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ABCA4-associated retinopathy complicated by didanosine-associated retinal toxicity

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ABSTRACT

Purpose: To describe a rare case of severe central and peripheral chorioretinal atrophy in a patient with *ABCA4*-associated retinopathy and prior didanosine exposure.

Observations: A 66-year-old man with a 20-year history of Stargardt disease and HIV/AIDS treated with didanosine for almost ten years in the late '90s presented with progressive bilateral visual loss and color desaturation. Best-corrected visual acuity was 20/400 in both eyes. Multimodal imaging revealed extensive retinal pigment epithelium and choroidal atrophy involving both the macula and mid-periphery, with macular thinning and structural damage confirmed on optical coherence tomography. The peripheral atrophy pattern was consistent with known didanosine toxicity, while the macular degeneration was typical of *ABCA4*-associated disease. Genetic testing identified three heterozygous *ABCA4* variants: one pathogenic nonsense mutation, one likely pathogenic missense mutation, and one variant of uncertain significance. Segregation analysis was not possible due to lack of parental samples.

Conclusions and importance: This case suggests that prior mitochondrial-toxic drug exposure may exacerbate the course of inherited retinal dystrophies, producing unusually severe panretinal degeneration. Clinicians should review medication history in patients with inherited retinal diseases and consider long-term retinal monitoring even years after discontinuing potentially toxic agents.

1. Introduction

Inherited Retinal Diseases (IRDs) are rare conditions but collectively represent one of the most common causes of blindness among working-age individuals. The degree of visual impairment and clinical course are highly variable, depending on whether the macula or the peripheral retina are affected first. Still, people with IRDs remain at risk of retinal complications from systemic diseases (e.g., diabetes mellitus, arterial hypertension) and from drug toxicities, which may further deteriorate visual function. Didanosine is a synthetic purine adenine nucleoside analogue in the nucleoside reverse transcriptase inhibitor class approved by the U.S. Food and Drug Administration in 1991 for use in combination antiretroviral therapy for HIV infection.[1] Although it is no longer considered a first-line agent, many patients who began treatment in the 1990s were exposed to didanosine for prolonged periods. Retinal toxicity associated with continued use of didanosine is well documented and typically presents with bilateral, symmetric, mid-peripheral scalloped areas of retinal pigment epithelium (RPE) atrophy, typically sparing the macula.[2] This typical sparing contrasts with the marked macular involvement seen in our patient.

Here, we describe a case of a patient affected with *ABCA4*-associated retinopathy/Stargardt disease, an IRD primarily affecting the macula, and HIV infection treated with didanosine, who developed extensive chorioretinal atrophy likely resulting from the combination of two distinct pathogenic mechanisms.

2. Report of a case

A 66-year-old man was referred to the Medical Retina Unit at IRCCS San Raffaele Hospital (Milan, Italy) for progressive bilateral visual deterioration and a subjective perception of color desaturation. He reported a diagnosis of Stargardt disease approximately 20 years earlier.

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He had also been diagnosed with HIV infection and AIDS, and had been on antiretroviral therapy since then, including didanosine in late 1990s.

At presentation, best-corrected visual acuity (BCVA) was 20/400 in both eyes. Refraction revealed mild myopia (−2.00 D in the right eye, −1.50 D in the left eye). Anterior segment examination and intraocular pressures were unremarkable. Both eyes were pseudophakic.

Fundus examination revealed extensive bilateral chorioretinal atrophy involving both the posterior pole and the peripheral retina (Fig. 1). Fundus autofluorescence (FAF) imaging demonstrated widespread mottled hypoautofluorescence in the mid-periphery, along with pronounced macular hypoautofluorescence consistent with the funduscopic findings (Fig. 2). Optical coherence tomography (OCT) revealed significant central retinal thinning, an enlarged foveal depression, and outer retinal hyper-reflectivity associated with extensive atrophy of both the RPE and the underlying choroid. A dense epiretinal membrane (ERM) was also identified in the right eye (Fig. 2).

Fluorescein angiography (FA) revealed a large central hypofluorescent zone involving the macular region and extending beyond the vascular arcades. This area was bordered by a hyperfluorescent rim in the far periphery, consistent with advanced retinal pigment epithelium loss and window defects (Fig. 1). Additionally, abnormal visualization of the underlying choroidal vasculature was noted, further supporting extensive chorioretinal atrophy.

Molecular diagnosis for a possible IRD was then pursued though Next-Generation Sequencing (NGS), leading to the identification of three heterozygous variants in the *ABCA4* gene (NM_000350): c.1714C > T p. (Arg572*), classified as pathogenic according to the American College of Medical Genetics and Genomics guidelines, c.2461T > A p. (Trp821Arg), classified ad likely pathogenic, and c.4417C>A p. (Leu1473Met), classified as of uncertain significance.[3] Segregation of the variants on the two alleles could not be determined because parental blood samples were unavailable.

3. Discussion

This case illustrates the overlapping effects of two independent causes of retinal degeneration: Stargardt disease and didanosine-induced retinopathy. Didanosine-induced retinal toxicity is rare, with fewer than 30 cases reported in the literature since its first description in 1992.[4] Unlike previously reported cases of didanosine toxicity, characterized by peripheral atrophy with macular sparing and relatively preserved visual acuity,[1,2,5] our patient exhibited both central and peripheral chorioretinal atrophy, with profound bilateral vision loss.

Didanosine is a nucleoside reverse transcriptase inhibitor (NRTI) that acts as an adenosine analog. It is known to cause mitochondrial toxicity by inhibiting DNA polymerase-γ, leading to disrupted mtDNA replication.[6] Systemically, NRTI-induced mitochondrial damage can manifest as hepatic steatosis, lactic acidosis, peripheral neuropathy, nephrotoxicity, and lipodystrophy. Ocularly, its toxicity resembles primary mitochondrial retinopathies such as chronic progressive external

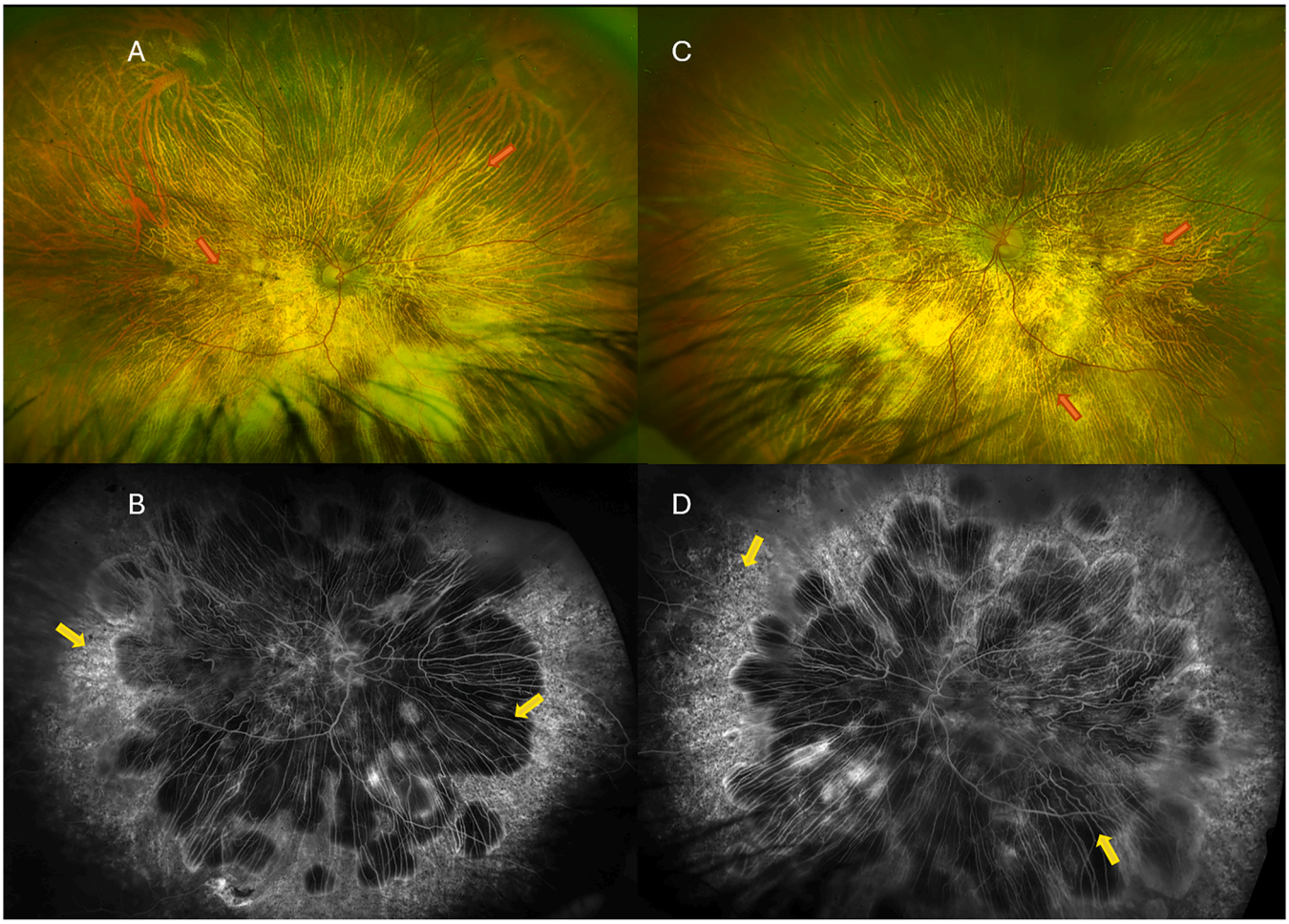

Fig. 1. Color fundus images of both eyes (A, C) show extensive chorioretinal atrophy involving the posterior pole (red arrow) and mid-periphery (red arrow). Late-phase fluorescein angiography (B, D) reveals central macular hypofluorescence extending beyond the vascular arcades (yellow arrow), with a peripheral hyperfluorescent rim and prominent choroidal vessel visualization (yellow arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

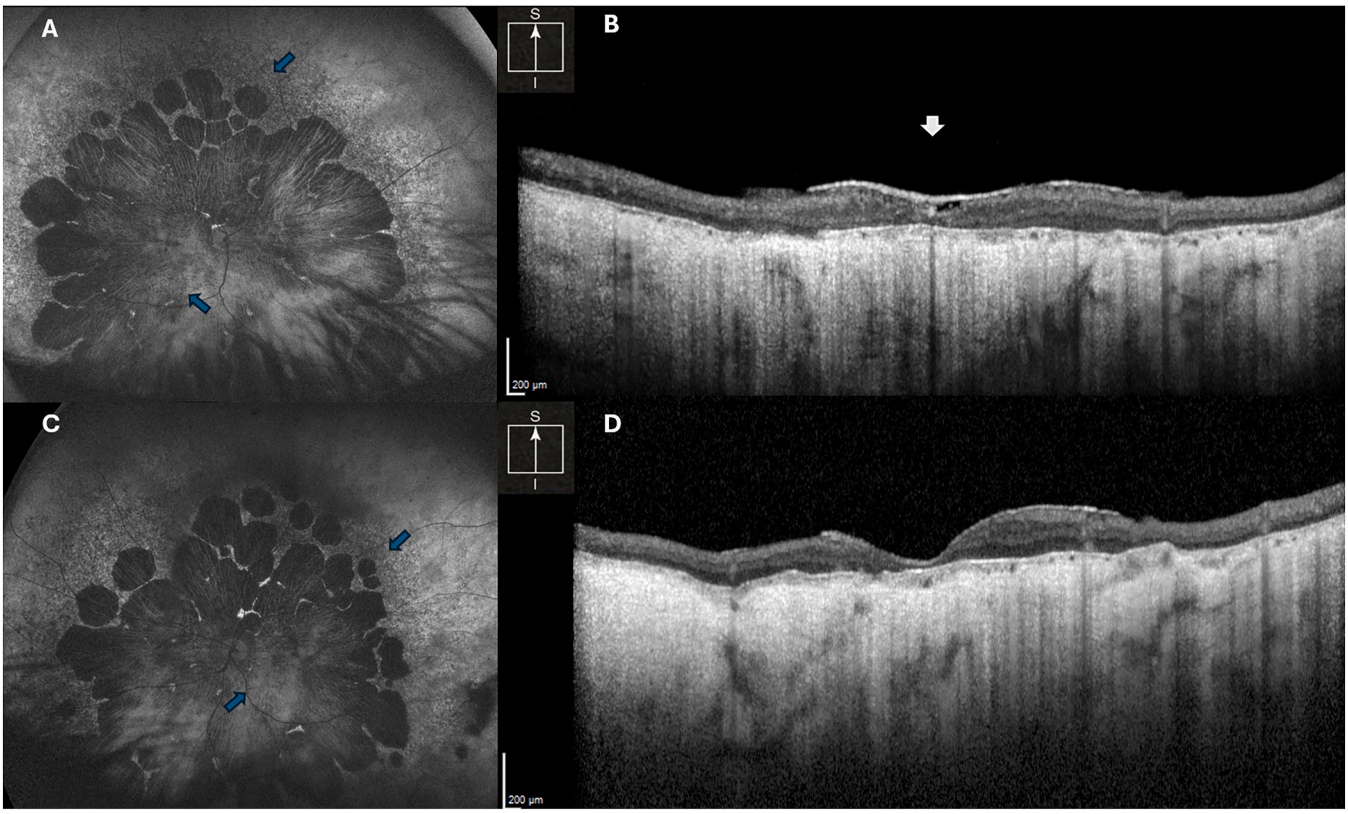

Fig. 2. Fundus autofluorescence (A, B) demonstrates diffuse mid-peripheral mottled hypoautofluorescence (blue arrow) and central confluent hypoautofluorescence (blue arrow). Spectral-domain OCT (C, D) shows foveal thinning, outer retinal hyper-reflectivity, and severe RPE and choroidal atrophy. A dense epiretinal membrane is noted in the right eye (white arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

ophthalmoplegia and Kearns-Sayre syndrome. The retina, especially the peripheral retina with its high density of rods and associated metabolic demands, is particularly vulnerable to such injury.[1] Retinal involvement due to didanosine toxicity was first described in 1992 by Whitcup et al.,[7] who reported children developing symmetric peripheral chorioretinal atrophy. In most documented cases, the macula is spared and visual acuity is preserved. One exception, reported by Hammer and Borruat,[8] described a patient with reduced vision despite a normal macula on OCT and fundus exam, with visual loss attributed to non-organic causes.

In our patient, the structural macular damage observed on OCT likely contributes to the poor visual acuity. This atypical central involvement is best explained by the underlying Stargardt disease, a predominantly macular dystrophy caused by *ABCA4* variants leading to toxic lipofuscin accumulation in the RPE. Although with an extreme variability in phenotypic and clinical severity. Such variability may be at least partly explained by genotype-phenotype correlations.[9] The combination of a nonsense variant p. (Arg572*) and a likely pathogenic missense variant p. (Trp821Arg) would be expected to result in an intermediate phenotype, while the third variant p. (Leu1473Met) remains of uncertain significance.[10,11] We hypothesize that the unusually severe retinal involvement observed may therefore reflect an additional contribution from didanosine toxicity. Didanosine-related mitochondrial toxicity, in contrast, primarily affects the peripheral retina due to the higher density and metabolic activity of rod photoreceptors.[1] Interestingly, retinal degeneration can continue even after discontinuation of didanosine. The underlying mechanism remains unclear, but it is hypothesized that irreversible cellular damage may be triggered during therapy, initiating progressive retinal cell loss long after drug exposure has ceased.[4]

Although *ABCA4*-associated retinopathy may present with cone-rod dystrophy and extensive chorioretinal atrophy - particularly in patients harboring biallelic severe variants,[10] which to the best of our knowledge[11] does not apply to our patient - we propose that in this case the interplay of these two mechanisms could have synergistically resulted in an extremely severe form of retinal degeneration.

Still, caution is warranted in definitively attributing the central versus peripheral retinal pathology to *ABCA4* or didanosine, as phasing could not be resolved in our patient and the p. (Leu1473Met) variant remains of uncertain significance, raising the possibility that it forms a more severe complex allele *in cis* with one of the other two variants. This raises the possibility that it may form a more severe complex allele *in cis* with one of the other two variants.

In conclusion, this case suggests that mitochondrial dysfunction induced by didanosine, in combination with *ABCA4*-associated retinopathy, likely contributed to the severe retinal atrophy and vision loss observed. It emphasizes the importance of advising patients affected with IRDs about possible retinal drug toxicities and complications from systemic conditions. Continued long-term monitoring is recommended, as retinal degeneration may continue even after discontinuing the causative agent.

CRediT authorship contribution statement

Annamaria Nunziata: Writing – original draft, Conceptualization. **Lorenzo Bianco:** Writing – review & editing, Data curation, Conceptualization. **Alessio Antropoli:** Validation, Data curation. **Alessandro Arrigo:** Validation, Supervision. **Francesco Bandello:** Validation, Supervision. **Ahmad M. Mansour:** Validation, Supervision. **Maurizio Battaglia Parodi:** Validation, Supervision, Conceptualization.

Patient consent

Consent to publish this case report has been obtained from the

patient in writing.

Authorship

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

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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