Imaging Tools for Detection of Inflammatory Choroidal Neovascularization

Subjects: Ophthalmology

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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. 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 may be a complication, especially 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 (type 2 lesion) 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.

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

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 are present on FA as early iso- or hyperfluorescence with late leakage [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 an RPE window defect) without leakage [2][3][4]. 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 [5][6][7]. Thus, FA alone may be insufficient to identify iCNV lesions and initiate appropriate therapy. Therefore, a multimodal approach with additional tests is recommended.

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 [8]. ICGA plays an important role in assessing pathologies involving the choroidal vasculature and choriocapillaris in chorioretinal inflammatory diseases. It is helpful in differentiating between iCNV and inflammatory lesions [9][10]. ICGA allows us to tell the difference between a recurrent inflammatory focus and iCNV: the former appears as an early hypofluorescent lesion, whereas the latter has been a hyperfluorescent lesion since early angiographic frames [8][9]. ICGA is also mandatory in the case of CNV associated with choriocapillaritis, such as multifocal choroiditis (MFC), where it shows the extent of occult choriocapillaris nonperfusion and hence the risk for CNV development [10][11]. CNV secondary to MFC is more frequent in inflamed areas; however, this may originate from an old chorioretinal scar as well. Low-grade chronic inflammation can be at the core of this process, and ICGA frequently shows areas of non-perfusion indicating ischemia, which may be the trigger of angiogenesis. In such cases, ICGA is essential in the evaluation of the choroidal status. Importantly, ICGA was shown to outperform FA in detecting occult CNV lesions [1]. 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 [12]. Thus, ICG helps identify both iCNV and inflammatory choroidal alterations in patients with uveitis, allowing clinical differentiation between these lesions and a more comprehensive evaluation of the disease [10].

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 [13]. 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 [13].

Inflammatory CNV usually develops between the RPE and neurosensory retina, demonstrating similar features on OCT imaging as classic (type 2) CNV [8]. In both cases, the lesions appear as hyperreflective structures located in front of a disrupted RPE, with solid tissue in the subretinal space [14][15][16][17]. 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 us to differentiate iCNV from other causes of CNV [6][14][18][19]. The inflammatory conditions associated with this sign include idiopathic multifocal choroiditis/punctate inner choroidopathy (MFC/PIC), intraocular tuberculosis, and acute syphilitic posterior placoid chorioretinitis [6][14][18][19]. Rajabian et al. and Berensztejn et al. reported “pitchfork signs” in patients with choroidal osteoma. The authors proposed that inflammation is the most important stimulus for the development of CNV in these cases [20][21]. However, recently, Falavrajani et al. [22] have described the “pitchfork sign” in five eyes with type 2 CNV and without any sign of ocular inflammation. They speculated that traction of the type 2 CNV complex on the outer retinal layers and consequent dragging of the layers or Müller cell activation could explain the presence of the “pitchfork sign” [22].

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 predicted the presence of FA leakage [14][17]. Thus, it was concluded that OCT can be used for monitoring disease progression and response to treatment [19][23].

Moreover, central retinal thickness evaluated by OCT is often used as an objective measure of iCNV activity [24][25][26]. Recently, Giuffrè et al. [27] demonstrated increased choroidal thickness under iCNV that decreases after therapy: the so-called “sponge sign”. The authors investigate choroidal thickness changes related to the clinical activity of inflammatory choroidal neovascularization in punctate inner choroidopathy/multifocal choroiditis as compared to myopic choroidal neovascularization. They found that choroidal thickness beneath inflammatory choroidal neovascularization significantly increased at baseline and decreased after therapy, reaching preclinical values. Conversely, no significant choroidal thickness changes were disclosed in myopic choroidal neovascularization eyes, under any location. 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 the choroidal neovascular membrane in doubtful cases (either inflammatory or myopic) and to guide therapeutic management [27].

OCT images can also help differentiate between iCNV lesions and non-neovascular alterations at the RPE level that are characteristic of 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 [4][16]. 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 involvement of the RPE or choriocapillaris (e.g., multifocal choroiditis and punctate inner choroidopathy) [14][25][26][28][29]. In such cases, the characteristics of the lesions can be determined by a combination of FA, ICGA, and OCT angiography (OCTA).

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. [30] 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 the detailed vascular structure of CNV. Therefore, it could be used as an alternative option for CNV identification and to guide therapeutic decision making [28]. Similarly, in a recent retrospective study of 14 patients, Zahid et al. [31] 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 its course. The utility of OCTA for the noninvasive diagnosis of iCNV and its subsequent follow-up was also confirmed by Yee et al. [32]. Finally, in a recent study, Aggarwal et al. [33] investigated the 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 the conclusion that OCTA is indispensable to exclude neovascular networks when FA, ICGA, and OCT results are inconclusive [32].

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 [14][33][34]. In such cases, OCTA allows noninvasive diagnostic imaging of iCNV and differentiation from inflammatory pathologies [14][33][34].

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

5. Near-Infrared Autofluorescence Imaging

Fundus autofluorescence (FAF) is a valuable imaging tool for multiple anatomical and physiological alterations in the ocular tissue [35]. Essentially, FAF is a map of lipofuscin distribution, which is the autofluorescent pigment of the eye naturally found in the RPE–photoreceptor complex [36]. It was reported that iCNV lesions may show a different pattern on FAF imaging than active inflammatory foci [14][35][36]. In FAF, normal autofluorescence may occur in active iCNV with preserved neurosensory retina [14][34][35][36][37]. Prolonged active CNV tends to present hyperautofluorescence, while hypoautofluorescent areas correlate with photoreceptor and RPE loss [14][34][37]. Active inflammatory foci may show an increased autofluorescence signal [35][36]. Therefore, the technique may be used for differentiating between inflammatory and CNV lesions.

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