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Surgical approach in a case of unilateral retinal pigment epithelium dysgenesis and literature review

Asterios Diafas [a], Anna Dastiridou [a], Asimina Mataftsi [a], Nikolaos Ziakas [a], Sofia Androudi [b,*]

[a] 2nd Department of Ophthalmology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, "Papageorgiou" General Hospital of Thessaloniki, Thessaloniki, Greece
[b] Department of Ophthalmology, University of Thessaly, Larissa, Greece

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ABSTRACT

Purpose: To present a case of unilateral retinal pigment epithelium dysgenesis (URPED) complicated with tractional retinal detachment and macular hole formation, and highlight the successful anatomical and functional restoration following surgical repair. To conduct an updated review of the literature.

Observations: A 16-year-old asymptomatic female presented with a unilateral atypical peripapillary lesion of the retinal pigment epithelium (RPE) in the left eye. At baseline, best corrected visual acuity (BCVA) was 20/20 and anterior segment examination was unremarkable. Fundus examination revealed an irregularly shaped atrophy of the RPE adjacent to the optic disc with scalloped border of RPE hyperplasia and a fibroglial proliferation in the overlying retina. Optical coherence tomography demonstrated mild changes of the RPE and the outer retina layers. Three years after initial diagnosis, the patient was referred to our clinic due to blurry vision. Complete ophthalmological evaluation revealed tractional retinal detachment with full thickness macular hole formation. Pars plana vitrectomy with epiretinal membrane removal and internal limiting membrane peeling led to anatomical recovery of the macular area with BCVA of 20/32 at four-months postoperatively.

Conclusions and importance: This is the first report of tractional retinal detachment and macular hole as rare complications of URPED. Systematic follow-up examinations seem to be essential for the prevention of permanent visual loss, whereas prompt surgical intervention can contribute to visual acuity restoration in complicated cases.

1. Introduction

In 2002, a rare posterior pole disorder was firstly recognized and described by Cohen et al., based on its characteristic fundoscopic appearance of central atrophic area and peripheral retinal pigment epithelium (RPE) hyperplasia and fibrosis. This unique clinical entity was initially named as "Unilateral, idiopathic leopard-spot lesion of the RPE".[1] In the literature, there are several conditions that appear with a "leopard-spot" pattern and this term was nonspecific and quite confusing. Thus, in 2009 the authors proposed altering the previous name to "Unilateral retinal pigment epithelium dysgenesis - URPED", mainly based on its pathognomonic characteristics in fundoscopy, fundus autofluorescence (FAF) and fluorescein angiography (FA). The URPED typically appears as a lesion with scalloped margins of mild fibrosis and atrophy, surrounding areas of RPE hyperplasia. In the mid-periphery, it is heterogenous with distinct lacunae of hyperplastic RPE, whereas the central area is characteristically atrophic. Additionally, FA pictures demonstrate an inverted pattern when compared to FAF ones. The hyperautofluorescent areas of the lesion on the FAF (i.e. the borders and the lacunae) are hypofluorescent on FA, while the central atrophic hypoautofluorescent area is seen as a well-defined hyperfluorescent lesion in FA due to window defect phenomenon.[2]

The limited number of published cases in the literature results in insufficient information regarding the natural history and the pathophysiological mechanisms involved in this rare clinical entity. The natural course of the lesions is stable, although slow progress over time has been reported in cases with long-term follow-up. The prognosis of visual acuity is generally good, except for the cases which develop complications, such as choroidal neovascularization (CNV), epiretinal membrane (ERM), retinal folds, retinal detachment (RD) and foveal atrophy.[2] Thus, the role of relatively new and non-invasive techniques of optical coherence tomography (OCT) and optical coherence tomography

* Corresponding author.
E-mail address: androudi@otenet.gr (S. Androudi).

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angiography (OCTA) is valuable in the assessment of URPED's vitreoretinal interface disorders and especially in monitoring the development and treatment of secondary CNV membrane.[3]

To the best of our knowledge, this is the first case of unilateral retinal pigment epithelium dysgenesis complicated with retinal detachment and macular hole formation that demanded immediate surgical intervention. This case emphasizes the importance of follow-up examinations as well as the early diagnosis in the final visual outcome despite the stable course in the majority of URPED cases. In addition to our case, we present a brief literature review summarizing the main characteristics of all reported cases (Table 1).

2. Case report

A 16-year-old girl was referred to our department due to an incidental finding in the posterior pole of the left eye during routine ophthalmological examination. The patient was asymptomatic with best corrected visual acuity (BCVA) being 20/20 in both eyes. Slit-lamp examination was unremarkable in both eyes, whereas intraocular pressure was 12 mmHg and 14 mmHg in the right and left eye, respectively. Despite that the posterior segment in the right eye appeared normal, the fundus of the left eye revealed a large solitary whitish-yellowish flat lesion with fringe-like margins, adjacent to the optic nerve that extended to the supero-temporal area including the corresponding vascular arcade (Fig. 1a). The central area of the lesion was characterized by thinned and atrophic RPE, whereas fibrosis and RPE hyperplastic changes were observed in the mid-peripheral lacunae and in the lesion's scalloped borders. A fibroglial proliferation was also noticed above the retina and the optic nerve head.

Ophthalmic history of the patient was negative, whereas the patient denied any history of ocular trauma or inflammation. The past medical history revealed a febrile illness of unknown origin and patient's hospitalization three months prior to presentation. The complete patient's physical examination was normal and chest x-ray was unremarkable for any pathology. Blood tests, including full blood count (FBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as well as a Quantiferon blood test were also negative. FAF showed hypoautofluorescence of the central atrophic area, allowing a clear view of the lesion's borders and the patches of RPE hyperplasia (Fig. 1b). Optical coherence tomography (OCT) revealed disruption of the outer layers of the retina with shallow RPE detachment nasally and thinning of the underling choroid (Fig. 1c), whereas incomplete posterior vitreous detachment (PVD) with vitreomacular adhesion (VMA) at the fovea and the optic nerve head was also documented. OCTA was negative for choroidal neovascular membrane formation.

The patient was advised as to the need of close observation and remained asymptomatic with BCVA being 20/20. Three years later, she was referred to our department complaining of blurred vision and gradual visual acuity decrease. Upon clinical examination, BCVA in the left eye was counting fingers (CF) at 1 m while fundoscopy showed fibroglial proliferation causing vascular tortuosity and local tractional retinal detachment (Fig. 2a). OCT confirmed the traction exerted to the retina by the overlying fibroglial tissue as well as the complete vitreous detachment at the fovea. It demonstrated also the retinal detachment with full thickness macular hole formation (Fig. 2b). The patient underwent pars plana vitrectomy (PPV) with epiretinal membrane and internal limiting membrane peeling. Sulfur hexafluoride (SF6) gas was injected intravitreally and a three-day head down posture was advised. At last follow-up, 4 months postoperatively, the retinal detachment and the macular hole were anatomically restored and BCVA was 20/32 (Fig. 2c).

3. Discussion

In this report we present the first case of surgically treated URPED-related complication and review all published cases of this rare clinical entity. It is well known that this condition is characterized by its unique clinical features and the pathognomonic inverted pattern on FA and FAF. However, its etiopathogenesis remains unclear, whereas there is limited published information about the disease progression.

In the literature, the natural course of URPED is unclear given the short follow-up period of the majority of reported cases, with the exception of a couple of well documented cases showing significant lesion enlargement and development (Table 1). Significant visual impairment has been described as a result of gradual lesion enlargement and continuous macular disorganization,[4] and visual loss has been mainly associated with the development of serious complications such as CNV. In 2002, Cohen et al.[1] firstly reported two URPED cases complicated with CNV that were treated with Krypton laser photocoaculation and maintained stable vision in short-term follow-up. Shimoyama et al.[5] also presented an 8-year-old boy with visual acuity reduction due to development of URPED-related CNV, which showed no response to either sub-tenon corticosteroid injection (triamcinolone acetonide) or intravitreal anti-VEGF agent (bevacizumab). URPED-related CNV regression and significant visual acuity recovery were reported in 2 cases after two[3] and six monthly intravitreal injections of bevacizumab,[6] although no information was provided about evolution over o longer follow-up period.

URPED is also associated with RPE changes and severe retinal disorganization. Riga et al.[4] demonstrated a case with severe vitreoretinal interface disorder comprising of retinal thickening and cystic disorganization, without any signs of neurosensory retinal detachment, whereas Gal-Or et al.[7] reported a sub-retinal RPE tumor originating from an URPED in a young woman, successfully treated with intravitreal anti-VEGF injections. This therapeutic approach resulted in tumor's thickness decrease and resolution of sub-retinal fluid (SRF) over the 5-month follow-up. In our case the fibroglial proliferation and ERM exerted significant tractional forces to the retina, causing mild local disorganization as well as retinal detachment and macular hole formation, rendering the surgical approach mandatory.

URPED is an exclusively unilateral condition, as also stated by its name. There is one reported case with abnormal findings in the fellow eye, in which despite the lack of abnormal findings in fundoscopy and in FA, multifocal stellate RPE lesions were noticed in FAF.[8] Regarding our case, both fundoscopy and FAF were completely normal in the non-affected eye, demonstrating the unilateral nature of the disease. However, the absence of subclinical findings in the fellow eye cannot be ruled out in published cases, given that not all of them were examined with FAF. The unilateral nature of the disease has also been shown by Yamasaki et al.,[9] who conducted electroretinography (ERG) in a 8-year--old boy with URPED. The affected eye demonstrated a pathological amplitude decrease in the photopic ERG and in the 30-Hz flicker test indicating cone dysfunction, whereas single-flash and scotopic ERG were normal in both eyes.

This unilateral and characteristic "leopard-spot" fundoscopic pattern also appears in a variety of diseases, which should always be included in the differential diagnosis of URPED. Chronic central serous chorioretinopathy (CSCR), commonly noticed in young males with a Type A personality being treated with high doses of corticosteroids, is characterized by a leopard-spot appearance on fundoscopy due to formed subretinal yellowish material in areas of chronic or recurrent neurosensory detachment.[10] Other systemic and ophthalmic diseases that would present with this fundoscopic pattern are large B-cell vitreoretinal lymphoma (VRL),[11] uveal effusion syndrome,[12] lymphocytic leukemia,[13] bilateral diffuse uveal melanocytic proliferation (BDUMP)[14] and hypertensive choroidopathy.[15]

Combined hamartoma of the retina and RPE (CHRRPE) and acute zonal occult outer retinopathy (AZOOR) are two uncommon clinical entities which were initially included in our differential diagnosis. Combined hamartoma of the retina and RPE (CHRRPE) is also a rare tumor with analogous fundoscopic features to URPED, i.e. vascular tortuosity, thickened and disorganized retina, epiretinal membrane,

Table 1
Unilateral retinal pigment epithelium dysgenesis: Characteristics of published cases.

	Author Year	Journal	Age Sex	History/ Presenting Symptoms/ VA	Findings/ Complications	Treatment/ Follow-up	Final VA
1	Cohen et al.[1] 2002	Arch Ophthalmol	34/ M	• Metamorphopsia • 20/20	• CNV • Localized serous RD	• Krypton laser photocoagulation • Stable over 2 years	20/20
2			27/ M	• History of boxing trauma • Incidental finding • 20/25	• ERM, Cystic changes • Vascular tortuosity, Retinal folds	• Enlarged RPE hyperplasia over 7 years	20/40
3			16/ F	• "Visual fatigue" • 20/20		• Stable over 6 months	20/20
4			24/ M	• History of DM type II • Visual loss • Metamorphopsia • 20/128	• Juxtafoveal CNV • Central macular detachment	• Krypton laser photocoagulation • Progression of the leopard-spot lesion the last 10 years • Stable over 6 months after presentation	20/ 128
5	Cohen et al.[2] 2009	Am J Ophthalmol	19/ M	• Incidental finding • 20/20		• Stable over 20 months	20/20
6			36/ F	• 20/32	• ERM • Vascular tortuosity, Retinal folds	• FU < 6 months	20/32
7			18/ M	• 20/40	• Vascular tortuosity	• No FU	20/40
8			42/ M	• History of trauma - Vehicle accident - No globe injury • 20/400	• ERM, Cystic changes • Localized RD	• FU < 6 months	20/ 400
9			16/ F	• 20/25	• Vascular tortuosity, Retinal folds	• FU < 6 months	20/25
10	Riga et al.[4]2020	Ocul Oncol Pathol	52/M	• Gradual visual loss • Metamorphopsia • 20/40	• ERM inferotemporally • Vascular tortuosity, Retinal folds • Retinal thickening and cystic degeneration • RPE atrophy evolving fovea	• Slow growth over 8 years	20/ 200
11	Ding et al.[22] 2020	BMC Ophthalmol	10/ F	• Incidental finding • Visual acuity decrease • 20/25		• Stable over 18 months	20/25
12	Florakis et al.[23] 2019	Retin Cases Brief Rep	47/ M	• Asymptomatic • 20/20		• No FU	20/20
13	Gal-Or O et al.[7] 2019	Retin Cases Brief Rep	30/ F	• Metamorphopsia • 20/25	• Sub-retinal presumed RPE tumor	• Intravitreal anti-VEGF • FU < 6 months	N/A
14	Preziosa et al.[3] 2019	Retin Cases Brief Rep	51/ F	• Progressive vision loss • 20/200	• CNV	• 2 intravitreal injections of bevacizumab • FU over 2 months	20/50
15	Yamasaki et al.[9] 2017	Retin Cases Brief Rep	8/ M	• 20/20		• Slight expansion of RPE atrophy over 2 years	20/20
16	Krohn et al.[17] 2018	Acta Ophthalmol	21/ M	• Enlarged blind spot • 20/20	• RPE atrophy evolving fovea • Thickened and disorganized retinal tissue	• Expansion of RPE atrophy • FU over 10 years	20/ 100
17	Renz et al.[8] 2012	Arch Ophthalmol	35/ F	• Photopsias and dimmer vision the last 6 years • Enlarged blind spot • 20/25	• Outer retinal thinning • Attenuation of the IS/OS junction • Bilateral findings	• No FU	N/A
18	Shimoyama et al.[5] 2014	Case Rep Ophthalmol	8/ M	• 20/20 • Visual disturbances 23 months after the first visit	• Enlargement of the lesion • Development of CNV • Slightly hyperemic optic nerve	• CNV resistant to treatment • Expansion of lesion and new CNV developed • FU over 7 years	20/50
19	Şekeryapan Gediz et al.[6] 2020	Turk J Ophthalmol	32/ M	• 20/32	• Retinal folds • Thinned and discontinuous vessels in the lesion area • Development of CNV, SRF, thickened retina over the CNV	• Monthly intravitreal injections of bevacizumab • Improvement (regression of SRF, persistence of IRF) • FU over 6 months	20/20
20	Berthout et al.[24] 2008	J Fr Ophtalmol	36/ F	• Progressive vision loss • Metamorphopsia • 20/32	• Retinal folds • Fibroglial membrane • Focal macular edema nasally	• No FU	N/A
21	Diafas et al. 2020		16/ F	• Initially asymptomatic - 20/20 • Progressive vision loss 3 years later - Counting Fingers in 1 m	• Fibroglial proliferation • Local tractional retinal detachment • Macular hole	• PPV with ERM-ILM peeling • FU over 4 months	20/32

CNV: Choroidal Neovascularization, RD: Retinal Detachment, ERM: Epiretinal Membrane, RPE: Retinal Pigment Epithelium, DB: Diabetes Mellitus, FU: Follow-up, VEGF: Vascular Endothelial Growth Factor, N/A: Non Applicable, IS/OS: Inner Segment/Outer Segment, SRF: Subretinal Fluid, IRF: Intraretinal Fluid, PPV: Pars Plana Vitrectomy, ILM: Internal Limiting Membrane.

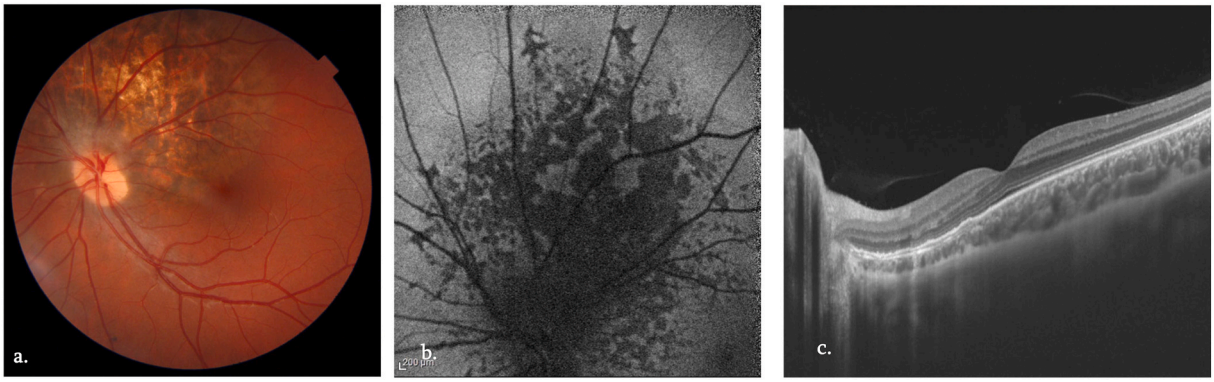

Fig. 1. (a) Fundus photograph at presentation depicts a large leopard-spot like atrophic area adjacent to the optic nerve (b) Fundus autofluorescence shows RPE changes (c) OCT image reveals shallow RPE detachment.

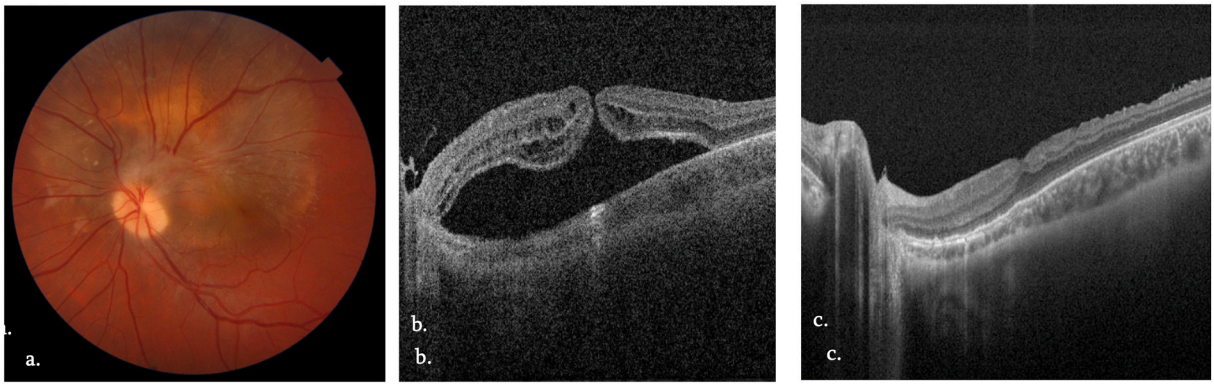

Fig. 2. (a) Preoperative fundus photograph shows the fibroglial proliferation causing vascular tortuosity and tractional retinal detachment (b) Retinal detachment and full thickness macular hole (c) Complete restoration of the macular hole 4 months postoperatively.

fibroglial proliferation and choroidal neovascularization.[16] Based on these clinical similarities, it has been hypothesized that URPED could be regarded as a forme fruste of CHRRPE.[17] However, the unique inverted pattern on FAF and FA images as well as characteristic fundoscopic findings, such as central RPE atrophy and peripheral hyperplastic RPE changes, make the diagnosis of URPED distinct.[2] URPED has also similar fundoscopic appearance with acute zonal occult outer retinopathy (AZOOR). AZOOR commonly presents with photopsia and visual field defects, and a subtly depigmented central area with drusen-like material accumulation at its outer margin. While the central atrophic area of the lesion is characteristically hypoautofluorescent, the lipofuscin presence creates hyperautofluorescent margins in a curvilinear shape, in contrast to the reticular fringe-like shape of URPED's borders.[18,19] Moreover, choroidal osteoma is a unilateral benign tumor that also presents as an orange-yellow elevated plaque in the macular and juxtapapillary area. Compared to URPED, the periphery of choroidal osteoma is well-defined, whereas the tumor's ultrasonographic hyper-reflectivity combined with sound attenuation usually establish the diagnosis.[20,21]

4. Conclusions

We hereby report the first URPED case complicated with retinal detachment and macular hole, that led to severe visual impairment and needed urgent surgical intervention. Despite the stationary or slightly progressive natural course that this clinical entity usually presents, our case provides new information about a relatively rapid evolution of vision-threatening complications, rendering the need for careful follow-up of these patients imperative.

Patient consent

Consent to publish this case report has been obtained from the patient(s) in writing – This report does not contain any personal identifying information.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The following authors have no financial disclosures: AD, AD, AM, NZ, SA.

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