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# Fundus autofluorescence features of central serous chorioretinopathy

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## 中心性浆液性脉络膜视网膜病变眼底自发荧光影像的特点

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**摘要**

**目的**:研究急性和慢性特发性中心性浆液性脉络膜视网膜病变眼底自发荧光影像模式及眼底荧光血管造影相关性发现。

**方法**:观察性研究案例。回顾性分析中心性浆液性脉络膜视网膜病变患者临床数据,眼底荧光血管造影及眼底自发荧光影像,并对其调查结果进行比较。

**结果**:该研究共纳入 17 例 25 眼。确诊为急性中心性浆液性脉络膜视网膜病变 5 眼,慢性疾病或复发性慢性疾病 20 眼。急性病例眼底自发荧光影像显示低荧光点与荧光血管造影检测出的荧光渗漏点位置相同。慢性特发性中心性浆液性脉络膜视网膜病变眼底荧光血管造影为视网膜色素上皮弥漫性萎缩区域,可透视荧光。眼底自发荧光影像的低荧光区域的形态和位置与眼底荧光血管造影的高荧光区域相对应,然而眼底荧光血管造影的低荧光区域与眼底自发荧光影像的高荧光区域相对应。在急性病例中,低自发荧光点不能准确指出视网膜色素上皮的渗漏点。

**结论**:中心性浆液性脉络膜视网膜病变眼底自发荧光影像模式能够描述疾病不同阶段的特征,具有无风险和可再生性,可替代荧光素血管造影术治疗中心性浆液性脉络膜视网膜病变。

**关键词**:脂褐质自发荧光;眼底自发荧光影像;中心性浆液性脉络膜视网膜病变

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## Abstract

• AIM: To define the fundus autofluorescence (FAF) patterns in acute and chronic idiopathic central serous chorioretinopathy (ICSCR) and correlate them with fundus fluorescein angiography (FFA) findings.

• METHODS: This is an observational case study in which we retrospectively reviewed the clinical data and FFA and FAF images of ICSCR patients and compared the findings.

• RESULTS: The study included 25 eyes of 17 patients. We detected acute ICSCR in 5 eyes, and chronic disease or recurrence in chronic disease in 20 eyes. FAF images in acute cases showed a sharply delineated hypoautofluorescent spot in exactly the same location as the pinpoint leak detected on fluorescein angiography. In FFA images of chronic ICSCR diffuse areas of RPE atrophy are visualized as transmission fluorescence. FAF images demonstrate hypo-autofluorescence that corresponds in shape and location to the areas showing the most intense transmission fluorescence on FFA, whereas areas with less transmission fluorescence on FFA correspond to hyper-autofluorescence on FAF. The hypo-autofluorescent spot pointing to the site of RPE leakage cannot be localized as precisely as in acute cases.

• CONCLUSION: FAF imaging in ICSCR is capable of depicting FAF patterns that are characteristic of various stages of the disease. It is a risk-free and reproducible alternative to fluorescein angiography in ICSCR.

• KEYWORDS: lipofuscin autofluorescence; fundus autofluorescence imaging; central serous chorioretinopathy
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## INTRODUCTION

Our knowledge of idiopathic central serous chorioretinopathy (ICSCR) dates back to 1866 when Albrecht von Graefe first described the clinical aspects of this condition. One hundred years later, Maumenee provided a fluorescein angiography description[1].

ICSCR typically affects individuals 20 to 45 years of age with a type A personality, and predominantly occurs in males. Men are 10 times more prone to developing ICSCR than are

women. Exposure to unusual emotional stress is a frequent association[2]. Classic presenting symptoms include metamorphopsia, micropsia, and positive scotoma. Visual acuity is often moderately decreased and may be improved to near normal with a small hyperopic correction. The typical biomicroscopic appearance is that of a well-defined, shallow, round or oval elevation of the neurosensory retina in the macular region. Simultaneous retinal pigment epithelial detachment (PED) is occasionally seen[2].

The sequence of events eventually resulting in ICSCR begins with inner choroidal exudation leading to PED. Pressure from serous elevation of the retinal pigment epithelium (RPE) causes a "blow-out" or micro-rip at or near the junction of the attached and detached pigment epithelium. Subsequently, exudates originating in the choroid sweep through the RPE dehiscence into the sub-retinal space, eventually leading to neurosensory detachment[3].

Fluorescein and indocyanine green angiography are the benchmark imaging modalities in ICSCR. Optical coherence tomography (OCT) can help in detecting subtle cases that may escape biomicroscopic recognition, and it facilitates quantification of neurosensory/RPE detachment for diagnostic and follow-up purposes.

Fundus autofluorescence (FAF) has been recently introduced as a novel imaging modality for various fundus disorders. This noninvasive technique relies on capturing the stimulatedemission of light from lipofuscin molecules in the RPE. In various diseases, large amounts of lipofuscin accumulate in the RPE as a metabolic byproduct and eventually induce RPE apoptosis. Variations in autofluorescence intensity in FAF images reflect the spatial distribution of lipofuscin within the RPE layer and may provide a disease-specific lipofuscin "signature"[3-7]. Since RPE changes provide hallmarks for acute and chronic stages of ICSCR in the form of RPE micro-rip and diffuse pigment epitheliopathy respectively, FAF imaging could be versatile in documenting the abnormal lipofuscin metabolism associated with these changes. Furthermore it might depict specific patterns that could be characteristic of different stages of ICSCR. In accordance with this hypothesis the current study aims at detecting different FAF patterns in ICSCR and correlating them with fluorescein angiographic findings.

## SUBJECTS AND METHODS

This is an observational case study conducted in the Retina Department of Vall d'Hebron Hospital, a teaching center affiliated with the Autonomous University of Barcelona. We retrospectively reviewed the clinical data and Fundus fluorescein angiography (FFA) and FAF images of all consecutive ICSCR patients seen in our practice between March 2010 and March 2013 and compared the findings. FAF was considered abnormal with visualization of hyper- or hypoautofluorescence relative to the previously reported normal FAF appearance[8-10] and to areas of normal FAF outside the detected lesion.

**Table 1 Patients characteristics**

| Patients characteristics | $n$(%) |
|---|---|
| M | 13 (76.5) |
| F | 4 (23.5) |
| Mean age (a) | 50 |
| ICSCR variant (per eye) | |
| Acute | 5 (20) |
| Chronic | 8 (32) |
| Chronic-recurrent | 12 (48) |
| Mean disease duration (mo) | |
| Acute ICSCR | 1 |
| Chronic ICSCR | 14.6 |
| Chronic-recurrent ICSCR | 13.5 |
| Mean baseline BCVA | |
| Acute | 20/40 |
| Chronic | 20/125 |
| Chronic-recurrent | 20/125 |
| Mean final BCVA | |
| Acute | 20/32 |
| Chronic | 20/100 |
| Chronic-recurrent | 20/80 |

The diagnosis of ICSCR was based on visual symptoms, neurosensory detachment detected on biomicroscopy and confirmed by active leakage of dye at the RPE level on fluorescein angiography, and by OCT imaging. The cut-off time to differentiate between acute and chronic ICSCR was set at 4mo. Patients presenting with conditions that could cause localized serous detachment of the macula, such as choroidal neovascularization, polypoidal choroidal vasculopathy, macular hole, optic pit maculopathy, or hereditary ocular diseases were excluded from the study.

FFA was performed with a type 1A Topcon TRC 50DX fundus camera (Topcon, Tokyo, Japan), outfitted with special filters to enable FAF imaging. Both imaging modalities were done on the same day. Image analysis was performed using ImageNet i-base software, version 1.05 (2009, Topcon Europe Medical, The Netherlands). The study was performed in accordance with the tenets of the Declaration of Helsinki of 2008.

## RESULTS

The study included 25 eyes of 17 patients (13 men and 4 women), with a mean age of 50y (range 37-64y). Nine patients had unilateral ICSCR, whereas eight patients presented with bilateral disease. We detected acute ICSCR in 5 eyes, chronic disease in 8 eyes, and recurrence in chronic disease in 12 eyes. Mean duration of the disease was 1, 14.6, 13.5mo in acute, chronic and chronic-recurrent cases, respectively. Mean duration of recurrent new episode in chronic-recurrent cases was 1.4mo. Baseline BCVA ranged from 20/100-20/32; mean 20/40 in acute cases, from 5/200-20/80; mean 20/125 in chronic cases and from 5/200-20/50; mean 20/125 in chronic-recurrent cases. Final BCVA ranged from 20/100-20/20; mean 20/32 in acute cases, from 10/200-20/40; mean 20/100 in chronic cases, and from 10/200-20/32; mean 20/80 in chronic-recurrent cases (Table 1).

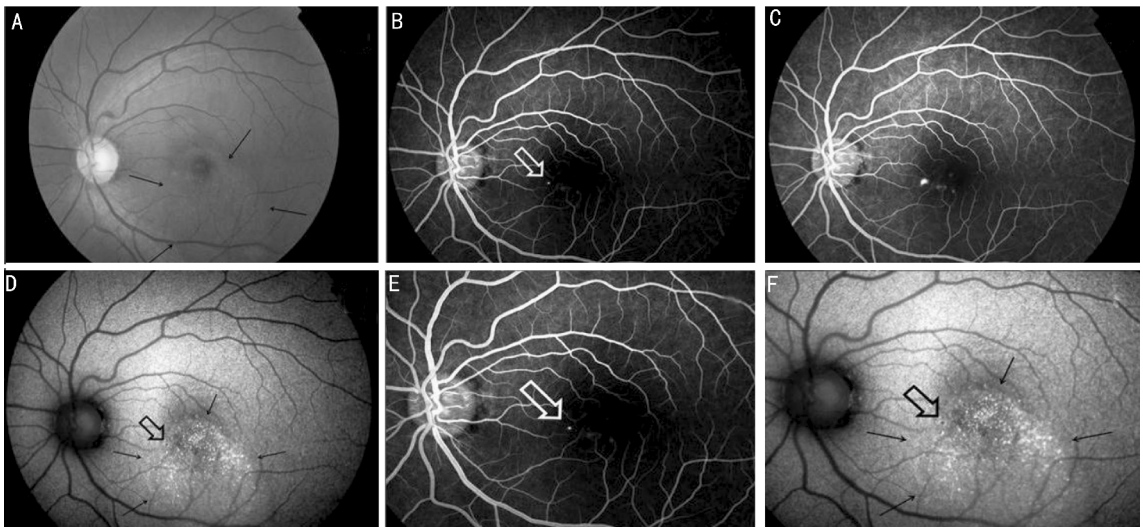


**Figure 1 Representative case of acute ICSCR in the left eye of a 42-year-old man with a 3mo history of metamorphopsia and micropsia. Best-corrected visual acuity (BCVA) was 0.7** A: Color fundus photo shows an approximately 3-disc-diameter (DD) ovoid area of neurosensory detachment (black arrows) encompassing the macula, and a yellowish spot at the fovea due to enhanced xanthophyll visibility. Multiple dot-like yellowish precipitates are dispersed within the area of detachment. B, C: Early and late venous phases of fluorescein angiography demonstrate pinpoint RPE leaks at the nasal border of the fovea (open arrow), gradually progressing to an ink blot pattern. Window defects due to RPE atrophy indicate previous episodes. D: FAF image shows a hypoautofluorescent pinpoint dot (open arrow) in the same location as the pinpoint leakage in B. The area of detachment is mainly isoautofluorescent, with hyperautofluorescent dots evenly distributed over the affected area (black arrows). E, F: Which are cropped for higher definition.

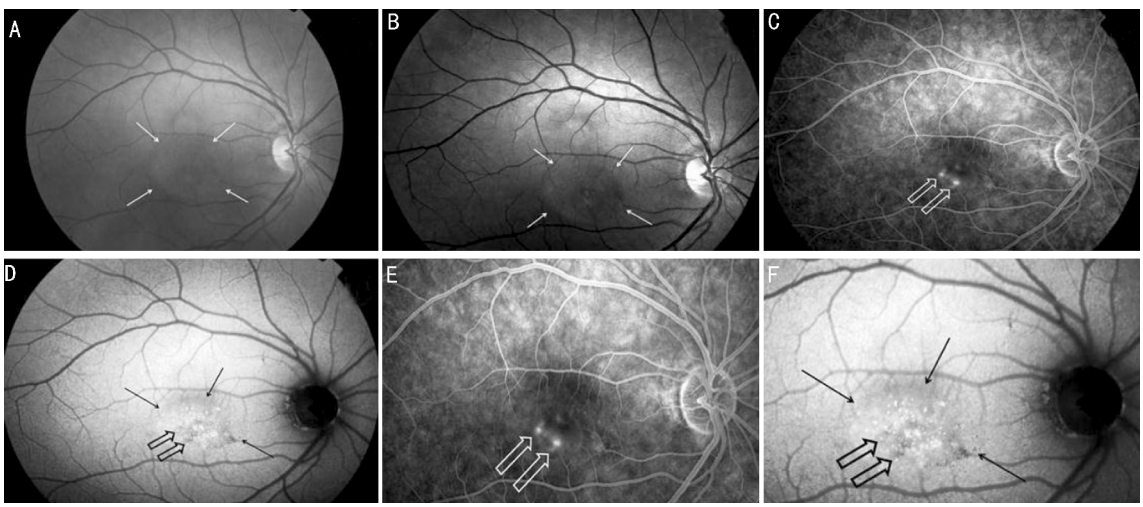


**Figure 2 Representative case of acute ICSCR in the right eye of a 45-year-old man with positive central scotoma and dyschromatopsia over the past 6wk** A, B: Color fundus and red-free photos show an approximately 2DD area of neurosensory detachment (white arrows). Color photo reveals a yellowish spot at the fovea and multiple yellowish dot-like precipitates dispersed within the area of detachment. C: Venous-phase fluorescein angiography demonstrates two pinpoint RPE leaks (open arrows). D: FAF image shows two hypoautofluorescent pinpoint spots (open arrows) in the same location as the leaks in C. The area of detachment is mainly isoautofluorescent, with hyperautofluorescent dots evenly distributed over the affected area (black arrows). E, F: Which are cropped for higher definition.

**Acute Idiopathic Central Serous Chorioretinopathy** FFA images in acute cases (Figures 1, 2) revealed pinpoint RPE leakage starting in the arteriovenous phase that gradually increased in size through successive frames in an expanding ink blot configuration. The area corresponding to neurosensory detachment in color and red-free photos demonstrated slight hypofluorescence due to blockage by sub-retinal fluid. Corresponding FAF images showed a sharply delineated hypoautofluorescent spot in exactly the same location as the pinpoint leak detected on fluorescein angiography. The area of neuro-sensory detachment was mainly isoautofluorescent, except for dispersed hyperautofluorescent dots in a freckle pattern homogenously distributed over the entire area. In the color fundus photo, this freckle pattern corresponded to yellowish dot-like precipitates spanning the area of neuro-sensory detachment (Figures 1, 2).

**Chronic and Chronic-recurrent Idiopathic Central Serous Chorioretinopathy** In FFA images of chronic ICSCR (Figure 3), diffuse areas of RPE atrophy are visualized as transmission fluorescence ("window defect"), sometimes with persistent multiple focal leaks. Corresponding color fundus photos show residual neurosensory detachment with

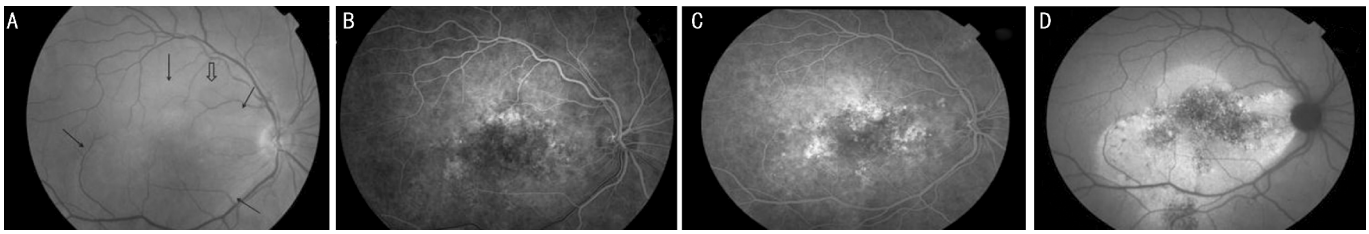


**Figure 3 Representative case of chronic ICSCR inthe right eye of a 44-year-old man who had experienced poor vision of two years' duration. Visual acuity was counting fingers at 1.5m** A: Color fundus photo shows a small PED (open arrow) and a large irregular area (black arrows) occupying the entire macular area and extending beyond the inferotemporal arcade. There is extensive RPE mottling and a shallow neurosensory detachment. B, C: Fluorescein angiography in arteriovenous and venous phases demonstrate early transmission fluorescence due to a window defect, with later appearance of multiple pinpoint RPE leaks. D: FAF image shows hypoautofluorescence corresponding to areas of maximum hyperfluorescence on FFA. The remaining area of residual or former neurosensory detachment was visualized as hyper-autofluorescent on FAF.

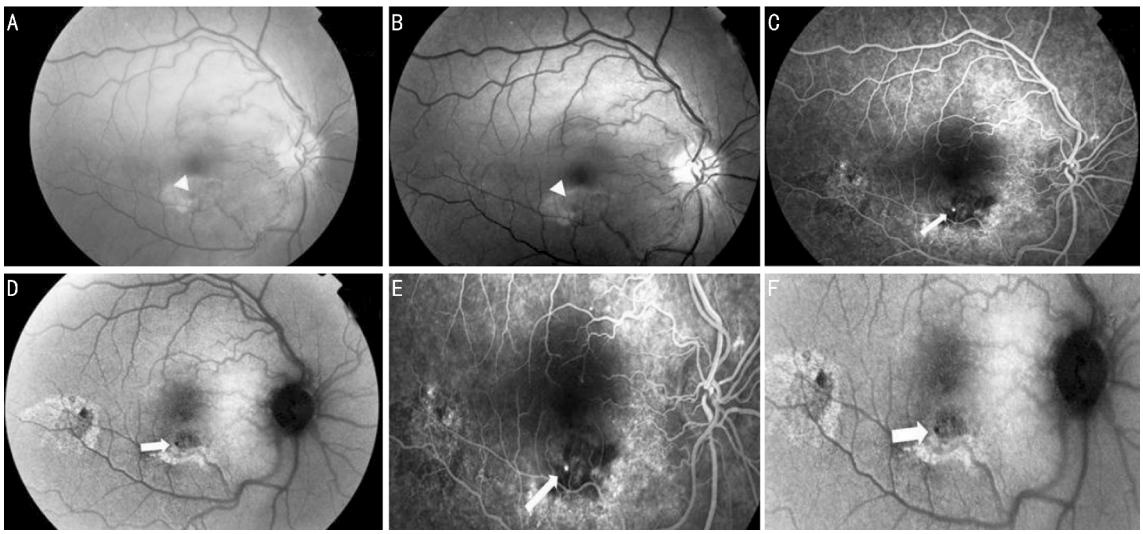


**Figure 4 Representative case of chronic-recurrent ICSCR in the right eye of a 44-year-old man. The patient, a known case of ICSCR, had recent complaints of blurred vision and metamorphopsia for the last 4mo** A, B: Color and red-free fundus photos show PED (arrowhead), shallow neurosensory detachment, and subretinal exudates. C: Venous-phase fluorescein angiography demonstrates a pinpoint RPE leak below the fovea (white arrow). The leak lies within an irregular area of blocked fluorescence (subretinal exudates) and stippled hyperfluorescence (RPE mottling). Window defects resulting from RPE atrophy with a central area of blocked fluorescence due to reactive RPE proliferation are seen temporally. D: FAF image shows hypoautofluorescent pinpoint dot (white arrow) in the same location as the pinpoint leak in C. E, F: Which are cropped for higher definition.

significant RPE mottling. FAF images demonstrate hypo-autofluorescence that corresponds in shape and location to the areas showing the most intense transmission fluorescence on FFA, whereas areas with less transmission fluorescence on FFA correspond to hyper-autofluorescence on FAF. The hypo-autofluorescent spot pointing to the site of RPE leakage cannot be localized as precisely as in acute cases (Figure 3). Chronic recurrent ICSCR (Figure 4) demonstrated evident RPE leakage in the ink blot pattern described above, in addition to signs and sequelae of previous episodes, including diffuse RPE epitheliopathy, and sub-retinal exudates.

## DISCUSSION

FAF imaging takes advantage of the intrinsic autofluorescence of lipofuscin, which is normally formed in the human RPE cell as a result of phagocytosis of the constantly shed photoreceptor outer segments. These outer segments are rich in polyunsaturated fatty acids, which render them particularly vulnerable to auto-oxidation, with lipofuscin release as a by-product. In normal circumstances, the RPE cell eliminates lipofuscin through active transport into the choroidal circulation[3-4,11-14]. Excessive accumulation of lipofuscin is indicative of RPE dysfunction, which leads to an imbalance between lipofuscin formation and clearance. FAF images are evaluated for the intensity of autofluorescence, whether iso-, hyper-, or hypo-autofluorescence, which in turn, corresponds to normal or abnormal lipofuscin distribution, and accordingly, to the RPE health status[3,15-19].

Normal autofluorescence or isoautofluorescence is characterized by a homogenous background autofluorescence that is most intense between 5° and 15° from the fovea, with no focal variations other than the optic disc and the blood vessels, which appear as dark structures. There is a gradual decrease of autofluorescence intensity in the inner macula towards the foveola due to a masking effect of yellow macular pigment[8-10,20-22]. FAF abnormalities in ICSCR may result from focal RPE dysfunction and from dispersion or accumulation of lipofuscin in the subretinal space due to photoreceptor outer segment shedding in this location[3,15].

According to Yannuzzi's theory of the pathogenesis of ICSCR[3], choroidal vascular hyperpermeability and exudation would exert mechanical pressure on the RPE and lead to a "blow-out" (*i. e.* an epithelial micro-rip or dehiscence), thereby enabling access of exudate to the subretinal space. In terms of fluorescein angiography, when the RPE rip is large enough, fluorescein dye will flow readily into the subretinal space in a "smokestack" leaking pattern. As RPE cellular proliferation compensates for the RPE defect, the leak acquires a pinpoint or expanding ink-blot configuration[23]. In terms of autofluorescence, the presumed RPE micro-rip would be visualized as hypoautofluorescence, simply because an absence of RPE cells at the rip site means there is no tissue there to accumulate and display lipofuscin. Yannuzzi[3] provided corroborating evidence to his theory in his study on FAF in acute ICSCR cases.

Our FAF findings in acute ICSCR are in accordance with Yannuzzi's theory and his study findings[3]. We detected a hypoautofluorescent spot in our acute ICSCR patients (Figures 1, 2) that corresponded to the pinpoint leak seen on fluorescein angiography. Similar findings have been reported by Karadimas *et al*[24], who used confocal scanning laser ophthalmoscopy (cSLO) to record autofluorescence and described a dark spot or target lesion that corresponded to the leak. Further supporting evidence for Yannuzzi's theory comes from the work of Framme *et al*[25], who also demonstrated decreased autofluorescence at the leak using cSLO.

In contrast, von Rückman *et al*[15] have provided a diametrically opposite description of the leaking point. In their study of FAF images obtained by cSLO, they reported hyperautofluorescence corresponding to the leak as a consistent finding in their acute ICSCR cases. These authors believe that focally increased autofluorescence at the leaking point is due to enhanced turnover of the photoreceptor outer segment and accordingly, to excessive lipofuscin accumulation.

Another interesting finding in our acute cases was subretinal hyperautofluorescent freckles uniformly distributed over the area of neurosensory detachment, which corresponded to yellowish dot-like precipitates in the color photo (Figures 1, 2). In Spaide and Klancnik's study[26] of FAF in ICSCR, this finding was reported as hyperautofluorescent granules. According to these authors, the dots represent autofluorescent material formed by shed photoreceptor outer segments combined with lipoproteins derived from serous fluid leaking through the RPE. Accumulation of this material is favored by the fact that the area of detachment in ICSCR is a loculated fluid-filled space with no means of escape. As ICSCR progresses to chronicity, accumulation of the material increases and it may aggregate into clumps and settle in the inferior portion of the detachment owing to gravity, with a marked increase in FAF intensity. The presence of these precipitates and their relation to the duration of ICSCR has also been described by Framme *et al*[25].

Our patients with chronic ICSCR demonstrated a mixed FAF pattern, with areas of enhanced intensity and others of decreased intensity (Figure 3). Inspection of this pattern in relation to color photography and FFA findings revealed that the intensity of autofluorescence correlated with the extent of chronicity, in the sense that areas of long-standing disease resulting in RPE atrophy demonstrated marked hypoautofluorescence, as well as maximum transmission fluorescence in FFA images. On the other hand, areas of relatively more recent duration (*i. e.* less chronic) demonstrated hyperautofluorescence. This irregular FAF pattern in chronic cases has been reported by a number of studies. In a prospective cohort of 69 eyes von Rückman *et al*[15] used the term mixed FAF in chronic ICSCR cases to describe areas of increased and decreased FAF as compared to background levels. Similarly, another study by Framme *et al*[25] comprising 85 patients with ICSCR used the term mottled FAF to describe irregular autofluorescence patterns associated with areas of residual neurosensory detachment seen in their chronic-recurrent ICSCR cases. Likewise, Spaide and Klancnik[26] reported in a series of 30 cases with ICSCR varying patterns of autofluorescence in which areas of central geographic atrophy of RPE associated with long-standing chronic ICSCR appeared hypoautofluorescence while their outer borders were hyperautofluorescent.

It is postulated that the higher the lipofuscin content of the RPE cell, the more autofluorescent it will appear on FAF and the less fluorescent on FFA due to absorption of short wavelength light. FAF, therefore, provides an indirect measure of the metabolic status of the RPE cell. Atrophic (dead) RPE cells do not contain lipofuscin and are severely hypoautofluorescent, whereas still viable cells have a varying content of lipofuscin and accordingly, a varying degree of hyperautofluorescence[3,15,26].

It is worthy of note that patients in our study who had severe hypoautofluorescent spots involving the fovea had the poorest visual outcome. This association corroborates the findings of Spaide and Klancnik [26] who reported a strong correlation between hypoautofluorescence and poor visual acuity should it affects the macular area.

In cases of chronic-recurrent ICSCR, FAF images demonstrated an overlap of acute and chronic signs, in which a dark spot corresponding to the reactivated or newly developed leakage point was clearly identified amidst an irregular FAF pattern characterizing chronic changes (Figure 4). In accordance with our findings, Framme *et al*[25] reported in their chronic-recurrent cases decreased or mottled FAF at the leakage point and hyperautofluorescence at areas of residual neurosensory detachment.

Limitations of this study include small sample size, retrospective design, and lack of images demonstrating different episodes of ICSCR in the same patient which would have rendered comparing different stages easier. Further studies including larger patient cohort and long follow-up period are needed to detect different phases of ICSCR in same patients starting from acute disease at presentation through

progression, if any, to chronic and/or chronic-recurrent stages as well as response to therapy.

Capture of the autofluorescent signal emitted by lipofuscin in cases of ICSCR proved to be a versatile imaging modality, with the capability of depicting FAF patterns that are characteristic of various stages of the disease. Its non-invasive nature renders it a risk-free and reproducible supplementary tool to fluorescein angiography and OCT in diagnosing ICSCR and for monitoring disease progression and response to therapy. It can also be a reliable alternative in cases where fluorescein angiography is contraindicated.

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