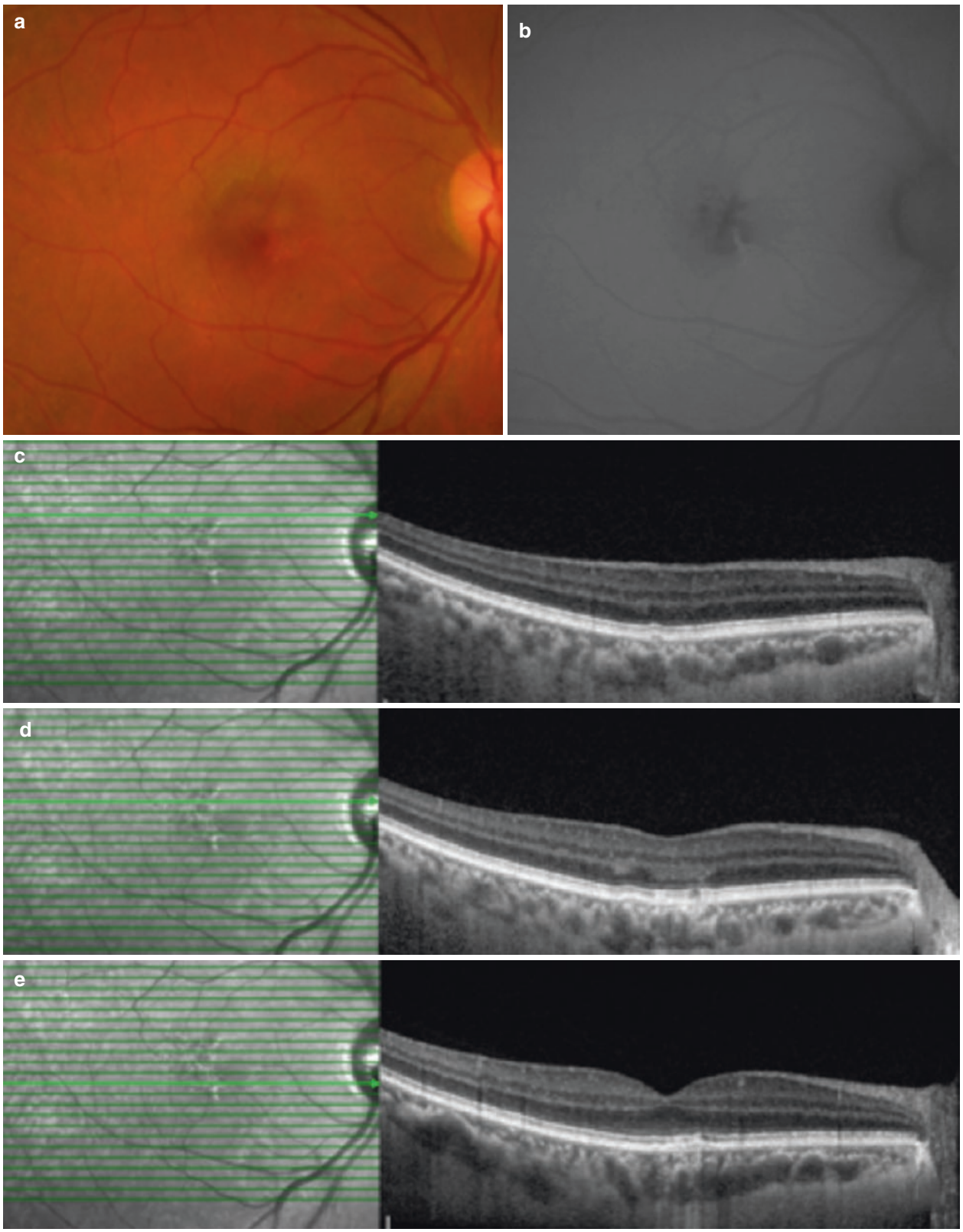


Fig. 5.2 A 50-year-old male with BPD presenting with mild reduced vision. VA 6/9 OD. (**a**) Color fundus photograph showing pigment deposition. (**b**) Fundus autofluorescence (FAF) imaged using a fundus camera showing areas of hyper/hypoautofluorescence corresponding to the pattern of lipofuscin deposition. (**c**–**e**) Series of spectral domain optical coherence tomography (SD-OCT) showing irregular RPE corresponding to area of hyperautofluorescence likely due to pigment clumping (**e**). The areas of hypoautofluorescence correspond to areas of ellipsoid zone and RPE disruption (**c**, **d**)

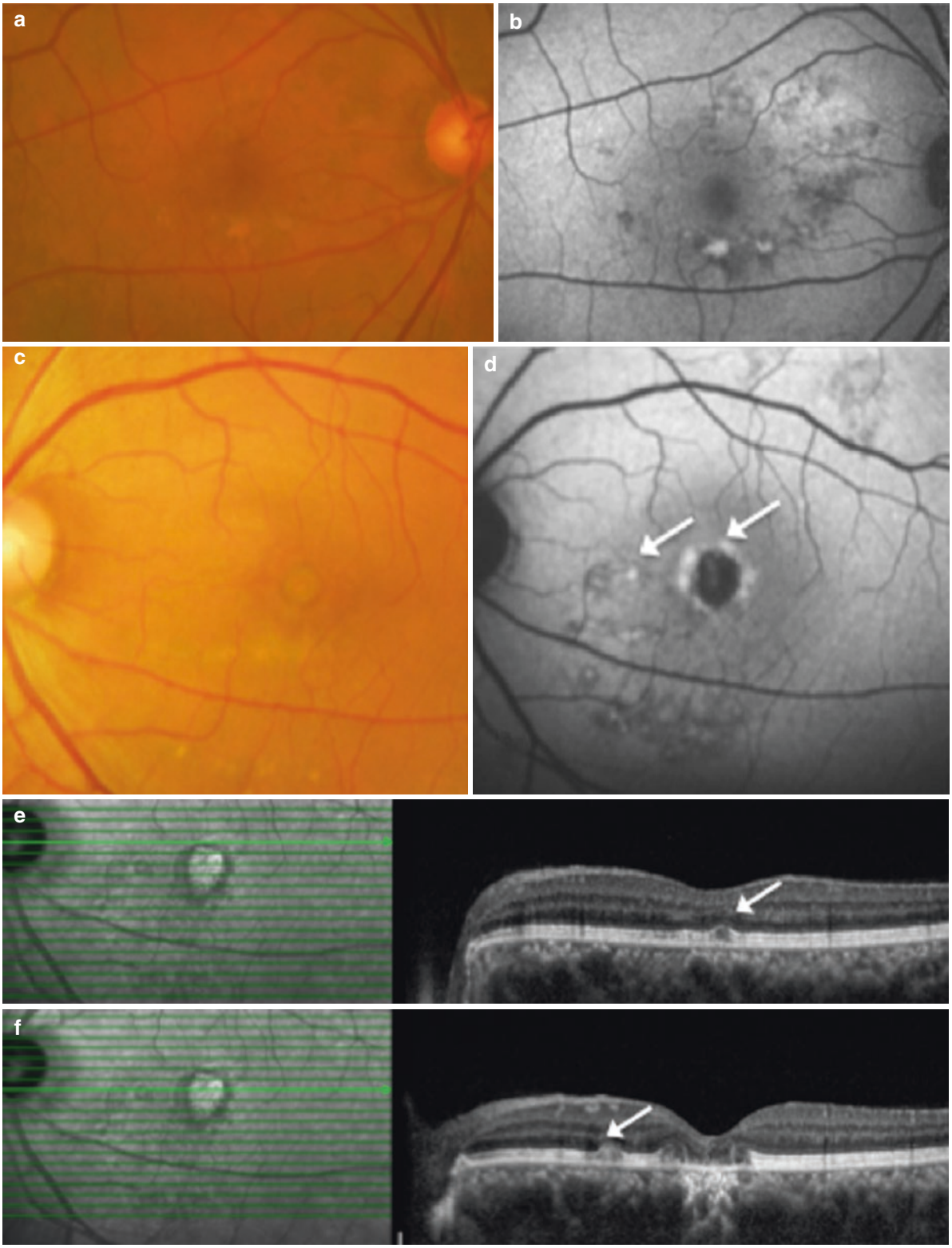


Fig. 5.3 A 43-year-old male with AOVPD presented with reduced left eye vision for 1 year. VA 6/18 OS. (**a**) Multifocal yellowish subretinal deposits surrounded by grayish pigmentary changes. (**b**) FAF shows these areas have hyperautofluorescent cores corresponding to yellow deposits. This is surrounded by hypoautofluorescent areas which are more obvious on FAF compared to color fundus photographs. (**c**, **d**) Later stage of AOFVD with a well-circumscribed yellowish foveal atrophic lesion which appears hypoautofluorescent on FAF. This lesion may be confused with an area of geographic atrophy in age-related macular degeneration. However, the surrounding fleck-like lesions which appear hyperautofluorescent should raise the suspicion that this may be a case of AOFVD. (**e**, **f**) Series of SD-OCT images showing loss of ellipsoid zone, disruption of outer retina, and RPE layer in the fovea area. However, there are areas of possibly early vitelliform lesions (white arrows) which correspond to hyperautofluorescent areas on 3D

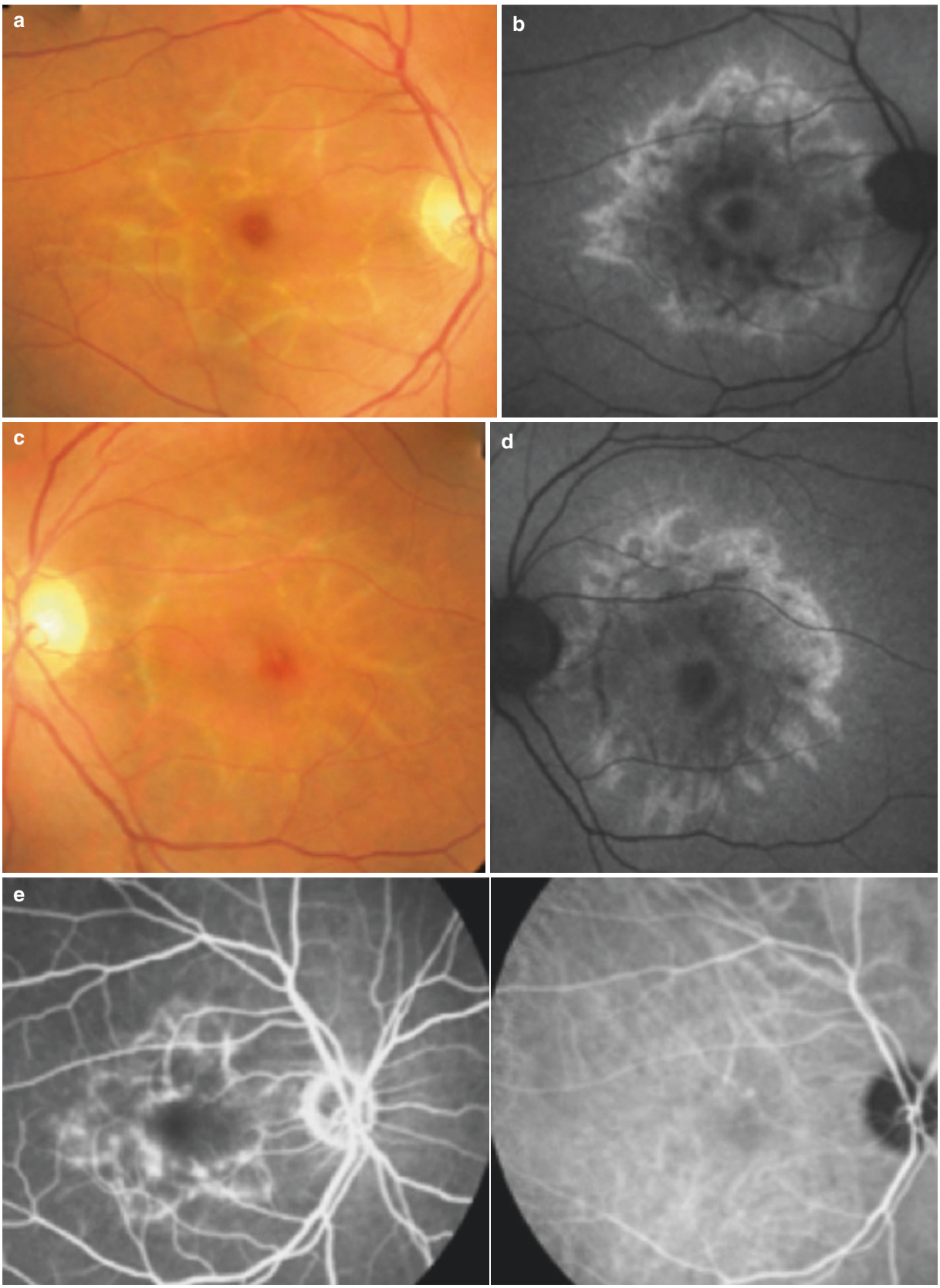


Fig. 5.4 A 56-year-old female who was referred for evaluation of retinal lesions. VA of 6/15 OD and 6/30 OS (proven *RDS* gene mutation). (**a**, **c**) Color fundus photographs showing a prominent reticular network of pale linear lesions at the macula. (**b**, **d**) On FAF, the linear structures appear hypoautofluorescent. However, a wider hyperautofluorescent ring can be seen encompassing the abnormal area. (**e**) The linear structures appear as hyperfluorescent window defects on FA which suggests there is RPE atrophy. The indocyanine green angiogram was unremarkable. (**f**, **g**) SD-OCT shows widespread disruption of the outer retinal layers

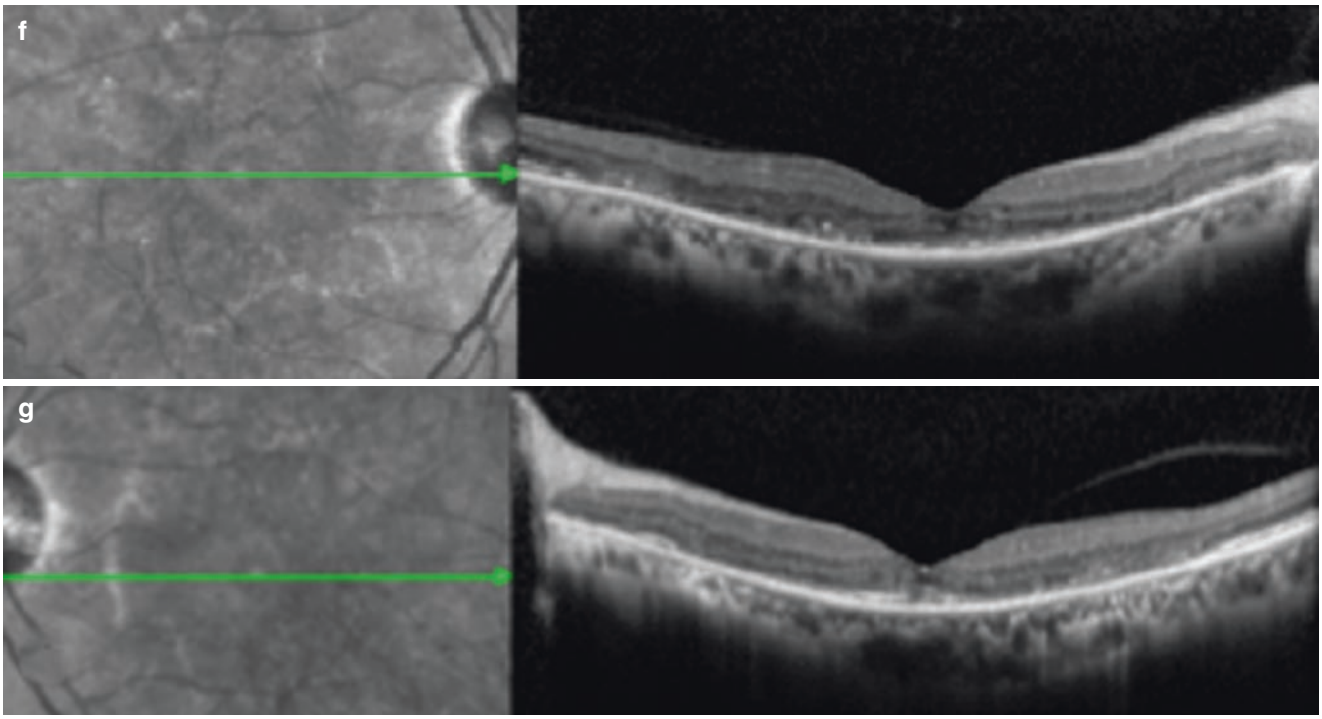


Fig. 5.4 (continued)

Multifocal Pattern Dystrophy Simulating Fundus Flavimaculatus

Occasionally, multifocal pattern dystrophy may also simulate other inherited retinal diseases such as Stargardt disease (Boon et al. 2007). Secondary CNV formation is a possible but rare sequelae of pattern dystrophy (Fig. 5.5). FA in these cases will not show a dark choroid which suggests lipofuscin deposition.

Investigations

On fundus autofluorescence (FAF), lesions in BPD may show increased as well as decreased autofluorescence, with corresponding changes in RPE lipofuscin within the lesion (Boon et al. 2008). The flecks in multifocal pattern dystrophy simulating Stargardt disease exhibit highly increased autofluorescence, with small adjacent zones of decreased autofluorescence. In AOVPD, various autofluorescence patterns described include normal, focal, patchy, ring-like, and linear with inconsistent correlation with visual acuity (Furino et al. 2008; Parodi et al. 2008).

OCT imaging in pattern dystrophy shows a variety of changes (Hannan et al. 2013; Kumar and Kumawat 2018). Features include hyper-reflectivity between the retinal pigment epithelium (RPE)/Bruch's complex and the ellipsoid zone. Ellipsoid zone and outer retinal layer disruption can also be observed. Abnormal focal hyper-reflectivity originating from the RPE toward the outer nuclear layer (ONL) may also be seen.

On FA, a butterfly-shaped defect can be more clearly seen especially when lesions are not clinically obvious. The lesion appears as blocked fluorescence due to pigment deposition, surround by hyperfluoresence (Tuppurainen and Mäntyjärvi 1994). The FA defects are also often more widespread and better manifested than color photographs.

Full-field electroretinogram (ERG) typically shows normal cone and rod amplitudes and implicit times. Some reduction may be seen if there are more extensive changes. EOG light peak to dark trough ratios are frequently normal and only modestly subnormal, in contrast to Best vitelliform macular dystrophy.

Electrophysiology is usually performed for patients with lack of mutations in *PRPH2*, or a fundus appearance which is apparent for more widespread involvement of the photoreceptors.

Management and Prognosis

Most patients with PD retain reasonable vision. Patients should be reassured that the prognosis of maintaining good central vision in one eye until late adulthood is good.

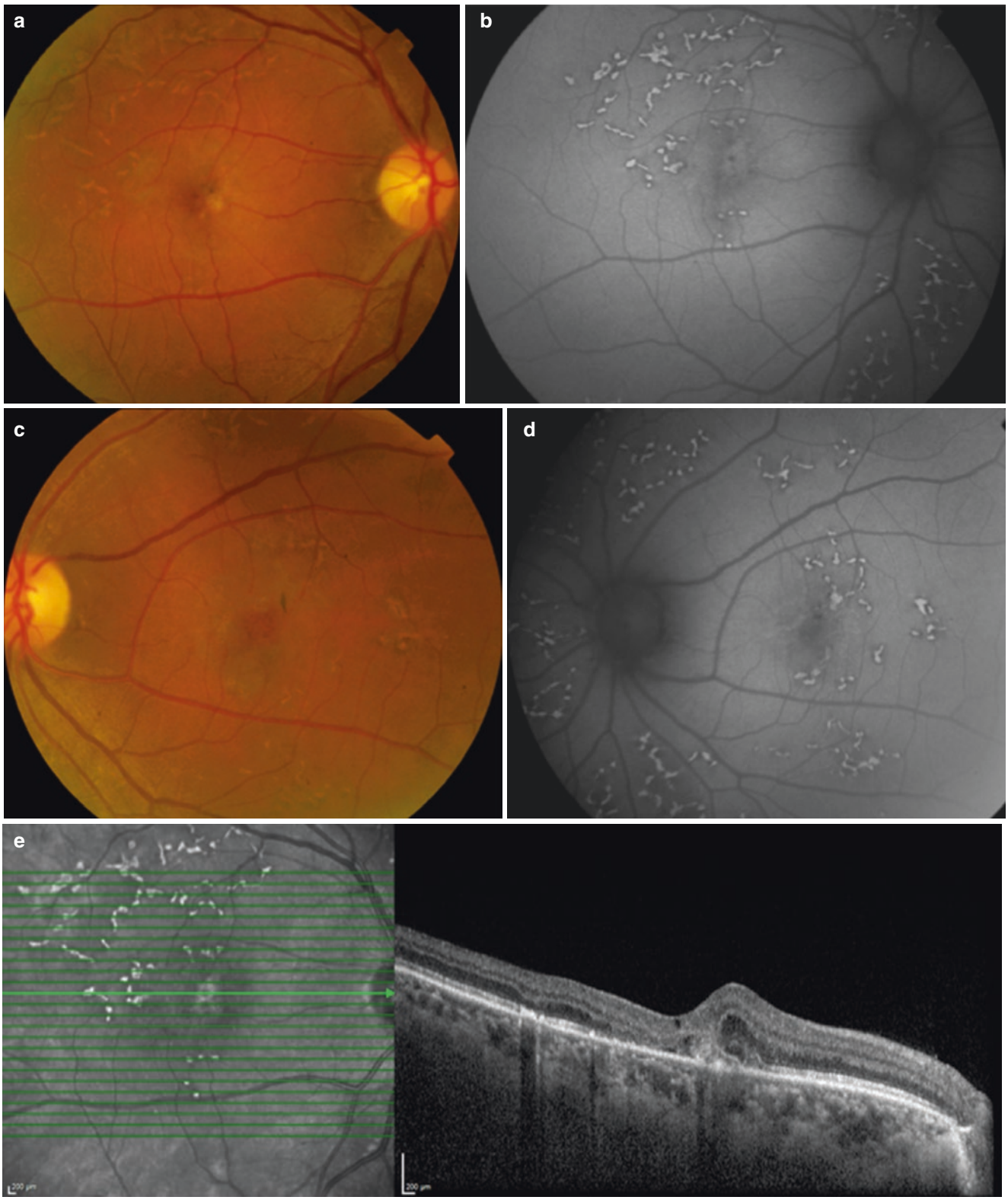
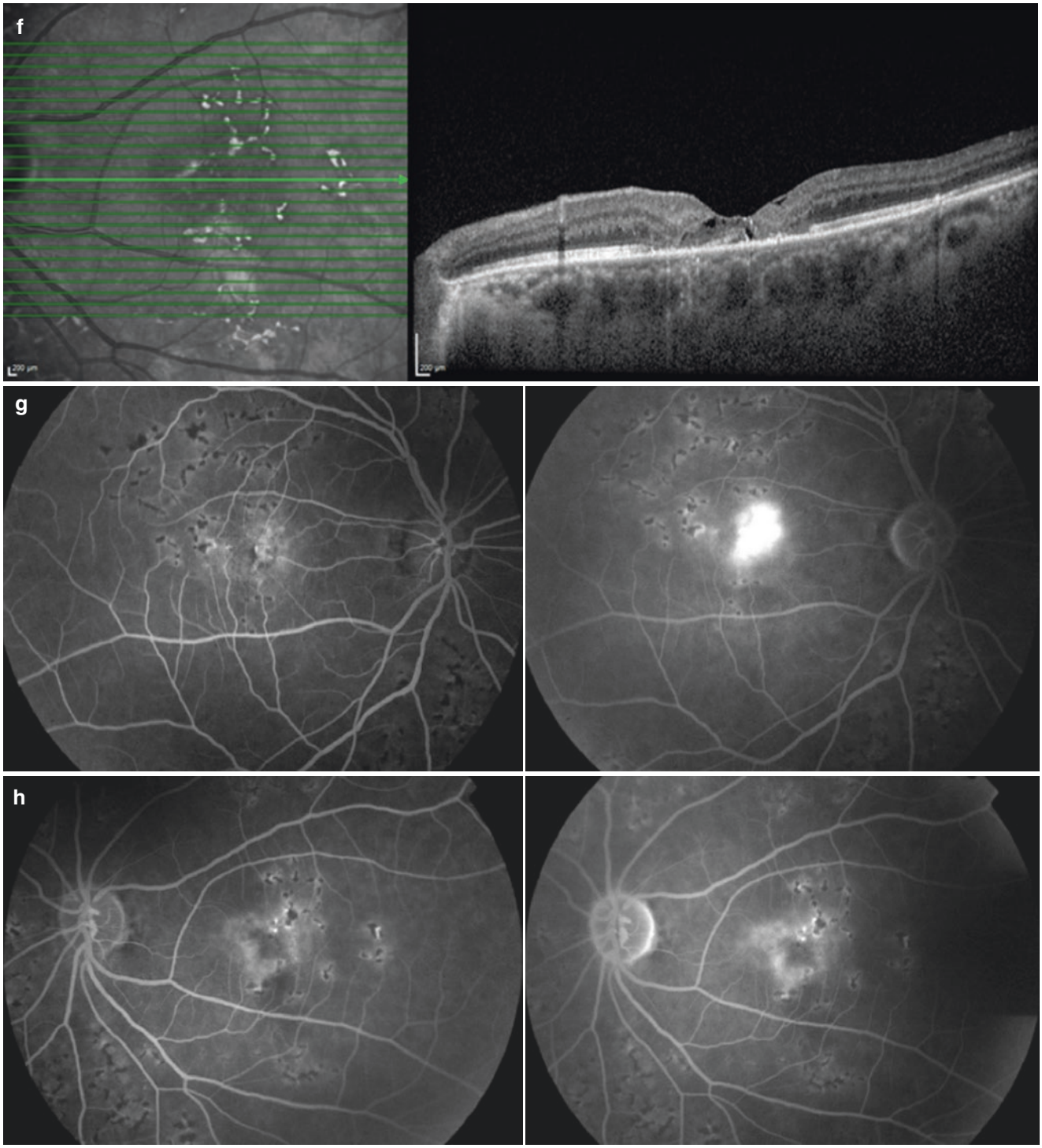


Fig. 5.5 (**a**, **c**) Color fundus photographs showing bilateral macula atrophic changes with yellowish fleck deposition. (**b**, **d**) Fundus AF showing hyperfluorescent areas corresponding to flecks. (**e**, **f**) SD-OCT shows loss of outer retina in both eyes. Retinal edema can be seen in the right resulting from a secondary CNV. (**g**) Early and late phase FA of the right eye demonstrating leakage from CNV. (**h**) FA of left eye showed no leakage. (**i**) Five years after presentation, in addition to yellowish flecks, RPE hyperplasia is seen temporal to the fovea. (**j**) Fundus AF showing hyperfluorescent areas corresponding to flecks and hypofluorescent areas at the fovea corresponding to area of RPE hyperplasia. (**k**) SD-OCT shows a hyperreflective lesion corresponding to a CNV scar. (**l**) Color fundus photograph showing RPE hyperplasia, in addition to flecks. (**m**) Fundus AF showing hypofluorescent area corresponding to area of RPE hyperplasia. (**n**) SD-OCT shows loss of outer retina in the left eye



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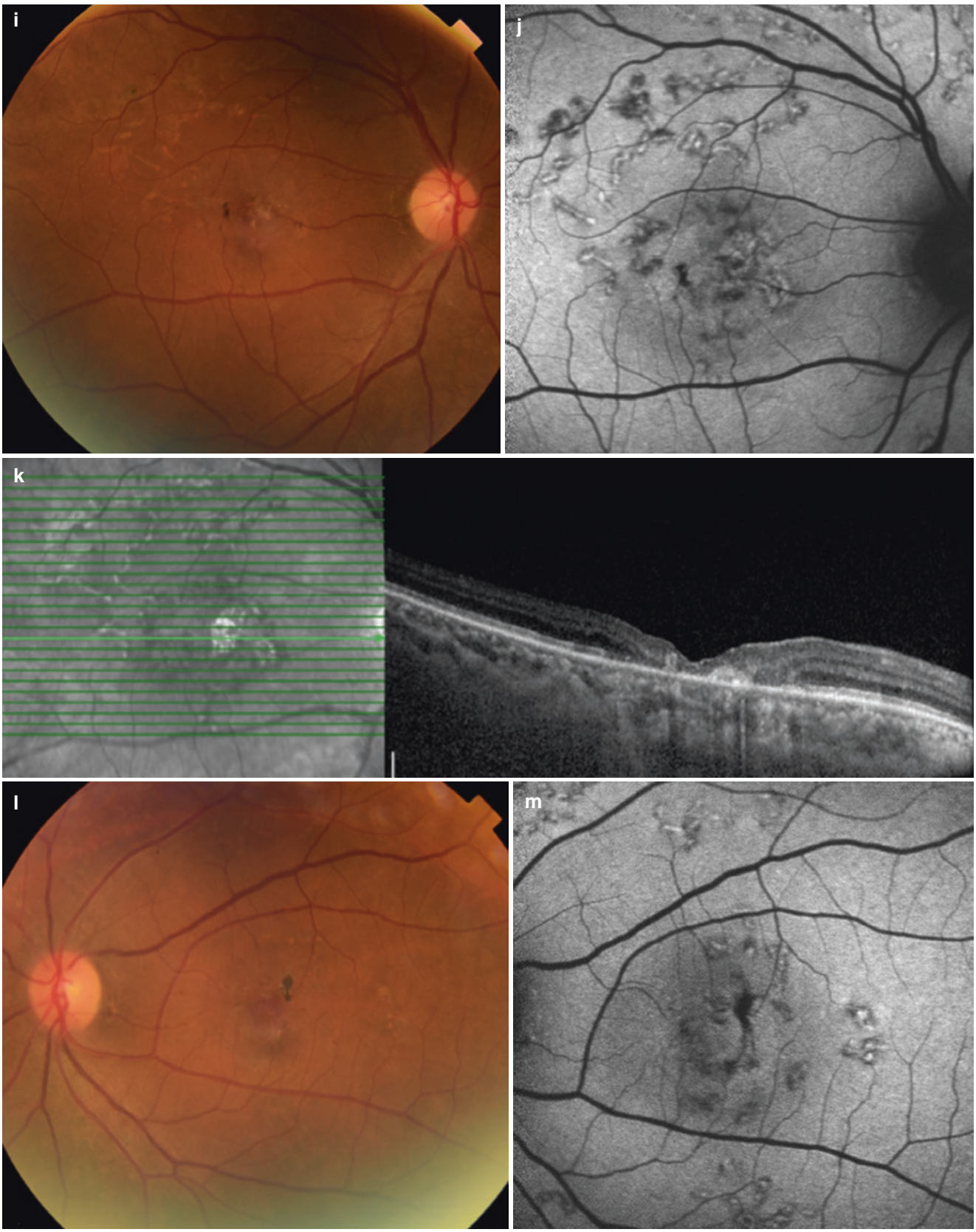

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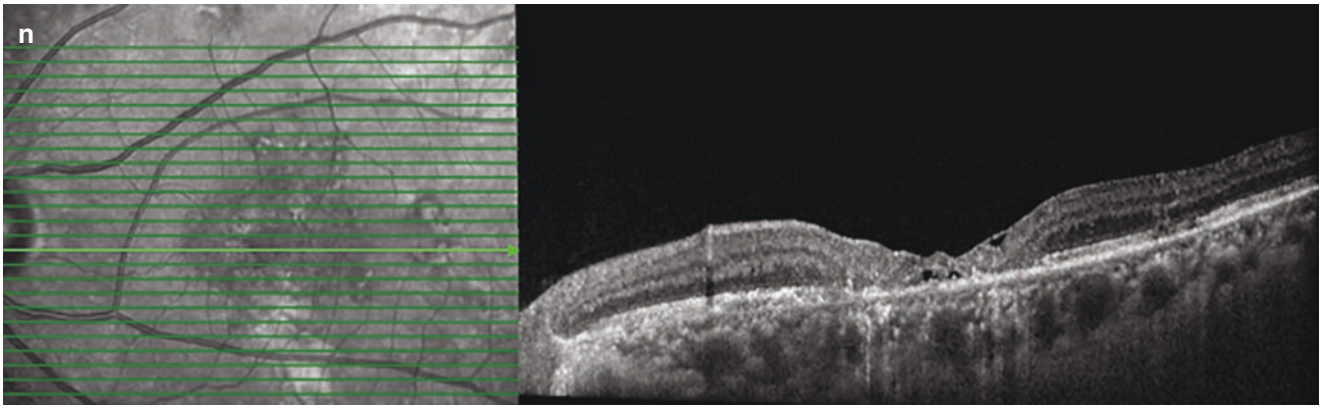

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In patients who experience difficulty in adapting when moving from a bright light into a dark area, the use of dark glasses when outside may help with symptoms. If CNV develops, anti-vascular endothelial growth factor injections are indicated. However, all patients should also be counseled regarding potential gradual visual deterioration in the long-term and potential implications on driving. It has been reported that about 50% of patients with PD eventually develop geographic atrophy or CNV (Francis et al. 2005).

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