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Case report

Presumed Doyne honeycomb macular dystrophy in two 72-year old twin sisters – case report

Sabina Kowalczyk[1], Mikołaj Guzikowski[1], Sebastian Sirek[2], Dorota Wyględowska-Promieńska[2]

[1]Students' Scientific Club, Department of Ophthalmology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
[2]Department of Ophthalmology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland

Address for correspondence:
lek. Mikołaj Guzikowski
Studenckie Koło Naukowe
Klinika Okulistyki, Wydział Nauk Medycznych ŚUM
ul. Ceglana 35, 40-514 Katowice
e-mail: mikolajguzikowski@gmail.com

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ABSTRACT

Introduction: Hereditary macular dystrophies constitute a group of rare disorders whose exact prevalence is unknown. They include Doyne honeycomb retinal dystrophy (DHRD), inherited in an autosomal dominant manner and associated with a missense mutation in the *EFEMP1* gene (2p16.1), which encodes a fibulin-like extracellular matrix protein containing an epidermal growth factor. Radially arranged, laminar, round drusen appear in childhood, whereas visual disturbances manifest only in the 4th and 5th decades of life.

Case reports: Two 72-year old female patients, who are twins, presented to the Outpatient Ophthalmology Clinic due to visual disturbances. Visual acuity (VA) was 0.04 in the right eye (RE) and 0.08 in the left eye (LE) in patient A, and 0.06 in RE and 0.2 in LE in patient B. Intraocular pressure (IOP) measured 18 mmHg in RE and 17 mmHg in LE in patient A, and 17 mmHg in RE and 11 mmHg in LE in patient B. The patients were qualified for further diagnostic evaluation of both eyes.

Results: OCT examination revealed confluent drusen and atrophy of the retinal pigment epithelium and photoreceptors in both patients. In patient A, an atrophic macular hole was additionally identified. The ganglion cell complex (GCC) measured an average of 120 μm in the RE and 120 μm in the LE in patient A, and 112 μm in RE and 113 μm in LE in patient B.

Conclusions: Patients with suspected DHRD require regular ophthalmological follow-up to monitor disease progression, correct refractive errors, and assess the degree of lens opacity.

KEYWORDS

hereditary macular dystrophies, Doyne honeycomb retinal dystrophy, drusen, fundus autofluorescence

INTRODUCTION

Hereditary macular dystrophies are a group of rare diseases whose exact prevalence is not known [1]. They include Doyne's honeycomb retinal dystrophy (DHRD), otherwise called autosomal dominant radial drusen. It is a genetically based disease, inherited in an autosomal dominant manner, and is associated with a missense mutation of the *EFEMP1* gene (2p16.1) encoding a fibulin-like extracellular matrix protein that contains an epidermal growth factor (EGF) [2]. It manifests in the form of radially arranged, laminar, round yellow-white drusen accumulating beneath the retinal pigment epithelium (RPE) in its posterior pole [3]. They have a characteristic honeycomb appearance, from which the name of the disease originates. Drusen appear in childhood, but they are asymptomatic, and the visual disturbances caused by them appear only in the 4th and 5th decades of life [4]. They include symptoms such as metamorphopsia, blind spots, and may even lead to loss of vision [5].

CASE REPORTS

Two 72-year-old female patients, monozygotic twins, presented to the Outpatient Ophthalmology Clinic due to visual disturbances in the form of blurred vision, a central scotoma, and metamorphopsia. The symptoms emerged in the 5th decade of life and gradually progressed until the time of presentation. Family history revealed that the patients have five additional siblings, making a total of seven children in the family. Among them, a 76-year-old brother and an 86-year-old sister are currently undergoing intravitreal anti-VEGF therapy due to neovascular (wet) age-related macular degeneration (AMD). The patients were unable to provide information regarding any history of ocular disorders in their parents.

Visual acuity (VA) was 0.04 in the right eye (RE) and 0.08 in the left eye (LE) in patient A, and 0.06 in RE and 0.2 in OL in patient B. Intraocular pressure (IOP) measured 18 mmHg in RE and 17 mmHg in LE in patient A, and 17 mmHg in RE and 11 mmHg in LE in patient B. The patients were qualified for further diagnostic evaluation of both eyes.

Optical coherence tomography (OCT) of both eyes was performed, demonstrating confluent drusen and atrophy of the retinal pigment epithelium and photoreceptors in both patients. In patient B, an atrophic macular hole was additionally identified. The ganglion cell complex (GCC) measured an average of 120 μm in OD and 120 μm in OS in patient A, and 112 μm in OD and 113 μm in OS in patient B (Figures 1, 2, 3 and 4).

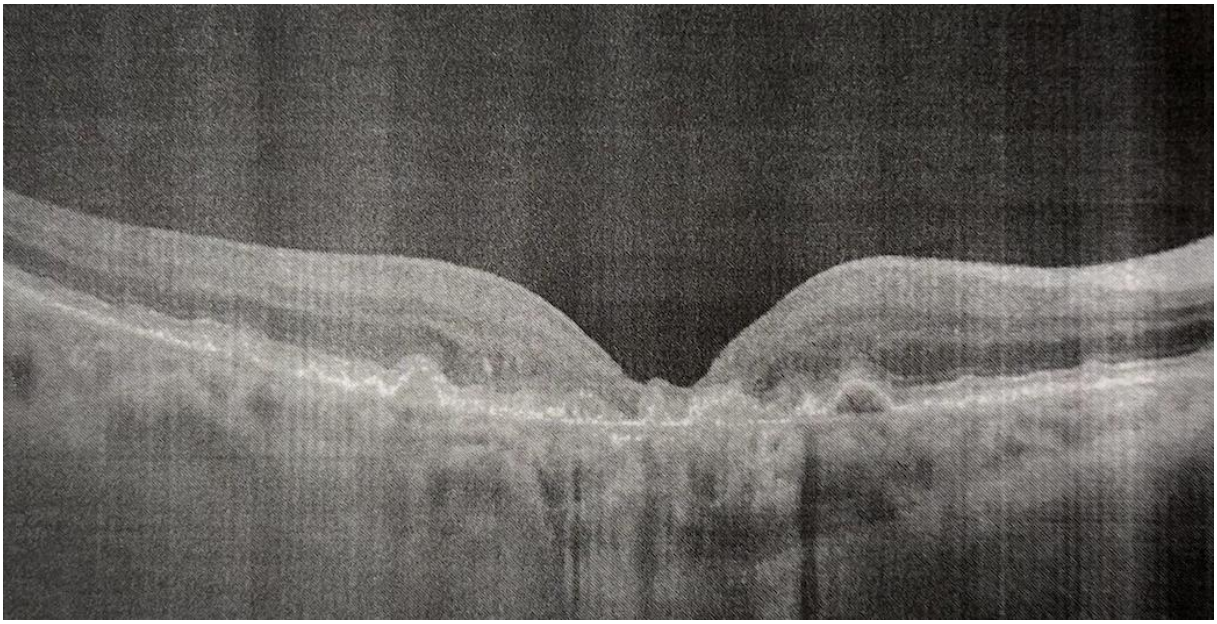

Fig. 1. OCT examination of the RE of Patient A

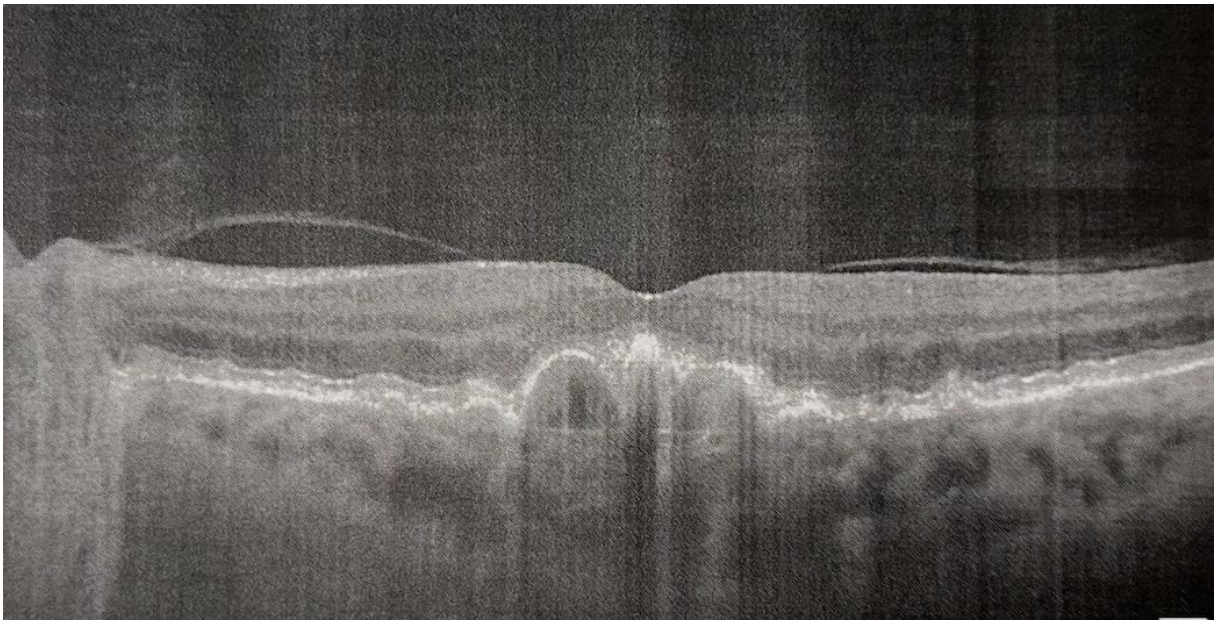

Fig. 2. OCT examination of the LE of Patient A

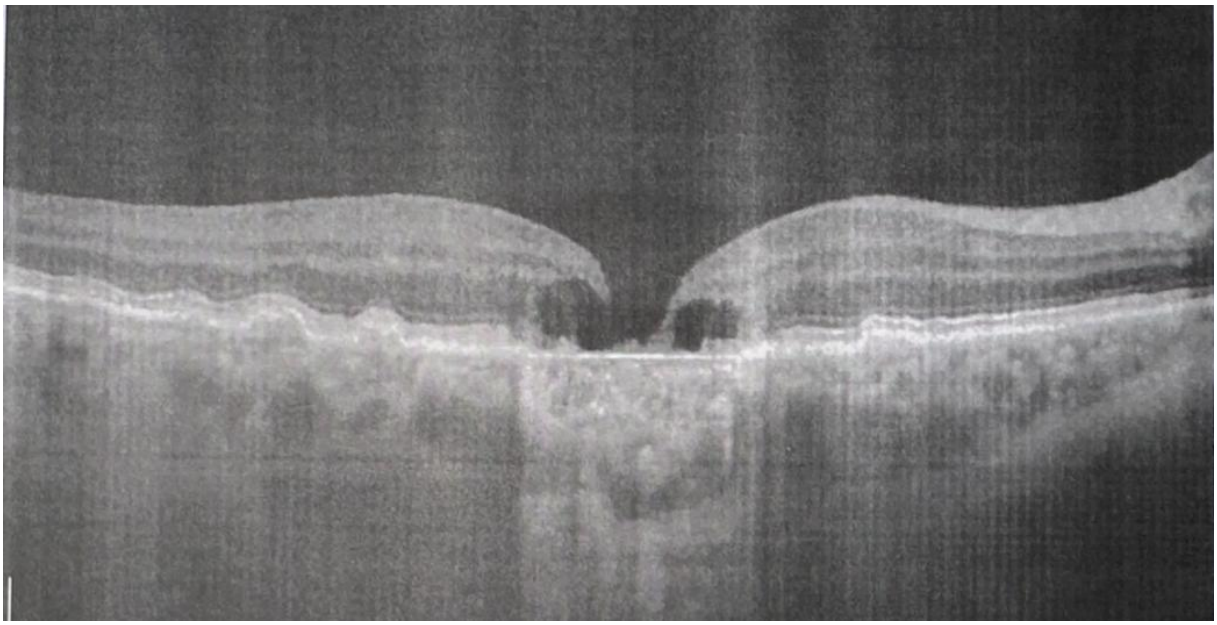

Fig. 3. OCT examination of the RE of Patient B

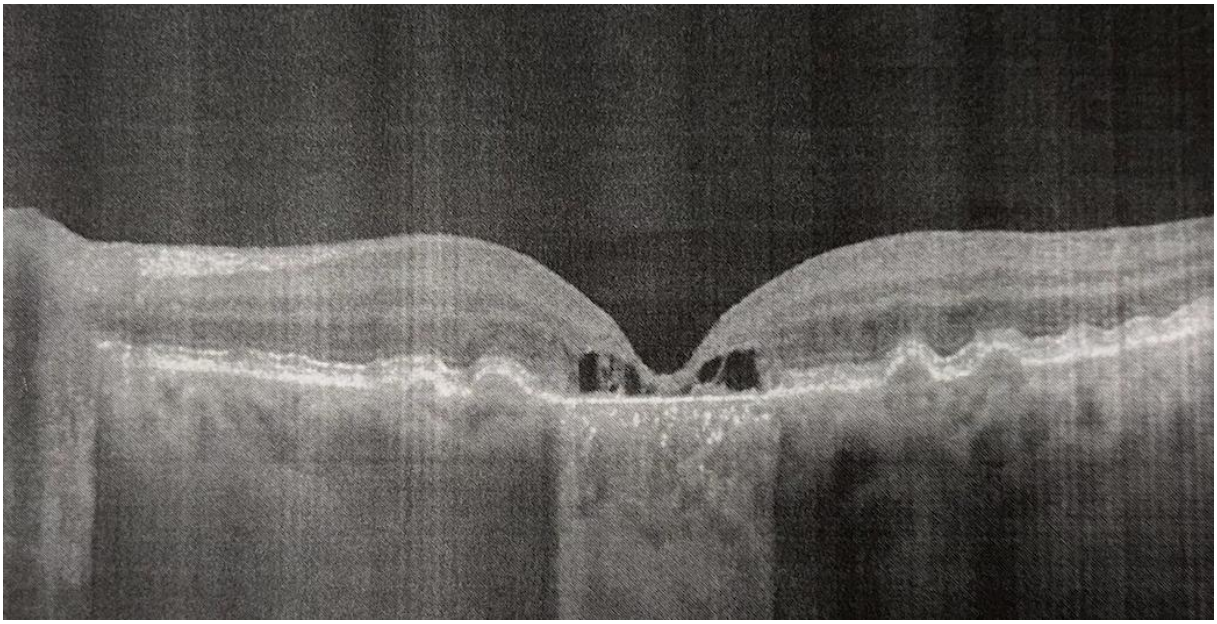

Fig. 4. OCT examination of the LE of Patient B

Next, fundus photography of both patients and fundus autofluorescence (FAF) examination were performed (Figures 5 and 6). Fundus photography revealed confluent drusen, as well as central and paracentral retinal pigment epithelium atrophy. FAF in patient A (Figure 5) revealed uniformly distributed drusen with increased autofluorescence in a radial pattern around the optic disc, without hypoautofluorescent areas, and preserved foveolar topography. In patient B (Figure 6), variable autofluorescence intensity was observed with hyperautofluorescent drusen in the nasal region of the optic disc, focal hypoautofluorescent areas in the central field.

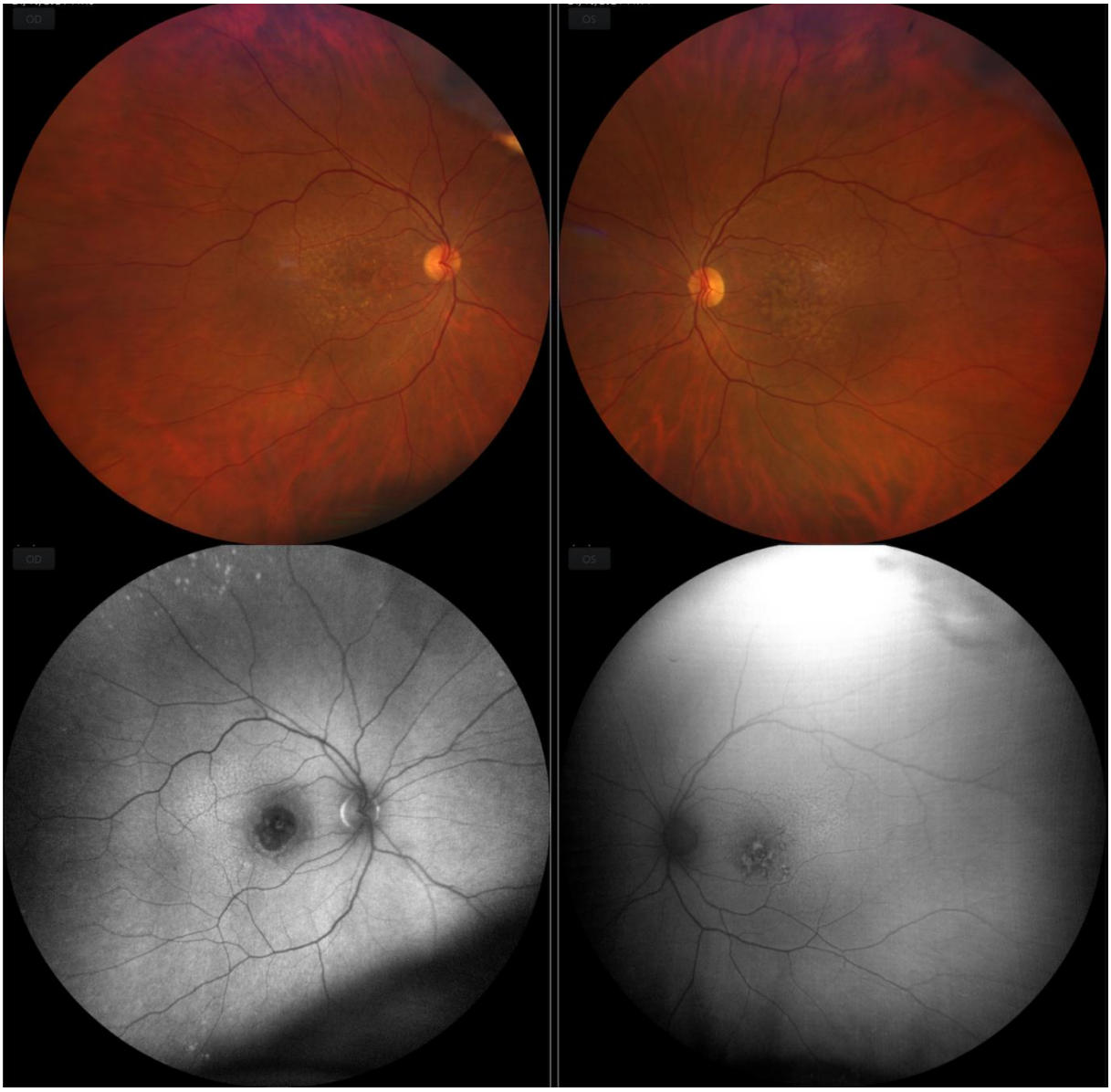

Fig. 5. Fundus photograph of Patient A (upper), FAF of Patient A (lower)

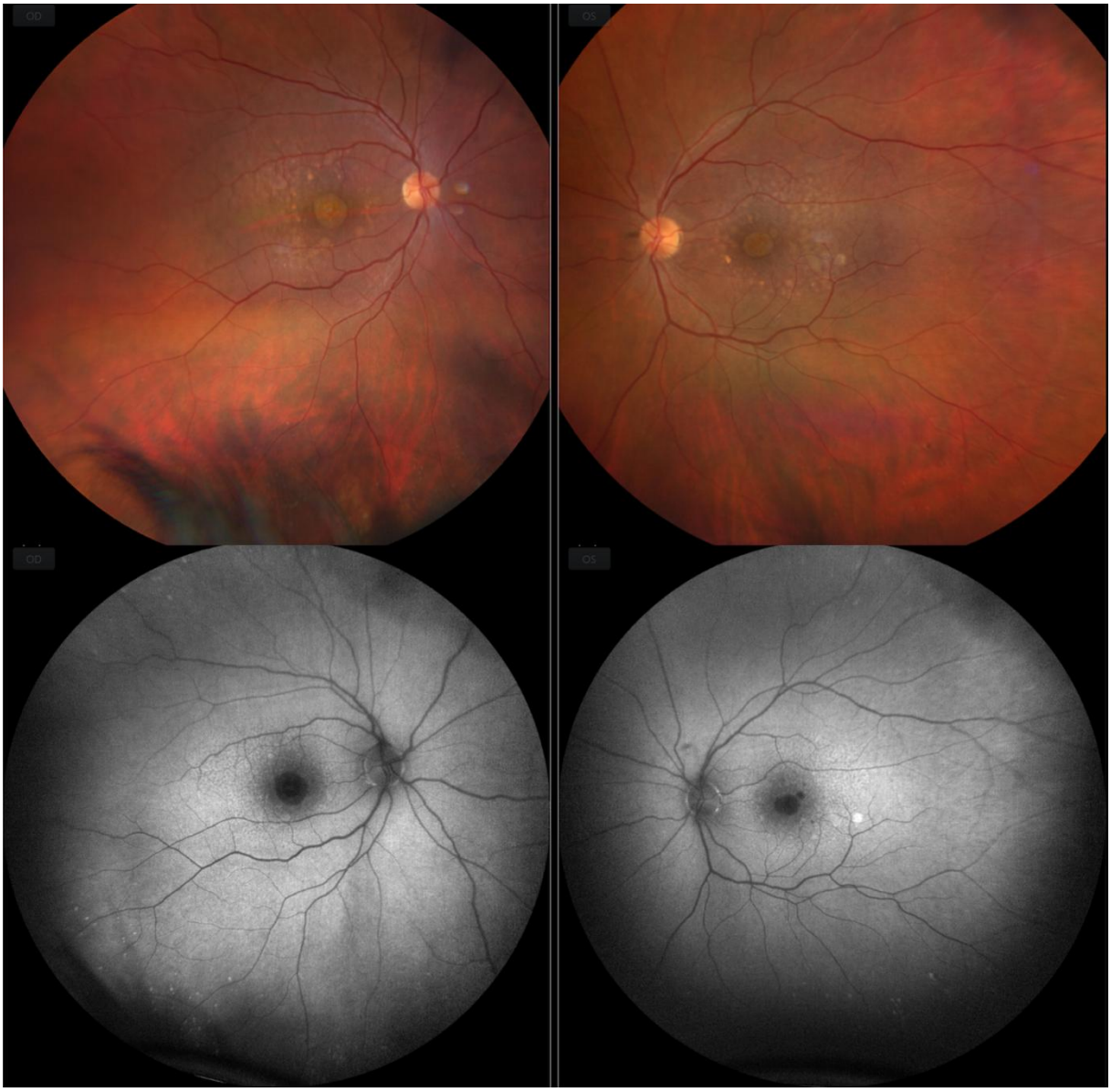

Fig. 6. Fundus photograph of Patient B (upper), FAF of Patient B (lower)

DISCUSSION

DHRD, also referred to as autosomal dominant radial drusen, is a genetically based disorder, inherited in an autosomal dominant manner, and is associated with a missense mutation in the *EFEMP1* gene (2p16.1), which encodes a fibulin-like extracellular matrix protein containing an epidermal growth factor (EGF) [2]. It manifests as radially arranged, laminar, round yellow-white drusen accumulating beneath the retinal pigment epithelium (RPE) in the posterior pole [3]. These drusen are not pathognomonic for DHRD and also occur in other retinal diseases; among them, the presence of large, soft, or confluent drusen is characteristic of AMD and is directly correlated with the progression of retinal atrophy and the risk of neovascularization [6,7]. Drusen induce apoptosis of the overlying RPE, impairing the exchange of oxygen and nutrients as well as the clearance of cytotoxic metabolic byproducts between the cells and the choroid [8,9,10].

There are certain similarities between drusen in DHRD and those in AMD. In DHRD, ocular histopathological studies have shown that fibulin-3 (F3) accumulates between the RPE and the

drusen formation site [11]. Similarly, AMD drusen exhibit comparable F3 immunoreactivity, which is absent at drusen sites in non-AMD eyes [12]. Additionally, Sohn et al. [12] demonstrated that drusen from patients with DHRD and AMD are eosinophilic and sudanophilic and contain membrane attack complexes, vitronectin, amyloid P, and tissue inhibitor of metalloproteinase-3 (TIMP-3). This indicates that differentiating the etiology of drusen in older patients, particularly between DHRD and AMD, is challenging, as seen in our patients. The literature also describes distinguishing features: Sohn et al. [12] observed strong type IV collagen staining in DHRD drusen, which is absent in AMD drusen. Querques et al. [13], using fundus autofluorescence (FAF), reported that increased autofluorescence of large drusen in DHRD corresponds closely to the actual drusen location, whereas in AMD, there is little correlation between drusen distribution and FAF.
Therapeutic options for drusen are relatively limited. Preventive treatment of drusen includes high-dose antioxidants such as vitamins C and E, lutein, zeaxanthin, and zinc, according to the Age-Related Eye Disease Study 2 (AREDS 2) [14]. Antioxidants neutralize reactive oxygen species and reduce lipofuscin accumulation in RPE cells and photoreceptors [15]. According to the guidelines of the Polish Ophthalmological Society, antioxidants are recommended in early stages. Currently, there are no effective drusen treatments available in Europe. In the United States, in February 2023, pegcetacoplan (Syfovre) was approved, slowing the progression of geographic atrophy [16]. According to recommendations from the Professional Association of German Ophthalmologists, the German Ophthalmological Society, and the German Retina Society, conventional laser photocoagulation of AMD drusen causes drusen regression but does not reduce the risk of AMD progression and therefore should not be performed [17].
In the presented clinical case, patient A demonstrated an atrophic macular hole (MH) on OCT. Kim et al. [18] studied surgical outcomes of MH associated with four types of AMD, including MH resulting from retinal thinning due to subretinal drusen or drusenoid pigment epithelial detachment (PED). The study reported a 100% MH closure rate in MH associated with retinal thinning from subretinal drusen or drusenoid PED after vitrectomy, with significant VA improvement. However, surgical outcomes were not significantly associated with the mechanism of macular hole formation ($P = 0.083$). Additionally, in two patients, drusen size decreased; in eight eyes it remained unchanged; in six eyes it increased; and one eye developed choroidal neovascularization (CNV). One patient with bilateral macular holes developed bilateral geographic atrophy.
Michalewska and Nawrocki [19] performed inverted internal limiting membrane (ILM) flap surgery on 18 eyes with full-thickness macular holes (FTMH) and dry (atrophic) AMD, achieving hole closure in 16 eyes after the first procedure and in all cases after the second. VA improved significantly ($P < 0.05$), gradually reaching approximately 20/40 at 18–36 months postoperatively. Tarkova et al. [20] retrospectively evaluated eyes undergoing 25-gauge pars plana vitrectomy (PPV) with intermediate dry AMD, achieving successful closure of idiopathic macular holes (IMH) in all

10 eyes. Initial VA ranged 0.1–0.6 and improved to 0.2–0.9 at the end of follow-up ($P < 0.05$). Berzack and Parekh [21] reported a 67-year-old male with FTMH and intermediate dry AMD in the left eye who underwent PPV with ILM peeling and SF6 injection, achieving complete macular hole closure and early stabilization of macular drusen. VA improved from 0.2 to 0.5 postoperatively. Berinstein et al. [22], in a retrospective study of 34 eyes undergoing PPV for macular holes with preoperative drusen, observed a 76% closure rate ($P = 0.1263$). Mean final VA was 0.3.
Based on these publications, surgical closure of macular holes in the presence of dry (atrophic) AMD and drusen can be achieved with high success. During manuscript preparation, we did not find reports describing macular holes in DHRD or potential surgical management. In our patients, only patient A exhibited an atrophic macular hole on OCT. Due to the relatively limited disease progression and diagnostic challenges in determining the precise etiology of drusen potentially related to DHRD, surgical intervention was not pursued.

CONCLUSIONS

Patients with suspected DHRD require regular ophthalmological follow-up to monitor disease progression, correct refractive errors, and assess the degree of lens opacity.

Use of AI tools statement

ChatGPT was used for language translation of the manuscript.

Conflict of interest

All the authors declare that they have no conflicts of interest.

Authors' contribution

Study design – S. Kowalczyk, M. Guzikowski, S. Sirek, D. Wyględowska-Promieńska
Manuscript preparation – S. Kowalczyk, M. Guzikowski
Literature research – S. Sirek, D. Wyględowska-Promieńska
Final approval of the version to be published – D. Wyględowska-Promieńska

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