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Occult inflammation detected by autofluorescence May Be the cause of idiopathic choroidal neovascularization

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ABSTRACT

Purpose: To describe retinal pigment epithelium (RPE) disease detected by fundus autofluorescence (FAF) imaging in eyes with idiopathic choroidal neovascularization (ICNV).

Methods: A retrospective review of patients seen during a 14-month period with the diagnosis of ICNV was performed to identify patients with RPE disease, defined as hypo or hyperautofluorescent lesions on FAF. The presence of ICNV was confirmed by clinical history, ophthalmoscopic examination, fluorescein angiography (FA), and spectral domain-optical coherence tomography (SD-OCT). The clinical diagnosis of an underlying inflammatory condition was based on the FAF appearance of multiple punched-out hyper or hypoautofluorescent spots in the retinal fundus.

Results: The mean age was 27 years (range, 21-33 years). Best-corrected visual acuity ranged from 20/25 to 20/200 with a median visual acuity of 20/80. Ten eyes of 8 patients presented RPE abnormalities on FAF. Of the 10 study eyes, ICNV was observed in 8 eyes. ICNV appeared as a type 2 neovascular membrane at the macular area on FA, and SD-OCT revealed neurosensory detachment in all study eyes. FAF demonstrated abnormalities of the RPE that were not appreciated on clinical examination or by other imaging modalities.

Conclusions: FAF may reveal an underlying inflammatory condition in patients diagnosed as ICNV, modifying the diagnosis and management.

1.

Choroidal neovascularization (CNV) is the most frequent source of legal blindness in older individuals in the United States, and age-related macular degeneration (AMD) is the most common cause for CNV in this age group.[1,2] CNV is also known to be a complication of chorioretinal inflammatory conditions, including multifocal choroiditis (MFC) and punctate inner choroidopathy (PIC).[3–5] Classically, these disorders occur in young individuals with myopia.[3–5] Idiopathic CNV (ICNV) represents a solitary or focal area of CNV in a retinal fundus that is otherwise normal on clinical and fluorescein angiographic examination in each eye occurring in patients aged 50 years or younger without predisposing conditions such as pathological myopia, trauma, angioid streaks, and macular dystrophies.[6,7] The majority of cases of ICNV experience unilateral disease although rarely the fellow eye may develop neovascular changes when followed for long periods.[7] These bilateral cases are thought to be the result of other diseases, such as macular dystrophies or inflammatory disorders.[8,9]

As ICNV eyes can develop choroidal features similar to those of inflammatory diseases by indocyanine green angiography (ICG), it was suggested that ICNV is related to chorioretinal inflammatory diseases.[10] In the present study, we report a patient cohort who were diagnosed with idiopathic CNV based on clinical and fluorescein angiography (FA) evaluation, but were found to have abnormalities on fundus autofluorescence (FAF) consistent with an underlying inflammatory condition.

2. Methods

The medical records and imaging studies of a consecutive and

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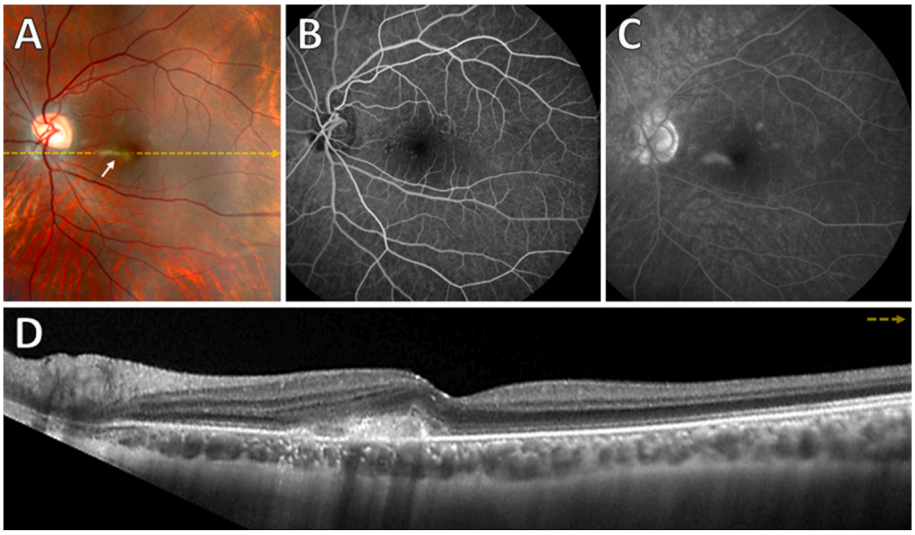

Fig. 1. (Case #2). A. Color fundus photograph from a 26-year-old female patient demonstrates a small and grayish juxtafoveal lesion **(arrow)**. The best-corrected visual acuity (BCVA) is 20/60 in the patient's left affected eye. **B and C.** Fluorescein angiogram (FA) shows early staining (**B**) and late small leakage (**C**) consistent with type 2 or classic choroidal neovascularization. Note that three hyperfluorescent dots are seen temporal to the fovea, and one hyperfluorescent dot is seen nasally to the choroidal neovascularization (CNV). **D.** Spectral-domain optical coherence tomography (SD-OCT) reveals a juxtafoveal CNV. Note the ellipsoid zone loss next to the optic nerve, shallow and small RPE detachment nasally to the CNV, and several hyperreflective dots majorly located at the inner choroid near the outer retinal lesions. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

multicenter series of patients with a diagnosis of ICNV from February 2018 to April 2019 were retrospectively reviewed after Institutional Review Board approval from Universidade Federal de São Paulo, São Paulo, Brazil. Eyes identified as manifesting a multifocal RPE disorder on FAF, consistent with an underlying inflammatory condition were included in this analysis. None of the study patients had a history of ocular or systemic disease known to be associated with CNV. Each patient had a work-up to rule out the presence of systemic disorders that could cause features similar to those of MCP or PIC. Patients who had undergone intravitreal anti-VEGF or triamcinolone injection, photodynamic therapy, or thermal laser photocoagulation for CNV were excluded from this study. All enrolled patients had undergone a comprehensive ophthalmic examination, color fundus photography and FAF. The diagnosis of ICNV was based on clinical history, ophthalmoscopic examination, FA, and spectral domain-optical coherence tomography (SD-OCT). The clinical diagnosis of an underlying inflammatory condition was based on the FAF appearance of multiple punched-out hyper or hypoautofluorescent spots found in the macular and

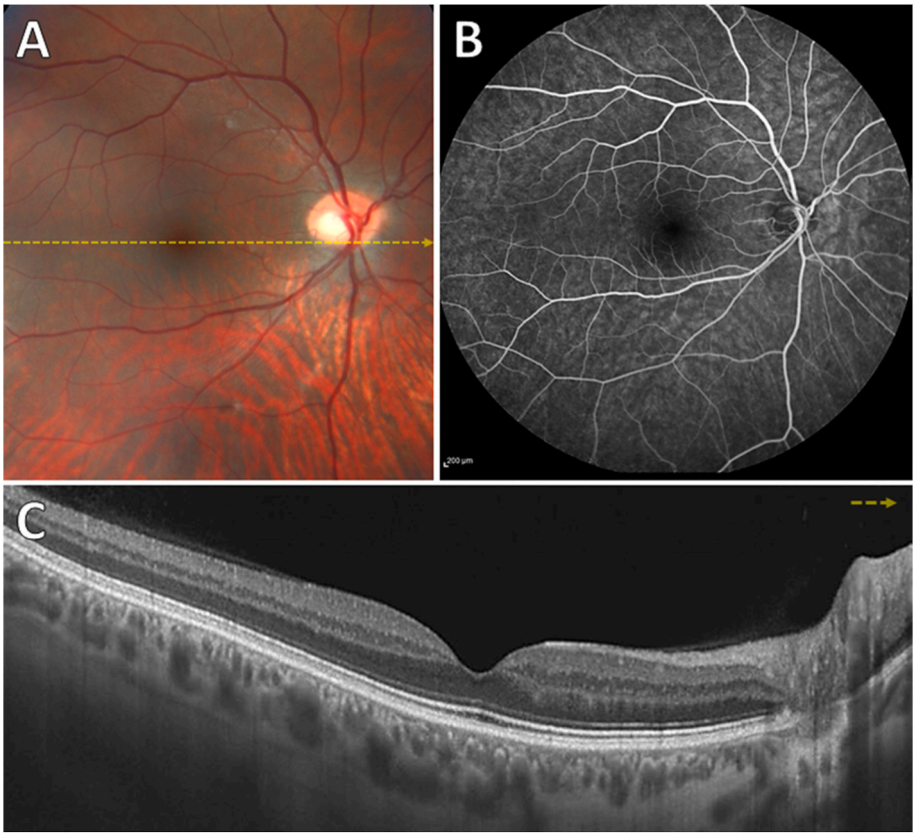

Fig. 2. (Case #2). The patient's right unaffected eye with a BCVA of 20/20. **A.** Color fundus photograph demonstrates a lack of any significant clinical findings. **B and C.** FA and SD-OCT are also unremarkable. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

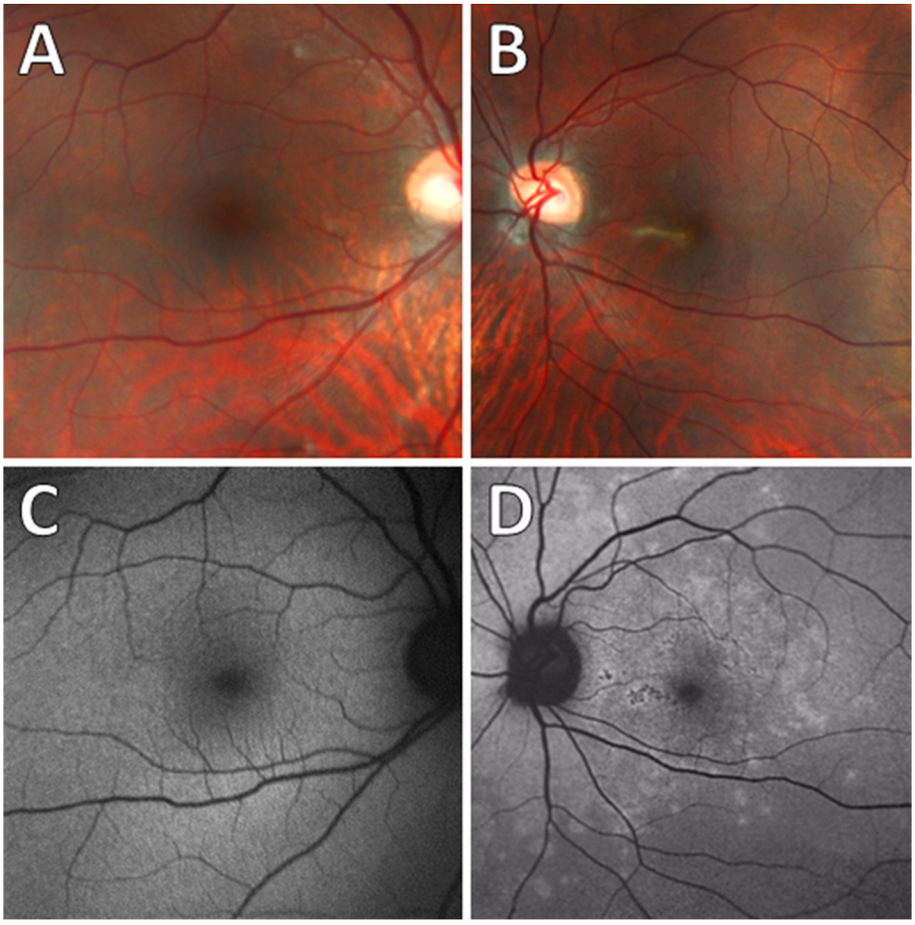

Fig. 3. (Case #2). A and B. Color fundus photographs of both eyes, with comparison to fundus autofluorescence (FAF) imaging (**C and D**). FAF shows peripapillary and macular hyperautofluorescent spots in the patient's left affected eye, suggestive of retinal pigment epithelium (RPE) abnormalities, that were unilateral. The corresponding color fundus photograph does not demonstrate similar RPE findings. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

peripapillary areas. The characteristics of these lesions, including shape, size, and distribution in the fundus were determined using FAF.

The FAF photographs (Triton, Topcon Medical Systems, Tokyo, Japan) were taken with an excitation filter with the bandpass wavelengths of 535–585 nm and a barrier filter with a bandpass of 615–715 nm. A swept-source (SS) OCT (Triton, Topcon Medical Systems, Tokyo, Japan) was used to obtain the B-scan OCT images. An integrative analysis of the ocular imaging was performed with special attention paid to the FAF findings.

3. Results

Eight eyes of 8 patients (5 men and 3 women) with ICNV having multifocal RPE disorder consistent with an underlying inflammatory condition were identified. All patients were white. The mean age of patients was 27 years (range, 21-33 years). Snellen best-corrected visual acuity ranged extensively from 20/25 to 20/200 with a median visual acuity of 20/80, and refractive error ranged from −1.00 D to −2.50 D. Anterior segment examination was unremarkable, and vitreous cells were observed in 6 eyes. Of the 8 study eyes, CNV was observed in their right (number of 6) and in their left (number of 2) eyes. Bilateral CNV was not observed in this series, and subfoveal involvement was observed in three eyes.

ICNV appeared as a membrane within the macular area with or without associated hemorrhage and subretinal fluid on fundus examination. FA demonstrated the presence of a type 2 or classic neovascular membrane, and SD-OCT showed neurosensory detachment at the macula in all study eyes (Fig. 1). The uncorrected visual acuity in the asymptomatic fellow eye was 20/20, with no detectable abnormalities in the macula or peripheral fundus on clinical examination with slit lamp biomicroscopy and indirect ophthalmoscopy. The FA and OCT studies of these eyes were also normal (Fig. 2).

On FAF, CNV appeared to be closely bounded by hyperautofluorescence, which seemed to be arising from more than one hyper or hypoautofluorescent spot. These hyper and hypoautofluorescent chorioretinal scars were located in the macular and peripapillary areas, and their size and shape were quite similar among the study patients, distant or adjacent to the areas of CNV. Color fundus photography failed to show these changes observed on FAF (Fig. 3). FAF revealed bilateral peripapillary and macular abnormalities of the RPE in two patients (Fig. 4). In one study patient, FAF highlighted areas of potential RPE abnormalities in the macular area in the affected eye. Although these areas were not apparent or barely detectable by clinical examination, close examination of the color fundus photographs readily revealed corresponding macular areas of RPE involvement. There was evidence of RPE abnormalities in the asymptomatic fellow eye as well (Fig. 5). Table 1 summarizes the clinical and imaging features of the study patients.

4. Discussion

ICNV is considered a diagnosis of exclusion, made in patients of age 50 years or younger when a single or focal area of CNV is observed in the absence of known acquired or inherited diseases such as inflammatory retinopathies, trauma, angioid streaks, high myopia, macular dystrophies, and choroidal tumors.[1] Currently, there is no agreement about mechanism for ICNV. The refractive error of patients with ICNV is not dissimilar from that of the general population, and there is no reported association of ICNV with HLA or gene polymorphisms. By definition, ICNV is unilateral, and in 19 cases of subfoveal ICNV followed for a

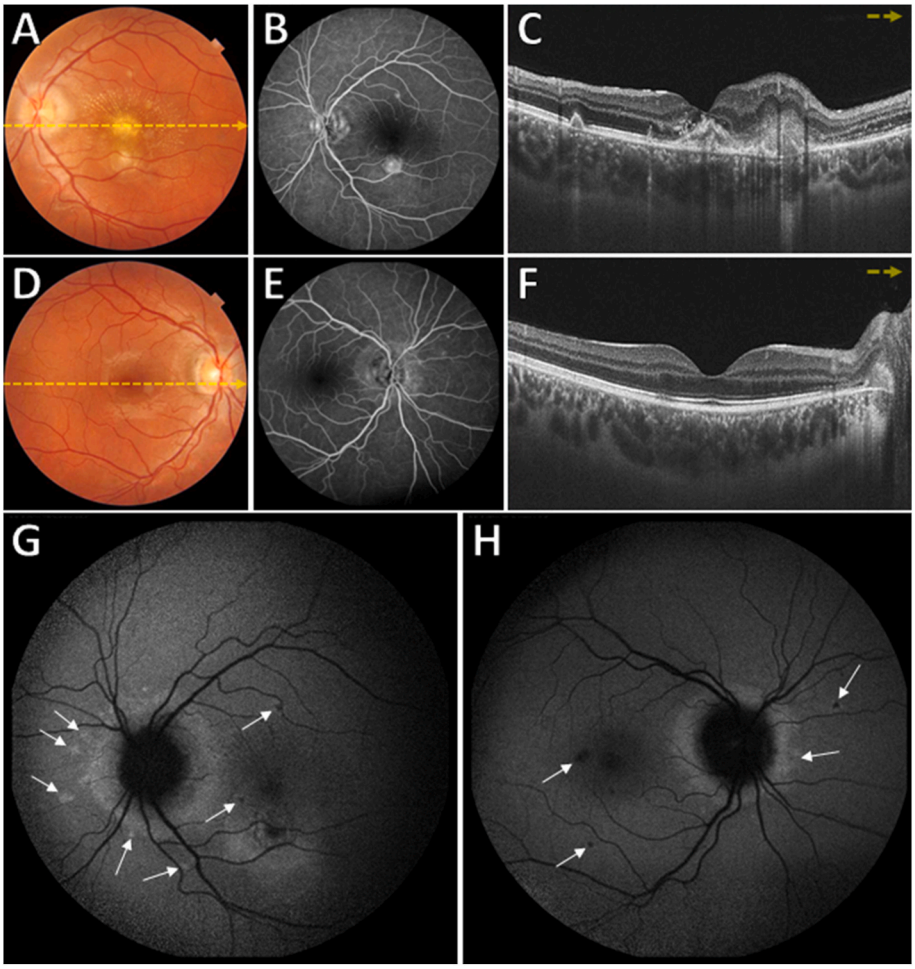

Fig. 4. (Case #5). A. Color fundus photograph from a 29-year-old female patient demonstrates an extensive macular exudation in the left eye. The BCVA is 20/200 in this eye. **B and C.** FA and SD-OCT of the left eye reveals a type 2 foveal CNV. **D.** Color fundus photograph of the patient's right unaffected eye shows an absence of any significant clinical findings. **E and F.** FA and SD-OCT of the right eye are also unremarkable. **G.** FAF of the left eye shows RPE peripapillary and macular abnormalities **(arrows)** in the patient's affected left eye. **H.** FAF of the right eye depicts subtle hypo and hyperautofluorescent spots in the peripapillary and macular areas **(arrows)**, suggestive of RPE abnormalities. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

median of 87 months, Ho et al. found no involvement of the fellow eye.[11] Retinal physicians, accordingly, tend to advise patients that development of neovascular disease in the fellow eye is not likely to occur. Although rare bilateral cases have been described, these are more likely early or subclinical presentations of bilateral disease rather than true ICNV.[12] The macular photocoagulation study group showed that approximately 10% and 50% of the study ICNV cases developed histoplasmosis like spots in either the study or fellow eye at 1 and 5 years follow-up examinations, respectively. A similar number of these ICNV cases developed drusen in the study or fellow eye at both 1 and 5 years follow-up examination.[8,13] Clinicopathologic findings in a young woman whose preoperative diagnosis was ICNV were the first evidence that granulomatous inflammatory mechanisms could also be implicated in the occurrence of ICNV.[14]

Idiopathic MFC is a broad term that normally includes PIC, MFC with panuveitis and presumed ocular histoplasmosis syndrome (POHS). PIC appears in young, myopic women but MCP does not, and it is normally associated with intraocular inflammation. The three of them have risk of developing CNV. Even though idiopathic MFC could indicate an ocular expression of an autoimmune illness in genetically susceptible people, the exact etiopathogenesis still remains uncertain.[15,16] FAF is a non-invasive imaging modality that provides indirect information on the level of metabolic activity of the RPE, and it is known to detect more widespread RPE involvement in retinal diseases than would be indicated by other means of imaging.[17–19] At first, the study patients were diagnosed as ICNV based on an otherwise normal clinical examination and FA, the standard characterization of the disease. Nevertheless, in all cases, FAF showed areas of RPE abnormalities throughout the fundus that were not clinically detectable or barely depicted by color fundus photographs. The areas of RPE involvement on FAF were identified within the macular area and around the peripapillary region. In two study patients, FAF demonstrated bilateral RPE changes. These bilateral cases were previously reported and possibly masqueraders themselves.[8,9] Discrete RPE changes may have existed in these patients masking a probable genetic or inflammatory disorder.

We believe that the RPE changes seen in ICNV patients indicate an underlying inflammatory condition. Although FAF is recognized to identify more widespread RPE involvement in these disorders than would be detected by other imaging methods,[16] some reports, using FA and ICG, have previously described early manifestation of inflammatory chorioretinal diseases in ICNV patients. Giovannini et al.[10] studying the choroid of ICNV individuals using ICG reported the presence of multiple hypofluorescent spots which were not visualized by fundus ophthalmoscopy or FA. In such patients, an inflammatory disease emerged afterward. Machida et al.[9] also proposed an inflammatory mechanism as a possible pathogenesis for ICNV. They reported four patients with ICNV who developed inflammatory chorioretinal diseases in the ipsilateral or contralateral eye. Abnormal choroidal findings (hypofluorescent and hyperfluorescent lesions) comparable to those seen in chorioretinal inflammatory diseases such as MFC, PIC and MEWDS were described using ICG in these ICNV patients. It indicates that ICNV may possibly be a component of the initial stages of such inflammatory choroidal disorders. Therefore, the singular choroidal neovascular process may change over time and could convert and fit to a more diagnostic criteria for choroidal inflammatory disease. Increased levels of serum inflammatory biomarkers, such as interleukin (IL)-2, IL-10, IL-17, FGF and VEGF, and haplotypic association with IL-10 and TNF loci have also been demonstrated in ICNV and MFC patients, respectively,[20,21] suggesting that both

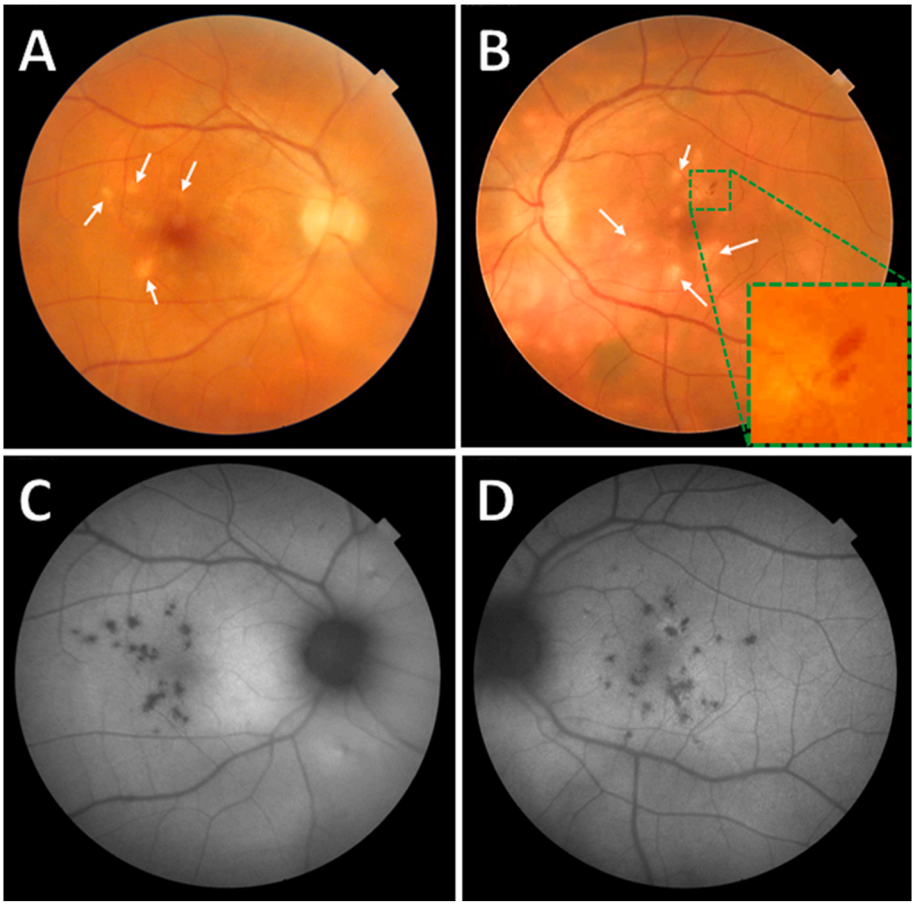

Fig. 5. (Case #8). A and B. Color fundus photograph from a 33-year-old male patient demonstrates a very small juxtafoveal hemorrhagic lesion (magnified view in the green square) in the patient's affected left eye. The BCVA is 20/25 in this eye. Close examination of the color fundus photographs of both eyes reveals RPE involvement within the macular area. **C and D.** FAF shows several hypoautofluorescent spots **(arrows)** within the macular area of both eyes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Clinical and imaging characteristics of 8 patients with occult inflammatory choroidopathy masquerading as idiopathic choroidal neovascularization.

Patient (#)	Diagnosis	Age (years)	Gender	BCVA (study eye)	Refractive Error	FA	FAF	OCT
1	MFC	24	Female	20/40	−1.50 D	Type 2 CNV	Peripapillary and macular hyperAF spots	Foveal CNV
2	MFC	26	Female	20/60	−1.75 D	Type 2 CNV	Peripapillary and macular hyperAF spots	Juxtafoveal CNV
3	PIC	30	Female	20/100	−1.00 D	Type 2 CNV	Macular hyperAF spots	Foveal CNV
4	MFC	25	Male	20/25	−2.00 D	Type 2 CNV	Macular hypoAF spots	Foveal CNV
5	MFC/AZOOR	29	Female	20/200	−1.75 D	Type 2 CNV	Peripapillary and macular hyper/hypoAF spots	Foveal CNV
6	PIC	21	Female	20/30	−1.25 D	Type 2 CNV	Macular hypoAF spots	Foveal CNV
7	MFC	28	Male	20/80	−2.50 D	Type 2 CNV	Macular hyperAF spots	Juxtafoveal CNV
8	MFC	33	Male	20/25	−1.50 D	Type 2 CNV	Macular hypoAF spots	Juxtafoveal CNV

Abbreviations#, number; BCVA, best-corrected visual acuity; CNV, choroidal neovascularization; FA, fluorescein angiography; FAF, fundus autofluorescence; MFC, multifocal choroiditis; OCT, optical coherence tomography; PIC, punctate inner choroidopathy.

diseases may have an inflammatory source in its physiopathology. Given the apparent inflammatory basis of the acute CNV in young people, some physicians may elect to manage the neovascularization with anti-inflammatory pharmacologic agents.[7,8]

The present study suggests that these RPE abnormalities represent an underlying inflammatory condition. Accordingly, we recommend that all patients with ICNV be examined with FAF for the possibility of occult RPE abnormalities, which may indicate a bilateral process, a need for more frequent future clinical surveillance, a guarded bilateral visual prognosis, and a possible modification in the management of the ICNV. Our study does have some limitations as the relatively small size of our ICNV cohort. However, it is expected that imaging additional ICNV patients with FAF would result in a more frequent identification of RPE abnormalities. Therefore, we may consider the likelihood that eyes with ICNV could actually represent an underlying inflammatory condition that have not yet revealed characteristic inflammatory chorioretinal spots.

Declaration of interest

None.

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