Didanosine retinal toxicity

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Abstract

Objectives: We report long-term follow-up for a didanosine-associated retinal toxicity (DART) case, demonstrating its progression once didanosine (DDI) administration was discontinued under multimodal imaging. We propose this case to enrich the literature on retinal DDI toxicity through diagnosis and to understand the fundamental role in multimodal retinal imaging for detection and monitoring of retinal toxicity.
Case description: A 69-year-old man with a loss of night vision and complained of slowly progressive peripheral field of vision constriction over the past 7 years. His visual acuity was 20/20 in the right eye and 25/20 in the left eye. The patient was identified with fundoscopy and multimodal imaging that showed bilateral retinal alterations in the mid-periphery well-delineated zones of RPE atrophy associated with relative loss of neurosensory retina and choriocapillaris. There was a progression of retinopathy during follow-up after 7 years since DDI was discontinued.
Conclusion: DART is a progressive disorder despite drug session. The use of multimodal images of the fundus and functional testing in patients with DDI toxicity allows a more precise study of their progression and study of the findings in these patients.
Keywords: HIV, didanosine retinal toxicity, toxic retinopathy.

Toxicidad retinal por Didanosina

Resumen

Objetivos: Reportamos el seguimiento a largo plazo de un paciente con toxicidad retinal asociada a

didanosina, demostrando bajo imágenes multimodales su progresión una vez que la administración del fármaco fue discontinuada. Proponemos este informe de caso para enriquecer la literatura sobre la toxicidad de la didanosina y entender el papel fundamental en la implementación de las imágenes multimodales para la detección y monitoreo de la toxicidad retinal.
Caso clínico: Un hombre de 69 años refirió pérdida de visión nocturna y disminución periférica lentamente progresiva del campo visual en ambos ojos durante los últimos 7 años. Su agudeza visual fue de 20/20 en el ojo derecho y 25/20 en el izquierdo. Mediante fundoscopía e imágenes multimodales se identificaron alteraciones retinales bilaterales con atrofia del epitelio pigmentario retinal asociadas a pérdidas relativas de retina neurosensorial y de la coriocapilaris, ubicadas en zonas bien delimitadas de la periferia media retinal. Se observó progresión de la retinopatía durante el seguimiento de 7 años desde que se suspendió el fármaco.
Conclusión: La toxicidad retinal asociada a la didanosina es un trastorno progresivo a pesar de la sesión de drogas. La implementación de imágenes multimodales y de exámenes funcionales en pacientes con esta toxicidad permite un estudio más preciso y detallado de su progresión.
Palabras clave: didanosina, toxicidad, retina, HIV, retinopatía tóxica.

Toxicidade retiniana por didanosina

Resumo

Objetivos: Relatamos o acompanhamento a longo prazo de um paciente com toxicidade retiniana associada à didanosina, demonstrando sua progressão sob imagens multimodais uma vez que a administração da droga foi descontinuada. Propomos este relato de caso para enriquecer a literatura sobre toxicidade da didanosina e entender o papel fundamental na implementação de imagens multimodais para a detecção e monitoramento da toxicidade retiniana.
Caso clinico: Um homem de 69 anos relatou perda de visão noturna e declínio do campo visual periférico lentamente progressivo em ambos os olhos nos últimos 7 anos. Sua acuidade visual era 20/20 no olho direito e 25/20 no esquerdo. Por meio de fundoscopia e imagens multimodais foram identificadas alterações retinianas bilaterais com atrofia do epitélio pigmentar da retina associada à perda relativa da retina neurossensorial e dos coriocapilares, localizados em áreas bem definidas da periferia médio-retiniana. A progressão da retinopatia foi observada durante o seguimento de 7 anos desde que a droga foi descontinuada.
Conclusão: A toxicidade retiniana associada à didanosina é uma doença progressiva apesar da sessão de drogas. A implementação de exames multimodais de imagem e de exames funcionais em pacientes com essa toxicidade permite um estudo mais preciso e detalhado de sua progressão.
Palavras-chave: didanosina, toxicidade, retina, HIV, retinopatia tóxica.

Introduction

The number of persons living with HIV worldwide reached approximately 37.7 million in 2020. In 2021, it was estimated that 28.2 million HIV-positive patients were accessing antiretroviral therapy (ART), an increase of 7.8 million people compared to 2010[1]. Nowadays, patients affected by the human immunodeficiency virus (HIV) benefit from effective therapy, ensuring a majority of them a long-term remission. Current treatments of HIV are based on a combination of antiviral drugs, some of which can manifest undesirable secondary effects.

Didanosine (DDI) is an antiviral agent that belongs to the nucleoside analog reverse transcriptase inhibitor (NRTI) class. The mechanism of action of DDI involves intracellular phosphorylation of the parent drug to its active metabolite, 2', 3'-dideoxyadenosine 5'-triphosphate (ddATP), which prevents HIV (human immunodeficiency virus) replication by inhibiting the action of the viral reverse transcriptase through competition with the naturally occurring nucleoside deoxyadenosine triphosphate for incorporation into the growing viral DNA chain. Incorporation of ddATP into viral DNA stops viral DNA elongation, therefore terminating HIV replication[2].

DDI has been a cornerstone of HIV management since it was made available in October 1991

when was approval for use as an antiretroviral agent by the Federal Drug Administration (FDA) and was initially marketed as Videx® by Bristol Myers Squibb (BMS), New York, USA. DDI was originally introduced as an alternative to zidovudine (ZDV) for patients who were intolerant of ZDV or experienced disease progression during ZDV monotherapy.

Combination treatment steadily improved life expectancy of patients with HIV infection, and HIV became a chronic disease. Nevertheless, longstanding treatment with antiretroviral agents led to an increasing body of literature on retinal toxicity. Intraocular toxicity from DDI was first reported in 1992 by Whitcup *et al.*, who described retinal lesions associated with DDI therapy in a 6-year-old HIV positive girl[3]. To date, since 1992, there have been numerous reported cases of didanosine-associated retinal toxicity (DART) amongst adults[4-9].

Herein we describe the long-term follow up of DART in an HIV-positive adult patient.

Case report

A 69-year-old white HIV-positive man was referred 7 years ago to the retina dystrophy consultation for presumed gyrate atrophy. The patient's complaints were a loss of night vision and peripheral visual difficulties.

His past medical history included type 2 diabetes (diagnosed in 2017), hyperlipidemia (since 1998), and HIV infection (since 1994). The patient had been diagnosed with HIV in 1994 and had been on highly active antiretroviral therapy (HAART) since 1996. His HAART history included zidovudine 500 mg/daily and didanosine 400 mg/daily (1996); zidovudine 500 mg/daily and lamivudine 300 mg/daily (1997); zidovudine 500 mg/daily, lamivudine 300 mg/daily and indinavir 2400 mg/daily (1998-2003); tenofovir 245 mg/daily, didanosine 400 mg/daily and lopinavir 800 mg/daily (2003-2005); abacavir 600 mg/daily, didanosine 250 mg/daily, atazanavir 300 mg/daily and ritonavir 100 mg/daily (2005-2006); atazanavir 400 mg/daily (2006-2009); abacavir 600 mg/daily, lamivudine 300 mg/daily, atazanavir 400 mg/daily and didanosine 250 mg/daily (2009-2014); tenofovir 245 mg/daily, lamivudine 300 mg/daily, darunavir 800 mg/daily and ritonavir 100 mg/daily (2014-2015); abacavir 600 mg/daily, lamivudine 300 mg/daily, darunavir 800 mg/daily and ritonavir 100 mg/daily (2015-2018).

To this day is in treatment with dolutegravir 10 mg/daily, darunavir 800 mg/daily, ritonavir 100 mg/daily, metformina 500 mg/daily (last glycosylated hemoglobin 7,2%) and rosuvastatine 10 mg/daily.

At presentation, his best-corrected visual acuity (BCVA) was 20/20 in the right eye and 20/25 in the left eye. His ocular movements were full, normal pupillary reactions, normal intraocular pressures and anterior segment examination were unremarkable.

Fundus examination showed bilateral patches of chorioretinal atrophy (with a nummular pattern of pigmentary changes) and stippled pigmentary clumps demarcated mid-peripheral, normal macula, and optic disc. There were no signs of diabetic retinopathy or maculopathy.

Widefield fundus photography (Optos, California Ultra-widefield Retinal Imaging System, Marlborough, USA) showed a 360° of mid-peripheral areas of chorioretinal atrophy, sometimes coalescent, as well as pigment accumulation mainly in the mid and far retinal periphery between the patches of geographic atrophy. On blue-light autofluorescence (FAF) imaging (Optos, California Ultra-widefield Retinal Imaging System, Marlborough, USA) confirmed the clinical findings of severe, demonstrated extensive retinal pigment epithelium (RPE) atrophy with extensive hypoautofluorescence in the nummular areas of atrophy affecting mid-peripheral fundus to the periphery, whereas the central macular areas demonstrated normal autofluorescence in both eyes (Fig. 1).

Posterior pole autofluorescence (FAF) imaging (Spectralis® HRA, Heidelberg Engineering Inc, Germany) revealed a normal macular area, the degree of hypo-autofluorescence correlates well with funduscopic areas of chorioretinal atrophy (nummular pattern), posterior interval pigmentary changes on fundoscopy match areas of mottled pattern hypo/hyper-autofluorescence.

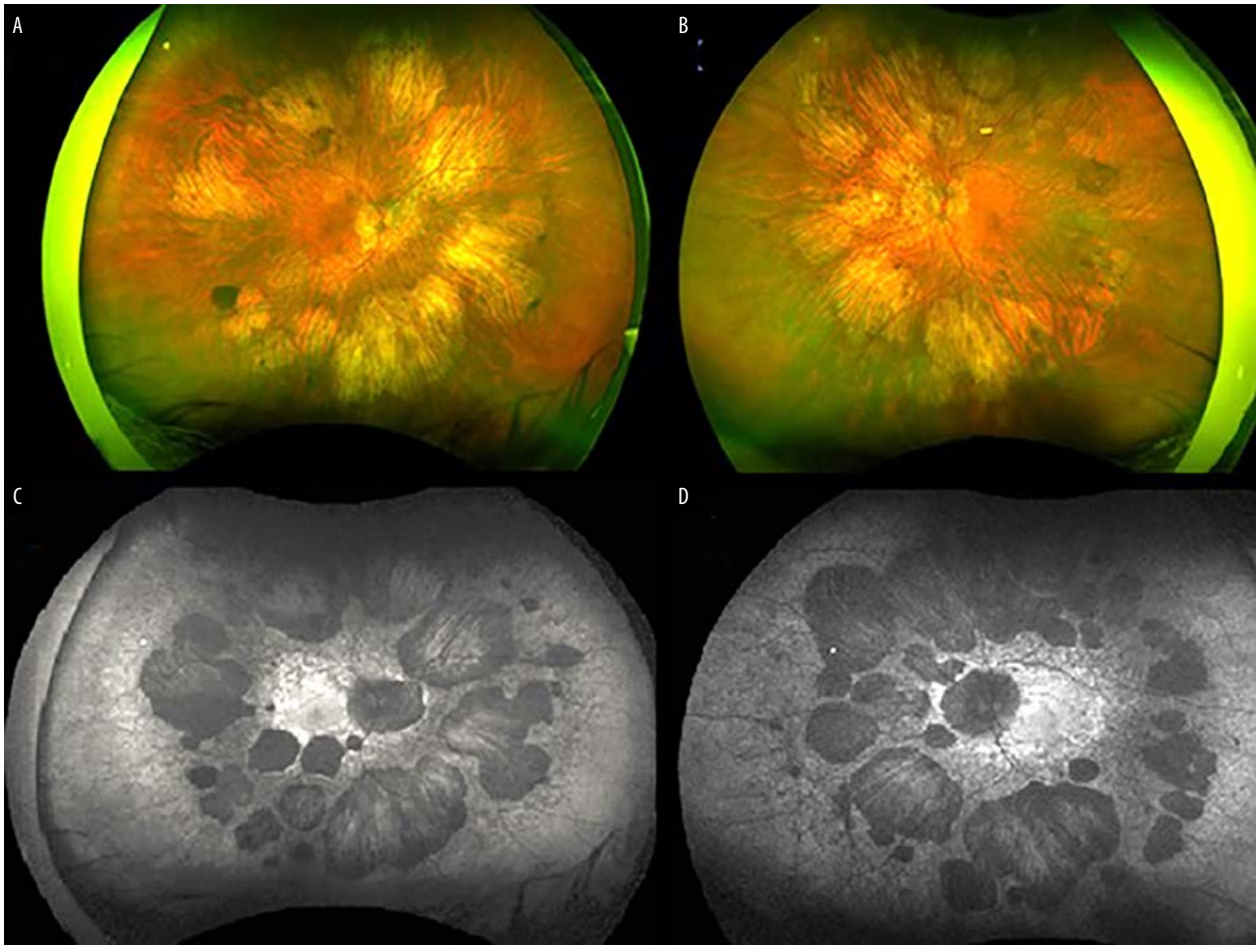

Figure 1. Fundus photographs of the right (a) and left (b) eye show extensive mid-peripheral atrophy at the level of the RPE. On autofluorescence imaging, the macula was spared in both eyes (c and d).

On optical coherence tomography (OCT) (Spectralis® HRA, Heidelberg Engineering Inc, Germany), the macula had a normal retinal architecture with an intact inner and outer retinal layer in both eyes. Peripheral OCT revealed complete loss of ellipsoid and thinning of RPE at the level of the atrophic lesions (Fig. 2).

Fluorescein angiography (AF) showed a granular mottled pattern of diffuse hyper fluorescence on the periphery and early window defects in an area of atrophy with late staining at the concentric margin of the atrophic lesions. The macula is not affected. (Fig. 3).

Goldman visual fields exhibited small central vision with extensive scotoma to the mid periphery and the electroretinography (ERG) showed undetectable rod response and extreme reduction of cones response in ERG cone and flicker (Fig. 4).

Discussion

The patient reported herein exhibited clinical and imaging features similar to cases of DDI retinopathy toxicity reported previously.

The findings reported in 9 cases by Haug *et al.* demonstrated the fundus findings consisted of concentric mid-peripheral chorioretinal atrophy and degeneration that was symmetrically present in each eye and sharply demarcated from the posterior pole, ranging from diffuse retinal pigment epithelial (RPE) mottling to severe patches of geographic atrophy[4].

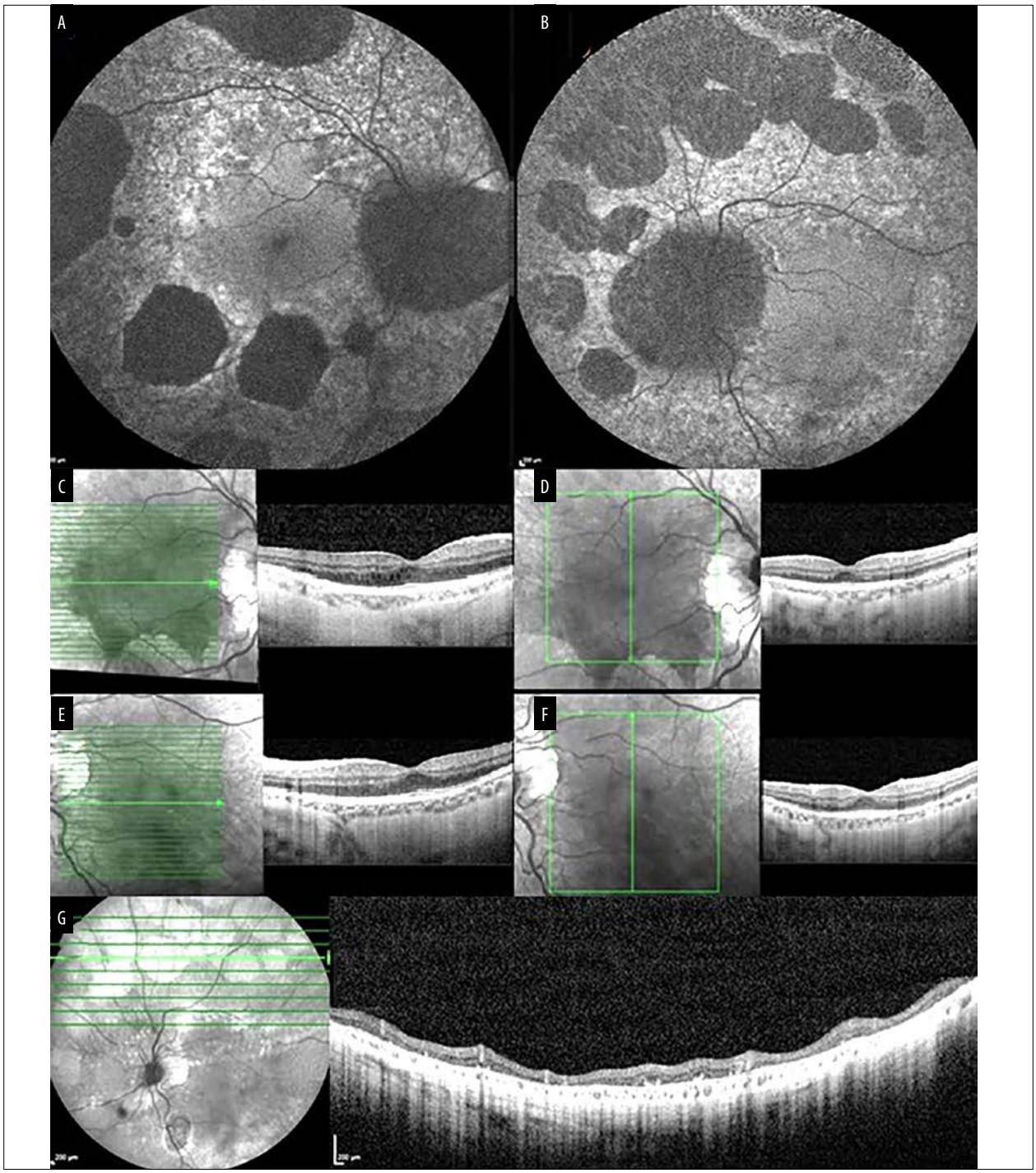

Figure 2. Posterior pole autofluorescence right eye (a) and left eye (b) show diffuse hypo-autofluorescence involving the mid-peripheral retina in both eyes corresponding to the areas of RPE atrophy. Spectral-domain optical coherence tomography scan of the right eye (c and d) and the left eye (e and f) demonstrating normal macula architecture and no apparent choroidal abnormalities. The scans horizontal and vertical were obtained using the Spectralis® HRA system (Heidelberg Engineering). Peripheral OCT scan (g) demonstrated patchy areas with loss of the external limiting membrane, myoid/ellipsoid, interdigitation zones, RPE, choriocapillaris, Sattler's, and Haller's layers.

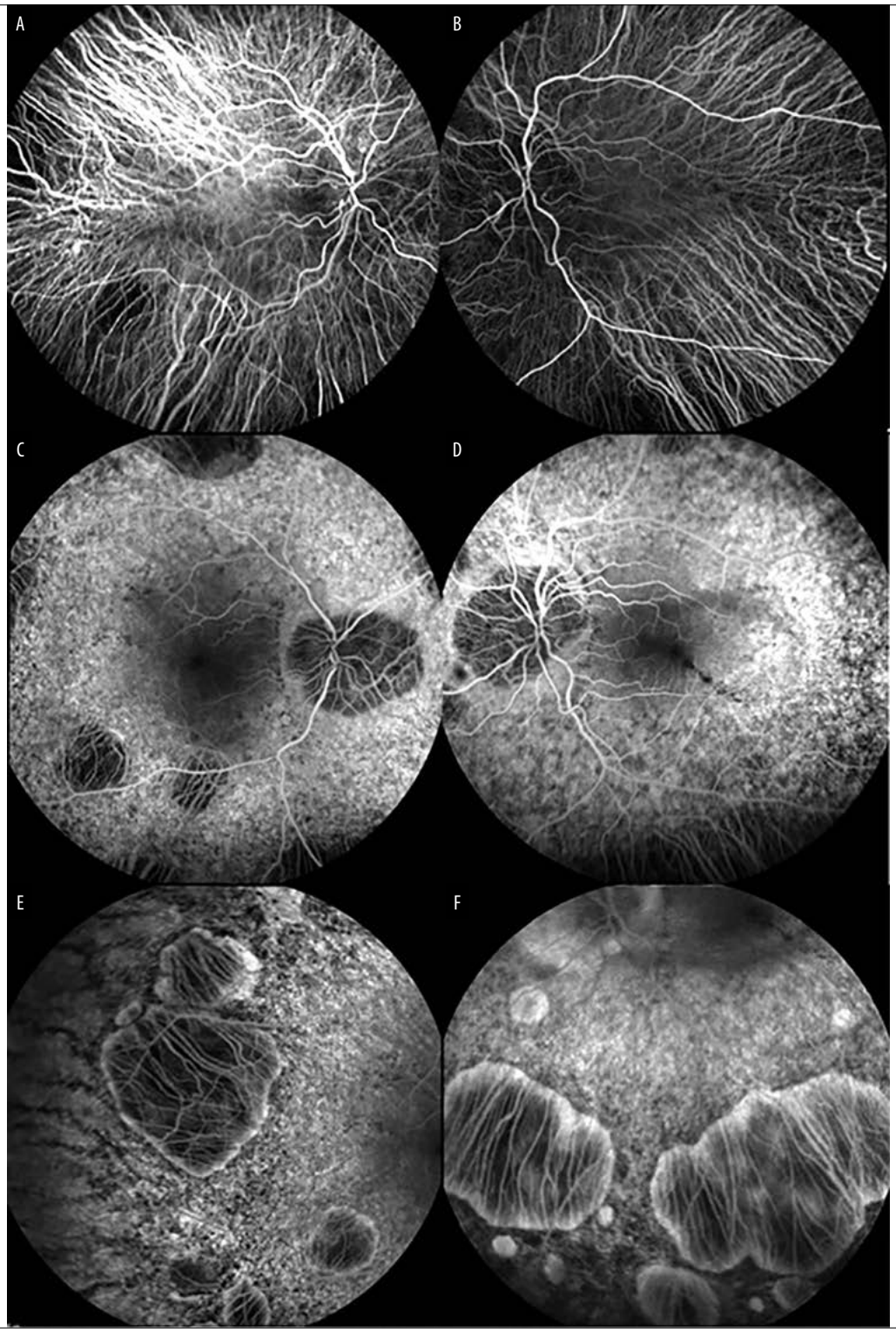

Figure 3. Fluorescein angiography in early time eyes right (a) and eye left (b) showed retinal and choroidal vasculature appeared not to be involved, medium time eyes right (c) and eye left (d); late time eyes right (e) and eye left (f) revealed RPE window defects corresponding to areas of RPE patches type atrophy.

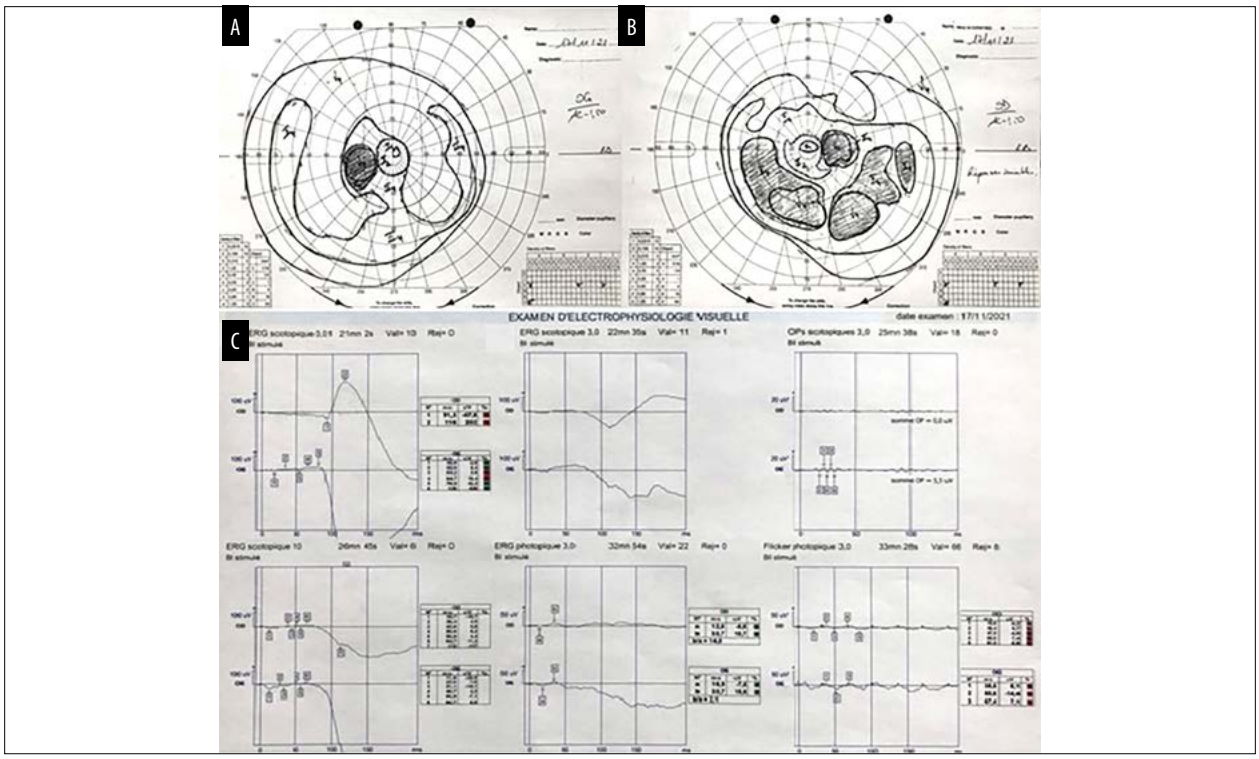

Figure 4. Goldman perimetry of the left eye (a) and of the right eye (b) showing an extensive deep mid periphery scotoma. ERG revealed bilateral rod depression (c).

Histopathologic retinal lesions were studied more extensively by Whitcup *et al* in HIV-related death children where demonstrated multiple areas of RPE loss surrounded by areas of hypertrophy and hyperpigmentation of the RPE[10]. Partial loss of the choriocapillaris and neurosensory retina were also noted. The macula was histopathologically spared, with a normal neurosensory retina, RPE layer, and choroid. Using transmission electron microscopy, they showed the presence of membranous lamellar inclusions and cytoplasmic bodies in affected peripheral RPE cells.

Our patient was treated with DDI for 9 years, with doses 400 mg/daily (1996 and 2003 to 2005) and 250 mg/daily (2005 to 2006 and 2009 to 2014).

Multimodal imaging evidence of progression over 6 years (2015-2021) even after cessation of DDI in 2014 (Figs. 5-9).

There was a progression of the retinopathy during the follow-up, after 7 years since DDI was suspended. This progression was observed in the increase of the atrophy of type patched in the midperiphery, the notable increase of the scotomas to the goldman visual field, and the dysfunction of reaction to the ERG. DDI clinically visible macular changes have not been reported as yet.

The location of atrophy in the retinal midperiphery is related to mitochondrial toxicity (MT). MT can occur as a consequence of HIV infection and from treatment with highly active antiretroviral therapy (HAART), many of the nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) are known to inhibit mitochondrial DNA (mtDNA) polymerase – γ, which is critically important for the synthesis of mtDNA[11].

In vitro toxicity of DDI on differentiated RPE cells has been investigated by Hu *et al.*[12]. They showed that DDI treatment generated cells undergo corresponding pathophysiological changes to adapt to the process, thus better tolerating oxidative stress; but they hypothesized that longer exposure to DDI, leads to increased glycolysis, and oxidative stress exceeds the tolerable level of the cells, showing loss of RPE mitochondrial function and causing serious damage. Also revea-

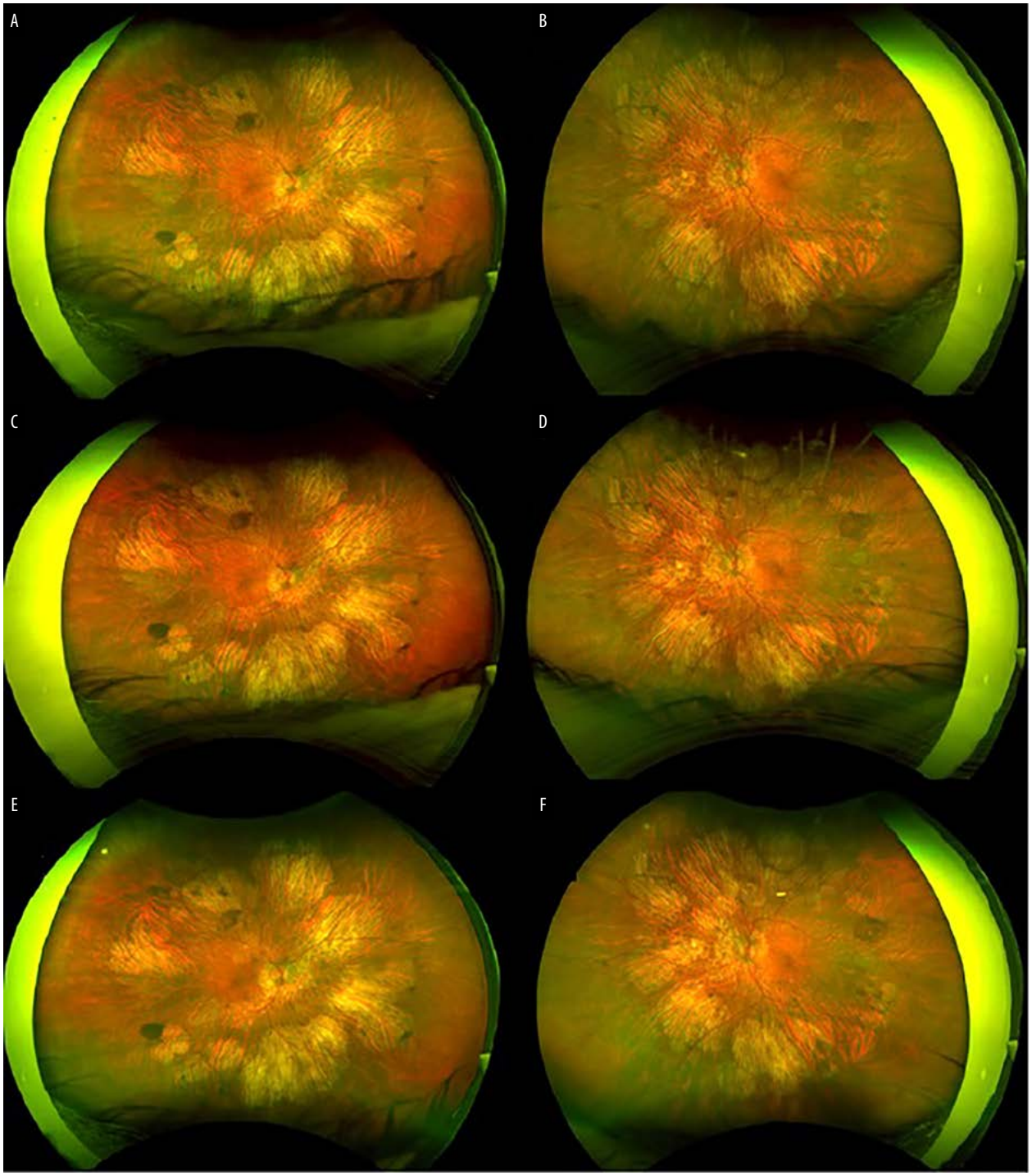

Figure 5. Wide-field fundus imaging (Optos) from follow-up didanosine retinal toxicity between 2015 to 2021. a) right eyes. b) left eye fundus photos 2015. c-d) fundal photos 2018. (e-f) fundal photos 2021.

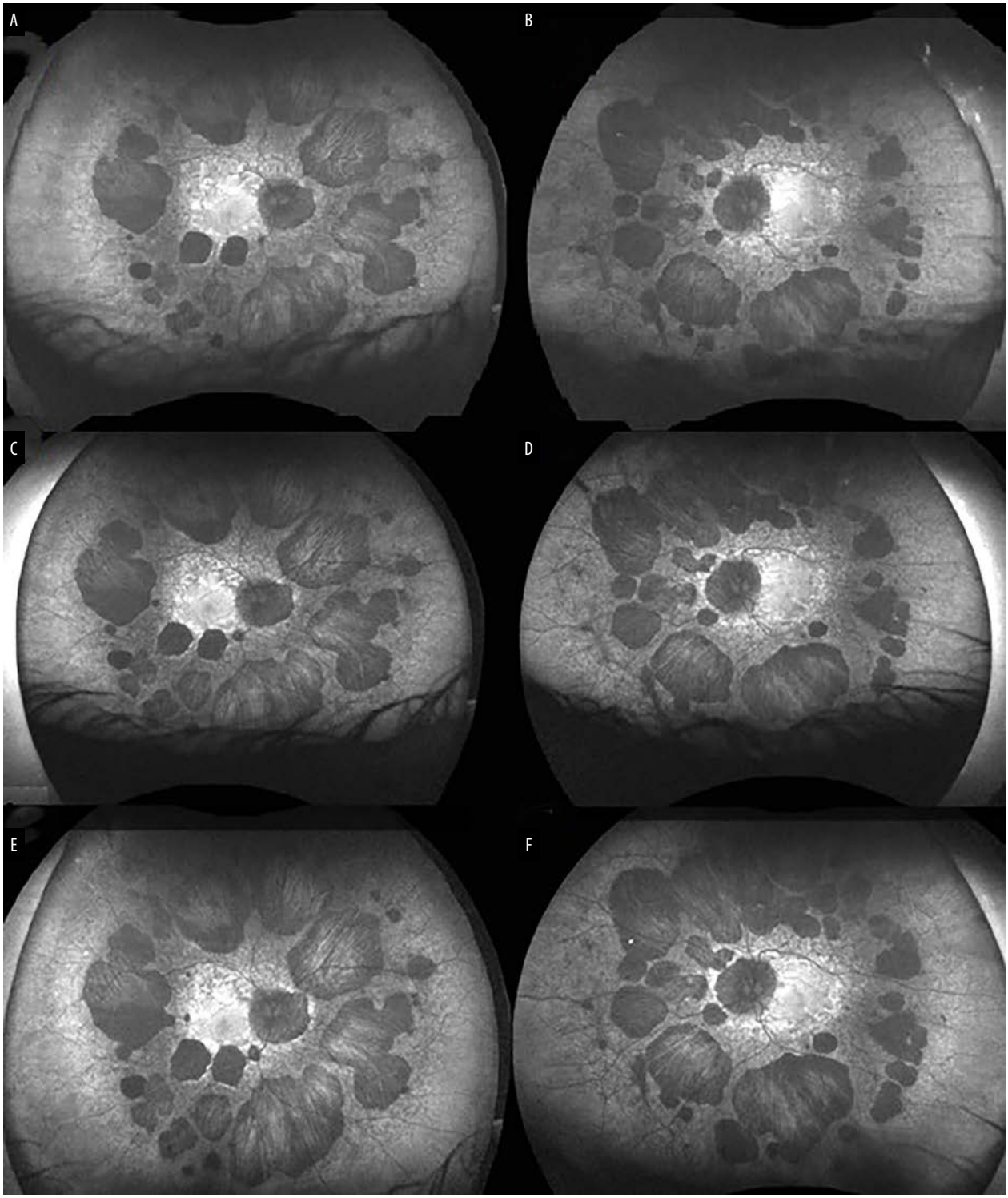

Figure 6. Wide-field fundus autofluorescence Optos, imaging from follow-up didanosine retinal toxicity between 2015 to 2021. a-b) AF photos 2015. c-d) AF photos 2018. e-f) AF photos 2021.

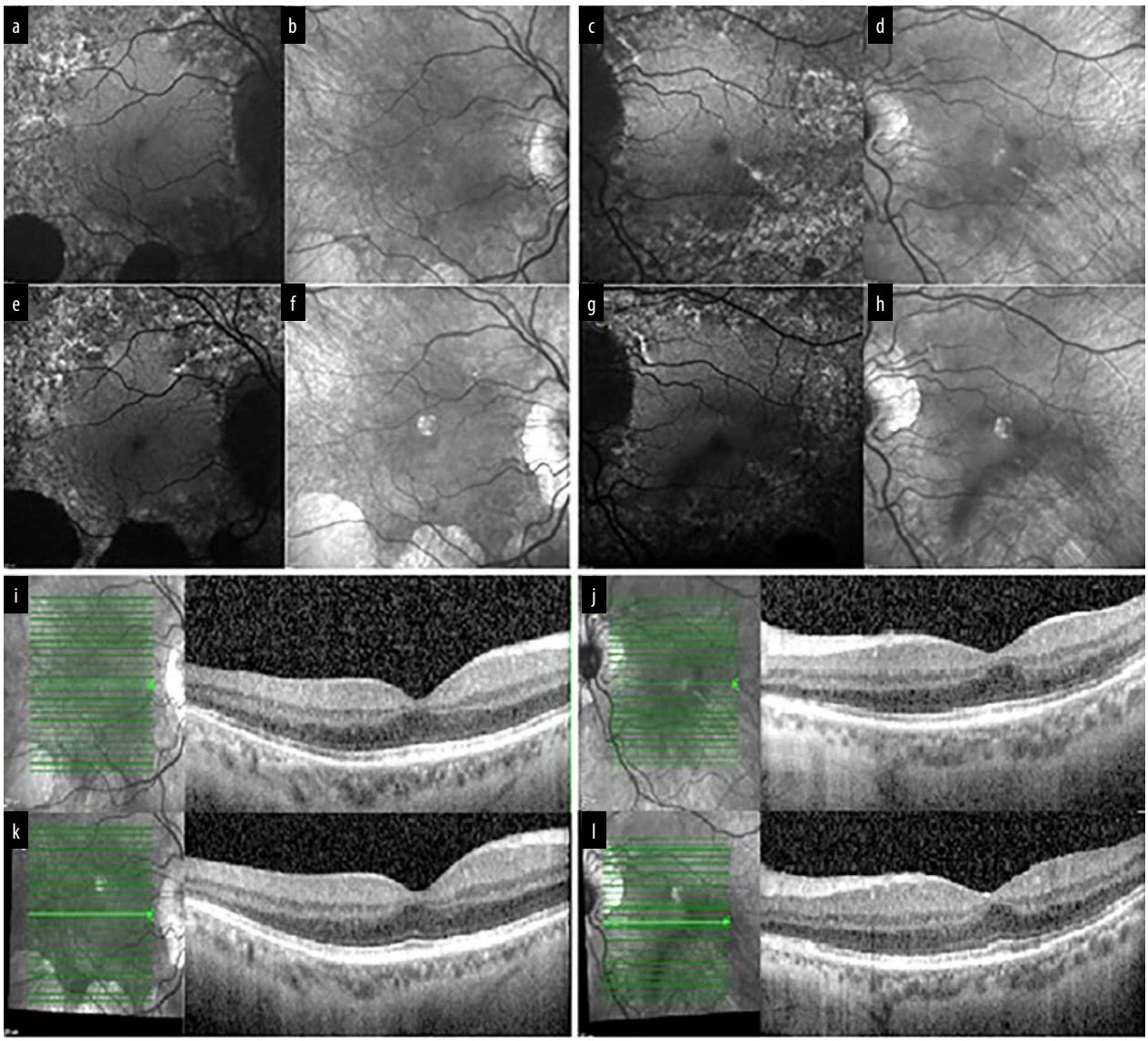

Figure 7. OCT Spectralis® multimodal imaging (a-d) 1 years after DDI cessation (2015) FAF eye right (a) and left eye (b), infrared reflectance eye right (b) and eye left (d). The peripheral chorioretinal atrophy seemed to have progressed in each eye as shown in the figures (e-h) comparison in 2021. OCT Spectralis macular scan show no changes since 2015 - eyes right (i) and eyes left (j) to 2021, eyes right (k) and eye left (l), comparison by Spectralis eye-tracking system.

ling up to 60% depletion of mtDNA after 6-24 days of DDI treatment.

DDI affects the mid-peripheral retina because mitochondrial depletion is thought to affect the energy-intensive rod system initially, and toxicity preferentially affects the peripheral retina, sparing the macula, could be related to the denser population of rods, which may lead to increased vulnerability of the RPE because of the high metabolic demand of rod outer segment turnover or possibly because of the distribution of the drug.

The differential diagnosis for peripheral chorioretinal degeneration includes inherited mitochondrial disorders such as chronic progressive external ophthalmoplegia, Kearns–Sayre syndrome, maternally inherited diabetes and deafness, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes. Genetic

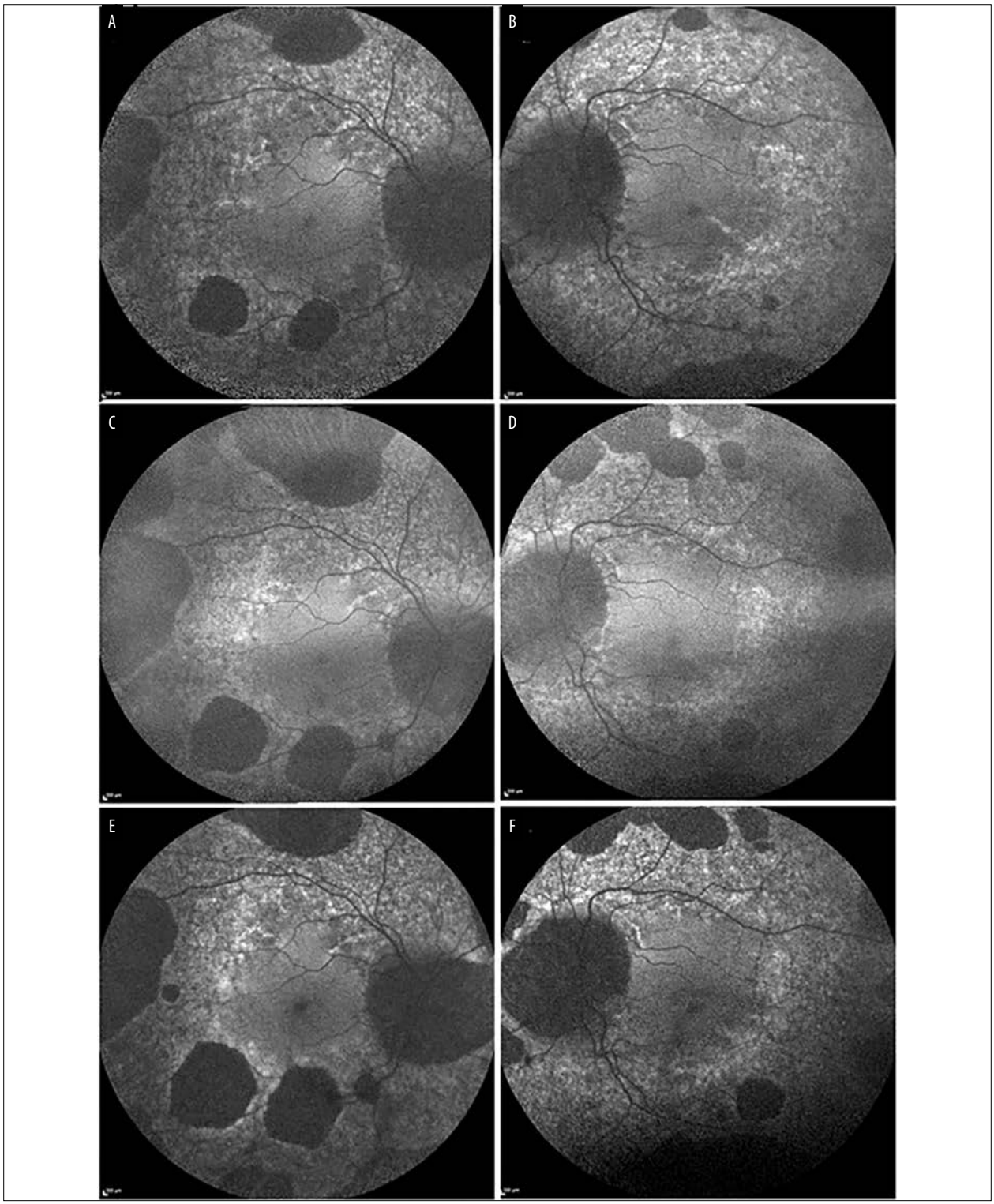

Figure 8. OCT Spectralis® imaging FAF shows an increase in hypoautofluorescence in atrophy patches in the middle periphery from 2015 to 2021. Eye right (a) and eye left (b) in 2015; eye right (c) and eye left (d) in 2018; eye right (e) and eye left (f) in 2021.

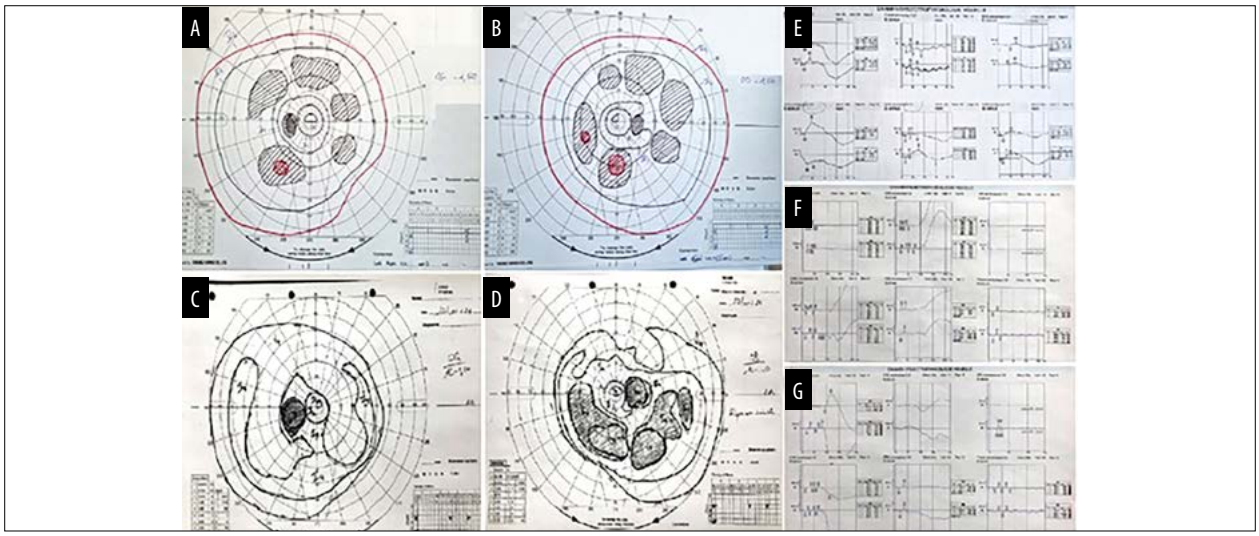

Figure 9. Goldman field of view shows an evolution of peripheral deep scotomas since 2018, eye left (a) and right eye (b) in 2018 to left eye (c) and right eye (d) in 2021. The ERG recording from 2015, 2018, and 2021 demonstrated generalized progression of retinal dysfunction with relatively to severe rod involvement and marked cone system involvement.

pathologies (i.e. retinitis pigmentosa, choroideremia, gyrate atrophy, and Bietti's dystrophy), inflammatory and infectious conditions, as well as iatrogenic entities (i.e. thioridazine toxicity), should also be considered.

The theory of the DART progression may occur as DDI is replaced with an alternative NRTIs which may also be toxic to mitochondria (including zalcitabine, stavudine, lamivudine, zidovudine, abacavir, tenofovir, and emtricitabine) or another explanation may be that the phenotypic retina changes of the mitochondrial cellular damage don't become apparent immediately but are delayed, even after cessation of DDI use.

In the case report of Haug *et al.* found at long-term follow-up (96 weeks) for five of nine cases[4]. At least three cases demonstrated progression of the peripheral chorioretinal atrophy despite DDI cessation. Of these three cases, all were currently taking tenofovir and two of the cases were also taking emtricitabine, possibly because of a potentiating effect of other NRTIs, such as tenofovir, which is now more commonly used than DDI.

Conclusion

In conclusion, the diagnosis of toxic retinopathy associated with didanosine was made based on clinical history, examination, and ophthalmologic exams with characteristically slowly progressive peripheral vision loss, symmetrical and concentric mid-peripheral chorioretinal atrophy and degeneration, macular and posterior pole sparing with preserved VA, FAF mid-peripheral atrophy with extensive hypoautofluorescence areas, AF with mid-peripheral patchy hyperfluorescent borders, OCT with outer retinal and RPE damage reaching INL in the zone with atrophy without macular changes. We found progress in retinopathy after discontinuing the administration of DDI, retinal imaging and functional testing plays an essential role in screening patients and follow-up, especially studies with FAF giving a functional correlate, that is very useful in monitoring patient progression.

DDI is no longer a first-line drug used for the treatment of HIV disease, and therefore, the newly diagnosed cases are in patients who

have been treated for HIV for many years, thus skewing the demographic to older patients.

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