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FEATURE REVIEW ON LINE

Pigmented Lesions of the Retinal Pigment Epithelium

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ABSTRACT

The primary eye care practitioner assumes an important role in clinical decisions involving the differentiation between malignant and nonmalignant pigmented lesions. A misdiagnosis may have profound consequences on patient management and visual or life prognosis. However, information on these lesions, particularly their appearance using advanced imaging, is fragmented throughout the literature. The purpose of this review is to describe these features in detail, so that the implications of this information on clinical practice are more readily apparent. Clinically relevant descriptions of pigmented lesions of the retinal pigment epithelium using traditional and advanced imaging modalities in the literature were collated and integrated with findings from patients seen at the Centre for Eye Health. The information was then organized and tabulated. Finally, a flow diagram was created to be used as a clinical reference in the differential diagnosis of pigmented lesions of the retinal pigment epithelium.
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Key Words: pigmented retinal lesions, congenital hypertrophy of the RPE, pigmented ocular fundus lesions of familial adenomatous polyposis, congenital grouped pigmentation of the RPE, reactive hyperplasia of the RPE, chair-side reference

Pigmented lesions of the retinal pigment epithelium (RPE) are commonly encountered by eye care professionals in clinical practice.[1] Such lesions include congenital hypertrophy of the RPE (CHRPE), congenital grouped pigmentation of the RPE (CGP-RPE), pigmented ocular fundus lesions of familial adenomatous polyposis (POFLs), reactive hyperplasia of the RPE, RPE adenoma, hamartomas of the RPE, and RPE adenocarcinoma.

Most pigmented lesions of the fundus are asymptomatic, occurring in patients presenting for routine primary eye care. Macular lesions may have a more profound effect on vision resulting in a variety of symptoms including reduced visual acuity, visual field loss, photopsias, metamorphopsia, and/or floaters.[2] Ocular or orbital pain may also be present, owing to raised intraocular pressure or inflammation. Retinal pigment epithelium changes noted in the fundus may be categorized by the underlying cellular change as atrophy (loss of cells), hypertrophy (increase in cell size), hyperplasia (increase in cell number), migration (movement of cells), metaplasia (differentiation to another cell type), hamartoma (exaggerated hypertrophy and hyperplasia of mature tissue in a normal location), and/or carcinoma (epithelial cell cancer).[3,4] These underlying cellular changes occurring in each lesion type dictate the lesion's appearance. The eye care practitioner must recognize relevant aspects of the patient's ocular and medical histories and use a variety of examination techniques to determine whether the lesion may be routinely monitored in their clinic or referred for further specialized review. Although some of these lesions may be innocuous, others (such as RPE adenocarcinoma) are sight threatening and therefore demand timely and accurate diagnosis. Furthermore, misdiagnoses may have profound negative consequences such as the enucleation of an eye with a suspected melanoma that actually had a nonmalignant lesion.[5,6] The aim is to recognize the differentiating clinical features of benign versus malignant RPE change so that appropriate management can be initiated.

Differentiating pigmented lesions of the RPE from each other and other clinical entities such as choroidal melanomas is currently difficult for several reasons: (1) there are a wide range of lesion types, (2) there are many characteristics that are used to differentiate these lesions and skill is required to make a distinction, and (3) the image characteristics of some of the pigmented lesions using modern technologies are still being established. In this evolving environment, up-to-date criteria should be applied to avoid errors in management. Ambiguity in classifying these lesions translates to a high incidence of misdiagnosis and associated errors in

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management.[7–9] For example, Law et al.[8] reported that only 403 of 1050 (38.3%) of new intraocular tumor patients referred to a tertiary ocular oncology care center were referred with the correct diagnosis. Thus, strategies that relieve the diagnostic ambiguity associated with these lesions are needed. In particular, educational strategies that increase awareness of "pseudomelanomas" and intraocular tumors would facilitate more accurate diagnoses and referrals.[6,8] Strategies involving advanced imaging technologies may also be useful, as effective use of imaging technologies has been shown to reduce the misdiagnosis rate of choroidal melanoma.[6] Multimodal diagnostic imaging and its widespread dissemination into clinical practice have been shown to improve the understanding and diagnosis of other retinal diseases such as age-related macular degeneration.[10]

This review collates current clinically relevant descriptions of pigmented lesions of the RPE using traditional and advanced imaging modalities. Although the term *pseudomelanoma* has been applied to at least 40 different conditions,[9,11] this review will focus on selected pigmented lesions of the RPE (for a review of choroidal melanomas and associated lesions, see Shields et al.[5]). For these pigmented lesions of the RPE, we propose a chair-side reference flowchart, which may be useful to streamline the thought process for clinicians when trying to differentiate these lesions, thus improving the diagnostic accuracy of these lesions.

METHODS

A review of the literature was performed followed by a retrospective review of noteworthy cases that presented between 2010 and 2014 to the Centre for Eye Health (CFEH) Sydney, Australia. The CFEH is a referral-only clinic that provides advanced imaging and consultations by specially trained optometrists and ophthalmologists. All patient records and images were independently reviewed by at least two experienced clinicians in concordance with CFEH's diagnostic protocols. Final images presented herein were all reviewed by ophthalmologist MH.

Images for cases present in this review were acquired using the Kowa 3D nonmydriatic retinal camera (Kowa, Japan), an Optomap Panoramic 200Tx ultra-widefield scanning laser ophthalmoscope (Optos PLC, Dunfermline, UK), Spectralis optical coherence tomography (Heidelberg Engineering, Heidelberg, Germany), and the Humphrey Field Analyzer (Carl Zeiss, Dublin, CA). Optomap scanning laser ophthalmoscope images may be separated based on its use of three laser wavelengths: green (532 nm), red (633 nm), and blue (488 nm). Green separation images (using the green laser) capture information from the neurosensory retina and RPE, whereas the red separation image (using the red laser) captures information from the RPE and choroid.[12]

Patient written consent was obtained in accordance with the Declaration of Helsinki and approved by the Biomedical Human Research Ethics Advisory Panel of the University of New South Wales, Australia.

Congenital Hypertrophy of the RPE

Epidemiology and Clinical Appearance

Congenital hypertrophy of the RPE refers to benign, typically asymptomatic lesions found in 1.2% of the population visiting an optometric practice.[1,13,14] These lesions are not associated with any systemic or other ocular disease[15,16] and their natural history is typified by slow, progressive basal enlargement. Clinically, typical CHRPE appear as unilateral, singular, round, flat, heavily pigmented lesions in the midperipheral fundus with sharply demarcated, smooth, or scalloped margins (Fig. 1A).[1,14,15,17,18] Lesion color is generally uniform and may vary from light brown or gray to black.[15] Within these lesions, there are often atrophied, window-like defects of variable size and shape called lacunae (Fig. 1B, C). Other characteristic features include marginal halo and overlying retinal vasculature abnormalities, such as attenuation and sheathing (Fig. 1D).[15–17]

Advanced Imaging Characteristics

The characteristics of CHRPE using advanced imaging are shown in Figs. 1 and 2. Using ultra-widefield fundus imaging, CHRPE lesions appear dark in red separation, green separation, and composite views of the fundus (Fig. 1A), suggesting a location within the RPE.[13,19] On fundus autofluorescence imaging, CHRPE display a characteristic uniform hypo-autofluorescence pattern whereas intralesional lacunae appear iso-autofluorescent (Fig. 2A, B).[19] On infrared imaging, CHRPE lesions are hyporeflective whereas the lacunae are hyperreflective (Figs. 1F and 2C).[19] Using optical coherence tomography (OCT), CHRPE generally appear as a slightly thicker and brighter RPE band (Fig. 2E).[13] Above the lesion, retinal disorganization and thinning, particularly of the outer nuclear layer, and absence of the inner segment ellipsoid zone are common (Fig. 2E, inset) and may correspond with observed visual field defects that become more absolute with time (Fig. 2D).[13,15,19,20] Other OCT findings include posterior optical shadowing in darkly pigmented CHRPE, increased optical transmission through large lacunae, and the presence of hyperreflective, intraretinal spots, cystoid edema, or a subretinal cleft (Figs. 1G and 2E, F). B-scan ultrasonography typically reveals CHRPE as a flat, acoustically solid mass.[19]

Histopathology

Histological analysis of CHRPE shows the RPE cells to be 1.5 to 2.0 times larger than normal in height while maintaining their typical monolayer arrangement.[21] Within these large cells, there are increased number and size of pigment granules.[21,22] Above the lesions, there is an associated loss of outer nuclear layer and photoreceptor segments[20] (Fig. 2G).

Distinguishing clinical features: lacunae and marginal halo.

RPE Adenoma and Adenocarcinoma

Epidemiology and Clinical Appearance

Rarely, RPE adenoma (benign epithelioma) or low-grade adenocarcinoma (malignant epithelioma) of the RPE can arise from CHRPE and necessitate treatment.[15] Such lesions are extremely uncommon, have no potential to metastasize, and adopt a nodular mass appearance that changes over time.[23] They may be associated with remote macular edema, adjacent intraretinal or subretinal

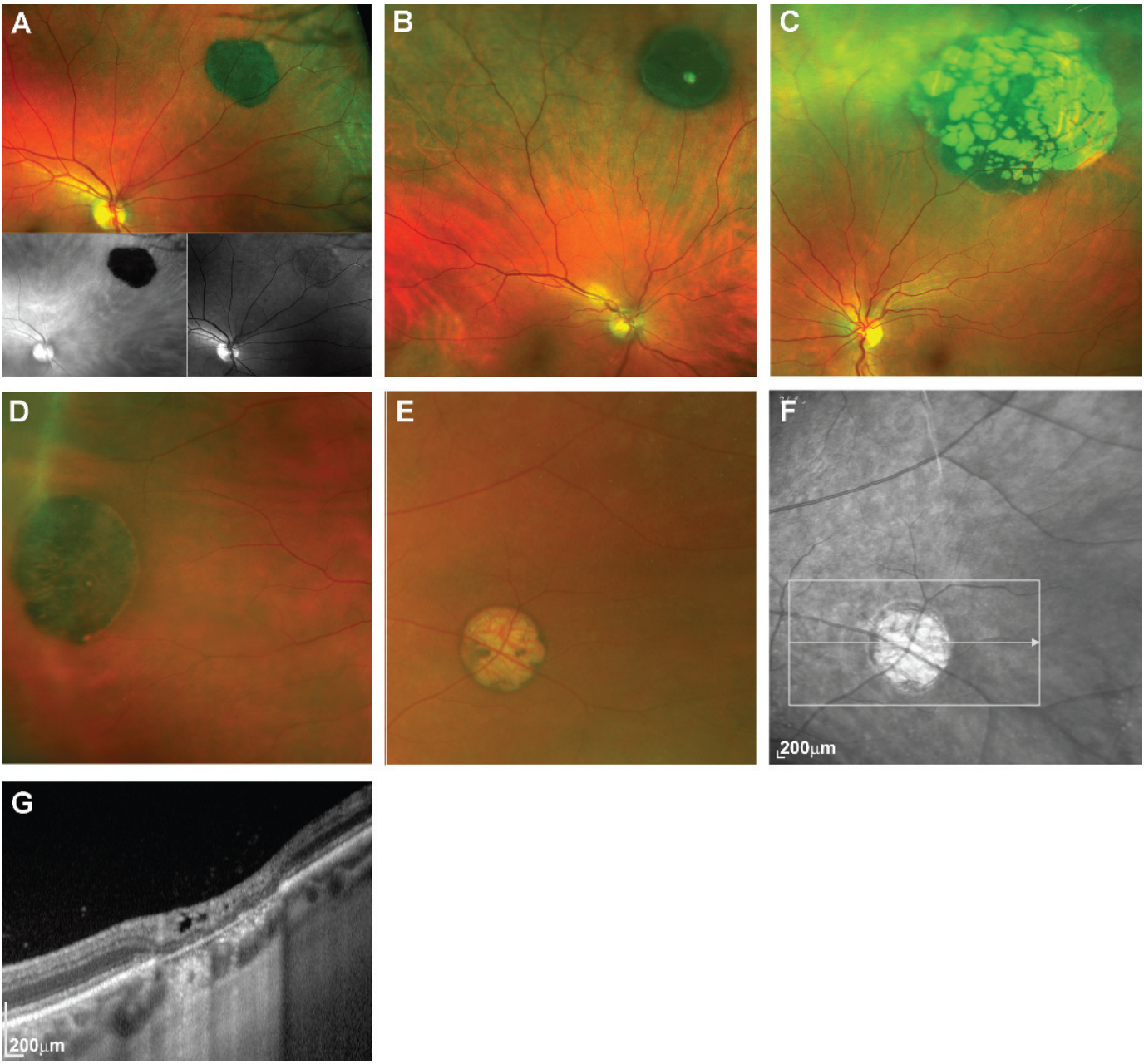

FIGURE 1.

Optomap ultra-widefield imaging results depicting the various presentations of CHRPE. Lesions are (A) typically singular, round, flat, and darkly pigmented occurring in the midperipheral fundus, with well-defined smooth edges and appear dark in individual red and green separation views suggesting a location within the RPE. Congenital hypertrophy of the RPE may also present with other clinical features such as (B) marginal halo and lacunae, (C) numerous lacunae and a scalloped border, or (D) overlying retinal vasculature sheathing. It may also appear nonpigmented (E) as in this case of a 63-year-old white woman, in which the infrared view (F) shows hyperreflectivity of the lesion associated with it being completely covered by a lacuna and (G) corresponding OCT line scan shows internal cystoid spaces.

exudation, retinal blood vessel development, surface wrinkling of the lesion, and/or intraocular inflammation.[20,23]

Advanced Imaging Characteristics

Because of their scarcity, imaging descriptions in the literature relating to RPE adenoma and RPE adenocarcinoma are limited to B-scan ultrasonography. Two independent case reports have shown RPE adenocarcinoma as moderately sonoreflective, elevated lesions in the fundus.[23,24] Similarly, RPE adenoma has been described in one case report as an elevated lesion with high internal reflectivity.[25] The appearance of these lesions using other advanced imaging modalities is limited to a single case study reporting on the usefulness of ultra-widefield photography for documentation and monitoring purposes.[25]

Histopathology

The histological distinction between benign RPE adenoma and malignant RPE adenocarcinoma is unclear.[23] However, the former

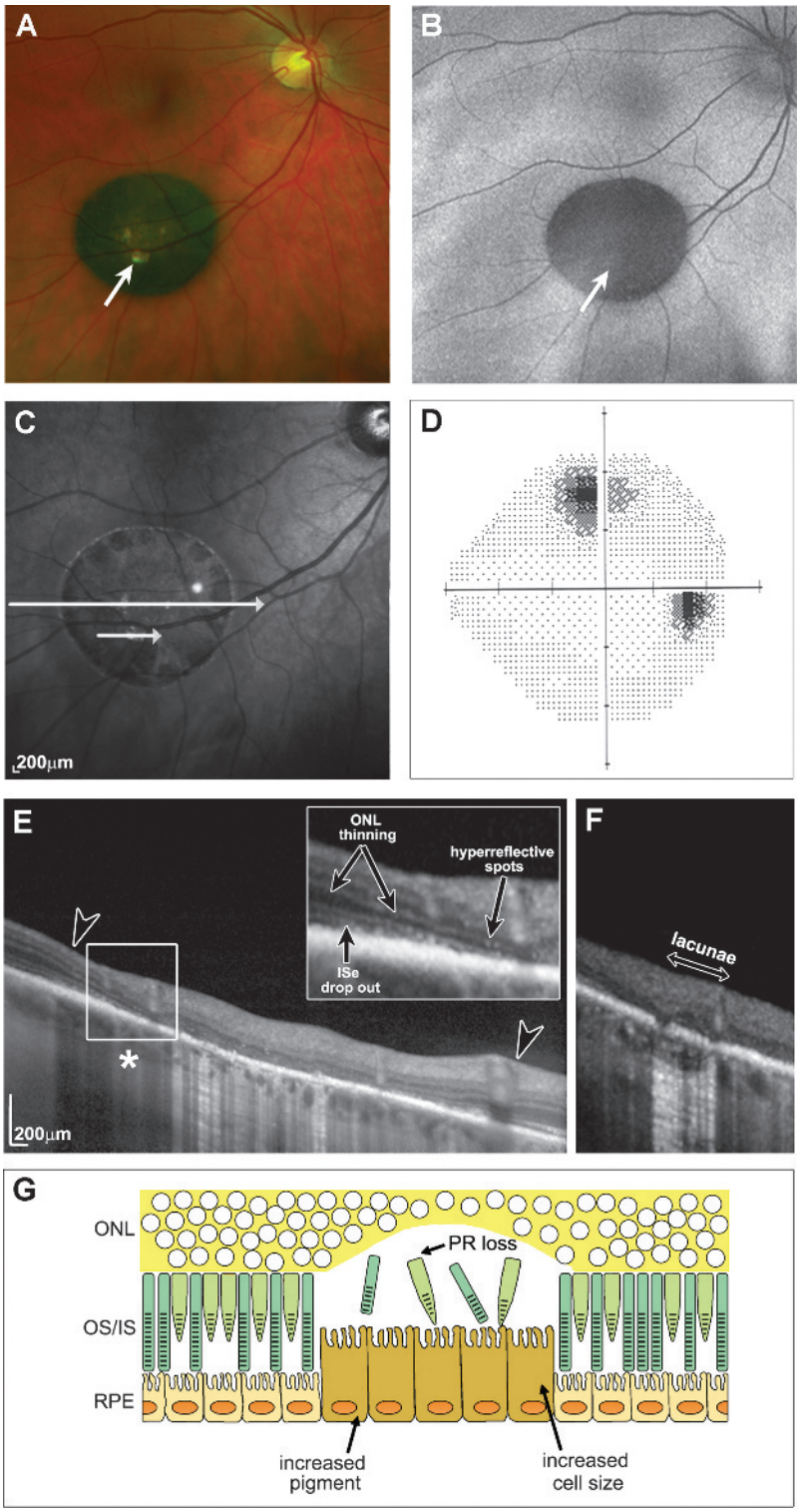

FIGURE 2.

A CHRPE lesion present in a 45-year-old white man. (A) Optomap imaging revealed a darkly pigmented, round lesion with smooth, well-demarcated borders, and internal lacunae (arrow). (B) Using fundus autofluorescence, the lesion displayed largely uniform hypo-autofluorescence and iso-autofluorescence of the lacunae (arrow). (C) On infrared imaging, the CHRPE appeared hyporeflective whereas the lacunae were discretely hyperreflective. Lines indicate the position of the OCT B-scans featured in E and F. (D) CHRPE-related absolute visual field defect. (E) Optical coherence tomography imaging showed just appreciable thickening and brightening of the RPE between the arrowheads, corresponding with the lateral extent of the CHRPE. There is also dropout of the inner segment ellipsoid zone, retinal thinning (particularly of the outer nuclear layer), and hyperreflective spots; refer to inset. Changes in the photoreceptor layers likely explain the corresponding visual field defect for the lesion. (F) Optical coherence tomography line scan through a large lacuna (shorter line on C) showing increased optical transmission into the choroid. (G) Histologic schematic of CHRPE showing tall RPE cells (1.5 to 2 times the height of normal peripheral RPE cells, arranged similarly in a monolayer) with increased number and size of intracellular pigment granules and associated loss of the outer nuclear layer, and photoreceptor inner and outer segments. The cytoplasm of CHRPE cells is intensely pigmented. ONL, outer nuclear layer; PR, photoreceptor; ISe, inner segment ellipsoid.

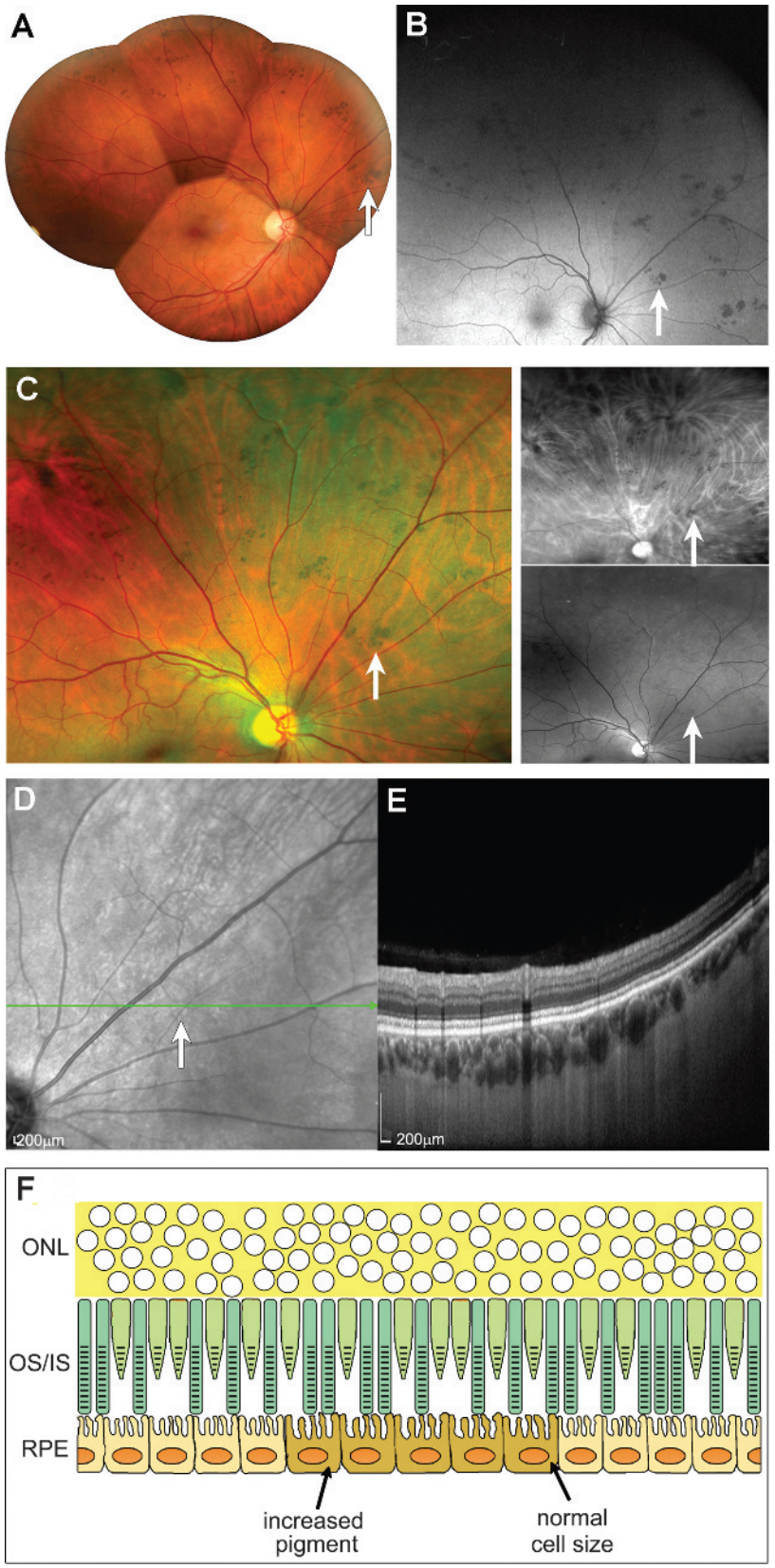

FIGURE 3.

Congenital grouped pigmentation of the RPE or bear tracks present in a 50-year-old woman. (A) Fundus photograph showing the lesions as clusters of hyperpigmented, well-circumscribed oval lesions in the superior retina. The multimodal imaging characteristics of these lesions have not been established. (B) Fundus autofluorescence showed that the lesions were hypofluorescent. (C) View of the lesions using Optomap ultra-widefield imaging, with individual red and green separation channels. (D, E) Infrared and OCT imaging showed no obvious abnormalities. (F) Histology schematic of ''bear tracks'' indicating increased concentration of pigment granules within otherwise normal RPE cells.

classically retains characteristics of RPE cells including basement membranes, cell junctions, and microvilli. Retinal pigment epithelium adenocarcinomas may be distinguishable from RPE adenomas by greater anaplasia, mitotic activity, and chorioretinal invasion.[4] The histopathology of RPE adenocarcinoma has specifically revealed proliferation and chorioretinal infiltration of atypical RPE cells.[23,24]

Distinguishing clinical features: nodular appearance, exudation, and vascularization.

Congenital Grouped Pigmentation of the RPE

Epidemiology and Clinical Appearance

Congenital grouped pigmentation of the RPE is characterized by multiple, small, brown-black, well-circumscribed flat lesions that cluster in a single quadrant of the fundus (Fig. 3A).[1,16] Lesions commonly increase in size toward the periphery, giving rise to its common name, ''bear tracks.''[1,26,27] A nonpigmented variant also exists, referred to as ''polar bear tracks'' or ''congenital grouped albinotic spots.''[26] Congenital grouped pigmentation of the RPE is not associated with heritable or systemic disease or visual symptoms.[16,17,28]

Advanced Imaging Characteristics

The advanced imaging characteristics of these lesions are presented in Fig. 3. These lesions are hypo-autofluorescent (Fig. 3B) and appear dark on red and green separation images using Optomap imaging (Fig. 3C). Interestingly, lesions are not visible on infrared imaging (Fig. 3D) and cause no appreciable change using OCT (Fig. 3E), suggesting grossly ''normal'' RPE and overlying retinal morphology. No other reports on multimodal findings of CGP-RPE are currently available.

Histopathology

The imaging findings in CGP-RPE correspond with their histopathology, which suggests increased concentration of pigment granules within otherwise normal RPE cells, that is, hypertrophy type change (Fig. 3F).[28]

Distinguishing clinical features: multiple, clustered, small lesions.

Pigmented Ocular Fundus Lesions of Familial Adenomatous Polyposis

Epidemiology and Clinical Appearance

Pigmented ocular fundus lesions of familial adenomatous polyposis refer to the congenital (present at birth) and familial pigmented ocular lesions occurring in patients with familial adenomatous polyposis (FAP) and Gardner and Turcot syndromes (Fig. 4).[1,17,29] Pigmented ocular fundus lesions of FAP are the most frequent extracolonic manifestation of FAP and are thus a highly reliable and early marker of disease.[16,30] The accurate identification of POFLs is critical as untreated FAP associated with malignant carcinoma of the colon is fatal in most cases.[1,30] The natural history of these lesions has scarcely been reported.

Pigmented ocular fundus lesions of FAP are typically benign and asymptomatic unless located in the macula[16,30]; large lesions can cause visual field scotomata.[30,31] Clinically, various types of POFLs have been described.[32,33] Lesions are generally multiple and bilateral (averaging seven between the two eyes[34]) and present scattered around the equator.[17,33,34] Most typically, the lesions appear punctiform—small (<0.1 disc diameter in size), round, dark

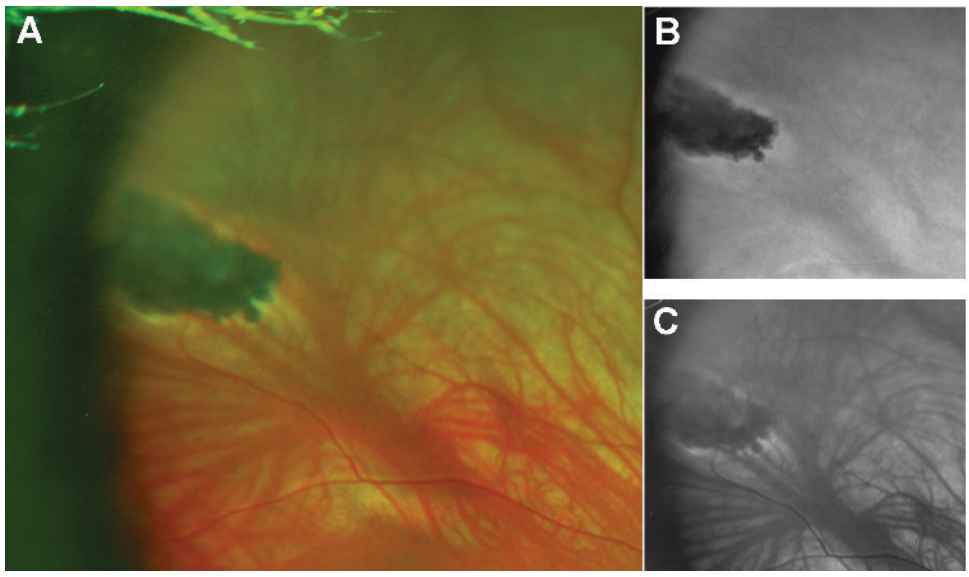

FIGURE 4.

Pigmented ocular fundus lesion present in a 28-year-old, asymptomatic white man with Gardner syndrome (typified by the presence of FAP, osteomas, and other soft tissue tumors) who was referred to CFEH for fundus imaging using ultra-widefield scanning laser ophthalmoscopy. (A) Composite view, showing a large lesion of dark and nonuniform coloration, located just beyond the equator in the right eye. The lesion also features a hypopigmented surrounding halo, which makes its appearance consistent with a large POFL. However, the unilateral and singular nature of this lesion is atypical of POFL, which more typically presents as multiple, oval or pisciform lesions in both eyes. (B, C) Persistence of the lesion in red and green separation images.

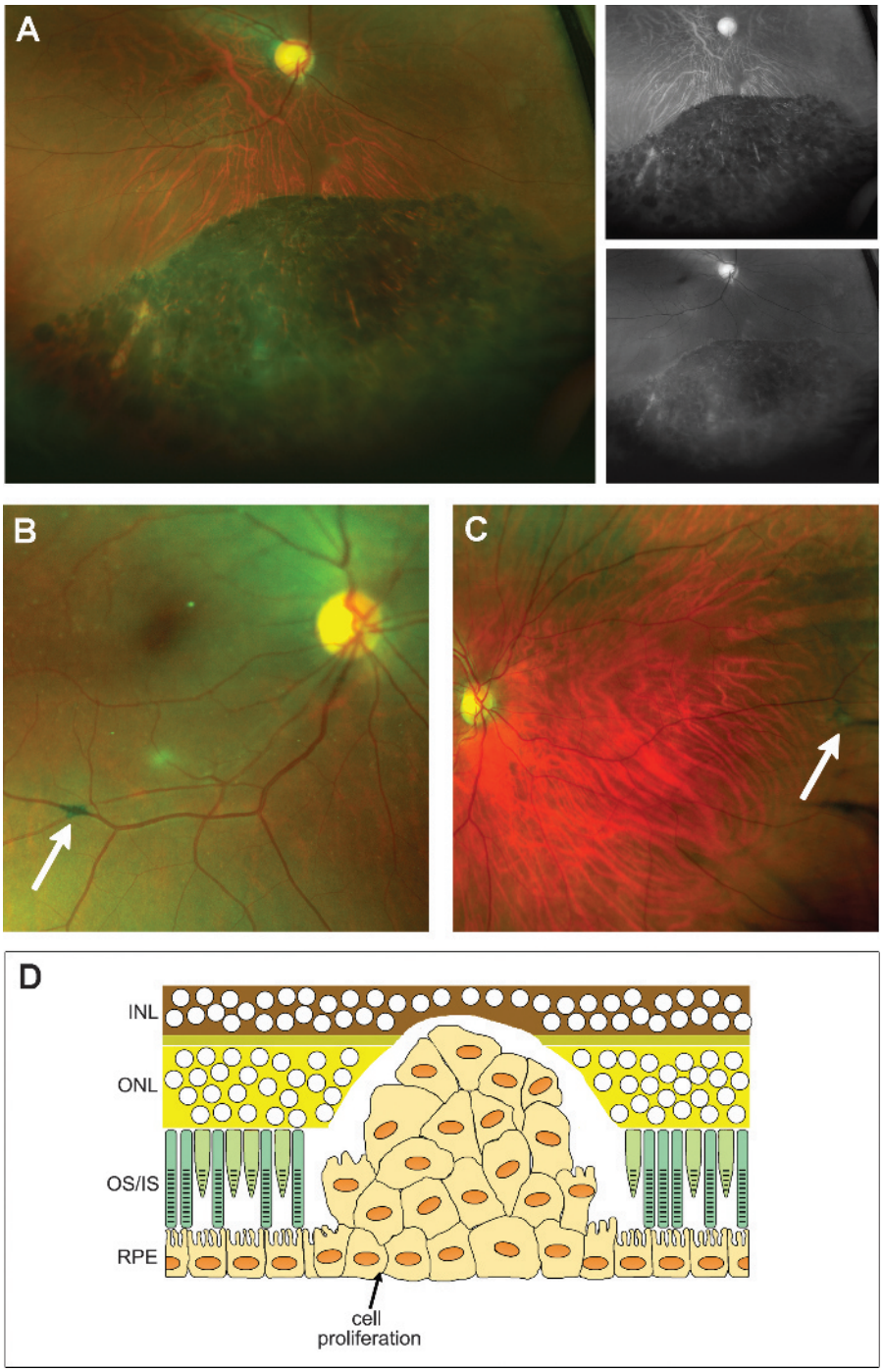

FIGURE 5.

The spectrum of Optomap ultra-widefield imaging results in reactive hyperplasia of the RPE. Lesions (A) may result from retinal detachment, (B) may be located paravascularly, or (C) may appear as small, intraretinal, spiculated foci. (D) The histology of reactive hyperplasia of the RPE represented in a schematic depicting proliferation of RPE cells appearing as a cellular mass.

brown or black as "satellite lesions" of larger variants.[33,34] In contrast, the larger lesions usually appear round, oval, or pisciform ("fishlike" featuring a posterior tapered tail) in shape and dark though sometimes nonuniform in color and encircled by a hypopigmented halo.[17,33,34] About one-third of patients with FAP will have no RPE lesions.[34] A diagnostic criterion of four or more lesions (irrespective of size or bilateral characteristics) or at least two lesions (one of which is large) is often set to provide a suitable sensitivity (0.68) and specificity (1) level.[34]

Advanced Imaging Characteristics

Reports regarding the appearance of POFL using advanced imaging technologies is restricted to OCT. Optical coherence tomography findings of POFLs may vary with the presentation and include increased reflectivity of the RPE layer, intraretinal extensions of hyperreflectivity, excavation into and absence of the RPE and Bruch membrane, and/or thinning of the outer retinal layers.[35] Retinal pigment epithelium extension into the retina

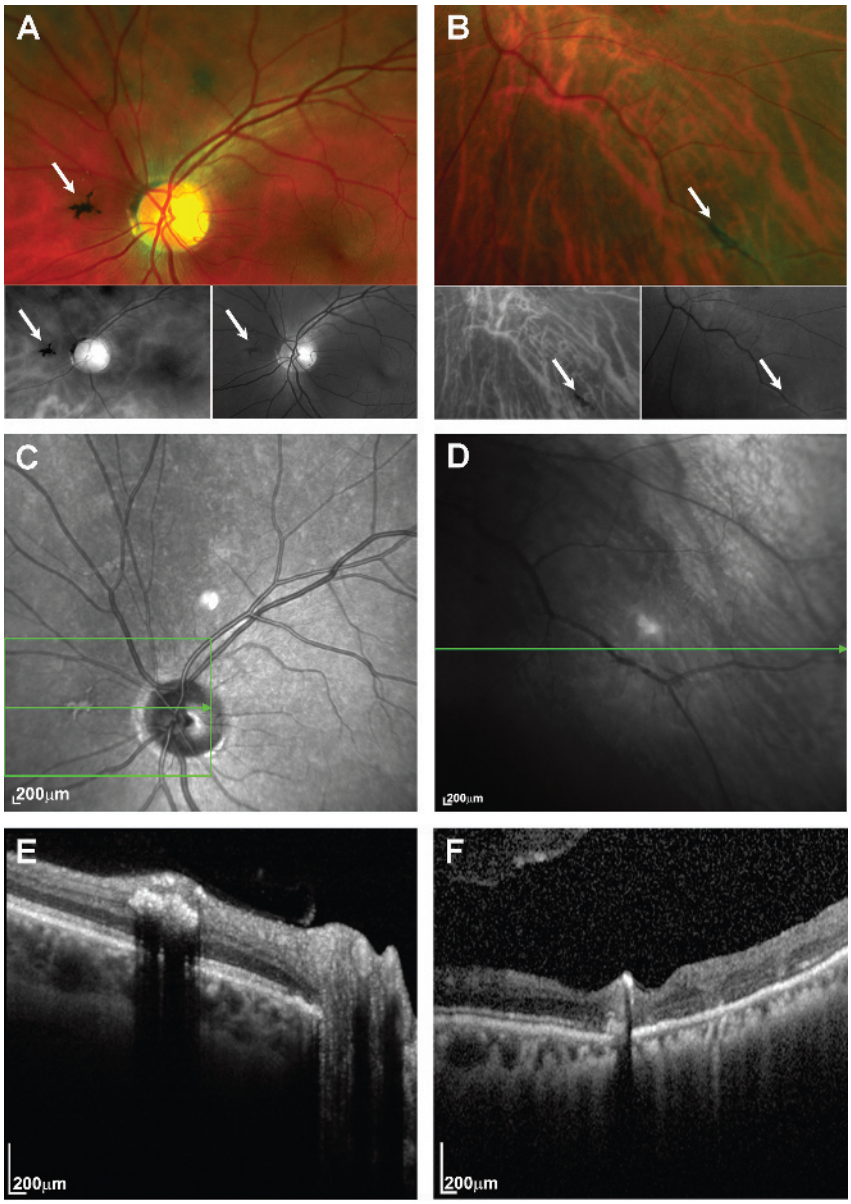

FIGURE 6.

Reactive hyperplasia of the RPE present in a 50-year-old white man. (A) Optomap wide field imaging showed a small hyperpigmented, irregular lesion nasal to the optic disc. (C) The lesion appears mostly hyperreflective under infrared imaging in this instance. (E) Optical coherence tomography imaging through the lesion shows the pigmentation in the inner retina owing to the migration of proliferating RPE. (B) An isolated paravascular, hyperpigmented lesion presenting in a 65-year-old Asian man. Its persistence in red and green separation views suggests that it involves the RPE. (D) Using infrared imaging, the lesion appeared less prominent and hyporeflective. (F) Optical coherence tomography image showing discrete inner retinal hyperreflectivity.

detectable by OCT is characteristic of POFL and may aid in its distinction from CHRPE.[35]

Histopathology

The histopathology of POFL shows a distinct hamartomatous component.[36] Three possible compositions have been identified: (1) RPE hypertrophy only, (2) a "mound" of RPE cells interposed between the RPE basement membrane and inner collagenous layer of Bruch membrane, and (3) a multilayered mound of hyperplastic cells.[37]

Distinguishing clinical features: often multiple (setting a criterion of at least four lesions, whatever the size and bilaterality, or at least two lesions, one of which is large, providing suitable sensitivity/specificity levels[34]); satellite and punctiform or large and pisciform with nonuniform coloration.

Reactive Hyperplasia of the RPE

Epidemiology and Clinical Appearance

Reactive hyperplasia of the RPE is a common, innocuous, stable condition of the RPE that may be idiopathic or arise as a result of intraocular inflammation, trauma, hemorrhage, or retinal detachment.[3,38] It classically presents as irregularly shaped, relatively flat, well-demarcated areas of pigment clumping (Fig. 5). Small

lesions can be described as intraretinal, spiculated (stellate shaped) pigmentation, or "focal hyperplasia of the RPE" (Fig. 5B, C) whereas atypical, larger lesions have been termed "nodular reactive hyperplasia of the RPE" and may be indistinguishable from less benign etiologies (such as RPE adenoma).[3,39,40] Although reactive hyperplasia of the RPE typically involves minimal changes over time, cases of neoplasms arising from focal hyperplasia of the RPE have also been described.[38]

Advanced Imaging Characteristics

The spectrum of multimodal characteristics of reactive hyperplasia of the RPE is shown in Figs. 5 and 6. Besides the cases presented here, there are few other reports regarding the appearance of reactive hyperplasia of the RPE using multimodal imaging. Optomap ultra-widefield monochromatic images have shown persistent visibility of the lesions in both views (Fig. 6A, B). Infrared imaging revealed variable, nonhomogeneous patterns of hyperreflectivity and/or hyporeflectivity (Fig. 6C, D). Areas of heavy pigmentation can be expected to exhibit hypo-autofluorescence. Optical coherence tomography imaging through these lesions shows areas of distinct hyperreflectivity in the inner retina, associated with posterior shadowing (Fig. 6E, F).[41]

Histopathology

Histologically, reactive hyperplasia of the RPE has been described as the benign proliferation of RPE cells appearing as a flat sheet or cellular mass (Fig. 5D).[40]

Distinguishing clinical features: irregular shape and appearance of "pigment clumping."

Congenital Simple Hamartoma of the RPE

Epidemiology and Clinical Appearance

Rare lesions of the RPE include hamartomas: focal, benign masses composed of cells that are of normal structure and in the correct tissue location. Congenital simple hamartoma of the RPE (or congenital hyperplasia of the RPE) is a mostly asymptomatic,

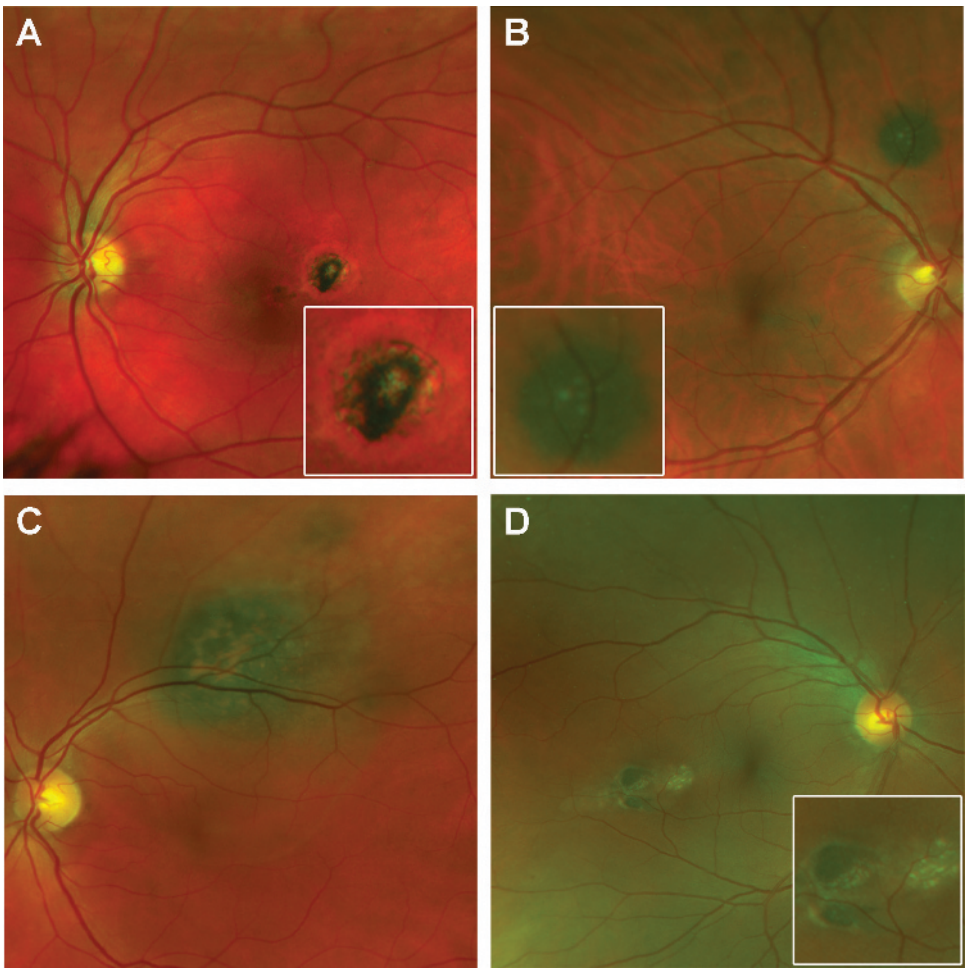

FIGURE 7.

Other chorioretinal lesions, as they appear using Optomap imaging, that may involve or mimic changes in the RPE. (A) Toxoplasmosis chorioretinitis lesion present in a 27-year-old white woman. The lesion appeared variably pigmented. (B) A choroidal naevus found in an asymptomatic 62-year-old white woman that was associated with overlying drusen. The lesion may also be distinguished from pigmented lesions of the RPE by its lighter coloration and less well-defined borders. (C) Small choroidal melanoma in a 62-year-old white woman associated with overlying lipofuscin and serous detachment of the retina. The patient subsequently underwent transpupillary laser thermotherapy. (D) A case of torpedo maculopathy observed in a 52-year-old white woman. The lesion was located at the temporal macula and features hypopigmented areas and a spindle shape pointed at the fovea.

nonprogressive lesion that appears clinically as a small, nodular, darkly pigmented lesion within the macula.[20,42–44] Other features may include feeder vessels, fine macular traction at the surface of the lesion, exudation, and vitreous cells.[20,43] Its pseudonym, "congenital hyperplasia of the RPE," is apt as it often displays the features classic of reactive hyperplasia of the RPE.

Advanced Imaging Characteristics

Reports in the literature regarding the appearance of these lesions using advanced imaging is restricted to OCT and fundus autofluorescence. On OCT, congenital simple hamartoma of the RPE appears well demarcated and highly reflective, occurring either superficially or involving full-thickness retina, associated with complete, "crisp" posterior shadowing.[42,43,45,46] Using fundus autofluorescence imaging, lesions display a uniform hypofluorescence pattern.[42]

Histopathology

The histopathology of congenital simple hamartoma of the RPE appears similar to reactive hyperplasia of the RPE as lesions may represent congenital proliferation and migration of RPE cells.[43]

Distinguishing clinical features: nodular shape, associated traction, and location at the macula.

Combined Hamartoma of the Retina and RPE

Epidemiology and Clinical Appearance

Combined hamartoma of the retina and RPE describes a relatively uncommon, benign, congenital hamartomatous malformation.[47] It typically appears as a unilateral, nonuniform, charcoal gray-white, fibroglial mass involving the neurosensory retina located at or adjacent to the optic disc.[20,43,48] Characteristically, the mass may be obscured by a gliotic semitranslucent epiretinal membrane and retinal folds.[47] An association with neurofibromatosis type 2 has been emphasized.[20,49] For further review, see Shields et al.[48]

Advanced Imaging Characteristics

The appearance of this lesion has been described in a small case series using ultrasonography and OCT.[47] Ultrasonography shows these lesions as elevated with medium to high and irregular internal reflectivity.[47] Similar findings have been shown using OCT; lesions appear as an elevated mass with intraretinal disorganization and hyperreflectivity associated with epiretinal membranes and posterior shadowing.[47]

Histopathology

In postmortem analysis, combined hamartoma of the retina and RPE demonstrates disorganized retinal cells, hyperplastic

TABLE 1.
Systematic evaluation of funduscopic characteristics of pigmented lesions of the RPE

	CHRPE	POFLs	CGP-RPE	Reactive hyperplasia of the RPE	Congenital simple hamartoma of the RPE	Combined hamartoma of the retina and RPE
Laterality (unilateral or bilateral)	Unilateral[1,14]	Often bilateral[17,33,34]	Unilateral[1,16]	Unilateral or bilateral	Unilateral	Unilateral[48]
Number (singular or multiple)	Singular[14]	Usually multiple[17,33,34]	Multiple[1,16]	Singular or multiple[40]	Singular	Singular[48]
Location	Midperipheral fundus[1,13,14]	Mostly scattered around the equator[17,33,34]	Clustered in a single quadrant[1,16]	Anywhere in the fundus[40]	Macula[20,44]	At or adjacent to the optic disc[20,48]
Color (light or heavy pigmentation homogeneity)	Heavily pigmented light brown, gray to black[14]	Heavily pigmented, large lesions sometimes feature areas of depigmentation[33,34]	Heavily pigmented brown-black[1,16] May be nonpigmented	Heavily pigmented[40]	Heavily pigmented [20,44]	Variable and nonhomogeneous charcoal gray-white[20,48]
Thickness or elevation (flat or elevated, tractional layers involved)	Flat[14,21]	Flat[35]	Flat[16]	Relatively flat Intraretinal[3,40]	Mildly elevated Tractional[20,44]	Tractional[20]
Size	Mean basal diameter of 4.5 mm[21]	Punctiform or large Most commonly <0.1 disc diameter in size[17]	Larger toward the periphery[26,28]	Variable[40]	<1 mm in size[44]	Extending to involve the macula[48]
Shape (regular or irregular round, oval, spiculated)	Round[1,14]	Round, oval, or pisciform[17,33,34]	Round[28]	Irregular, stellate[3]	Nodular[44]	Irregular[20]
Borders (distinct or diffuse presence of halo)	Smooth or scalloped Well-demarcated Associated halo[14]	Well demarcated May be associated with a depigmented halo[33,34]	Well demarcated[28]	Well demarcated	Well demarcated [20]	Ill-defined[20,48]
Surface features (subretinal fluid, drusen, lipofuscin, internal atrophy)	Lacunae, Vascular attenuation and sheathing[14]				Feeder vessels, exudation, and vitreous cells[43]	Disorganized retina, hyperplastic glial cells, and vascular tortuosity[50]

glial cells, and vascular tortuosity.[50] The lesions often feature prominent, overlying tractional changes affecting the vessels and neurosensory retina, which may explain presenting reductions in visual acuity.[50]

Distinguishing clinical features: nonuniform charcoal gray-white coloration and ill-defined borders.

The Differential Diagnosis of Pigmented Lesions of the RPE

This review has focused on selected pigmented lesions of the RPE. However, a number of other chorioretinal lesions lead to pigmentation changes in the fundus and may involve or mimic changes in the RPE.[5,16,51] Lesions that may mimic pigmented lesions of the RPE, commonly encountered in clinical practice, include ocular toxoplasmosis, choroidal naevi, choroidal melanomas, and torpedo maculopathy (Fig. 7).[52]

Ocular toxoplasmosis (Fig. 7A) lesions classically appear as variably pigmented areas of scarring in the posterior eye. Their nonhomogeneous pigmentation and apparent additional involvement of layers anterior and posterior to the RPE assist in their differential diagnosis.[53] Choroidal naevi (Fig. 7B) often present with a similar appearance to classical CHRPE. However, the former often appears lighter with a less well-defined outline, associated with overlying drusen. The clinical features of choroidal melanoma have been thoroughly described elsewhere.[5] They constitute a serious malignancy. In contrast to pigmented lesions of the RPE, choroidal melanomas typically appear as solitary, elevated, subretinal masses that feature the orange pigment lipofuscin on the lesion surface (Fig. 7C). Torpedo maculopathy (Fig. 7D) refers to often asymptomatic, torpedo-shaped lesions of the macula. The features that distinguish torpedo maculopathy from pigmented lesions of the RPE include its location at the temporal macula, hypopigmentation, and its spindle shape directed toward the fovea.[54]

As shown so far, a systematic approach to the evaluation of pigmented lesions generally will enable the early identification of differentiating features. This approach is facilitated using advanced imaging technologies and best applied using knowledge of the underlying cellular change. Furthermore, careful consideration of the epidemiology and natural history of these lesions is necessary so that the clinician may recognize benign versus malignant changes and initiate appropriate management.

The funduscopic characteristics that may be useful for correct diagnosis and monitoring of pigmented lesions are shown in the first column of Table 1. Using these features, we systematically tabulated the characteristics of the lesions featured in this review. From Table 1, it is clear that there is a certain degree of descriptive ambiguity. Specifically, lesions could not be discriminated using one characteristic alone because of the considerable overlap between lesions and heterogeneity within a lesion type. In addition, certain characteristics appeared to be less useful than others in distinguishing pigmented lesions of the RPE. Most importantly, although the tabulation is informative, it is cumbersome and not easily integrated into the consulting room of the busy eye care professional.

Based on these considerations, we attempted to refine the information from Table 1 into a simplistic, more user-friendly tool. Specifically, we ranked the characteristics from Table 1 based on ambiguity and number of possible descriptors and formulated a series of flowcharts that could be used as chair-side references for clinical evaluation of pigmented RPE lesions. The final result was

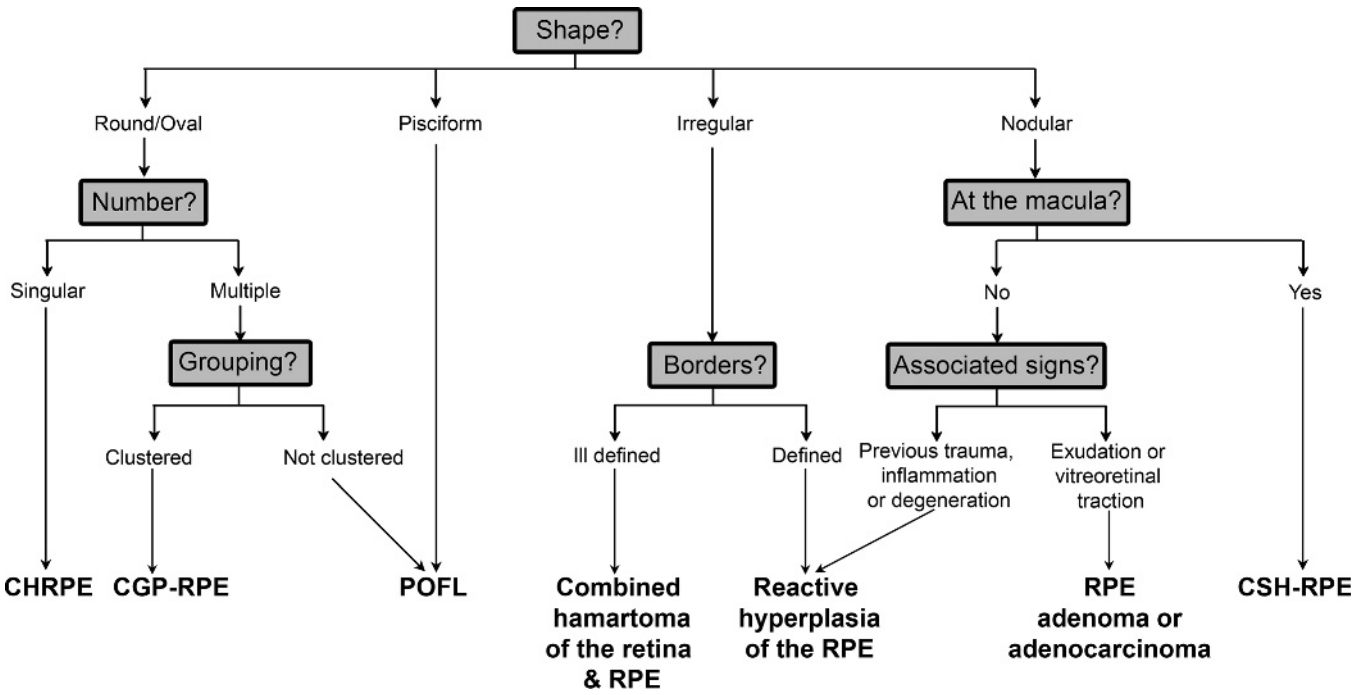

FIGURE 8.

Chair-side reference flowchart designed to aid in the differential diagnosis of pigmented lesions of the RPE. More detailed descriptions are available in Tables 1 and 2.

TABLE 2.
Multimodal imaging characteristics of pigmented lesions of the RPE

	CHRPE	POFLs	CGP-RPE	Reactive hyperplasia of the RPE	Congenital simple hamartoma of the RPE	Combined hamartoma of the retina and RPE
OCT	Thicker, brighter RPE[12] Disorganization, thinning (particularly the ONL) Absence of the ISe[12,21] Posterior shadowing[12,21]	Increased RPE reflectivity Intraretinal extensions of hyperreflectivity Excavation and absence of the RPE and Bruch membrane Thinning of outer retinal layers[26]	No appreciable changes*	Inner-retina hyperreflectivity Posterior shadowing[34]	Hyperreflectivity occurring superficially or involving full-thickness retina Complete posterior shadowing[35]	Not established
FAF	Uniform hypo-AF[21] Iso-AF lacunae[21]	Not established	Uniform hypo-AF*	Hypo-AF	Uniform hypo-AF[35]	Not established
IR	Hyporeflective Hyperreflective lacunae[21]	Not established	Not visible*	Variable, nonhomogeneous hyperreflectivity and hyporeflectivity*	Not established	Not established
B-scan	Flat, acoustically solid mass[21]	Not established	Not established	Not established	Not established	Not established

*Based on observations from this review.
FAF, fundus autofluorescence; IR, infrared; ONL, outer nuclear layer; ISe, inner segment ellipsoid; AF, autofluorescence.

a flowchart that can be used for the systematic evaluation of lesions in an intuitive and streamlined fashion (Fig. 8). The flowchart is a simplification of the differential diagnosis process and has limited applicability to atypical lesions. However, it should enable easy visualization of the thought process required to differentially diagnose these lesions by prompting the user to assess specific funduscopic characteristics. The diagnosis can then be further verified through reference to the specific lesion in Table 1.

Table 2 highlights the characteristics of pigmented lesions using multimodal imaging. Interestingly, we found that multimodal imaging was not essential to the differential diagnosis of pigmented lesions and that a chair-side reference could be composed from funduscopic characteristics alone. This, however, may be attributed to these technologies not being well established for many of the lesions discussed in this review. Further research is needed to fully understand the role of advanced imaging in characterizing these lesions, especially as it relates to the evaluation of conditions associated with greater risk of ocular morbidity and mortality.

CONCLUSIONS

The general eye care practitioner assumes an important role in the differential diagnosis of life- and sight-threatening fundus lesions. The funduscopic characteristics of pigmented lesions of the RPE are well established. Information on these lesions using multimodal imaging is fragmented throughout the literature and not always available. Review of this information revealed that a multimodal imaging approach may not be explicitly required in the differential diagnosis of pigmented lesions of the RPE. Rather, traditional methods alone may be effective for determining the diagnosis of these lesions and the practitioner may find that a streamlined aid, such as the chair-side reference flowchart proposed, is beneficial. Overall, this chart would be helpful in clinical differential diagnoses and should at least prompt the practicing clinician to adopt a systematic evaluation of pigmented lesions of the RPE.

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REFERENCES

1. Coleman P, Barnard NA. Congenital hypertrophy of the retinal pigment epithelium: prevalence and ocular features in the optometric population. Ophthalmic Physiol Opt 2007;27:547–55.
2. Hemmerdinger C, Damato B. Pigmented lesions of the choroid and retina. Optician 2008;236:22–6.
3. Jampel HD, Schachat AP, Conway B, Shaver RP, Coston TO, Isernhagen R, Green WR. Retinal pigment epithelial hyperplasia assuming tumor-like proportions. Report of two cases. Retina 1986; 6:105–12.
4. American Academy of Ophthalmology. 2013-14 Basic and Clinical Science Course, Section 4: Ophthalmic Pathology and Intraocular Tumors. San Francisco, CA: American Academy of Ophthalmology; 2013.

5. Shields CL, Manalac J, Das C, Ferguson K, Shields JA. Choroidal melanoma: clinical features, classification, and top 10 pseudomelanomas. Curr Opin Ophthalmol 2014;25:177–85.
6. Accuracy of diagnosis of choroidal melanomas in the Collaborative Ocular Melanoma Study. COMS report no. 1. Arch Ophthalmol 1990;108:1268–73.
7. Khan J, Damato BE. Accuracy of choroidal melanoma diagnosis by general ophthalmologists: a prospective study. Eye (Lond) 2007; 21:595–7.
8. Law C, Krema H, Simpson ER. Referral patterns of intraocular tumour patients to a dedicated Canadian ocular oncology department. Can J Ophthalmol 2012;47:254–61.
9. Shields JA, Augsburger JJ, Brown GC, Stephens RF. The differential diagnosis of posterior uveal melanoma. Ophthalmology 1980; 87:518–22.
10. Nivison-Smith L, Milston R, Madigan M, Kalloniatis M. Age-related macular degeneration: linking clinical presentation to pathology. Optom Vis Sci 2014;91:832–48.
11. Rennie IG. Things that go bump in the light. The differential diagnosis of posterior uveal melanomas. Eye (Lond) 2002;16:325–46.
12. Sherman J. Panoramic Ophthalmoscopy: Optomap Images and Interpretation. Thorofare, NJ: SLACK Inc; 2007.
13. Shields CL, Materin MA, Walker C, Marr BP, Shields JA. Photoreceptor loss overlying congenital hypertrophy of the retinal pigment epithelium by optical coherence tomography. Ophthalmology 2006; 113:661–5.
14. Krohn J, Froystein T, Dahl O. Topography of solitary congenital hypertrophy of the retinal pigment epithelium in the ocular fundus. Acta Ophthalmol 2009;87:921–2.
15. Shields CL, Mashayekhi A, Ho T, Cater J, Shields JA. Solitary congenital hypertrophy of the retinal pigment epithelium: clinical features and frequency of enlargement in 330 patients. Ophthalmology 2003;110:1968–76.
16. Traboulsi EI. Pigmented and depigmented lesions of the ocular fundus. Curr Opin Ophthalmol 2012;23:337–43.
17. Turell ME, Leonardy NJ, Singh AD. A unique presentation of grouped congenital hypertrophy of the retinal pigment epithelium. Ophthalmic Genet 2011;32:162–4.
18. Gass JD. Focal congenital anomalies of the retinal pigment epithelium. Eye 1989;3:1–18.
19. Fung AT, Pellegrini M, Shields CL. Congenital hypertrophy of the retinal pigment epithelium: enhanced-depth imaging optical coherence tomography in 18 cases. Ophthalmology 2014;121:251–6.
20. Yannuzzi LA. The Retinal Atlas. Philadelphia, PA: Saunders/ Elsevier; 2010.
21. Lloyd WC, 3rd, Eagle RC, Jr., Shields JA, Kwa DM, Arbizo VV. Congenital hypertrophy of the retinal pigment epithelium. Electron microscopic and morphometric observations. Ophthalmology 1990; 97:1052–60.
22. Champion R, Daicker BC. Congenital hypertrophy of the pigment epithelium: light microscopic and ultrastructural findings in young children. Retina 1989;9:44–8.
23. Shields JA, Eagle RC, Jr., Shields CL, Brown GC, Lally SE. Malignant transformation of congenital hypertrophy of the retinal pigment epithelium. Ophthalmology 2009;116:2213–6.
24. Trichopoulos N, Augsburger JJ, Schneider S. Adenocarcinoma arising from congenital hypertrophy of the retinal pigment epithelium. Graefes Arch Clin Exp Ophthalmol 2006;244:125–8.
25. Shah SP, Jain A, Coffee RE, McCannel TA. Optos Panoramic 200MA ultrawide-field imaging of peripheral RPE adenoma. Semin Ophthalmol 2009;24:37–9.
26. Kim DY, Hwang JC, Moore AT, Bird AC, Tsang SH. Fundus autofluorescence and optical coherence tomography of congenital grouped albinotic spots. Retina 2010;30:1217–22.
27. Meyer CH, Holz FG. Documentation of congenital hypertrophy of the retinal pigment epithelium with wide-field funduscopy. Semin Ophthalmol 2009;24:251–3.
28. Shields JA, Tso MO. Congenital grouped pigmentation of the retina. Histopathologic description and report of a case. Arch Ophthalmol 1975;93:1153.
29. Traboulsi EI, Apostolides J, Giardiello FM, Krush AJ, Booker SV, Hamilton SR, Hussels IE. Pigmented ocular fundus lesions and APC mutations in familial adenomatous polyposis. Ophthalmic Genet 1996; 17:167–74.
30. Tiret A, Parc C. Fundus lesions of adenomatous polyposis. Curr Opin Ophthalmol 1999;10:168–72.
31. Santos A, Morales L, Hernandez-Quintela E, Jimenez-Sierra JM, Villalobos JJ, Panduro A. Congenital hypertrophy of the retinal pigment epithelium associated with familial adenomatous polyposis. Retina 1994;14:6–9.
32. Berk T, Cohen Z, McLeod RS, Parker JA. Congenital hypertrophy of the retinal pigment epithelium as a marker for familial adenomatous polyposis. Dis Colon Rectum 1988;31:253–7.
33. Traboulsi EI, Krush AJ, Gardner EJ, Booker SV, Offerhaus GJ, Yardley JH, Hamilton SR, Luk GD, Giardiello FM, Welsh SB, et al. Prevalence and importance of pigmented ocular fundus lesions in Gardner's syndrome. N Engl J Med 1987;316:661–7.
34. Tiret A, Taiel-Sartral M, Tiret E, Laroche L. Diagnostic value of fundus examination in familial adenomatous polyposis. Br J Ophthalmol 1997;81:755–8.
35. Tzu JH, Cavuoto KM, Villegas VM, Dubovy SR, Capo H. Optical coherence tomography findings of pigmented fundus lesions in familial adenomatous polyposis. Ophthalmic Surg Lasers Imaging Retina 2014;45:69–70.
36. Hennessy MP, Collins F, Coroneo MT. The distinction between multiple retinal pigment epithelial hamartomata (MRPEH) in familial adenomatous polyposis (FAP) and congenital hypertrophy of the retinal pigment epithelium (CHRPE). Aust N Z J Ophthalmol 1993;21:275–6.
37. Kasner L, Traboulsi EI, Delacruz Z, Green WR. A histopathologic study of the pigmented fundus lesions in familial adenomatous polyposis. Retina 1992;12:35–42.
38. Shields JA, Shields CL, Slakter J, Wood W, Yannuzzi LA. Locally invasive tumors arising from hyperplasia of the retinal pigment epithelium. Retina 2001;21:487–92.
39. Heegaard S, Larsen JN, Fledelius HC, Prause JU. Neoplasia versus hyperplasia of the retinal pigment epithelium. A comparison of two cases. Acta Ophthalmol Scand 2001;79:626–33.
40. Shields JA, Shields CL, Shields JA. Intraocular Tumors: An Atlas and Textbook, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
41. Trabucchi G, Brancato R, Pierro L, Introini U, Sannace C. Idiopathic juxtafoveolar retinal telangiectasis and pigment epithelial hyperplasia: an optical coherence tomographic study. Arch Ophthalmol 1999;117:405–6.
42. Teke MY, Ozdal PC, Batioglu F, Elgin U, Ozturk F. Congenital simple hamartoma of retinal pigment epithelium: clinical and imaging findings. Case Rep Ophthalmol Med 2012;2012:654502.
43. Grant LW, Seth RK. Congenital simple hamartoma of the retinal pigment epithelium. Semin Ophthalmol 2014;29:183–5.
44. Madgula IM, Adatia FA, Sagoo MS, Wescott M. Simple hamartoma of the retinal pigment epithelium in a man of African descent. Can J Ophthalmol 2009;44:e35–6.

45. Shukla D, Ambatkar S, Jethani J, Kim R. Optical coherence tomography in presumed congenital simple hamartoma of retinal pigment epithelium. Am J Ophthalmol 2005;139:945–7.
46. Shields CL, Shields JA, Marr BP, Sperber DE, Gass JD. Congenital simple hamartoma of the retinal pigment epithelium: a study of five cases. Ophthalmology 2003;110:1005–11.
47. Avitabile T, Franco L, Reibaldi M, Pulvirenti MA. Combined pigment epithelial and retinal hamartoma: long-term follow-up of three cases. Can J Ophthalmol 2007;42:318–20.
48. Shields CL, Thangappan A, Hartzell K, Valente P, Pirondini C, Shields JA. Combined hamartoma of the retina and retinal pigment epithelium in 77 consecutive patients visual outcome based on macular versus extramacular tumor location. Ophthalmology 2008; 115:2246–52.e3.
49. Grant EA, Trzupek KM, Reiss J, Crow K, Messiaen L, Weleber RG. Combined retinal hamartomas leading to the diagnosis of neurofibromatosis type 2. Ophthalmic Genet 2008;29:133–8.
50. Kang HM, Koh HJ, Chung EJ. Spectral-domain optical coherence tomography of combined hamartoma of the retina and retinal pigment epithelium in neurofibromatosis. Korean J Ophthalmol 2013;27:68–71.
51. Shields JA, Mashayekhi A, Ra S, Shields CL. Pseudomelanomas of the posterior uveal tract: the 2006 Taylor R. Smith Lecture. Retina 2005;25:767–71.
52. Pian D, Ferrucci S, Anderson SF, Wu C. Paramacular coloboma. Optom Vis Sci 2003;80:556–63.
53. Butler NJ, Furtado JM, Winthrop KL, Smith JR. Ocular toxoplasmosis II: clinical features, pathology and management. Clin Experiment Ophthalmol 2013;41:95–108.
54. Trevino R, Kiani S, Raveendranathan P. The expanding clinical spectrum of torpedo maculopathy. Optom Vis Sci 2014;91:S71–8.

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