Letter to the Editor

Inherited Retinal Dystrophies in the Differential Diagnosis of Uveitis: Clinical Clues from a Case

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Dear Editor,

Inherited retinal dystrophies (IRD) may present with inflammatory findings in some cases, which complicates the differential diagnosis and can lead to misdiagnosis as uveitis. We would like to emphasize that accurate clinical differentiation plays a decisive role not only in establishing appropriate treatment strategies but also in the timing and planning of re/habilitative approaches.

A 27-year-old female patient was evaluated at two separate centers for suspected intermediate uveitis and was subsequently referred to our clinic due to the lack of a typical response to treatment. Her medical history revealed that she initially presented with complaints of stinging and ocular discomfort. Following the detection of vitreous cells and macular edema, she received two bilateral intravitreal triamcinolone acetonide (Kenakort-A®; Deva Holding A.Ş., İstanbul, Türkiye) injections, followed by the initiation of systemic corticosteroid (methylprednisolone, Prednol®; Gensenta İlaç Sanayi ve Ticaret A.Ş., İstanbul, Türkiye) therapy at a dose of 64 mg/day. At the second center, azathioprine (Imuran®; Excella GmbH & Co. KG, Feucht, Germany) at a dose of 150 mg/day was added to this treatment.

No pathology was detected on systemic evaluations and her personal/family history was unremarkable except for a positive QuantiFERON-TB Gold test, for which she had been started on 300 mg/day isoniazid (I.N.H.®; Koçak Farma İlaç ve Kimya Sanayi A.Ş., Kapaklı, Tekirdağ, Türkiye). On ophthalmological examination, visual acuity (Snellen decimal) was 1.0 in the right eye and 0.8 in the left eye. Anterior segment examination revealed no findings suggestive of active or prior uveitis. Intraocular pressure was measured as 20 mmHg bilaterally via applanation tonometry. No vitreous reaction was observed on fundus examination, but the presence of a peripapillary white gliotic appearance bilaterally and waxy pallor of the optic disc, arteriolar attenuation, and perivascular white gliotic sheathing in the left eye was noted. In addition, granular pigmentary changes were detected in the mid-peripheral retina (Figure 1A, B).

Fundus fluorescein angiography (FFA) was evaluated with a confocal scanning laser ophthalmoscopy system

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(Heidelberg Retina Angiograph 2, Heidelberg Engineering, Germany). Optic disc margins and vascular structures were normal bilaterally, with no leakage observed. Transmission (window) defects secondary to retinal pigment epithelial (RPE) changes were present in the mid-peripheral areas. The macula and peripapillary region appeared relatively spared (Figure 1C, D).

Fundus autofluorescence (FAF) images were obtained by confocal scanning laser ophthalmoscopy (Spectralis HRA + OCT, Heidelberg Engineering, Germany). A symmetrical, well-defined hyperautofluorescent ring was observed in the macula. The characteristic appearance of peripapillary hyperautofluorescence with preserved autofluorescence around the optic disc was noted (Figure 1E, F).

Optical coherence tomography (OCT) images were acquired using spectral-domain OCT (Spectralis OCT, Heidelberg Engineering, Germany). Irregularities and focal disruptions were observed bilaterally in the perifoveal region of the ellipsoid zone (EZ), while the subfoveal EZ band was preserved (Figure 1G, H). Bilateral cystoid macular edema (CME) was present. Involvement of the inner retinal layers with the presence of retinoschisis cavities was observed bilaterally. It was noted that the retinal layers had lost their characteristic laminated appearance.

Visual field testing was performed using the SITA-Standard 24-2 program (Humphrey Field Analyzer II, Carl Zeiss Meditec, USA). Bilateral concentric constriction was detected (Figure 2A, B).

Electroretinography (ERG) was performed in accordance with the 2022 ISCEV (International Society for Clinical Electrophysiology of Vision) standards (MonPack One, Metrovision, Perenchies, France). Scotopic responses were completely extinguished, and photopic responses were significantly reduced. This combination was interpreted as consistent with advanced rod-cone dystrophy (Figure 2C).

As the findings were compatible with IRD, azathioprine was discontinued, while systemic corticosteroid treatment was tapered and stopped. Topical brinzolamide (Britil®; World Medicine İlaç Sanayi ve Ticaret A.Ş., İstanbul, Türkiye) was added for the management of CME. Genetic analysis identified a homozygous c.1028G>T (p.Trp343Leu) missense variant in the *CC2D2A* gene. According to the American College of Medical Genetics and Genomics criteria, the variant was classified as a variant of uncertain significance (VUS).

The demonstration of microinflammatory processes and altered immune responses in some subtypes of IRD suggests that clinical presentations resembling inflammation may have a pathophysiological basis.[1,2] However, this biological foundation indicates that inflammatory findings should not be interpreted as primary uveitis.[3] Cases have been reported in the literature where IRD was misdiagnosed as

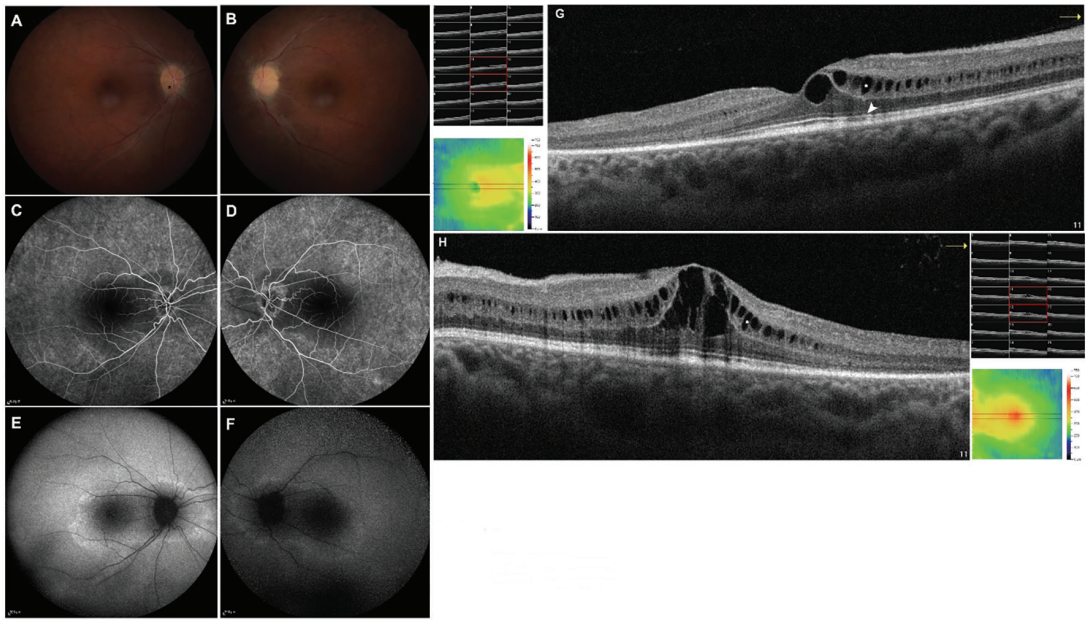

Figure 1. Color fundus photographs of the right (A) and left (B) eyes. Perivascular sheathing was observed over the optic disc (A, black asterisk). Fundus fluorescein angiography frames of the right (C) and left (D) eyes. Fundus autofluorescence images of the right (E) and left (F) eyes. Optical coherence tomography scans of the right (G) and left (H) eyes. Irregularities and focal disruptions in the EZ (G, white arrow) and retinoschisis cavities (G/H, white asterisks) were observed

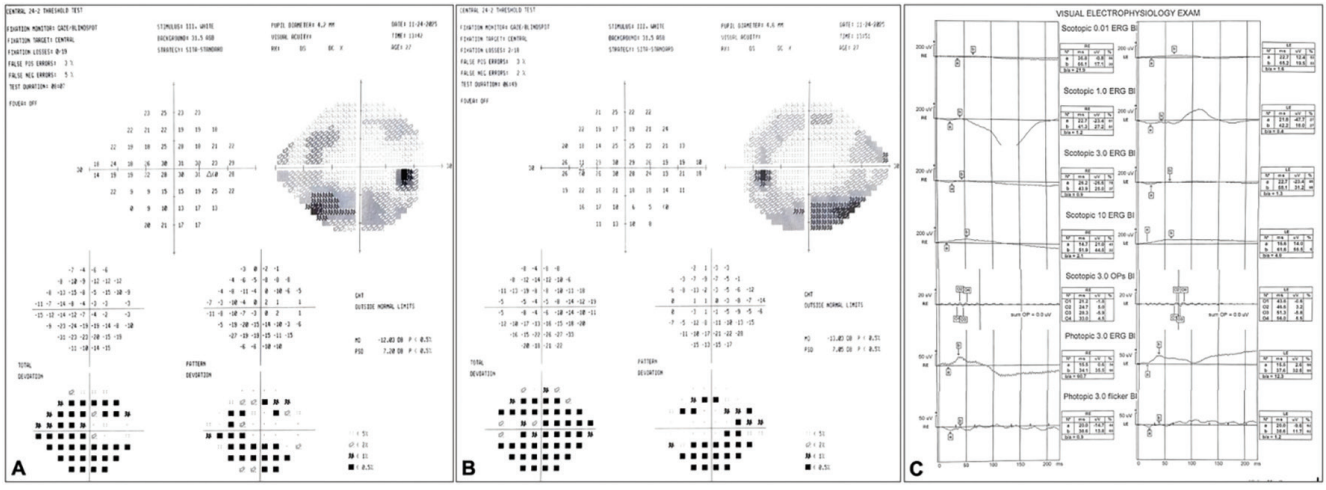

Figure 2. Visual fields of the right (A) and left (B) eyes and the electroretinogram (C)

uveitis, leading to the development of ocular and systemic complications secondary to long-term corticosteroid use.[4] Although there is currently no curative treatment for IRD, early diagnosis is important for the timely initiation of re/habilitative care, the planning of supportive approaches, and the evaluation of gene-targeted treatment options in applicable cases.[5]

In clinical practice, recognizing the clinical and imaging findings suggestive of IRD is essential. In this patient group presenting with uveitis-like findings, the absence of sudden visual loss, the lack of clues favoring IRD in the medical history, and the inability to identify an etiology for uveitis are common characteristics.[3] In our case, vision was preserved, posterior pole findings were detected incidentally during a routine examination, and no guiding information was obtained from the personal or family history.

On ophthalmological examination, the inflammatory phenotype associated with IRD typically exhibits bilateral and symmetrical involvement. A pronounced discrepancy between the severity of inflammation and visual function is an important clinical clue that may suggest an underlying dystrophic process.[6] Anterior chamber inflammation is absent in most cases. The accompanying presence of perivascular sheathing can be a misleading finding in favor of uveitis. In the presented case, the absence of inflammatory cells in the anterior chamber, the bilateral and symmetrical nature of the findings, and their restriction to the posterior segment supported a diagnosis of IRD.

In the early stages of the disease, FFA may have limited specificity in the differential diagnosis. In the advanced stages of the degenerative process, optic disc or retinal vascular leakage can be observed in late-phase (6-8 minutes) FFA frames.[3] The primary notable finding in the presented case was the observation of extensive RPE loss, excluding a limited preserved area between the optic disc and the macula. The absence of leakage in the optic disc and retinal vascular structures was interpreted as consistent with an early-stage inflammatory pattern.

In cases of IRD associated with uveitis, FAF imaging offers important clues for differential diagnosis. While a sharply demarcated, bilateral, and symmetrical parafoveal hyperautofluorescent annulus (ring sign) is frequently observed in the macular region in IRD, a patchy and asymmetrical distribution is generally seen in uveitis.[7,8] Furthermore, the presence of preserved autofluorescence around the optic disc (peripapillary sparing) is considered a characteristic finding of IRD. The "speckled pattern" consisting of hyperautofluorescent mottling observed around degenerative areas is another finding considered indicative of IRD.[3] In our case, the parafoveal hyperautofluorescent ring and the area of preserved peripapillary autofluorescence strongly supported the diagnosis of IRD. Additionally, this autofluorescence pattern correlated with the limited area of preserved RPE between the fovea and optic disc on FFA (Figure 1C-F).

In the literature, irregularities or focal disruptions in the EZ are described as characteristic OCT findings for IRD. CME is a frequent component of IRD-associated inflammation, and involvement of the inner retinal layers, particularly retinoschisis areas in the inner nuclear layer, constitutes another commonly observed structural change in this disease group. Reports indicate that sectoral thickening (microedema) of the retinal nerve fiber layer (RNFL) can also occur.[9] Although the OCT findings in our case were consistent with the literature, no significant sectoral thickening was detected on RNFL analysis.

In functional evaluations, the discrepancy between the ERG and visual field in very early stages is a valuable clinical parameter for differentiating IRD from uveitis.[10] The

relative preservation of the visual field despite significantly diminished electrophysiological responses is interpreted as consistent with early-stage IRD, where photoreceptor outer segment involvement is limited. In our case, the extinguished scotopic ERG responses indicate that the rod system was affected. Furthermore, the development of concentric constriction of the visual field suggests that the disease was at an advanced functional stage.

In cases where the possibility of IRD is overlooked during the diagnostic process, the pattern of response to treatment can provide important clues for the differential diagnosis.[3] Inflammatory findings accompanying IRD may show partial and transient improvement with systemic or local corticosteroid therapy, tending to recur shortly thereafter. This transient response-relapse behavior has been reported in misdiagnosed IRD cases.[2] Therefore, careful evaluation of the treatment response is diagnostically significant.

Given that the *CC2D2A* variant identified in our patient was classified as a VUS, its causal relationship with the clinical phenotype has not yet been established with certainty. Nevertheless, biallelic *CC2D2A* variants have been reported to be associated with isolated rod-cone dystrophy, and the CC2D2A protein has been shown to localize to the photoreceptor connecting cilium/transition zone and to play a role in outer segment protein trafficking.[11,12] These findings suggest a potential biological link between the inflammatory presentation in our patient and ciliary dysfunction and indicate that the inflammatory phenotype in CC2D2A-associated retinal dystrophies may not yet be sufficiently characterized.

In conclusion, keeping IRD in mind in the differential diagnosis of unusual clinical presentations mimicking inflammation enables not only diagnostic accuracy but also the appropriate planning of the patient's long-term follow-up and management. Diagnostic delays can negatively impact not only clinical decisions but also the timing of re/habilitative and psychosocial support processes, thereby leading to a decline in the patient's quality of life.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of the clinical findings and visual materials included in this study for scientific purposes.

Declarations

Author Contributions

Surgical and Medical Procedures: N.Y., P.Ö., Concept: D.Y., N.Y., Design: D.Y., N.Y., Data Collection or Processing: D.Y., P.Ö., E.Ş., N.Y., Analysis or Interpretation: D.Y., P.Ö., E.Ş., N.Y., Literature Search: D.Y., N.Y., Writing: D.Y., P.Ö., E.Ş., N.Y.

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