CASE REPORT

Case Series: Multimodal Imaging Reveals the Spectrum of Pattern Dystrophies of the Retinal Pigment Epithelium

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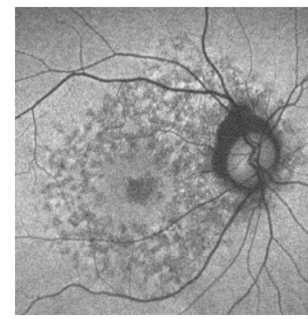
SIGNIFICANCE: Pattern dystrophies of the retinal pigment epithelium, often misdiagnosed as other macular conditions, were once considered a rare retinal disease. However, an increasing number of cases have recently been discovered owing to advancements in multimodal imaging and increased awareness of the condition.

PURPOSE: The purposes of this study were to increase awareness of pattern dystrophies and to review how to accurately diagnose and manage pattern dystrophies by understanding their presentation on fundus autofluorescence, optical coherence tomography, and electrodiagnostic testing.

CASE SERIES: Three cases of patients diagnosed as having pattern dystrophies are reported. In case 1, fundus autofluorescence, optical coherence tomography, and electrodiagnostic testing aid in diagnosing multifocal pattern dystrophy. The same tools are used to diagnose adult-onset foveomacular vitelliform dystrophy in case 2 and reticular pattern dystrophy in case 3.

CONCLUSIONS: Fundus autofluorescence, optical coherence tomography, and electrodiagnostic testing facilitate the proper diagnosis of patients with pattern dystrophies. With increased awareness of pattern dystrophies and increased use of multimodal imaging, pattern dystrophies will likely no longer be considered rare.



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Pattern dystrophies encompass a group of heterogeneous diseases affecting the retinal pigment epithelium. There are five pattern dystrophies, including the following: adult-onset foveomacular vitelliform dystrophy, butterfly, multifocal, reticular, and fundus pulverulentus. Each presents with a specific pattern in the posterior pole, which is a result of excess lipofuscin in areas of retinal pigment epithelial stress.[1,2] Abnormal accumulation of lipofuscin is the hallmark of pattern dystrophies.[1,3] Adult-onset foveomacular vitelliform dystrophy is the most commonly reported pattern dystrophy in the literature,[3] whereas fundus pulverulentus is considered the rarest, with very few cases reported. Agarwal et al.[4] describe cases where patients with fundus pulverulentus progressed to other pattern dystrophies, leading to speculation if it is truly its own disease entity or a variant or precursor of the other four.

As implied by the name *dystrophy*, there is a genetic component to this disease. However, most patients with pattern dystrophies do not have a gene mutation identified.[5,6] This raises the question of whether the disease is truly a dystrophy or actually just a type of degeneration.[3] On the other hand, many patients present with bilateral and symmetrical retinal findings,[1] supporting that it is indeed a dystrophy with underlying genetic influence. Of the patients who do have a gene mutation identified, an autosomal dominant *PRPH2* gene mutation is most common.[5] Other recently identified gene mutations associated are the *IMPG1*, *IMPG2*, *CTNNA1*, and *OTX2* genes.[6]

Because most pattern dystrophies do not have identifiable gene mutations and because one genotype does not correlate with one specific phenotype (and vice versa), genetic testing does not provide a concrete diagnosis. Instead, pattern dystrophies remain a clinical diagnosis. Diagnoses are made using clinical examination and multimodal imaging, including fundus autofluorescence and optical coherence tomography. Electrodiagnostic testing also helps rule out other retinal diseases.[5]

Fundus autofluorescence is a fundus photography that uses a unique filter, typically excitation of 488 nm, which highlights areas of lipofuscin.[7] Areas that hyperfluoresce are areas of the retina with excess lipofuscin, corresponding to stressed or diseased retinal pigment epithelium. Areas that hypofluoresce are areas that do not have any lipofuscin production because of an underlying nonfunctioning, atrophic retinal pigment epithelium. Because lipofuscin is the hallmark of pattern dystrophies and fundus autofluorescence highlights lipofuscin, this instrument is key in diagnosing pattern dystrophies.[1,8]

Optical coherence tomography is used to localize the lesion within the layers of the retina. In pattern dystrophies, excess lipofuscin is produced by the stressed retinal pigment epithelium. This lipofuscin lies above the retinal pigment epithelium and under the photoreceptors in the interdigitation zone. As lipofuscin accumulates, it can extend into the inner retina toward the junction between the photoreceptor inner and outer segments, termed the *ellipsoid zone*.[9] On optical coherence tomography, the lipofuscin from pattern dystrophies presents itself as hyperreflectivity above the retinal pigment epithelium, sometimes extending upward through the ellipsoid zone. This zone is an important landmark because there is a direct correlation between the integrity of this line under the macula and the preservation of visual acuity.[1–3,8,10]

Electrodiagnostic testing aids the diagnosis by ruling out other hereditary retinal diseases. Electrooculography tests the overall function of the retinal pigment epithelium by comparing the maximal light with minimal dark response. This comparison, termed the *Arden ratio*, has a reference value of 1.8 or greater. Electroretinography tests the

overall function of the photoreceptors, bipolar cells, and Müller cells. Pattern dystrophies are localized retinal diseases; most of the retina still maintains good health and function. Therefore, patients with pattern dystrophies typically have normal electrooculography and flash electroretinography results. There are reports of patients who have a subnormal electrooculography result; however, the reasoning for this is not completely understood.[3]

Past literature claims that pattern dystrophies are rare diseases with few cases reported. With the advancement of multimodal imaging, more and more patients with pattern dystrophies are being discovered.[11] The disease is likely not as rare as previously thought. No identifiable health information was included in this case series (Fig. 1).

CASE 1

A 47-year-old woman was referred to rule out Stargardt disease. Her best-corrected visual acuity was 20/20 in each eye. Dilated fundus examination revealed areas of hypopigmented fleck-like lesions surrounding the maculae. Ultrawide-field fundus photography, fundus

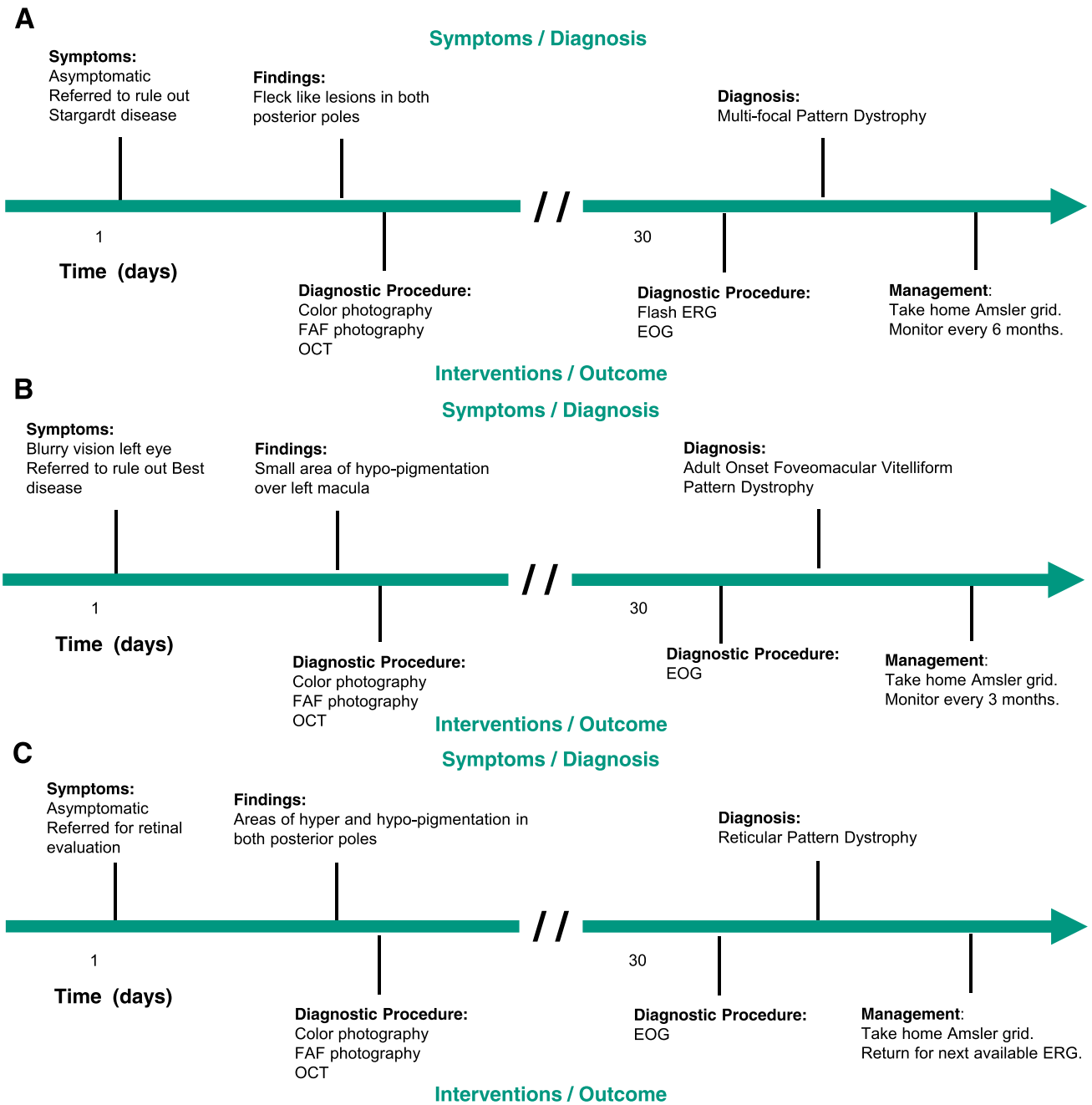

FIGURE 1. Clinical timeline. (A) Case 1: a 47-year-old woman was referred to rule out Stargardt disease and diagnosed as having multifocal pattern dystrophy. (B) Case 2: a 63-year-old man was referred to rule out Best disease and diagnosed as having adult-onset foveomacular vitelliform pattern dystrophy. (C) Case 3: a 57-year-old woman was referred for retinal evaluation and diagnosed as having reticular pattern dystrophy. EOG = electrooculography; ERG = electroretinography; FAF = fundus autofluorescence; OCT = optical coherence tomography.

autofluorescence, and optical coherence tomography spectral domain images were obtained.

Pseudocolored images of the posterior poles showed hypopigmented fleck-like lesions surrounding the maculae (Figs. 2A, B). Fundus autofluorescence highlighted that lipofuscin made up the multifocal fleck-like lesions (Figs. 2C, D). The lesions appeared symmetrical between the two eyes. The lesions were more evident on fundus autofluorescence (Figs. 2C, D) than on pseudocolored imaging (Figs. 2A, B).

Optical coherence tomography of the right eye depicted an area of hyperreflectivity above the retinal pigment epithelium extending upward through the interdigitation zone and disrupting the ellipsoid zone (Fig. 2E). Although there were scattered areas of hyperreflectivity above the retinal pigment epithelium in both eyes, the ellipsoid zone

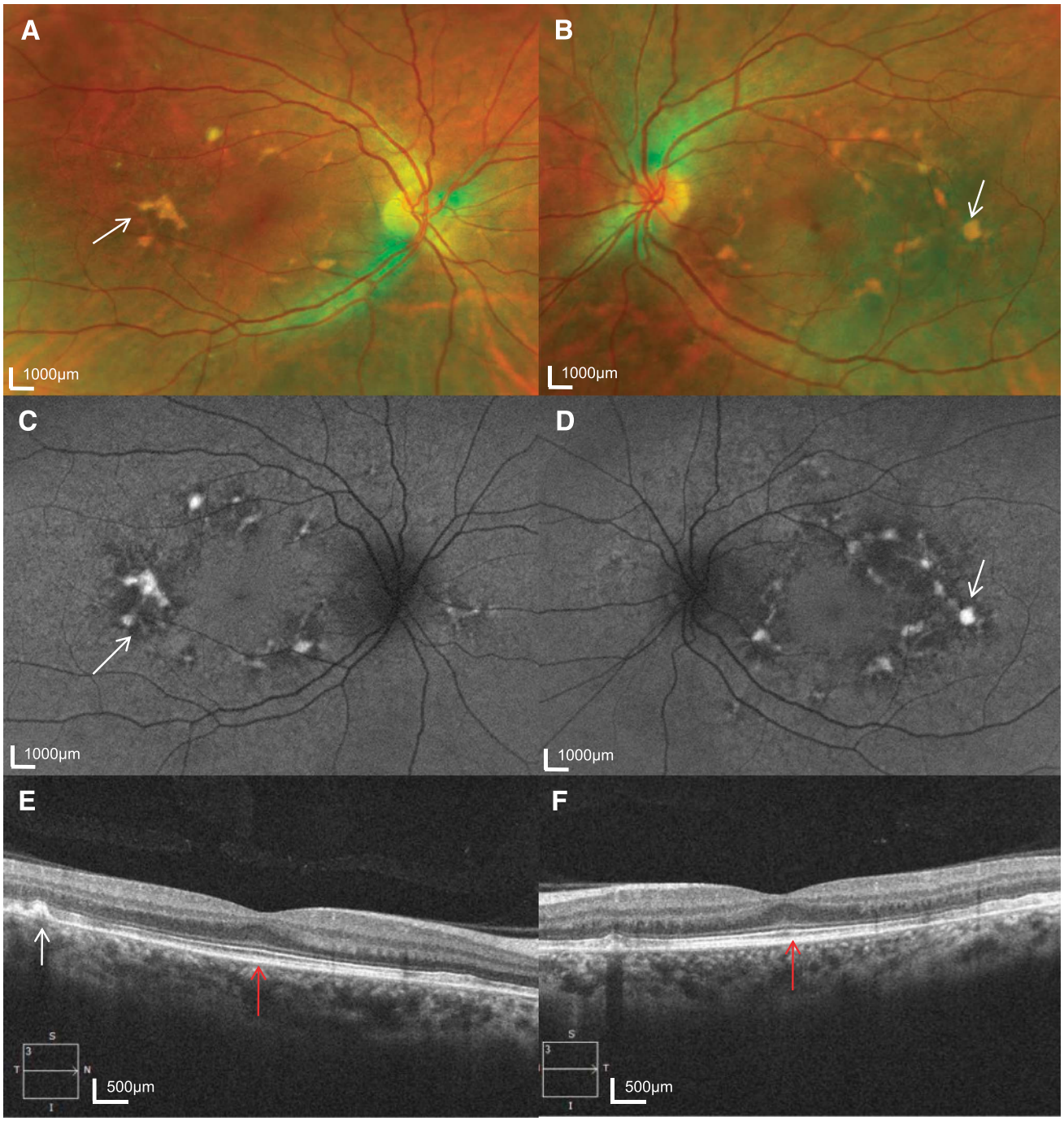

FIGURE 2. Case 1 imaging. Pseudocolored fundus images, OD (A) and OS (B): the white arrows point to hypopigmented fleck-like lesions surrounding the maculae. Fundus autofluorescence, OD (C) and OS (D): white arrows point to the hyperfluorescent multifocal fleck-like lesions. Optical coherence tomography, OD (E) and OS (F): the white arrow on OCT OD points to an area of hyperreflectivity above the RPE extending upward through the interdigitation zone and disrupting the ellipsoid zone. The red arrows point to the intact ellipsoid zone under the macula in both eyes. OCT = optical coherence tomography; OD = right eye; OS = left eye; RPE = retinal pigment epithelium.

below both the maculae remained intact, explaining the patient's visual acuity of 20/20 in each eye (Figs. 2E, F).

The results from flash electroretinography and electrooculography were normal; Arden ratios were 2.110 in the right eye and 2.802 in the left eye. Based on the age at onset, fundus autofluorescence pattern, optical coherence tomography, and normal electrodiagnostic testing results, the patient was diagnosed as having multifocal pattern dystrophy, and Stargardt disease was ruled out (Fig. 5). The patient was given a take-home Amsler grid to monitor visual changes at home. She was scheduled to return every 6 months to monitor for progression.

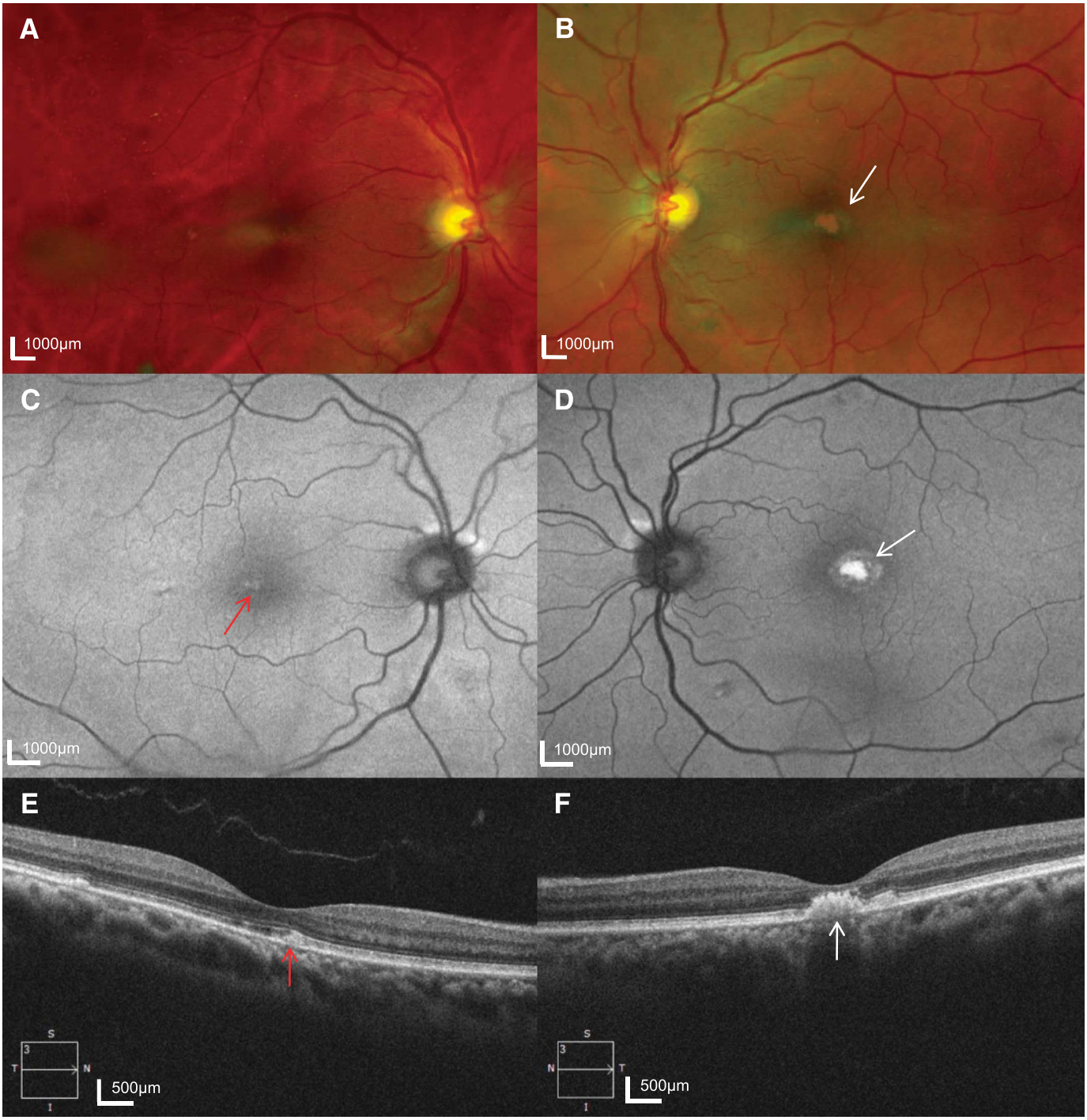

FIGURE 3. Case 2 imaging. Pseudocolored fundus images, OD (A) and OS (B): the white arrow points to a round hypopigmented lesion on the left macula. Fundus autofluorescence, OD (C) and OS (D): the white arrow points to a one-third disc-diameter hyperfluorescent area of lipofuscin over the left macula. The red arrow points to a very small area of hyperfluorescence over the right macula. Optical coherence tomography, OD (E) and OS (F): the white arrow points to an area of hyperreflectivity above the RPE in the left macula that disrupts the overlying ellipsoid zone. The red arrow points to a very small area of hyperreflectivity above the RPE of the right eye. OD = right eye; OS = left eye; RPE = retinal pigment epithelium.

CASE 2

A 63-year-old man was referred to rule out Best disease. Ocular history was remarkable for mild cataracts in both eyes. His best-corrected visual acuity values were 20/25 in the right eye and 20/100 in the left eye. Dilated fundus examination revealed a small round elevated area of hypopigmentation on the left macula. Ultrawide-field fundus photography, fundus autofluorescence, and optical coherence tomography spectral domain images were obtained.

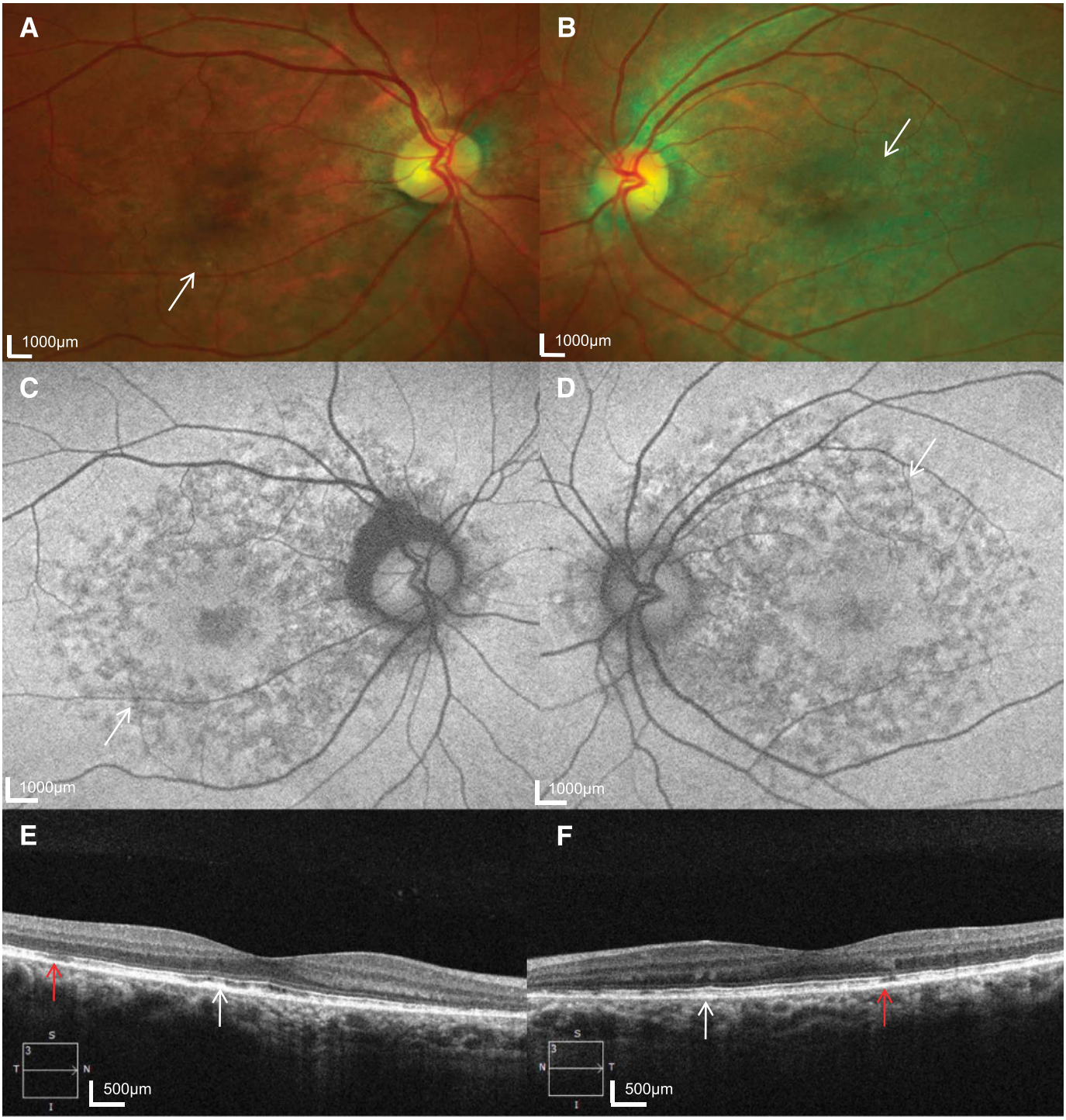

FIGURE 4. Case 3 imaging. Pseudocolored fundus images, OD (A) and OS (B): the white arrows point to mildly visible hypopigmented and hyperpigmented lesions around the maculae and optic nerves. Fundus autofluorescence, OD (C) and OS (D): white arrows point to symmetric hypofluorescent and hyperfluorescent lesions in a reticular-like pattern around the maculae and optic nerves. Optical coherence tomography, OD (E) and OS (F): the white arrows point to areas of hyperreflectivity above the RPE. The red arrows point to areas in which the ellipsoid zone is missing. OD = right eye; OS = left eye; RPE = retinal pigment epithelium.

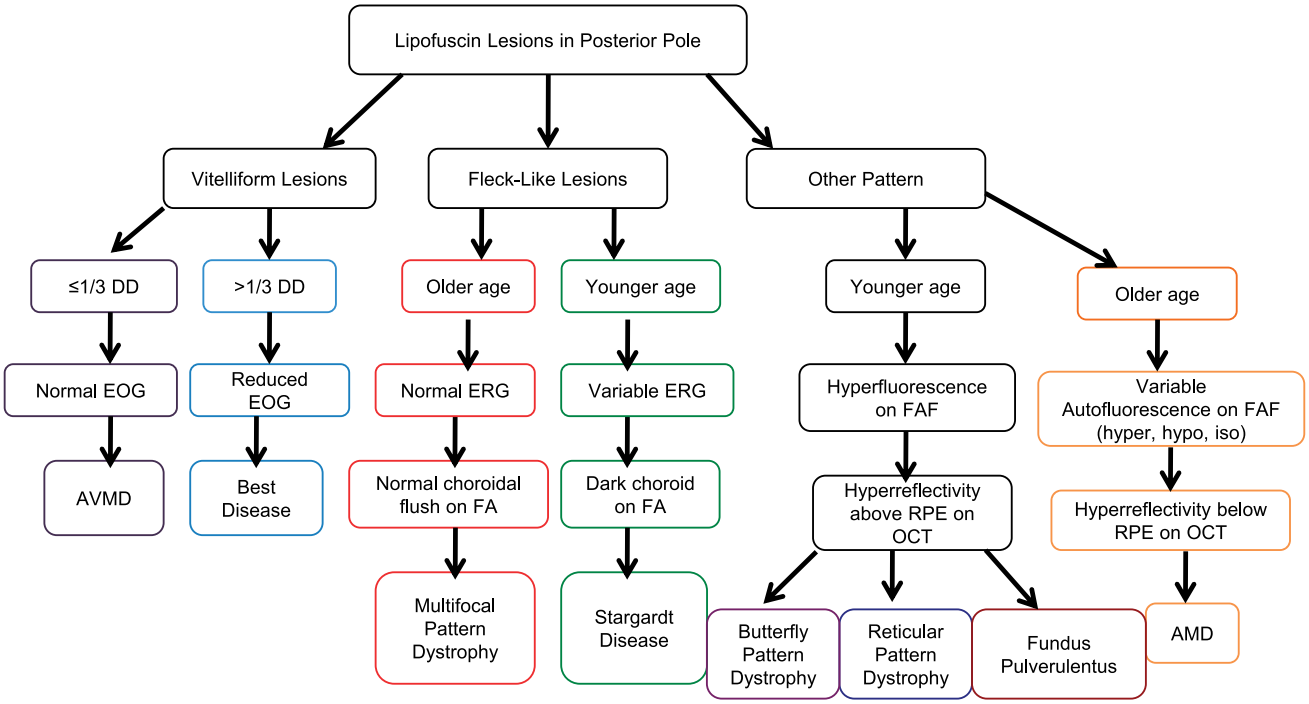

FIGURE 5. Summary flowchart. AVMD = adult-onset foveomacular vitelliform dystrophy; DD = disc diameter; EOG = electrooculography; ERG = electroretinography; FA = fluorescein angiography; FAF = fundus autofluorescence; OCT = optical coherence tomography; RPE = retinal pigment epithelium.

Pseudocolored image of the left posterior pole showed a round hypopigmented lesion on the macula (Fig. 3B). Fundus autofluorescence revealed a one-third disc-diameter hyperfluorescent area of lipofuscin over the left macula (Fig. 3D). There was a very small visible area of hyperfluorescence in the right macula (Fig. 3C).

Optical coherence tomography of the left eye showed an area of hyperreflectivity over the macula (Fig. 3F). The hyperreflectivity, representing the lipofuscin, was above the retinal pigment epithelium extending upward through the interdigitation zone and disrupting the ellipsoid zone. This disruption in the ellipsoid zone explained the left eye's visual acuity of 20/100. On optical coherence tomography of the right eye, there was a very small area of hyperreflectivity above the retinal pigment epithelium (Fig. 3E), corresponding to the very small area of hyperfluorescence seen on fundus autofluorescence (Fig. 3C). However, the ellipsoid zone of the right eye was intact, explaining the visual acuity of 20/25.

The result from electrooculography was normal, with Arden ratios of 4.273 in the right eye and 4.350 in the left eye. Based on the fundus autofluorescence pattern, optical coherence tomography, and normal electrooculography testing result, the patient was diagnosed as having adult-onset foveomacular vitelliform dystrophy, and Best disease was ruled out (Fig. 5). The patient was given a take-home Amsler grid to monitor visual changes at home. He was scheduled to return every 3 months to monitor for progression.

CASE 3

A 57-year-old woman presented for retinal evaluation. She had no pertinent ocular history. Her best-corrected visual acuity was 20/25 in each eye. Dilated fundus examination revealed areas of hyperpigmentation and hypopigmentation surrounding both the optic nerves and the maculae. Ultrawide-field fundus photography, fundus autofluorescence, and optical coherence tomography spectral domain images were obtained.

Pseudocolored images depicted mildly visible hyperpigmented and hypopigmented lesions around the optic nerves and maculae (Figs. 4A, B). These lesions were more notable in fundus autofluorescence images; hyperfluorescence and hypofluorescence are revealed in a reticular pattern within the posterior poles (Figs. 4C, D). The lesions appeared symmetrical between the two eyes.

Optical coherence tomography showed areas of hyperreflectivity above the retinal pigment epithelium (Figs. 4E, F). There were also areas where the ellipsoid zone was missing. Although mildly attenuated, the ellipsoid zones under the maculae were still intact, explaining the visual acuity of 20/25 in each eye.

The result from electrooculography was normal in the right eye, with an Arden ratio of 2.583, but unreliable in the left eye. The patient is scheduled to return for an electroretinography. Based on the age at onset, fundus autofluorescence pattern, optical coherence tomography, and normal electrooculography testing result of the right eye, the patient was diagnosed as having reticular pattern dystrophy (Fig. 5). The patient was given a take-home Amsler grid to monitor visual changes at home. She will be monitored for progression at her follow-up examinations.

DISCUSSION

Past literature has incorrectly concluded that pattern dystrophies are rare. Two theories explain why. First, many patients with pattern dystrophies do not develop macular lesions and therefore remain asymptomatic. Most clinicians do not perform additional testing on asymptomatic patients, and hence, these cases remain undiagnosed. Second, pattern dystrophies are not well known and consequently are often misdiagnosed as age-related macular

degeneration, central serous chorioretinopathy, or nonspecific retinal changes.[11] With the use of new diagnostic instruments, such as fundus autofluorescence and optical coherence tomography, clinicians have the ability to diagnose more cases of pattern dystrophies. Refer to Fig. 5.

The main differential diagnosis and the most common misdiagnosis for pattern dystrophy is age-related macular degeneration. However, main characteristics of both diseases can help clinicians differentiate the two. Patients with pattern dystrophies are usually diagnosed between the ages of 40 and 60 years, whereas patients with age-related macular degeneration are usually diagnosed at 50 years or older.[12] Vision loss in patients with pattern dystrophies is typically mild (between 20/20 and 20/60), whereas patients with age-related macular degeneration typically have a worse visual acuity outcome, varying between mild (20/20) and severe (counting fingers). Age-related macular degeneration has a white predilection,[8] but there is no race predilection identified in pattern dystrophies thus far.

The hallmark of age-related macular degeneration is the presence of drusen, whereas the hallmark of pattern dystrophies is the presence of lipofuscin in patterns without drusen. Recognizing the presence of either lesion is vital for correct diagnosing. Fundus autofluorescence and optical coherence tomography can aid clinicians in differentiating drusen from lipofuscin. On fundus autofluorescence, lipofuscin has a bright hyperfluorescent appearance. Drusen, however, have a variable fluorescence; they can hyperfluoresce, hypofluoresce, or isofluoresce. When drusen hyperfluoresce, they do not appear as bright as lipofuscin does. Also, pattern dystrophies tend to have more symmetrical retinal appearances, as demonstrated in cases 1 and 3, which is an important differential.[8] Optical coherence tomography can also differentiate drusen from lipofuscin. Lipofuscin presents as hyperreflectivity above the retinal pigment epithelium, sometimes extending upward through the ellipsoid zone. Drusen, on the other hand, usually present as hyperreflectivity below the retinal pigment epithelium. There have been reports of subretinal drusenoid deposits that are located above the retinal pigment epithelium; however, these are rare and are still distinguishable from lipofuscin by their focal round appearance.[13] Breaks in Bruch's membrane are more likely to occur in age-related macular degeneration than in pattern dystrophies because drusen are usually underneath the retinal pigment epithelium adjacent to Bruch's membrane, as opposed to lipofuscin, which is above the pigment epithelium. Both diseases can result in atrophy or in choroidal neovascularization; however, these are much more common in age-related macular degeneration.[1,8,10]

Other differential diagnoses for pattern dystrophies are Stargardt disease and Best disease. Multifocal pattern dystrophy can be mistaken for Stargardt disease because of the fleck-like lipofuscin lesions seen in both diseases clinically on fundus photography and most obviously on fundus autofluorescence. The patient from case 1 presented with similar lesions. Stargardt disease is associated with an autosomal recessive *ABCA4* gene mutation, whereas in pattern dystrophy, an autosomal dominant *PRPH2* gene mutation is most often associated. Compared with patients with pattern dystrophy, patients with Stargardt disease present with an earlier age at onset and a worse visual prognosis, ranging from 20/40 to 20/400. Optical coherence tomography imaging alone cannot be used to differentiate between Stargardt disease and multifocal pattern dystrophy because lipofuscin, regardless of the disease etiology, will show up as hyperreflectivity above the retinal pigment epithelium. Electroretinography varies based on the type of Stargardt disease.[14] A dark choroid on fluorescein angiography is pathognomonic for Stargardt disease, whereas patients with pattern dystrophy retain normal choroidal flush.[1,5]

Adult-onset foveomacular vitelliform dystrophy is often mistaken for Best disease because of the vitelliform lesions present in both diseases. Best disease is due to an autosomal dominant *BEST1* gene mutation. Compared with adult-onset foveomacular vitelliform dystrophy, patients with Best disease present with an earlier age at onset and a worse visual prognosis, ranging from 20/40 to counting fingers. The vitelliform lesions in pattern dystrophies are usually smaller, around one-third of a disc diameter, as seen in the patient from case 2. An abnormal electrooculography result is pathognomonic for Best disease. It is abnormal because Best disease is a diffuse retinal pigment epithelial disease that affects the entire retina, although the vitelliform lesion is often only visible in the macular region. Patients with pattern dystrophies, a localized disease, retain a normal electrooculography result.[3]

CONCLUSIONS

Correct diagnosis is essential for proper treatment and management of patients with pattern dystrophies. It is important to differentiate pattern dystrophies from other diseases with similar clinical presentations. Patients with pattern dystrophies must be monitored for atrophy and choroidal neovascularization, although the risk is relatively low. With increased awareness of pattern dystrophies and with the advancement of fundus autofluorescence and optical coherence tomography, there is an increase in the number of cases diagnosed, and there will continue to be so. As more and more cases are uncovered, pattern dystrophies may no longer be considered a rarity.

ARTICLE INFORMATION

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