New Trends in the Management of Inflammatory Choroidal Neovascularisation

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Abstract

Choroidal neovascularisation (CNV) can be a severe, sight-threatening sequela in patients with uveitis. CNV can occur in both infectious and non-infectious diseases. In the majority of cases, fluorescein angiography, indocyanine green angiography and optical coherence tomography allow the clinical characteristics of the CNV to be accurately determined. An infectious disease should be looked for so that patients can be given a suitable therapy when available. Regarding non-infectious inflammatory CNV, the treatment strategy should be aimed at controlling inflammation. Systemic corticosteroids with or without immunosuppressants are suggested, even when the CNV occurs with apparently inactive uveitis. In this case, chronic sub-clinical inflammation can be the basis for the CNV pathogenesis. Additional therapies aimed directly at the neovascular process, such as intravitreal antivascular endothelial growth factor agents, are recommended, particularly when the therapy shows insufficient efficacy. However, the current data are still only based on case reports or small series. For such reasons, further trials are mandatory to validate the preliminary results.

Keywords

Choroidal neovascularisation (CNV), uveitis, steroids, immunosuppression, vascular endothelial growth factor (VEGF), choroiditis

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Choroidal neovascularisation (CNV) is one of the most severe causes of visual impairment in patients with uveitis. The disruption of homeostasis between the retinal pigment epithelium (RPE) and Bruch's membrane can generate a vicious circle leading to choroidal neoangiogenesis. Both non-infectious and infectious uveitis can present CNV as a possible complication. Infectious uveitis is provoked by infective agents that directly affect the retino-choroidal space, whereas non-infectious uveitis, also called endogenous uveitis, is likely to be an autoinflammatory disease.

The balance between physiological and pathological pro-angiogenic factors is based on the equilibrium of inhibitory and stimulating agents. This balance controls cell proliferation and inflammatory mediator production by the cells themselves. The imbalance between inhibitory[1] and stimulatory activities[2] of different mediators produced *in vivo* by the RPE[3] is thought to be the trigger of neovessel formation.

Animal models[4] have proved that neoangiogenesis can occur even in the absence of evident inflammatory activity and can be the late complication of chronic low-grade inflammation. Exploration of choroidal inflammation using only biomicroscopy and fluorescein angiograpy (FA) is not sufficient. Only choroidal foci causing alterations of the retina red reflex can be detected through the screen of the RPE by fundoscopy and/or FA. The choroid can only be analysed using indocyanine green angiography (ICGA), as this method is able to show choroidal abnormalities.

Thanks to ICGA semiology, it has been possible to re-classify choroidal inflammation according to the structures that are predominantly involved. The ischaemic consequences of non-perfusion of the choriocapillaris involve the chorio–retinal interface, the RPE and the outer retina. This leads to the production of mediators involved in vascular endothelial growth factor (VEGF) production and, consequently, to CNV pathogenesis. As choroidal neovessels grow, they may extend into the sub-RPE or subretinal space.[5] The location, growth pattern and type (1 or 2) of CNV depends on the patient's age and the underlying disease. Bleeding and exudation occur with further growth, accounting for the visual symptoms. Type 2 neovascular membranes are the ones that commonly occur in inflammatory diseases.

As previously stated, CNV can occur in both infectious and non-infectious diseases. In the infectious diseases toxoplasmosis,[6] *Toxocara canis*,[7] tuberculosis[8] and viral retinopathies,[9] CNV can present as choroidal neoangiogenesis. Non-infectious uveitis has also been associated with CNV, such as punctate inner choroidopathy (PIC), multifocal choroiditis (MC), acute posterior multifocal placoid pigment epitheliopathy (APMPPE) and Vogt-Koyanagi-Harada (VKH) disease. The following sections describe the major posterior infectious and non-infectious uveitis entities most often associated with CNV.

Infectious Uveitis

Although several protozoa can affect the retina, such as *Trypanosomiasis*,[10,11] *Leishmania*[12] and *Pneumocystis carinii*,[13]

Toxoplasma gondii[6] is the protozoan that most commonly affects the eye. It is the only one that has been associated with CNV. *Toxoplasma gondii* belongs to the genus *Toxoplasma* and is a ubiquitous, endocellular parasite in humans.[14–16] Congenitally acquired toxoplasmosis was originally thought to make up the majority of toxoplasmic retinochoroiditis. This was the case until recently, when most toxoplasmic retinochoroiditis infections were recognised as being acquired.[16,17] The association between *Toxoplasma retinochoroiditis* and CNV is frequent and very well known.[6] CNV typically grows close to the edge of an old atrophic scar, even though CNV can occasionally be synchronous with active toxoplasmic retinochoroiditis. FA is useful for the diagnosis of CNV, particularly to distinguish it from the reactivation of retinochoroiditis. The typical angiographic hallmarks of the choroiditis are early hypofluorescence and late staining for the atrophic areas, and late hypofluorescence when pigment clumps are present. The adjacent CNV has the typical dirty grey aspect on fundoscopy, presenting an early hyperfluorescence and late leakage on FA. Optical coherence tomography (OCT) can be useful for the appraisal of CNV,[18] showing liquid within the adjacent or overlying retina. It is also useful for verifying the efficacy of CNV treatment.

As stated earlier, in very rare cases CNV can occur concomitantly with reactivation of retinochoroiditis. As far as treatment is concerned, in the rare cases where CNV is associated with recurrent retinochoroiditis, the classic combination of antitoxoplasmic antibiotics with corticosteroids should be given.[19] The other options available for the treatment of CNV associated with toxoplasmic retinochoroiditis are laser therapy[20] and photodynamic therapy (PDT).[21] At this time, anti-VEGF drugs have shown promising results.[22] These techniques can therefore be considered the most reasonable options for such disease.

CNV can be a rare sequela of bacterial infectious choroiditis.[23–32] Choroidal colonisation by the bacteria can occur after bacterial metastasis, such as endocarditis, aortic valve infection, renal and bone abscesses and intravenous drug abuse. CNVs secondary to bacterial choroiditis are generally membranes that grow close to the primary chorioretinal lesion or in the neighbouring area of an old atrophic scar.

Viruses, such as rubella or West Nile virus, can cause the development of CNV, mostly as a late complication.[33–37] The most recent virus associated with CNV is the West Nile virus, which Khairallah et al.[37] reported for the first time in 2006. In the case presented, FA proved there was an extensive ischaemic capillaropathy in the macula and a few months later a CNV developed near a chorioretinal scar.

Most fungal diseases have been described as potential pathogens of the eye. Several papers have reported the severe complications of various fungi, such as *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigatus*. In these diseases CNVs have been reported, although these are anecdotal cases only.

Helmiths are parasitic worms that can infect humans and, potentially, affect the eyes. Despite this, only *Toxocara canis* generates the choroidal lesions leading to neoangiogenesis, and such cases are rare. The CNV typically occurs near an active or quiescent choroidal granuloma, showing early hyperfluorescence and late leakage of the dye at FA. ICGA can demonstrate an occult CNV underlying the area close to the granuloma.[38]

With the exception of toxoplasmosis, cases described in the literature are only reports. There are no indications of a possible method that can offer good control of the CNV.[38]

Treatment is based on the combination of systemic drugs and other techniques, such as argon laser photocoagulation, PDT, surgical removal and intravitreal anti-VEGF drugs. No trials and/or case series are available in the literature, therefore clinical rationale should be followed. Considering the data emerging from recently reported anecdotal cases, intravitreal anti-VEGF drugs seem to be the best option with or without other systemic medications. They offer a less aggressive control of the CNV, reducing the risk of exuberant scarring and optimising the outcome of the disease.

Non-infectious Uveitis

Posterior pole non-infectious uveitis can be a severe disease, threatening the visual acuity directly or secondarily by its complications.

MC is the posterior uveitis with the highest rate of CNV formation. It is found in 32–46% of patients.[39–41]

In 1973, Nozik and Dorsch[42] described two cases resembling presumed ocular histoplasmosis, characterised by multifocal choroidal spots and panuveitis. More than 10 years later, Dreyer and Gass[39] reported 28 additional cases with anterior uveitis, vitritis and multiple lesions in the posterior pole, which they called 'MC and panuveitis'. Today, it should probably more simply be called MC, since the panuveitis is not frequently associated with the chorditis.

CNV generally appears to be anterior to the RPE, located in the macular region or peripapillary area. The reason why CNV is so frequent in multifocal chorditis may be explained by the widespread involvement of the choriocapillaris in many of these cases.

CNV secondary to MC is more frequent in inflamed areas, even though it may originate from an old chorioretinal scar. Low-grade chronic inflammation can be the basis of such a process, and ICGA frequently shows large areas of non-perfusion causing ischaemia, which could be the trigger of neovessel formation. ICGA plays an important role in evaluation of the choroid in multifocal chorditis as the choroidal involvement is better detected by ICGA than FA.[43]

OCT can be very helpful, as in all cases, in studying the position of CNV with reference to the RPE and giving information on the presence of liquid in the overlying or adjacent retina.

PIC is another sub-type of MC, presenting multiple choroidal spots and, often, CNV. Active, yellowish spots can be characterised by an overlying serous detachment of the neurosensory retina[44] corresponding to those areas where the patient complains of scotomas and/or metamorphopsias. Choroidal spots can evolve into faded chorioretinal lesions or atrophic chorioretinal scars. Yellowish lesions tend to depigment and become creamy, surrounded by a hyperpigmented edge. Focal chorioretinal scars can be the site of origin of the CNV. CNV complicates PIC as frequently as it does in multifocal chorditis. The occurence of CNV is estimated at 17–40% of eyes, often causing severe and permanent visual impairment.[44,45]

Clinical and angiographic aspects are similar to CNV in MC. As in MC, ICGA is the best modality for proving choroidal involvement,[46] which is usually found to be prominent.

In 1932, Junius[47] described a posterior pole intraocular inflammation presenting a serpiginous pattern. Several reports added more cases in the following years[48,49] and serpiginous choroiditis (SC) became a distinguished entity. SC is a rare, severe, recurrent and, generally, bilateral disease. It is thought to primarily involve the choriocapillaris and secondarily the RPE and the rest of the choroid.[47] The disease typically starts in the peripapillary region and tends to progress centrifugally to the macula, assuming the typical serpiginous pattern. CNV is a well-known complication of SC and occurs in 10–25% of affected patients.[50–53]

CNV typically occurs near the edge of both active and inactive lesions. FA can be helpful in proving the CNV and should always be performed. During the active stage of the disease, CNV cannot easily be recognised as it shows a hyperfluorescence similar to the hyperfluorescent borders of the disease. As FA usually underestimates the areas involved, ICGA is essential in the evaluation of choroidal involvement and for the longitudinal management of SC.

ICGA enables far better delineation of choroidal lesions than corresponding fluorescein frames, showing sub-clinical abnormalities of the choroid appearing as a hyperfluorescent areas in the late phases of ICGA with a weak leakage.[54] This allows one to hypothesise that sub-clinical, low-grade inflammation may be one problem leading to neovessel pathogenesis.

A very peculiar type of MC is the one secondary to *Histoplasma capsulatum*. Although the trigger is an infectious disease, ocular histoplasmosis syndrome (OHS) or presumed OHS (POHS) seems to be an immune reaction, possibly triggered by the fungus itself.

POHS is characterised by disciform macular detachment associated with peripheral chorioretinal scars and peripapillary atrophy, which are the classic triad of this disease. The primary cause of visual impairment in POHS is the occurrence of CNV in the macula, which results in exudation and subsequent scarring. As the disease can be considered autoinflammatory, Dees et al. reported the use of immunesuppressants for the control of CNV secondary to presumed ocular histoplasmosis. Patients were treated with the combination of steroids, cyclosporin A and, in some cases, azathioprine, achieving good control in all cases considered.[55]

Although the diseases reported above are more frequently associated with CNV, theoretically any posterior pole ocular inflammation can be complicated by a neoangiogenetic process. Some of the non-infectious uveitis that have been associated with choroidal neoangiogenesis include:

- subretinal fibrosis and uveitis syndrome;[41]
- APMPPE;[56]
- birdshot retinochoroidopathy;[57]
- multiple evanescent white dots syndrome (MEWDS);[58–60]
- VKH disease;[61]
- sympathetic ophthalmia;[62] and
- sarcoidisis.[63]

Figure 1: Active Extrafoveal Choroidal Neovascular Membrane Showing Leakage at the Late Phase of the Fluorescein Angiography (arrow)

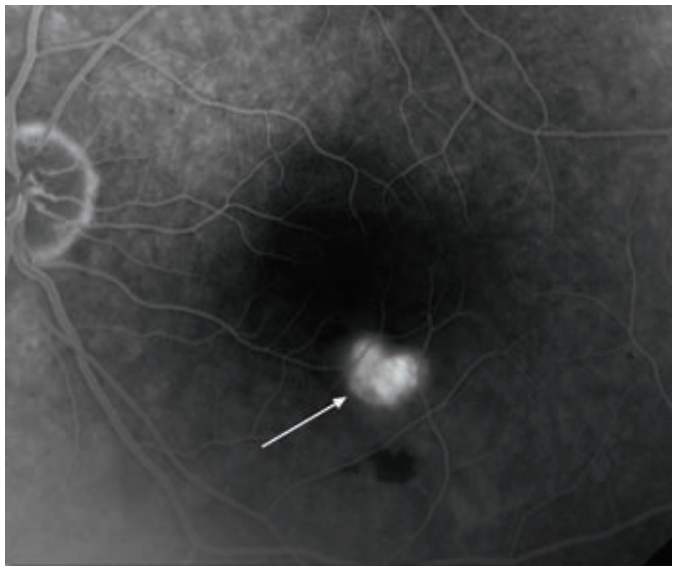
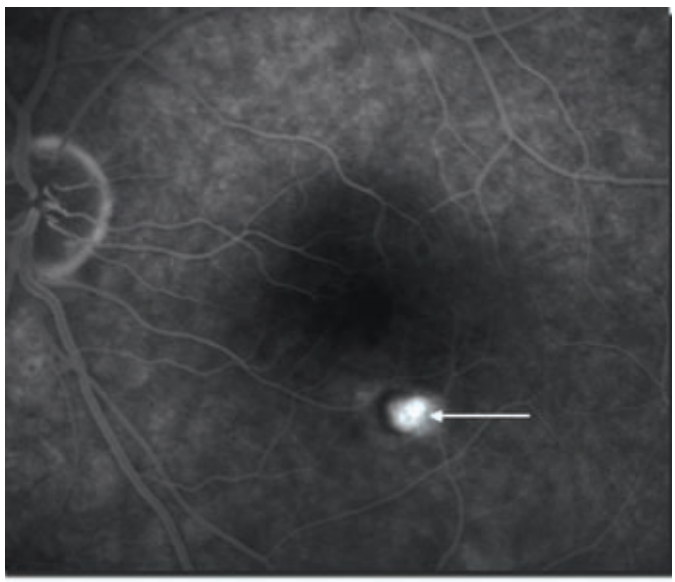


Figure 2: After Oral Steroids at 1mg/kg, Gradually Tapered, the Neovascular Membrane Showed an Evident Reduction of Leakage in the Late Phase of the Angiogram, as well as a Reduction in Size (arrow)



The clinical characteristics of CNV in all of these entities are similar to those observed in other posterior uveitis and are generally type 2 membranes.

Subtle choroidal inflammation can be the promoter of the neoangiogenic process, even for those CNVs that apparently have no evidence of choroidal inflammation. The prototype of such a case is so-called idiopathic CNV. This is the case when CNV is the only reliable finding in the retina and no other abnormalities are reported. It appears as a yellowish lesion surrounded by a dark rim of fresh blood.

FA is not contributory in understanding a clinical pattern, which can be evocative of posterior pole ocular inflammation. The role of

Figure 3: Active Punctate Inner Choroidopathy Showing Multiple Macular Spots and an Active Juxta-foveal Choroidal Neovascularisation (arrow) that Was Treated with Systemic Steroids and Mycophenolate Mofetil

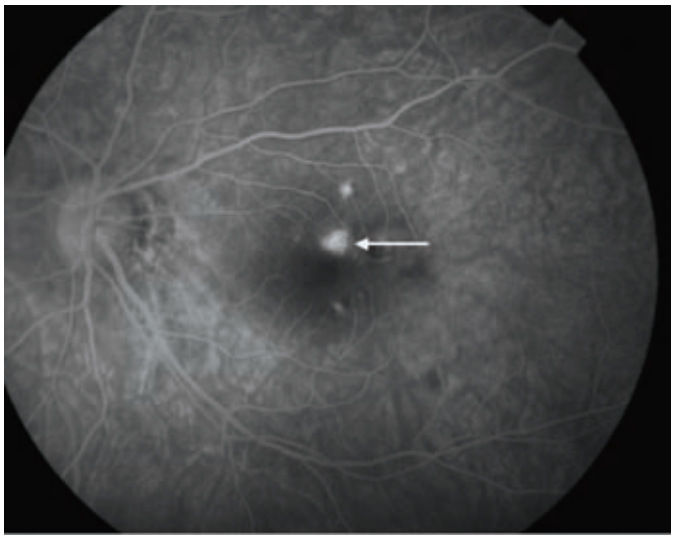
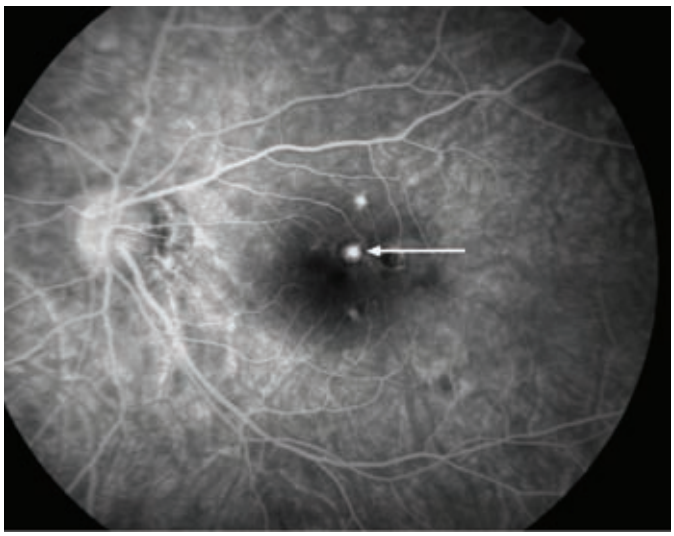


Figure 4: Two Months Later, the Membrane Showed No Leakage, Surrounded by an Evident Hypofluorescent Ring (arrow); The Patient Was on Only Oral Mycophenolate Mofetil at that Time



inflammation in the pathophysiology of idiopathic CNV has been postulated on the basis of ICGA.[64] It is further supported by the preceding publications, which have shown CNV as a possible sequela.[4] The supposed role of inflammation in idiopathic CNV is important for the treatment strategy. More than in other CNVs, idiopathic CNV should be treated as an inflammatory neovascularisation[65] (see *Figures 1* and *2*).

The strategy for the management of non-infectious inflammatory CNV is changing, albeit the core of the treatment is still based on control of the triggering inflammation. The histopathological features, pathophysiology and preliminary results of some studies suggest a relatively unique method for management.[66]

As there are no guidelines for the management of inflammatory CNVs, there is no flow-chart that can be followed for their treatment. All of the methods proposed present the results as safe and effective, but it is not clear which one could offer the most advantages. There are no randomised controlled trial data available directly comparing different techniques. In addition, no trials have been carried out on CNVs secondary to specific uveitis entities.

The rationale for combined therapy lies in the pathophysiology of the inflammatory CNV itself. Indeed, the association of medical treatment with other methods offers control of both the triggering factor of inflammation and the neovascular process.

Several techniques have been proposed for the management of CNVs, such as laser photocoagulation,[67] periocular and systemic steroids,[68] PDT,[69,70] immunesuppression[55] and surgical removal.[71] The use of systemic steroids should be considered mandatory, as the inflammatory process is not only loco-regional, but there is also evidence of involvement of the whole immune system.[72]

As reported above, the safety and efficacy of immunosuppression[55] for the control of new choroidal vessels in uveitis have been described. The choice of immunosuppressant should be established on the basis of the characteristics of the drug itself. Some immunosuppressive drugs, such as cyclosporin A,[73] tacrolimus and sirolimus,[74] are known to produce nephrotoxicity. This nephrotoxicity induces over-expression of soluble mediators that have an important role in CNV pathogenesis.[75]

The steroid-sparing drug that is gaining consideration in this area is mycophenolate mofetil. It is effective in reducing such biomechanisms,[76] improving arteriolopathy and decreasing the amount of soluble mediators involved in CNV pathophysiology. For such reasons, mycophenolate mofetil is a promising drug for the long-term control of inflammatory CNV[77] (see *Figures 3* and *4*).

When PDT was introduced, laser treatment changed, limiting argon laser photocoagulation to extrafoveal neovascular membranes. This reduced the risk of iatrogenic damage. PDT has been used following various strategies: some patients have been treated electively with medical therapy and PDT,[69] while others have received PDT when they have not achieved control of CNV with other treatments.[70] At this time, PDT has only a marginal role and the new anti-VEGF drugs have a prominent position in the management of inflammatory CNV.[78]

The same considerations can be made for surgical removal of CNV: after the introduction of intravitreal anti-VEGF drugs,[78] surgery is indicated only for extensive peri-papillary membranes,[79] albeit previously this technique was reported to be safe and effective.[71]

Although there are no direct comparisons between different treatments, the rationale may suggest medical treatment as the first choice for juxta/sub-foveal CNV. When this fails in controlling the CNV activity, anti-VEGF intravitreal drugs should be considered, with or without PDT.

Discussion

Uveitic CNV is a rare but severe complication of uveitis. In most cases the clinical findings obtained by FA, ICGA and OCT allow clinicians to accurately determine the characteristics of the CNV.

In the case of active inflammation, an infectious disease should be looked for and a suitable therapy offered when available.

Regarding non-infectious uveitis, the treatment strategy should be aimed at controlling inflammation with the help of corticosteroids, usually given systemically but sometimes locally in unilateral disease, and/or immunosuppressive agents. Corticosteroids with or without immunosuppressants are also suggested for CNV associated with apparent inactive inflammatory disease: subclinical inflammation can be present and can create the conditions for the pathogenesis of CNV.[78,79]

Additional therapies aimed directly at the neovascular process are recommended, particularly in those cases showing aggressive behaviour. If steroids with or without immunosuppressive therapy show an insufficient response, anti-VEGF therapy should be rapidly introduced.

Argon laser photocoagulation should probably be avoided, even in CNV outside the fovea, because intravitreal administration of anti-VEGF therapy seems be more effective and have a longer-lasting action. Similarly, PDT seems to be no match for anti-VEGF drugs, and recent evidence directs the clinician to use these new types of therapy. However, as for all other methods evaluated, these results are still only based on case reports or small series. For these reasons, further study – possibly multicentre, randomised controlled trials – are mandatory to validate these preliminary results. ■

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