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Review

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Comprehensive Review

Diagnostic Challenges in Inflammatory Choroidal Neovascularization

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Abstract: Inflammation plays a key role in the induction of choroidal neovascularization (CNV). Inflammatory choroidal neovascularization (iCNV) is a severe but uncommon complication of both infectious and non-infectious uveitides. It is hypothesized that its pathogenesis is similar to that of wet age-related macular degeneration (AMD), and involves hypoxia as well as the release of vascular endothelial growth factor, stromal cell-derived factor 1-alpha, and other mediators. Inflammatory CNV develops when inflammation or infection directly involves the retinal pigment epithelium (RPE)–Bruch's membrane complex. Inflammation itself can compromise perfusion, generating a gradient of retinal-choroidal hypoxia that additionally promotes the formation of choroidal neovascularization in the course of uveitis. The development of choroidal neovascularization is extremely common in conditions such as punctate inner choroidopathy, multifocal choroiditis, serpiginous choroiditis, and presumed ocular histoplasmosis syndrome. Although the majority of iCNV cases are well defined and appear as the "classic" type on fluorescein angiography, the diagnosis of iCNV is challenging due to difficulties in differentiating between inflammatory choroiditis lesions and choroidal neovascularization. Modern multimodal imaging, particularly the recently introduced technology of optical coherence tomography (OCT) and OCT angiography (noninvasive and rapid imaging modalities) can reveal additional features that aid the diagnosis of iCNV. However, more studies are needed to establish their role in the diagnosis and evaluation of iCNV activity.

Keywords: uveitis; inflammatory choroidal neovascularization; multimodal imaging; fluorescein angiography; indocyanine green angiography; optical coherence tomography; optical coherence tomography angiography; near-infrared autofluorescence

1. Introduction

Uveitis-related choroidal neovascularization (CNV), known as inflammatory CNV (iCNV), is an uncommon complication of uveitis. At the same time, it is one of the most severe causes of visual impairment in patients with uveitis [1-3]. Inflammatory CNV is the third cause of CNV following wet age-related macular degeneration (AMD) and pathological myopia [2,3]. Inflammatory CNV develops more frequently in patients with posterior uveitis (2.7%) and panuveitis (0.8%) as compared with those with anterior and intermediate uveitis (0.1%) [4]. CNV is a clinically important complication of both infectious and non-infectious uveitis and is found to be more frequent in some specific clinical entities. Its incidence in non-infectious posterior uveitis has been reported to reach 2% [5]. A higher incidence of CNV was reported in multifocal choroiditis, punctate inner choroidopathy, serpiginous choroidopathy, birdshot retinochoroidopathy, and Vogt–Koyanagi–Harada disease [6-18]. On the other hand, data on the incidence of iCNV secondary to infectious uveitis are scarce and are derived mainly from case series and case reports. The prevalence of iCNV depending on the etiology of uveitis is presented in Table 1.

Table 1. Prevalence of inflammatory choroidal neovascularization (iCNV) depending on the etiology of uveitis.

Type of uveitis	Prevalence of iCNV, [references]
Non-infectious	
Multifocal choroiditis	32–50% [4-7]
Punctate inner choroidopathy	17-40% [1,4,8,9]
Serpiginous choroidopathy	10-25% [4,10,11]
Vogt–Koyanagi–Harada disease	9-15% [4,7,9,12]
Birdshot chorioretinitis	5% [4,13]
Intermediate uveitis	single cases reported [14,15]
Behçet disease	very rare [4,16]
Acute posterior multifocal placoid pigment epitheliopathy	single cases reported [4,16-18]
Sympathetic ophthalmia	single cases reported [16,19]
Sarcoidosis	single cases reported [4,9,16]
Multiple evanescent white dot syndrome	single cases reported [4,20,21]
Infectious	
Histoplasmosis	5-17.4% [4,9,16,22-25]
Candidiasis	rare; prevalence unknown [26-28]
Toxoplasmosis	0.3-19% [29-32]
Toxocariasis	single cases reported [33-35]
Tuberculosis	single cases reported [36-39]
Rubella retinopathy	single cases reported [40-43]
West Nile virus	single cases reported [44-46]

According to Baxter et al. [4], the presence of epiretinal neovascularization is associated with an over three-fold higher risk of iCNV. Moreover, the risk of CNV was significantly greater in eyes with active inflammation vs those with inactive inflammation. The presence of anterior chamber cells grade 2+ as defined by the Standardization of Uveitis Nomenclature Working Group was shown to be associated with iCNV. However, increased vitreous cells and vitreous haze were not significantly associated with an altered risk of incident CNV in patients with uveitis [4]. Previous diagnosis of CNV in the contralateral eye was associated with a several-fold higher risk of CNV in the second eye. However, the eyes of patients with bilateral uveitis were less likely to develop CNV than affected eyes of patients with unilateral uveitis [4].

The underlying pathophysiology of iCNV is likely similar to the pathophysiology of CNV in other conditions associated with CNV, such as age-related macular degeneration (AMD) or pathologic myopia. Inflammatory CNV may thus be considered not as a distinct form of CNV, but rather as associated with a set of circumstances that permit their development [1,8].

It was demonstrated that vascular endothelial growth factor (VEGF) plays a key role in CNV development [2,3]. Moreover, CNV has an extravascular component consisting of fibroblasts and leukocytes that express C-X-C motif chemokine receptor 4 (CXCR4). Retinal pigment epithelial (RPE) cells showed an increased production of tumor necrosis factor as well as interleukins IL-1, IL-2, IL-6, and IL-10, accounting for the inflammatory component of CNV [47, 48]. Also other mediators are involved in CNV development, such as nitric oxide, angiostatin, endostatin, C-C chemokine receptor type 3 (CCR3), and pigment epithelium-derived growth factor (PEDF) contrasting the neovascularization [49].

D'Ambrosio et al. [8] assessed the immunohistochemical staining grading of three structures of CNV, namely, the RPE, vascular network, and fibroblasts for SDF1, CXCR4, and VEGF receptor 2. The authors revealed differences in the CXCR4 staining of the vascular meshwork of iCNV as

compared with AMD-related CNV, suggesting that capillaries have a different role in membrane development [8].

There are two pathophysiological mechanisms by which uveitis can promote the development of iCNV [2,47]. The first one is associated with inflammation-mediated damage of the RPE-Bruch's membrane complex, which disrupts the outer blood-retinal barrier and permits neovascular upgrowth from the choroid. The damage can be induced by an angiogenic stimulus mediated by local inflammation, or it can result from the combination of both [2]. Activated inflammatory cells secrete enzymes that damage cells and cause degradation in the Bruch's membrane. Proangiogenic cytokines released by these inflammatory cells may promote CNV growth through breaks in the membrane and into the sub-RPE space, potentially leading to edema, exudation, hemorrhages, and fibrosis, resulting in profound central vision loss [1,2]. Thus, a higher risk of damage of the RPE–Bruch's membrane complex related with adjacent chorioretinal inflammation may explain the higher incidence of iCNV in patients with panuveitis and posterior uveitis [50]. It is noteworthy that the RPE is often intact in individuals with iCNV [2]. The proposed mechanism of iCNV development is thus the focal breach of the RPE due to infection or inflammation leading to the growth and entry of new vessels into the outer retinal space [50]. The second theory explains that retinal and choroidal inflammation directly compromises perfusion, generating a gradient of retinal-choroidal hypoxia that promotes the formation of choroidal neovascularization [2]. It should also be noted that in some cases "idiopathic" choroidal neovascularization may herald the subsequent development posterior uveitis [51].

Inflammatory CNV is typically diagnosed when a patient with uveitis reports a sudden deterioration of vision and/or metamorphopsias [2-4,52]. In advanced cases of iCNV, central scotoma may be present. Some of active extrafoveal lesions can be asymptomatic and may be detected only during an ophthalmological examination or on imaging studies alone [1,6,52,53].

In patients with posterior uveitis, the identification of iCNV is challenging due to related abnormalities including choroiditis as well as chorioretinal scarring and inflammatory lesions [52,53]. Difficulties in a differential diagnosis of iCNV and active inflammatory lesions arise from the characteristic presence of intraretinal or subretinal fluid as well as serous retinal detachment in both [1,8,52]. An accurate characterization of inflammatory lesions is important for the diagnosis of an underlying pathology and implementation of adequate treatment.

The aim of this paper was to discuss current multimodal imaging tools for the diagnosis of iCNV, with an emphasis on technological advances and future perspectives.

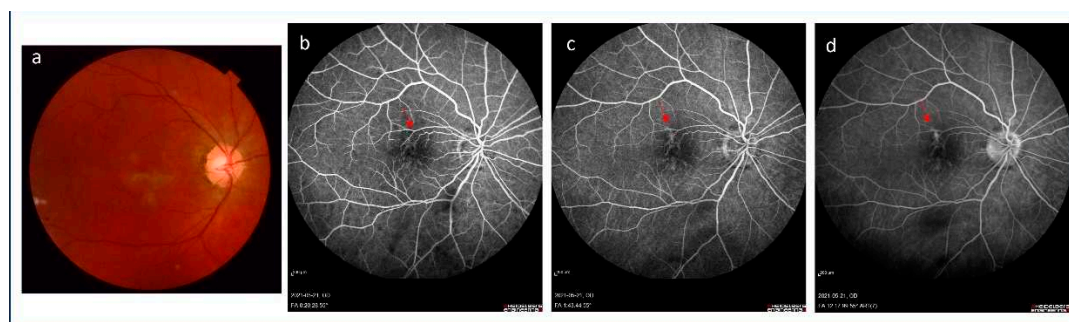## 2. Imaging tools for the detection of iCNV

2.1. Fluorescein angiography

Fluorescein angiography (FA) has been widely employed in the diagnosis of CNV secondary to various ocular pathologies. Since iCNV is often a classic type of neovascular membrane (type 2), it can be visualized by FA. CNV lesions present on FA as early iso- or hyperfluorescence with late leakage [54].(Fig.1) Similarly, active inflammatory lesions show features of early isofluorescence (although mostly hypofluorescence) and late leakage, while inactive atrophic lesions are characterized by early hypo- or isofluorescence with late staining (suggesting RPE window defect) without leakage [4, 55, 56] (Fig. 2) These highly similar FA features of iCNV and inflammatory lesions pose a diagnostic challenge. In conditions such as multifocal choroiditis, serpiginous choroiditis, or Vogt–Koyanagi–Harada disease, which present with scarring and pigmentation due to extensive retinal involvement, the detection of hyperfluorescence associated with CNV may be particularly difficult [52,53,57]. Thus, FA alone may be insufficient to identify inflammatory CNV lesions and initiate an appropriate therapy. Therefore, a multimodal approach with additional tests is recommended.
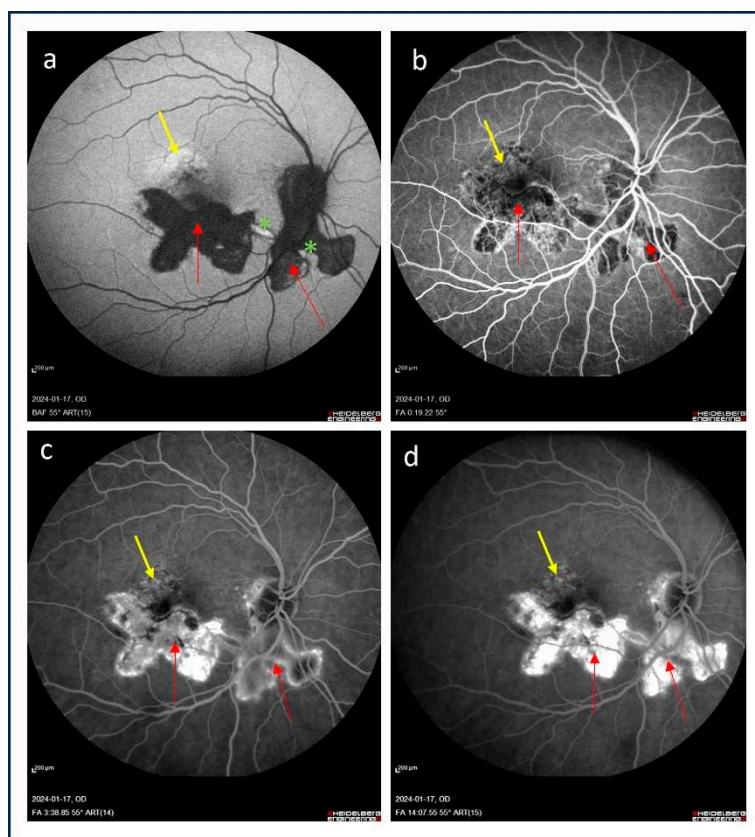
Figure 1. (a) Fundus autofluorescence image, showing hipoautoflurescence of inactive postinflammatory lesions (red arrows) and hiperautofluorescence of active inflammatory lesions (green asterix) (b-c) Fluoresceine angiography images, showing early isofluorescence with late staining of the lesions as a result of retinal pigmented epithelium window defect, without features f inflammatory choroidal neovascularization.

Figure 2. (a) Color picture of the fundus showing inactive inflammatory foci in macula region with changes at retinal pigmented epithelium level; (b-c) Fluorescein angiography images demonstrated early isofluorescence with late staining of the lesions as a result of reinal pigmented epithelium window defect without features of inflammatory choroidal neovascularization.

2.2. Indocyanine green angiography

One of the imaging techniques for the visualization of the choroid is indocyanine green angiography (ICGA), which allows a better visualization of the choroid compared with FA [58]. ICGA plays an important role in assessing pathologies involving the choroidal vasculature and choriocapillaris in chorioretinal inflammatory diseases. It is helpful in differentation between iCNV and inflammatory lesions [59, 60]. ICGA allows to tell the difference between a recurrent inflammatory focus and CNV: the former appears as an early hypofluorescent lesion, whereas the latter as a hyperfluorescent lesion since early angiographic frames [58,59]. ICGA is also mandatory in the case of CNV associated with choriocapillaritis such as multifocal choroiditis, where it shows

the extent of occult choriocapillaris nonperfusion and hence the risk for CNV development [60, 61]. Importantly, ICGA was shown to outperform FA in detecting occult CNV lesions [54]. While iCNV is typically a classic lesion that can be easily visualized by FA, ICGA has been recently reported to be more accurate in assessing the size of neovascular lesions, especially in patients with idiopathic CNV, which shares several clinical features with iCNV [62]. Thus, ICG helps identify both iCNV and inflammatory choroidal alterations in patients with uveitis, allowing a clinical differentiation between these lesions and a more comprehensive evaluation of the disease [60] (Fig. 3 and Fig.4).
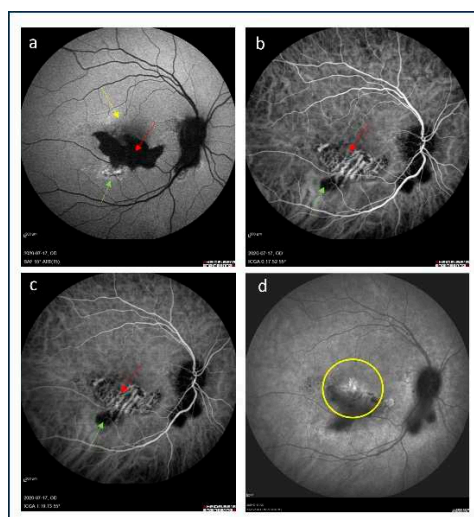
Figure 3. (a) Fundus autofluorescence image shows hypoautoflurescence of inactive postinflammatory lesion in macula (red arrow) with hyperautofluorescent area representing the active inflammatory focus at its lower margin (green arrow), at the upper border of the hypofluorescent lesion the hyperfluorescent area is present (yellow arrow); (b-c) Early and middle frames of indocyanine green (ICG) angiograms reveal a visibility of the choroidal vessels in the area of the inactive postinflammatory focus and small hypocyanescent area at its lower border corresponding to active choroidal inflammation; (d) Late ICG angiogram demonstrates homogeneous hypocyanescence of the postinflammatory lesion with evidence of late hypercyanescence at its upper margin. The patient was diagnosed for inflammatory choridal neovascularization.
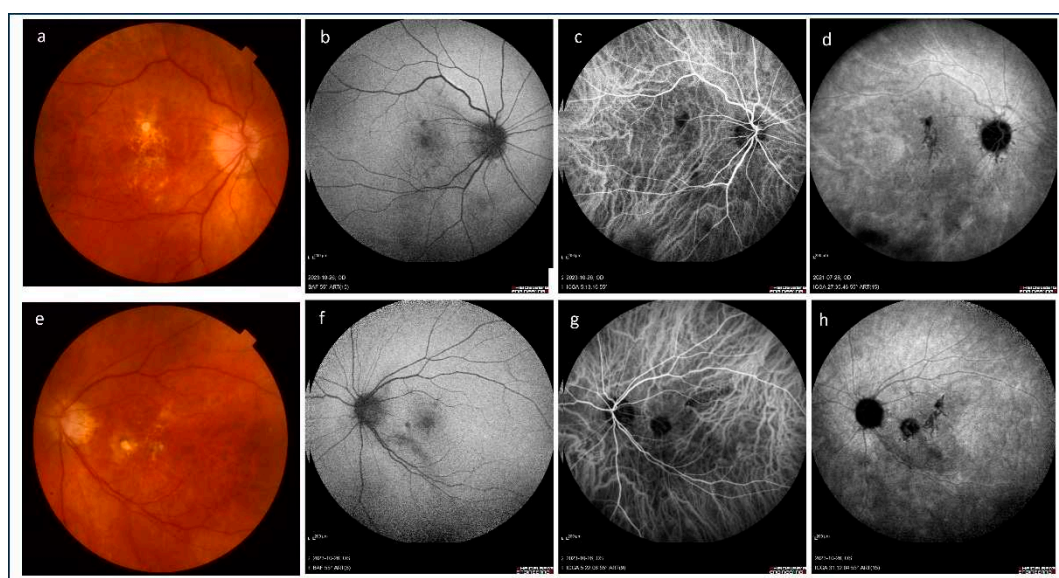

Figure 4. (a and e) Color pictures of the fundus presenting well-defined and partially pigmented chorioretinal scars at the sites of previous inflammation in macula of both eyes; (b and f) Fundus autofluorescence demonstrated hypoautofluorescent foci which correlate with photoreceptor and

retinal pigment epithelium damage; (c-d and g-h) Early and late frames of indo cyanine green angiograms revealed the presence of homogenous hypocyanescent foci related to retinal pigment epithelium damage due to postinflammatory scarring, no feature of inflammatory choroidal neovascularization is observed..

2.3. Optical coherence tomography

Optical coherence tomography (OCT) is a noninvasive and highly repeatable imaging technique that has revolutionized the management of retinal and choroidal diseases. By providing the quasi-histological sections of the ocular structure , it allows clinicians to identify ocular pathologies and assess response to treatment [63]. Moreover, the enhanced depth imaging modality of OCT can be used to evaluate choroidal thickness and structural modifications, which is particularly valuable in the treatment of uveitis [63].

Inflammatory CNV usually develops between the RPE and neurosensory retina, demonstrating similar features on OCT imaging as classic (type 2) CNV [58]. In both cases, the lesions appear as hyperreflective structures located in front of a disrupted RPE, with solid tissue in the subretinal space [1,64-66]. However, there is a single OCT feature that can help distinguish between iCNV and other classic CNVs. This is the so called "pitchfork sign", characterized by finger-like hyperreflective lesions extending from the CNV into the outer retinal layers, and it allows to differentiate iCNV from other causes of CNV [1,53,67]. It was reported that the OCT features of CNV activity such as retinal thickening, subretinal and intraretinal fluid, intraretinal hyperreflective flecks, and undefined boundaries of subretinal material (Fig. 5a) predicted the presence of FA leakage [1,66]. Thus, it was concluded that OCT can be used for monitoring disease progression and response to treatment [68,69].
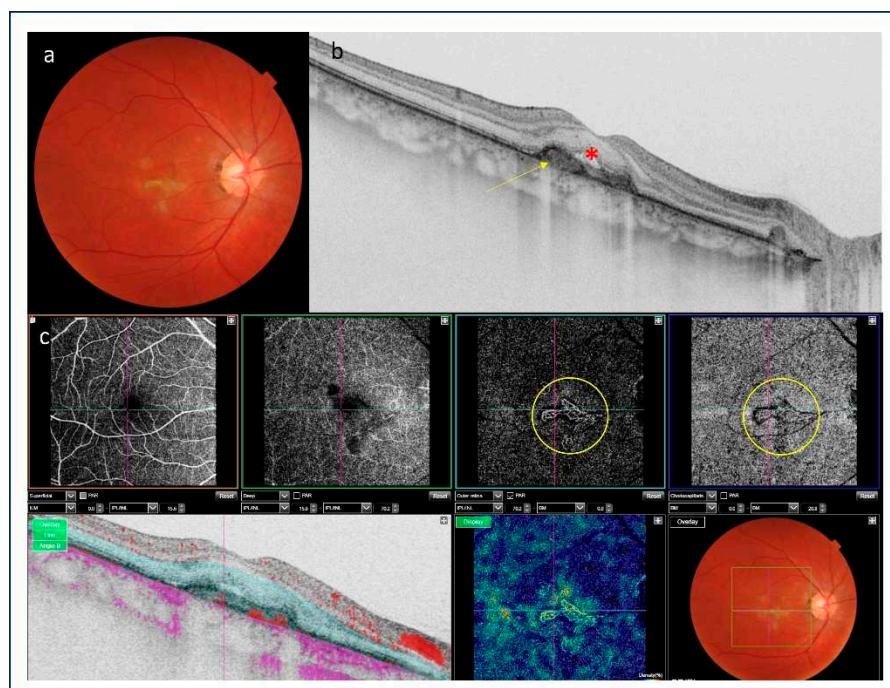
Figure 5. (a) Color picture of the fundus shows macular subretinal fibrosis; (b) Optical coherence tomography revealed hyperreflective material under the retinal pigment epithelium (yellow arrows), subretinal fluid is present (red asterix), (c) Optical coherence tomography-angiography demonstrated pathological vessels in outer retinal layer presenting inflammatory choroidal neovascularization. .

Moreover, central retinal thickness evaluated by OCT is often used as an objective measure of iCNV activity [70-72]. Recently, Giuffrè et al. [73] demonstarted increased choroidal thickness under iCNV that decreases after therapy: the so called "sponge sign". Thus OCT-based choroidal thickness evaluation may represent an additional useful tool to monitor inflammatory choroidal

neovascularization activity. Moreover, choroidal thickness under CNV could be used to discriminate the origin of choroidal neovascular membrane in doubtful cases (either inflammatory or myopic) and to guide therapeutic management [73].

OCT images can also help differentiate between iCNV lesions and nonneovascular alterations at the RPE level that are characteristic for several types of uveitis. For example, acute inflammatory foci in multifocal choroiditis show a deeper penetration of the OCT signal, a feature that is usually not seen in iCNV [56,65]. However, when distinguishing CNV lesions from iCNV, the use of OCT alone may be limited as these lesions display similar features of outer retinal or RPE hyperreflectivity, intraretinal edema, sub-RPE fluid, and exudation in conditions with the involvment of the RPE or choriocapillaris (e.g., multifocal choroiditis and punctate inner choroidopathy) [1,71,72,74,75]. In such cases, the characteristics of the lesions can be determined by a combination of FA, ICGA, and OCT angiography (OCTA).

2.4. Optical coherence tomography angiography

The usefulness of OCTA as a noninvasive technique for the detection of iCNV has been reported by several investigators. Cheng et al [76] assessed the ability of OCTA to detect iCNV and differentiate it from inflammatory lesions as compared with conventional FA in 26 patients with multifocal choroiditis. The authors concluded that OCTA outperformed FA in differentiating CNV from inflammatory lesions as the latter do not show any blood flow signals. It also permitted the visualization of detailed vascular structure of CNV. Therefore, it could be used as an alternative option for CNV identification and to guide therapeutic decision making [74]. Similarly, in a recent retrospective study of 14 patients, Zahid et al. [77] used OCTA to evaluate neovascular flow signals in macular chorioretinal lesions occurring in idiopathic multifocal choroiditis. They concluded that OCTA may be a useful tool for understanding the pathophysiology of the disease and monitoring disease course. The utility of OCTA for the noninvasive diagnosis of iCNV and its subsequent follow-up was also confirmed by Yee et al. [78]. Finally, in a recent study, Aggarwal et al. [79] investigated OCTA features of tuberculosis-associated choroiditis in comparison with conventional imaging modalities including FA, ICGA, and OCTA. This was the first study to demonstrate that OCTA can identify type 1 neovascular networks. The research led to a conclusion that OCTA is indispensable to exclude neovascular networks when FA, ICGA, and OCT results are inconclusive [78] (Fig.5c, Fig. 6b and Fig.7c).
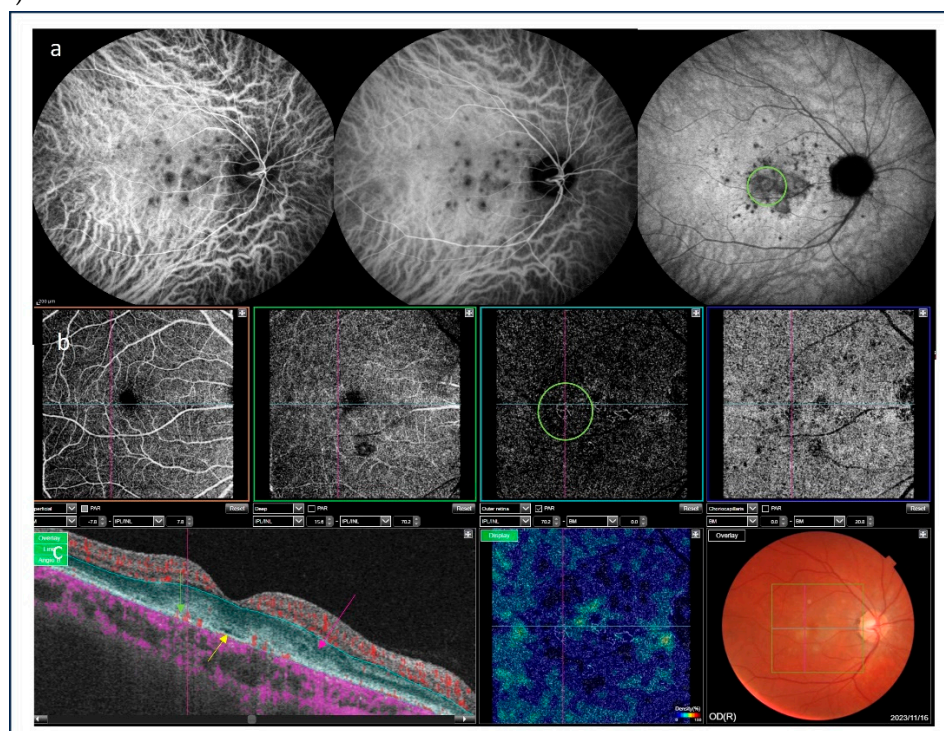
Figure 6. (a) Early and middle stages of indocyanine green angiography presented hypocya nescence spots indicating active inflammatory lesions, late stage showed hypercyanescent. plaque (green circle); (b) Optical coherence tomography angiography revealed the presence of small inflammatory choroidal neovascularization in outer retina layer (green circle); (c). Optical coherence tomography showed the presence of a trace of subretinal fluid (yellow arrow), blood flow in outer retinal layers (green arrow) and intraretinal fluid (pink arrow) indicating the presence of inflammatory choroidal neovascularization.
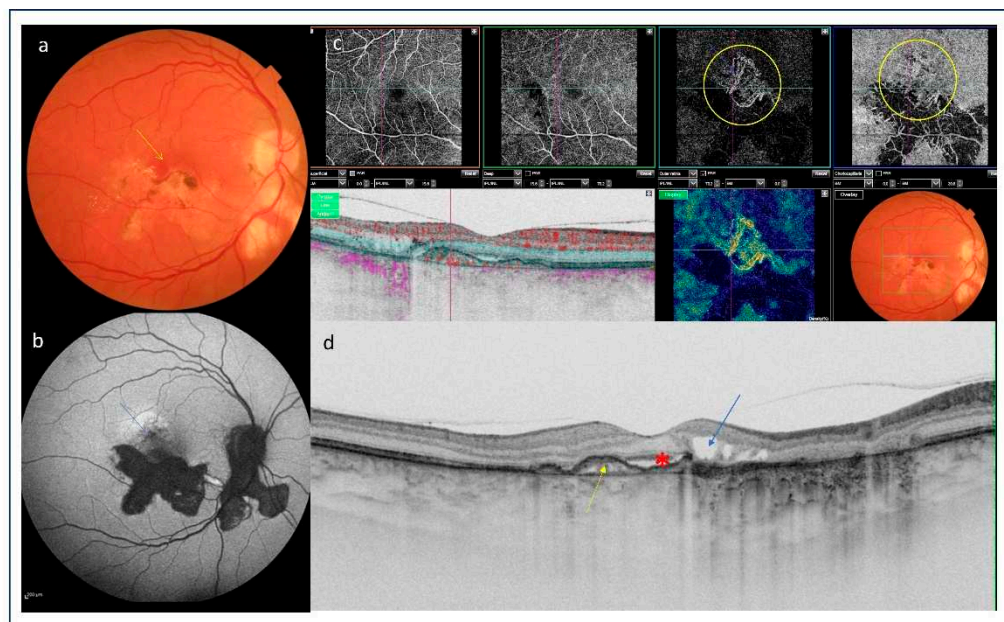
Figure 7. (a) Color picture of the fundus shows the presence of partially pigmented inactive inflammatory lesion related to serpiginous choroidopathy suspected for inflammatory choroidal neovascularization; (b) Fundus autofluorescence image shows hypoautoflurescence of inactive postinflammatory lesion in macula with hyperautofluorescent lesion above it; (c) Optical coherence tomography angiography demonstrated the net of pathological vessels in outer retina layer; (d) optical coherence tomography revealed the presence of subretinal mass (yellow arrow) with subretinal (red asterix) and intraretinal fluid (blue arrow) showing the evidence of inflammatory choroidal neovasularization.

In patients with posterior uveitis, the identification of iCNV is challenging due to related abnormalities including associated pathologies such as choroiditis, chorioretinal lesions, and choroidal scarring [1,79,80]. In such cases, OCTA provides objective evidence of CNV lesions because it has an advantage of differentiating iCNV lesions from inflammatory lesions as these do not show any neovascular flow signals [80]. Thus, OCTA allows noninvasive diagnostic imaging of iCNV and differantation from inflammatory pathologies [1, 79,80].

While the above studies prove the role for OCTA in the diagnosis and follow-up of patients with iCNV, larger prospective studies are needed to determine its advantages over conventional imaging.

2.5. Near-infrared autofluorescence imaging

Fundus autofluorescence (FAF) is a valuable imaging tool for multiple anatomical and physiological alterations in the ocular tissue [81]. Essentially, FAF is a map of lipofuscin distribution, which is the autofluorescent pigment of the eye naturally found in the RPE–photoreceptor complex [81]. It was reported that iCNV lesions may show a different pattern on FAF imaging than active inflammatory foci [1,81,82]. In FAF, normal autofluorescence may occur in active iCNV with preserved neurosensory retina [1,80-83]. Prolonged active CNV tends to present hyperautofluorescence, while hypoautofluorescent areas correlate with photoreceptor and RPE loss [1,80,83] (Fig.1a and Fig.7b). Active inflammatory foci may show increased autofluorescence signal

[81,82] (Fig.3a). Therefore, the technique may be used for differentiating between inflammatory and CNV lesions.

3. Conclusions

The detection of inflammatory CNV remains a challenge due to the presence of choroiditis lesions, scarring, and pigmentation that make it difficult to visualize CNV lesions. Available case reports and case series point to the benefits of using OCTA in combination with conventional imaging modalities such as FA, OCT, and ICGA. This multimodal approach may improve the detection and follow-up of iCNV lesions. OCTA is also an important addition to FA and ICGA in terms of providing important information on retinochoroidal abnormalities associated with uveitis: the severity of inflammation or the presence of any vascular changes and focal lesions. It may offer advantages over traditional modalities in the detection of neovascular flow in uveitis, but it should be used as an additional tool rather than a replacement of the existing ones. Also FAF requires further research to reveal whether this imaging modality can be used to differentiate between iCNV and inflammatory lesions and between AMD-related CNV and CNV related to inflammatory disease.

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