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Diffuse Pigmented Lesions in the Outer Retina: An Unusual Fundus Appearance

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Abstract

Purpose: This report describes and provides a differential diagnosis for a patient with unusual bilateral retinal pigmented lesions. **Methods:** A 40-year-old woman was found to have multiple flat, gray lesions scattered across her fundi, becoming larger and more confluent toward the periphery. There were small drusenlike deposits in her foveae. The hyperpigmented lesions demonstrated hypoautofluorescence with thickening of the retinal pigment epithelium and disruption of the overlying layers on optical coherence tomography (OCT). Full-field electroretinography revealed generalized reduced a- and b-wave amplitudes. **Results:** Chest x-ray, breast ultrasound, mammography, and pelvic ultrasound findings were negative for malignant etiologic factors. Panel testing results for hereditary retinal dystrophy were negative. **Conclusions:** Although the clinical and OCT appearance of the lesions is similar to congenital grouped pigmentation, the symmetric and bilateral nature of ocular findings coupled with electroretinographic changes suggest a possible retinal dystrophy. This case adds to the phenotypic diversity of pigmented fundus lesions.

Keywords

congenital grouped pigmentation, congenital hypertrophy of the retinal pigment epithelium (CHRPE), hyperpigmented lesions, retinal dystrophy

Introduction

Pigmented fundus lesions are often identified incidentally on clinical examination.[1] Although frequently benign, several entities are associated with vision- and life-threatening complications. Clinicians should be familiar with the various patterns of retinal pigmentation because they may be the first indicator of an underlying malignancy that requires systemic evaluation and appropriate referral.[1]

Most pigmented lesions identified by fundus examination are unilateral.[1] Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is present in approximately 1% to 4% of the general population and exists in solitary and multifocal forms.[2] Multifocal CHRPE, also known as congenital grouped pigmentation or "bear tracks," is a sporadic condition associated with clusters of well-defined, flat, hyperpigmented lesions scattered throughout the fundus.[3] Although these lesions are benign and unilateral, the presence of multiple, bilateral pigmented ocular fundus lesions can be associated with familial adenomatous polyposis (FAP) or Gardner syndrome.[3] These hamartomas have a characteristic appearance, with a surrounding depigmented halo and a "comet tail" configuration, and are present in 70% of patients with FAP syndrome.[3]

We present a patient with unusual bilateral hyperpigmented outer retinal lesions detected incidentally. Many of the lesions were clustered together as seen in multifocal CHRPE; however, the lesions were diffuse, extensive, bilateral, and involved the maculae and thus are not characteristic of typical bear tracks.[3] In addition, our patient had bilateral hypopigmented drusenlike lesions in the foveae that were hyperautofluorescent. Our patient underwent a work-up that included full-field electroretinography (ffERG) and genetic testing with no specific etiologic factors identified to account for her clinical presentation. Our search of the medical literature did not find any other similar cases with similar presentation.

Methods

A 40-year-old woman of Chilean origin was referred to a retina specialist after she developed symptoms of floaters in her right eye. She denied any associated photopsias or vision loss. Her past ocular history was significant for one prior episode of iritis in her left eye. There was no history of ocular trauma and no

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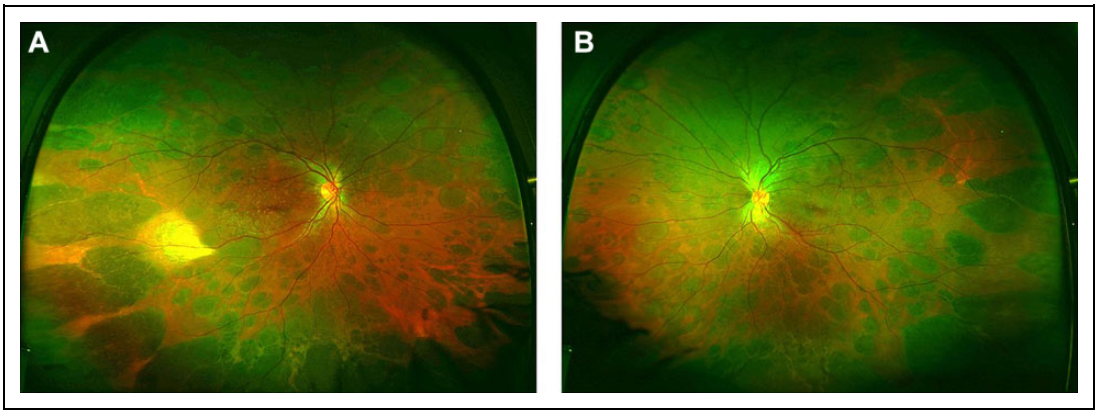

Figure 1. Widefield fundus photos (Optos) of the (A) right and (B) left eye demonstrating extensive multiple, round, flat, hyperpigmented lesions of varying sizes scattered throughout the retinae. There are small punctate hypopigmented drusenoid deposits in the maculae. Incidentally, there is an apparent region of myelinated nerve fiber layer along the inferotemporal vascular arcade in the right eye.

family history of ocular disease or blindness. Her medical history was unremarkable; she was not on any systemic medications, and she had no known allergies.

Results

When examined, the patient's best-corrected visual acuity was 20/20 OD and 20/20 OS. Her refractive correction was –0.25 + 0.75 × 097 OD and –1.00 + 2.25 × 074 OS. Intraocular pressures measured by Tono-Pen (Reichert Technologies) were 19 mmHg OD and 13 mmHg OS. Her pupils were equal and reactive to light and accommodation with no afferent pupillary defect. Anterior segment examination revealed clear corneas and lenses with no signs of anterior chamber inflammation.

Dilated posterior segment examination revealed multiple round and ovoid, gray, flat, hyperpigmented lesions of varying sizes scattered throughout the retina bilaterally (Figure 1). The lesions extended from within the arcades outward toward the periphery and became larger and more confluent closer to the periphery. There were no changes in the architecture of the retinal vessels as they coursed over the lesions. Small, soft yellow drusenlike deposits were identified in the foveal region. Vitreous syneresis was identified in the right eye, accounting for her symptoms of floaters. The vasculature was healthy with no signs of vasculitis of the retinal arterioles or veins. Incidentally, a small area of myelinated nerve fiber layer adjacent to the inferotemporal vascular arcade was noted in the right eye.

Spectral-domain optical coherence tomography (SD-OCT) (Heidelberg Engineering) demonstrated a quiet vitreous cavity with preservation of the inner retinal layers. Marked disruption and attenuation of the outer retinal layers including the outer nuclear layer and ellipsoid zone was identified. These areas corresponded to the areas of hyperpigmentation seen clinically (Figure 2). The RPE band appeared more hyperreflective in the areas corresponding to the lesions. The appearance of the choroid was unremarkable, with no evidence of choroidal thickening. There was a mild epiretinal membrane evident in the right eye. Widefield fundus autofluorescence (Optos) was performed, and all the lesions appeared to be uniformly hypoautofluorescent. The yellow deposits previously identified in the foveae were hyperautofluorescent (Figure 3).

Owing to the diffuse, atypical, symmetric appearance of these lesions, further testing with ffERG using DTL electrodes (Model 4200c, LKC Technologies) and the standard International Society for Clinical Electrophysiology of Vision (www.ISCEV.org) protocol was arranged. There was a nonspecific, generalized, mild to moderate reduction of the amplitudes of rod- and cone-driven responses in both eyes (Table 1).

The patient's serum was collected for DNA testing to investigate for genetic etiologic factors. A retinal dystrophy panel test consisting of 266 genes with known associations with retinal disorders was performed (Blueprint Genetics). No disease-causing or plausible novel variants were identified.

Although her retinal examination was not characteristic of a paraneoplastic disease such as bilateral diffuse uveal melanocytic proliferation (BDUMP), the patient was further questioned about the possibility of a malignant cause. She denied any symptoms consistent with urogenital or intraabdominal malignancy. She also denied any personal or family history of breast or colon cancer. She did, however, report a history of ovarian cancer diagnosed in her mother at age 55 years and in 2 maternal cousins at ages 40 and 55 years. The patient's chest x-ray, breast ultrasound, mammogram, and pelvic ultrasound results were negative for malignancy.

The patient's clinical appearance was neither characteristic of BDUMP nor in keeping with the pigmented lesions present in FAP syndrome. Given the presence of bilateral, grouped, hyperpigmented lesions, evidence of increased RPE reflectivity on OCT, and negative genetic and malignant work-up, her fundus appearance would appear to be in keeping with extensive grouped CHRPE. However, the depressed rod- and cone-driven ERG amplitudes in combination with drusenoid changes in the foveae and an overall symmetric fundi appearance would suggest a retinal dystrophy. We have not come across a similar posterior segment appearance in the literature. At follow-up 1 year later, she denied any vision change, and her examination and findings have remained the same.

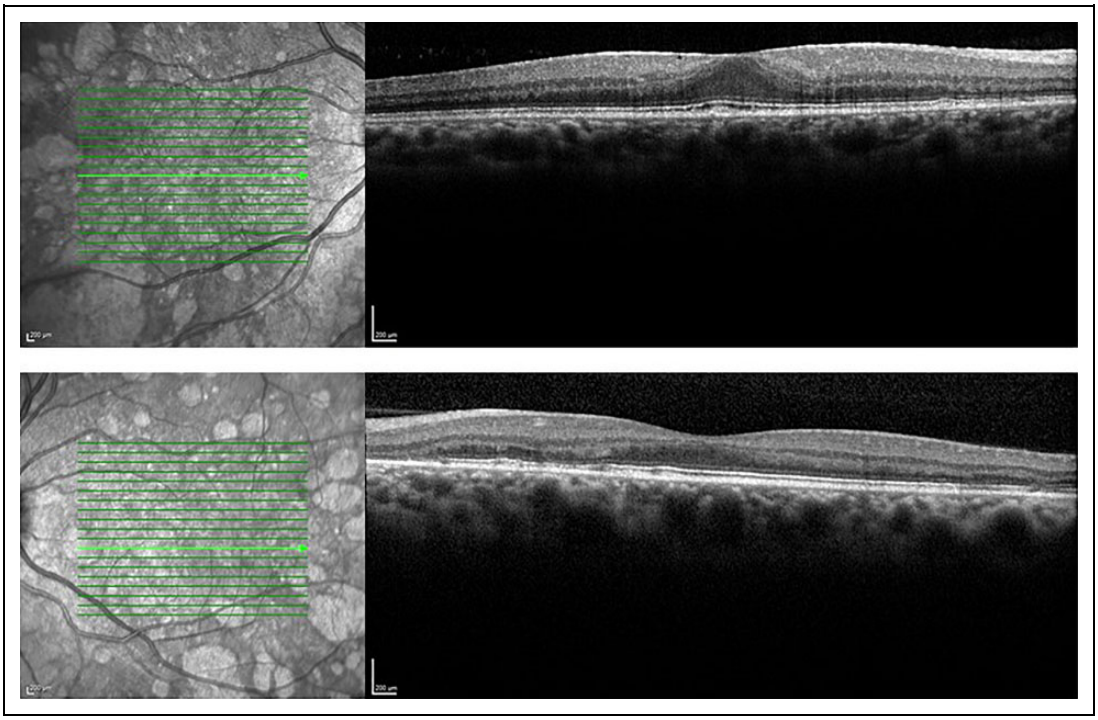

Figure 2. Spectral-domain optical coherence tomography (Heidelberg Engineering) of the (above) right and (below) left maculae illustrating en face and cross-sectional retinal images. There is a stippled hyperreflective signal in the outer retinal layers of both eyes. The retinal pigment epithelial layer demonstrates increased reflectivity, especially in the left eye, with attenuation of overlying outer retinal layers corresponding to the hyperpigmented lesions apparent clinically. Incidentally, there is a mild epiretinal membrane in the right eye.

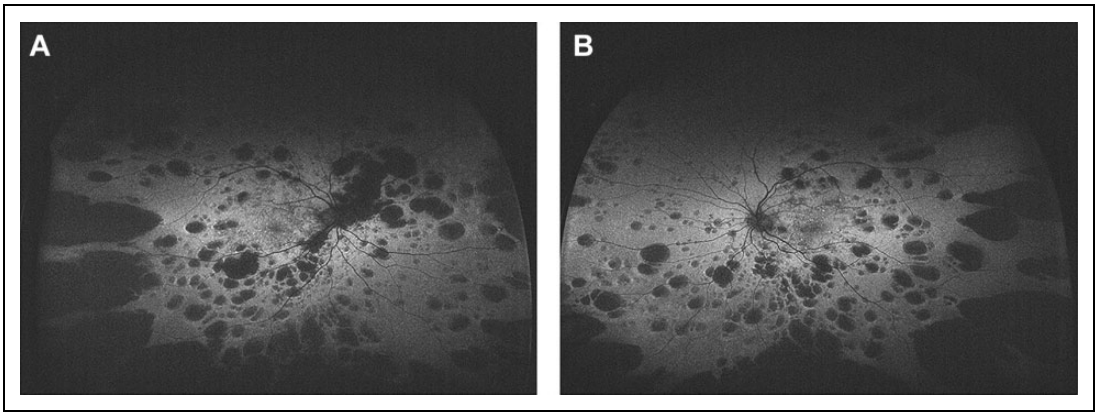

Figure 3. Widefield autofluorescence photos (Optos) of the (A) right and (B) left eye demonstrating uniform hypofluorescence corresponding to the hyperpigmented lesions apparent clinically. There are hyperreflective deposits in the maculae that correspond with the hypopigmented drusenoid deposits apparent on examination.

Conclusions

There is an extensive differential diagnosis for pigmented fundus lesions that includes CHRPE, congenital grouped pigmentation, choroidal nevi, reactive hyperplasia of the RPE, and retinal dystrophies, to name a few. Some of these conditions, such as reactive hyperplasia of the RPE, would become more apparent when a history of uveitis or ocular trauma is obtained.[4] In addition, rod-cone retinal dystrophies such as retinitis pigmentosa can be accompanied by symptoms of nyctalopia, constricted peripheral visual fields, and reduced visual acuity; a family history of similar symptoms may also be elicited.[5] Other lesions, such as CHRPE, bear tracks, and choroidal nevi, can be detected in the absence of symptoms.

When considering the incidental finding of extensive, diffuse, bilateral hyperpigmented lesions in our patient, the differential diagnosis can be narrowed. CHRPE represents well-circumscribed lesions in the RPE that are largely unilateral. They can be solitary or grouped, and they are typically dark gray or black but may occasionally be hypopigmented.

Table 1. Full-Field Electroretinogram of the Right and Left Eye Demonstrating Generalized Mild to Moderate Reduction in the Amplitudes of Rod- and Cone-Driven Responses.

	Waveform Amplitudes		
Electroretinogram Phases	Right Eye	Left Eye	Normative Data Range
Photopic[a]			
a-wave	12.1 μV	18.5 μV	16-20 μV
b-wave	48.1 μV	62.5 μV	83-105 μV
30 Hz flicker[a]	31.5 μV	48.8 μV	68-118 μV
Scotopic dim flash b-wave[a]	91.7 μV	97.7 μV	119-157 μV
Scotopic bright flash[a]			
a-wave	92 μV	115.7 μV	136-150 μV
b-wave	115.4 μV	159.9 μV	248-306 μV

[a]International Society for Clinical Electrophysiology of Vision standard conditions.

These lesions are asymptomatic and are not associated with systemic disease.[6] Multifocal CHRPE tends to have a sectoral distribution but can be extensive.[2] With fundus autofluorescence imaging, CHRPE appears hypoautofluorescent. OCT imaging shows that it is associated with thickened or irregular RPE and loss of outer retinal layers overlying the lesions, especially the outer plexiform layer.[7] ERG and electro-oculogram results are generally normal.[8] Our patient presented with extensive hyperpigmented lesions that appeared like multifocal CHRPE clinically and on OCT imaging. However, the bilateral and symmetric nature of the lesions coupled with reduced rod- and cone-driven amplitudes of the ffERG and drusenoid foveal changes would not be typical for multifocal CHRPE.

Lesions appearing like CHRPE but occurring in an irregular, multifocal, and bilateral distribution may represent the pigmented ocular fundus lesions seen in FAP or Gardner syndrome. These lesions are, however, distinct in that they tend to be smaller than CHRPE and are often tear-shaped or oval with a characteristic rim of surrounding hypopigmentation. These lesions also tend to be located closer to the posterior pole than CHRPE or bear tracks.[4] Despite our patient having extensive bilateral pigmented lesions, the appearance of each lesion is not characteristic of those seen in FAP syndrome. Furthermore, our patient denied any personal or family history of intestinal polyps or colorectal cancer.

Another paraneoplastic phenomenon that presents with bilateral pigmented fundus lesions is BDUMP. Clinically, the hallmark of BDUMP is the presence of multiple round or oval red patches at the level of the RPE that show intense early hyperfluorescence on fluorescein angiography. Other associated findings include thickening of the uveal tract, multiple elevated pigmented and nonpigmented uveal melanocytic tumors, exudative retinal detachment, and rapid progression of cataracts.[9] In this condition, the ffERG has reduced scotopic and photopic amplitudes. Associated OCT findings include RPE atrophy, presence of subretinal fluid, pigment deposition, and photoreceptor loss.[10] A variety of cancers have been associated with BDUMP; however, urogenital carcinoma, especially ovarian carcinoma, is the most commonly associated malignancy.[10] Although we have presented a case with bilateral, multiple round lesions in the outer retina, there are several features that make a diagnosis of BDUMP less likely. Notably, our patient's preserved vision, young age, and absence of symptoms or signs of systemic malignancy support an alternative diagnosis. In addition, her lesions appeared hypofluorescent as opposed to the characteristic hyperfluorescence seen in BDUMP.

Finally, bilateral, symmetric, pigmented fundus abnormalities can be a feature of a retinal dystrophy. The classic features of retinitis pigmentosa, including optic disc pallor, midperipheral intraretinal bone-spicule pigmentation, and arteriolar attenuation, were not present in our patient. Furthermore, there is no family history of a similar documented fundus appearance; however, we have yet to examine her immediate family members. Although classic retinitis pigmentosa is unlikely in our patient, her presentation may be in keeping with an underlying retinal dystrophy given her symmetric, bilateral condition with associated ERG changes. However, panel testing results of known genes associated with retinal dystrophies were negative in our patient.

In summary, we present a 40-year-old patient with an unusual fundi appearance in the absence of symptoms. Although this case may represent a remarkably atypical presentation of congenital grouped pigmentation or multifocal CHRPE, there are several features that point toward a retinal dystrophy as the cause. A gene abnormality other than those tested in the retinal dystrophy panel may be responsible. To investigate this further, however, would likely require a broader approach using whole-exome sequencing.

Ethical Approval

This study followed the tenets of the Declaration of Helsinki. Given the nature of this study as a case report, formal review by a research ethics board was not required.

Statement of Informed Consent

Consent was obtained from the patient for the publication of this case report, including medical record details, fundus photos, and electrophysiologic and ancillary testing.

Declaration of Conflicting Interests

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