RETINAL PIGMENT EPITHELIAL DETACHMENT: THREE CASE REPORTS
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ABSTRACT

Pigment epithelial detachment (PED) is a common entity in age-related macular degeneration and central serous chorioretinopathy. Nevertheless, it can manifest rarely without an obvious causative factor. The authors report 3 cases of PED that were atypical in terms of pattern and age presentation. The second case is associated with sickle cell disease, which has not been reported in literature as far and that could add to our knowledge of this disease entity. Methods: The three cases underwent ophthalmological examination, optical coherence tomography, fundus autofluorescence, fundus fluorescein angiography, full-field electroretinogram and visual evoked potential. Full medical evaluation was done. Results: Bilateral ocular fundus examination showed multiple, rounded lesions scattered all over the fundus in three cases and peripheral retinal pigment epithelial pigmentary changes in the periphery in two cases. Medical evaluation showed one case of sickle cell disease. Conclusion: The number of reports on atypical pigment epithelial detachment and their correlation is limited. In addition its occurrence with sickle cell disease in the second case is a novel correlation which has to be reported and followed-up.

INTRODUCTION

Retinal pigment epithelial detachment (PED) is a condition where the retinal pigment epithelium (RPE) separates from the underlying Bruch's membrane due to disruption of the junctions between them1,2. PEDs have been described in many choroidal disorders however, the most common form is that associated with advanced stages of exudative or neovascular age-related macular degeneration (AMD) and other disorders of choroidal neovascularization. Most of those patients have macular drusen in both eyes3. PED is also a common finding in Idiopathic central serous chorioretinopathy (CSC), other choroidal diseases like polypoidal choroidal vasculopathy, and some hereditary chorioretinal degenerations as multifocal Best’s vitelliform dystrophy4-8. In addition to the differential diagnosis when managing these patients, there are inflammatory choroiditis as sarcoidosis, Vogt-Koyanagi-Harada disease and infectious choroiditis. Various systemic disorders were reported to be associated with PED like malignant
hypertension, leukemia, lymphoma and some renal diseases\textsuperscript{9-13}. Whether or not the pathogenesis of PED in all these disorders have a common background is in doubt. Many cases presented with PED have none of these ocular or systemic causes and are considered idiopathic. The pathophysiological process of the development of PED is not well known, however many theories were put to explain this pathological event. The most common one is that of Gass\textsuperscript{12}, which stated that there, is a pathological interruption of the normal anatomic junction between the basement membrane of the RPE and the inner collagenous layer of Bruch’s membrane allowing serous fluid leakage from the underlying choriocapillaris or the choroidal neovascularization to gain access into the sub-RPE space. Another hypothesis, which could be the most accepted now, is that fluid accumulates in the sub-RPE space due to failure of elimination of the metabolic waste products of the RPE cells, which are unable to reach the choroidal circulation\textsuperscript{14}. The aim of this report is to describe three cases of atypical presentation of bilateral multiple PED.

Case 1

A 50-year-old woman having bilateral blurring of vision for 3 months. On examination, her best-corrected visual acuity (BCVA) was 20/25 in both eyes. Color vision was normal in both eyes. Amsler grid test was found negative for metamorphopsia in both eyes. Slit-lamp examination revealed unremarkable anterior segment in both eyes and intraocular pressure (IOP) of 12 mmHg in both eyes using the Goldmann applanation tonometer (Haag-Streit USA, Mason, Ohio). Bilateral fundus examination showed multiple, round translucent and yellowish white lesions scattered all over the fundus, more condensed in the macular area between the optic nerve head and the fovea, some were confluent in both eyes. Peripheral RPE pigmented changes are present in the peripheral fundus bilaterally. Cup/Disc ratio was about 0.1 in both eyes (Figure 1). Measurement of the diameter was done for these lesions and it was found that the size varies; however, the largest was around 0.67 mm in diameter. Fundus Auto Fluorescence-FAF- (TOPCON corp., Tokyo, Japan) showed bilateral positive auto-fluorescence for some lesions. Fluorescein fundus angiography-FFA- (TOPCON corp., Tokyo, Japan) of the fundus showed early simultaneous hyperfluorescence in all lesions, which became more hyperfluorescent in the late frames with preserved size and shapes throughout the whole frames and some of them showed dense hyperfluorescence. There was no leakage in any of the lesions at any frame in both eyes (Figure 2). Peripheral pigmentary changes appeared as hypofluorescent areas. Primary diagnosis of bilateral drusen with PED was made. Spectral-domain optical coherence tomography of the macula (cirrhus OCT\textsuperscript{TM}, Carl Zeiss) demonstrated multiple dome-shaped elevations with hyper-reflective RPE shadows with mixture of underlying optically-empty and optically-opaque multiple PED areas, some of them with drusenoid-filled spaces. The more dense lesions appeared as hyper-reflective RPE shadows with underlying hyper-reflective areas of drusen (Figure 3). Electrophysiological studies were done using the LKC’s visual diagnostic systems (LKC Technologies, Inc., Gaithersburg, USA). The flash visual evoked potentials (VEP) revealed bilateral subnormal response with normal amplitude and delay in latency while the pattern VEP showed bilateral overall reduction in amplitude with normal latency. Full-field
Electroretinogram (fERG) showed reduced b-wave amplitude and delay in latency. Full medical evaluation, including ocular and systemic history, complete blood count, blood chemistry, erythrocyte sedimentation rate, antinuclear antibodies, angiotensin-converting enzyme, chest radiographs, quantiferon test, and consultation for rheumatologic examination failed to find any systemic etiology. There were no systemic medications intake and family history was irrelevant. No treatment was advocated for her. In her follow-up visits along one year, ocular examination showed the same fundus picture in both eyes with the same level of visual acuity. OCT images showed the same lesions. Regular follow-up visits were advised for her.

Figure 1: Fundus Photography of both eyes. Bilateral multiple, round and translucent and yellowish white lesions scattered all over the fundus, more condensed in the macular area between the optic nerve head and the fovea. Note the pigmentary changes in the peripheral fundi.

Figure 2: Upper) FAF images show autofluorescence of some of the lesions. Middle & lower) FFA demonstrate bilateral early simultaneous hyperfluorescence in all lesions with constant size & shape & without leakage throughout all the frames.

Figure 3: OCT scans of the right eye (upper) & left eye (lower) show multiple dome-shaped elevations with a hyper-reflective RPE shadow & underlying optically empty areas of the multiple PED areas and other optically opaque hyper-reflective areas of drusen. The inner segment/outer segment (IS/OS) layer is disrupted at the area of the lesions. The dome-shaped elevations are irregular in contour in some of the lesions specially the optically-free ones. Note the RPE map of both eyes showing multiple dome-shaped elevations.
Case 2

A 47-year-old woman is having bilateral diminution of vision for the prior one year. She is a known case of sickle cell anemia (HbSS disease) with reported crises and multiple blood transfusions; last time was one year back. On examination, her BCVA was 20/40 in her right, and 20/80 in her left eye. Color vision was normal in her both eyes. Amsler grid test was found to be affected in both eyes with a paracentral line distortion. Slit-lamp examination revealed unremarkable anterior segment in both eyes and an IOP of 14 mmHg in both eyes using the Goldmann applanation tonometer (Haag-Streit USA, Mason, Ohio). Fundus examination showed multiple, round translucent lesions occupying the whole macular area, some were confluent in both eyes however they were more numerous in the left fundus. Similar lesions were present outside the macular area outside the arcades in the four quadrants. Peripheral RPE changes were present in the peripheral fundus bilaterally but much less than the first case. Cup/Disc ratio was about 0.2 in both eyes (Figure 4). We tried to correlate other known findings of sickle-cell retinopathy to the findings. The patient did not give any history of previous visual disturbances during her life. The fundus was free from any signs of sickle-cell retinopathy or any lesions denoting previous vascular occlusion. The anterior segment was free also from any lesions or any abnormal cork-screw vessels. FAF showed bilateral positive auto-fluorescence for some of the lesions. FFA showed bilateral early simultaneous hyperfluorescence in all lesions, which became more hyperfluorescent in the late frames with preserved size and shapes throughout the whole frames. There was no leakage in any of the lesions at any frame in both eyes (Figure 5). Primary diagnosis of PED areas was made. Spectral-domain optical coherence tomography of the macula (cirrus OCT™, Carl Zeiss) demonstrated multiple dome-shaped elevations with hyper-reflective RPE shadows with underlying optically-empty multiple PED areas (Figure 6). Electrophysiological study was done using the LKC’s visual diagnostic systems (LKC Technologies, Inc., Gaithersburg, USA). It showed almost the same results as the first case. An extensive medical evaluation, like the previous case was done which revealed sickle-cell disease only. She is on Folic acid for the last 10 years. No other systemic medications. Positive family history of sickle-cell disease is present. No treatment was advocated for her. In her follow-up visits along one year, no vascular occlusive attacks occurred. Ocular examination showed the same fundus picture in both eyes with the same level of visual acuity. OCT images showed the same PED lesions. Regular follow-up visits were advised for her.

Case 3

A 45-year-old woman presented with bilateral diminution of vision for the prior six months which was stationary. On examination, her BCVA was 20/20 in the right eye and 20/25 in the left eye. Color vision was normal in both eyes. Amsler grid
test was found mildly positive for metamorphopsia in the left eye. Slit-lamp examination revealed unremarkable anterior segment in both eyes and an IOP of 14 mmHg in both eyes using the Goldmann applanation tonometer (Haag-Streit USA, Mason, Ohio). Bilateral fundus examination showed multiple, round translucent white lesions scattered all over the fundus, with the larger lesions located in the macular area. There was no peripheral RPE pigmentary changes like the previous two cases. Cup/Disc ratio was about 0.3 in both eyes (Figure 7). The lesions had variable diameter; however, the largest was around 1.7 mm in diameter (Figure 7). Fundus angiography-FFA-(TOPCON corp., Tokyo, Japan) of the fundus showed early simultaneous hyperfluorescence in all lesions, which became more hyperfluorescent in the late frames with preserved size and shapes throughout the whole frames and some of them showed dense hyperfluorescence. There was no leakage in any of the lesions at any frame in both eyes (Figure 8). No peripheral pigmentary changes like the previous two cases, although the hyperfluorescent lesions were more numerous. Primary diagnosis of bilateral drusen with PED was made. Spectral-domain optical coherence tomography of the macula (Topcon 3D OCT-2000) demonstrated multiple dome-shaped elevations with hyper-reflective RPE shadows with underlying optically-empty multiple PED areas (Figure 9). Electrophysiological study was done using the LKC’s visual diagnostic systems (LKC Technologies, Inc., Gaithersburg, USA). It showed almost the same results as the previous two cases. Full medical and laboratory evaluation turned out to be normal. No treatment was advocated for her. In her follow-up visits along six months, ocular examination showed the same fundus picture in both eyes with the
same level of visual acuity. OCT images showed the same lesions. Regular follow-up visits were advised for her.

DISCUSSION

PED has been classified on clinical and angiographic appearances by different observers. By literature reviewing, we found a lot of classifications and explanations. Poliner et al\textsuperscript{15} classified PED as serous, turbid, and hemorrhagic in 3 groups. Casswell et al\textsuperscript{16} classified PED into 5 groups according to FFA appearances as follows: (i) early hyperfluorescence, (ii) late hyperfluorescence, (iii) shallow and limited hyperfluorescence, (iv) irregular hyperfluorescence (fibrovascular PED, hyperplastic, or elevated area of RPE, field that can block fluorescence, serous detachment of RPE, hemorrhagic detachment of RPE, drusenoid detachment of RPE), and (v) large confluent drusen area. Hartnett et al\textsuperscript{17} classified PED into six groups: (i) pseudovitelliform PED, (ii) confluent drusen type PED, (iii) serous PED, (iv) vascular PED, (v) hemorrhagic PED, and (vi) retinal vascular anomaly PED. Gass et al\textsuperscript{18} reported similar cases in middle-age healthy subjects without any associated ocular or systemic problems. These patients had visual acuities ranging from 20/30 to 20/16 initially with neither FFA nor OCT evidence of CNV. Yi et al\textsuperscript{19} also reported a similar case of a 32-year-old woman with bilateral multiple PEDs without any known pathology, throughout the posterior poles of both eyes. Several subretinal hemorrhages were noted in the right eye. FFA found multiple small, round, uniformly hyperfluorescent lesions in both eyes and the blocked fluorescence caused by subretinal hemorrhages in the right eye adjacent to numerous PEDs. Neither FFA nor ICG found any evidence of CNV. Sawa et al\textsuperscript{20} reported on a 46-year-old man who had idiopathic bilateral multiple serous PEDs for more than 7 years, especially in the macular area of the left eye. Later in the left eye, a bullous exudative neurosensory
retinal detachment developed as a result of a leakage point at the edge of the largest PED. The leaking point in the left eye was treated with laser photocoagulation. This patient had a final visual acuity of 20/20. Siegel et al\textsuperscript{21} reported 1 case and Roberts and Haine\textsuperscript{22} described 2 cases with multiple idiopathic serous PEDs with relatively good vision; they believed that these presentations were possible variants of CSC. They emphasized the striking similarities between the clinical entity of multiple serous PED and CSC, as both diseases display similar age of onset, show a predilection for men, and have a correlation with psychological stress. The authors postulated that these represent variants of the same disease process and defined this a variant form of CSC as multiple lesions consisting of an elevation of the RPE with minimal or no neurosensory detachment. Bandello et al\textsuperscript{23} described an uncommon case of a 25-year-old woman affected by bilateral idiopathic multiple serous detachments of the macular retinal pigment epithelium. During the FFA follow-up, in either macular area, one of these detachments resulted in a typical CSC active leakage point. These findings detail that idiopathic serous detachments of the retinal pigment epithelium may represent predisposing changes for the development of macular neurosensory retinal detachment. However, there is no study available indicating from which PED CSC may develop. In 1976, Noble et al\textsuperscript{7} described cases of middle-age patients with idiopathic multiple, but relatively few, isolated serous PED, of which fundus photographs and fluorescein angiograms suggested a diagnosis of atypical CSC. Lewis\textsuperscript{6} reviewed the clinical course of idiopathic serous PED in patients younger than age 55 who did not receive any treatment. He reported follow-up data from 32 eyes of 21 patients with serous PED, 10 of whom had multiple bilateral PED. There was no accompanying evidence of AMD or other ocular or systemic diseases in all patients. Almost all of these eyes had a final visual acuity of 20/50 or better after an average follow-up period of 7 years. He reported similarities in the characteristics and clinical course between idiopathic serous PED and CSC. In a similar fashion, Klein et al\textsuperscript{24} reviewed data of untreated eyes with serous PED. Patients were younger than 50 years of age and displayed no accompanying fundus pathology. During the course of the study neither CNV nor secondary complications developed in any of the patients. The final visual acuity was 20/30 or better in all eyes. The former two reports postulated that serous PED may well be considered a form of CSC in which the PEDs, rather than an overlying sensory retinal detachment, are the predominant feature. PED is a common finding in CSC. Patients with CSC, which can be called idiopathic choroidal vascular hyperpermeability, are more likely to have type A personality\textsuperscript{25}. A case-control study determined the use of corticosteroids and having hypertension as an important risk factor for patients with CSC\textsuperscript{26}. There are two main types of CSC, “typical” or “classic” type is usually seen in younger patients. This type causes an acute localized detachment of the retina with mild to moderate loss of visual acuity associated with one or a few focal leaks seen during fluorescein angiography and “diffuse retinal pigment epitheliopathy,” “decompensated RPE,” or “chronic CSC”, which has widespread alteration of pigmentation of the RPE in the posterior pole related to the chronic presence of shallow subretinal fluid\textsuperscript{27,28}. In acute CSC cases, neurosensory detachment associated with PED is a common finding in OCT. In chronic CSC cases, loss of photoreceptor outer segments, flattened foveal contour,
thinning of the retina, and widespread RPE irregularities could be observed on OCT. Serous PEDs are reported frequently in conjunction with central serous chorioretinopathy\textsuperscript{29}. In addition, some originally serous PEDs have been shown to transform to typical CSC, which include other components as well. After photoocoagulation treatment of isolated serous PEDs, and regression of the lesion is a similar finding with CSC. Curing with the same treatment may suggest a similar pathogenesis for PED and CSC\textsuperscript{30}. Giovannini et al\textsuperscript{31} observed that PEDs were frequently associated with choroidal leakage and venous dilatation, and this supports the hypothesis that an idiopathic serous PED is a variant of CSC. Other than CSC, AMD is another disease in which PED could be detected. AMD occurs more frequently in the elderly; however, symptoms such as drusen, subretinal neovascularization, intraretinal or subretinal fluid, and geographic atrophy generally accompany PED. PEDs detected in AMD are usually fibrovascular PEDs. FFA findings, particularly slow filling, delayed filling, irregular filling, and notching, indicate the presence of PED in AMD. Demonstrating the polypoid dilatation areas in the indocyanine green angiography (ICG) in polypoid choroidal vasculopathy (PCV), which is recognized as a subtype of AMD, may be useful for definitive diagnosis. Other findings are similar to that of AMD\textsuperscript{17,32}. Lumbroso et al\textsuperscript{33} investigated the relationship between morphological differences and etiology in PED by using enhanced deep imaging spectral domain OCT (EDI SD-OCT). Examination of 30 eyes of 22 patients revealed that PED shape was circular in 88.8% of CSC patients, with a smooth inner appearance, while irregular or multilobular in 76.2% of AMD patients with granular inner appearance. Clear PED generally accompanied CSC. Hashas A et al\textsuperscript{34} described a 27-year-old female patient with multiple isolated serous PED, without other symptoms of CSC and another eye disease. The authors concluded its isolated nature, and mentioned that monitoring of their patient for a long period of time will clarify if this is a pure isolated PED case or the initial stage of CSC. Our atypical three cases of PEDs are reported because they showed unusual picture being numerous, multiple and scattered all over both fundi. The three patients were younger than the usual spectrum of age of AMD which is considered the most common cause of PED, and slightly older than the usual age for CSC (50-, 47-, & 43-year-old, respectively) and were females (CSC has more male predilection). Most lesions’ contents are clear apart from drusenoid material in the first case giving the picture of serous and drusenoid PED neither giving any sign of subretinal neovascularization neither in OCT nor in FFA. The first and third cases were medically free completely, the second one gave a history of sickle-cell anemia with history of multiple sickle crisis and repeated blood transfusions. The OCT images of the patients showed the characteristic features of PED as shown in the figures with the first case showing some lesions filled with opaque drusenoid-like material, irregular dome contour of the lesions and disruption in the IS/OS region. FFA was done also to detect any site of focal leakage but it showed only hyperfluorescent constant areas, excluding wet AMD diagnosis. The first case had peripheral pigmented lesions resembling krill disease (acute retinal pigment epitheliitis). Although we could not apply it in this case due to the lack of the typical picture mentioned in Krill disease regarding the sudden deterioration of vision and later recovery of the cases with residual pigmentary changes, it presented with
decreased VA and central scotoma in healthy young adults and thus can be confused with CSC. However, it can be differentiated from CSC with hypopigmented halos surrounding macular lesions and also with the lack of leakage from hyperfluorescent pigment clusters, which are similar to Elschnig spots. The peripheral retinal PED and mottling with hyperpigmented and hypopigmented spots is not usual in this type of cases and neither reported in AMD nor in CSC except in central areas of the fundus which might suggest a widespread RPE malfunction. The third case has the largest diameter central PED reaching the size of the optic disc and has the lesions extending more peripherally and numerously than the other two cases. Considering the age of the first patient (50-year-old) and the drusenoid-like PED, we were inclined to consider this either an atypical case of AMD or an atypical chronic retinal pigment epitheliitis regarding the peripheral picture of both fundi. The second case of sickle-cell disease is the first case to be reported in the literature to have concomitant PED (to our knowledge after Pubmed, Medscape & Scopus engine searches). The FFA and OCT findings were typical of serous PED with minimal peripheral pigmentation. Should we consider it a sequelae of sickle-cell repeated crises in the choroidal circulation? Or is it merely a timely coincidence? The fundus picture is totally free of other signs of sickle-cell retinopathy. This case might be categorized as sickle-cell disease sequelae or an atypical case of CSC in a sickle cell disease patient. The third case with the largest and most numerous PEDs without peripheral pigmentary changes might be an atypical variant of CSC. We did not have access to ICG to check the choroidal vessels. The diminished ERG and VEP amplitudes could be attributed to the widespread PEDs but cannot explain it.

CONCLUSION

Three cases of PED which can be categorized as atypical due to their peculiar presentation and association of the second case with sickle-cell disease which is not presented before. The cause and course of atypical PED are yet to be elucidated with the emergence of more cases in the literature.

DISCLOSURE

The authors have no financial interest in any of the materials mentioned in this article.

REFERENCES


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