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Inflammatory Choroidal Neovascularisation

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ABSTRACT

Inflammatory choroidal neovascularization is uncommon severe sight threatening complication of uveitis, more frequent in posterior uveitis. Hypoxia, release of vascular endothelial growth factor and other mediators seem to be involved in its pathogenesis. Multimodal imaging including the recent optical coherence tomography angiography greatly aid in diagnosis and management. Management of these neovascular membranes consists of anti-vascular growth factor agents, with or without concomitant anti-inflammatory and/or corticosteroid therapy. Besides effective eradication of inflammation in uveitis, the ideal therapeutic goal should include timely detection and treatment of inflammatory CNVM, as the ultimate visual outcome would depend on the control of both.

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Introduction

Inflammatory choroidal neovascularization (i-CNV) is the third common cause of choroidal neovascularization worldwide, after age related macular degeneration (AMD) and pathologic myopia [1]. The CNV develops due to angiogenic drive which is mediated by either local inflammation, secondary to degenerative disruption of the retinal pigment epithelium (RPE) Bruch's membrane complex or both. CNV may occur in wide range of both infectious and non-infectious uveitis etiologies.

Fundus fluorescein angiography (FFA), indocyanine angiography (ICG) and optical coherence tomography (OCT) have been used as tool in diagnosis and localization of CNV. The development of optical coherence tomography angiography (OCTA) has high value in monitoring the progression of CNV. The management options include steroids, immunosuppressive, laser, photodynamic therapy (PDT) and anti VEGF agents. However all the treatment options have their limitations, the treatment guidelines are ambiguous.

The natural course and visual prognosis of inflammatory CNV are generally more favorable than the CNV from AMD. It can be due to its classic nature, smaller size of the membrane and younger age as compared to AMD related CNV [2]. The cause of significant delay in diagnosis of inflammatory CNVM is multifactorial including multifactorial etiology; nonspecific and variable presentation, subtle clinical signs at the beginning, relatively rare occurrence, low index of suspicion, asymptomatic nature of peripapillary CNVM, intense scarring, tendency to misdiagnosis. Although, CNV associated with uveitis is rare, the visual prognosis is poor if left untreated. To control underlying primary uveitic disease is most crucial aspect of management.

Etiology and Pathogenesis

CNV is an important sequel of wide range of ophthalmic pathologies of which most common cause in the elderly is age-related macular degeneration, while in the young, CNV is frequently due to secondary to high myopia, hereditary disorders, angioid streaks, and inflammation [3,4]. Uveitis tends to affect working age population, hence i-CNV frequently afflicts patients during their most productive and active years. Various etiologies of infectious uveitis resulting in cnvm include tuberculosis, toxoplasmosis, toxocariasis, histoplasmosis, congenital rubella, west nile virus while noninfectious etiologies include Vogt–koyanagi-harada syndrome, punctate inner choroidopathy, multifocal choroiditis, geographic helicoid peripapillary choroidopathy, acute multifocal placoid pigment epitheliopathy, sympathetic ophthalmia, behcets disease, sarcoidosis.

The process begins with focal infection of the choroid at time of the initial benign infection which resolves as an atrophic scar disrupting the Bruchs membrane. The resulting break in the Bruchs membrane provides an opening in the barrier and subsequent tissue rearrangement through which the new vessels gain access into sub retinal space. The potential paradigm for inflammatory neovascularization is that posterior segment intraocular inflammation activates both resident tissue macrophages and infiltrating macrophages generating VEGF release; complement activation, cytokine and chemokine production.

VEGF acts with other chemical mediators resulting in choroidal and retinal neovascularization. Therefore, intravitreal injection of antiVEGF could be a treatment approach which directly affects the pathogenic pathway of CNVM formation without causing collateral damage. CNV has also an extravascular component consisting fibroblasts, leucocytes, tumor necrosis factor alfa and IL-1 recruiting macrophages accounting for the inflammatory component of CNV [5]. Other mediators that play a role is nitric

oxide that induces the membrane formation. The transforming growth factor beta is responsible for the process of recruiting choroidal fibroblasts, but at the same time it induces the production of VEGF which leads to the formation of new active foci.

Diagnosis

In active uveitis, the clinical symptoms and signs of active intraocular inflammation take precedence over the signs of inflammatory CNVM, leading to its missed or delayed diagnosis. Many i-CNVs lesions, especially extrafoveal may be asymptomatic and detected by clinical examination or imaging alone. Commonly, i-CNV lesions may be missed initially due to associated features such as inflammatory lesions, scars, pigmentation, and intra- or subretinal fluid accumulation leading to imprecise evaluation of activity of the underlying disease [6]. However, the advances in ocular imaging tools have largely overcome the clinical challenges in their diagnosis. Fluorescein angiography (FA) has been used for long time to assess the presence and activity of a CNV in uveitic patient. On FA, CNV lesions present with early iso- or hyperfluorescence with late leakage.

Active uveitic chorioretinal lesions show early hypofluorescent with late leakage and inactive atrophic lesions show early hypo-/isofluorescence with late staining without any leakage [7-9]. Thus, there are very subtle differences between CNV lesions and active/inactive retinochoroidal inflammatory lesions on FA which makes differentiation very challenging and inconclusive in these conditions. Hence, the multimodal imaging approach is always recommended. Indocyanine green (ICG) angiography is an imaging technique that allows a better visualization of the choroid than FA [10]. It can be used in identifying possible occult components and allowing these lesions to be differentiated from recurrent inflammatory lesions leading more comprehensive evaluation of disease. The introduction of optical coherence tomography (OCT) has profound impact in management of retinal and choroidal diseases into clinical practice [11].

On OCT, these lesions appear as hyper-reflective structures anterior to a disrupted RPE, with solid tissue visualized in the subretinal space [12,13]. One distinctive OCT feature of i-CNV that distinguish from type 2 CNV is the "pitchfork sign" which is finger-like hyper-reflective projections extending from CNV area into outer retinal layers [14]. On OCT, the activity of CNV is associated with retinal thickening, subretinal fluid, intraretinal fluid, intraretinal flecks which can be used to monitor CNV progression and response to therapy [15]. Inflammatory chorioretinal lesions may present with very similar features making OCT very challenging in these conditions. Hence, the combination of imaging tools such as FA and ICGA, as well as OCTA, may be more useful in such condition [16].

The recently introduced OCTA is a noninvasive technique and helps in reconstruction of retinochoroidal microvascular network by using endoluminal flow as contrast. The study by Cheng et al concluded that OCTA has an advantage of differentiating i-CNV from inflammatory lesions as these do not show any blood flow signals [17]. It provides objective evidence of the presence of CNV lesions and aids in the decision-making for the use of anti-VEGF agents. It has disadvantages such as motion artifacts, inaccurate segmentation, and projection artifacts. To enable better correlation of FA, ICGA, and OCT with OCTA, further studies are required so that the detection and treatment rates can be improved especially in missed cases of i-CNV.

Management

In order to keep the inflammation under control, identifying underlying infectious diseases are mandatory using the correct medical therapy. Besides effective eradication of inflammation in uveitic eyes, the ideal therapeutic goal should also include timely detection and treatment of Inflammatory CNVM, as the ultimate visual outcome would depend on the control of both. By reducing the VEGF stimulus to the growth of new vessels and decreasing inflammation, corticosteroid remains a valuable option for the treatment of i-CNVs. It inhibit the proliferation of vascular endothelial cells and their secretion of proangiogenic mediators. It also decrease vascular permeability by stabilizing basement membrane of CNVM. The visual outcome of corticosteroids in inflammatory CNVM has been variable.

Since inflammatory responses are central to the development of inflammatory CNVM, immunosuppressive agents are increasingly being used in its management. It can limit angiogenesis owing to their anti-inflammatory property Anti-VEGF therapies have been used for management of i-CNVs associated with both infectious and non-infectious uveitic entities. In the face of uncertainty, it seems to be the wisest approach to control the inflammatory stimulus by use of systemic steroids and simultaneously treating neovascular component with intravitreal injections of anti-VEGFs [Figure 1a & 1b]. Rarely reported complications after intravitreal injection of anti-VEGF include ocular hypertension, reactivation of uveitis, subfoveal retinal pigment epithelium rip, submacular fibrosis, submacular hemorrhage or spread of chorioretinal atrophy [18]. Spaide et al had suggested a two-component model of CNV, vascular and extravascular [19].

Therapies like Photodynamic therapy (PDT) which have been used to treat subfoveal CNV are known to target the vascular component of the model. However, it usually only stabilizes but does not improve visual acuity. PDT is known to increase VEGF expression leading to recurrence of CNV. Sub retinal fibrosis and atrophy are known complications of PDT; hence its use has been limited. PDT has been variably used in the management of i-CNV often combining it with corticosteroids/immunosuppressive or anti-VEGF therapy [20]. If the inflammation is unilateral, local therapies such as intravitreal triamcinolone acetonide, dexamethasone implant, or methotrexate can be considered which also help in reducing size of the CNV lesion.

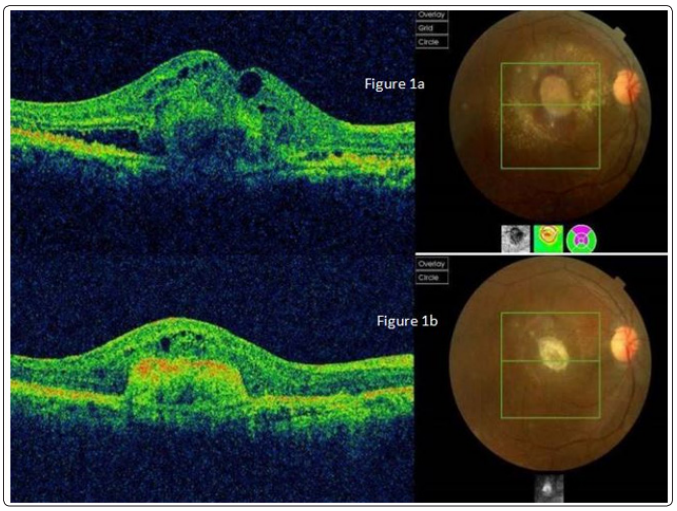

Figure (1a): Showing OCT and fundus photographs of a patient with active subfoveal CNVM in right eye **(1b)** same patient showing scarring CNVM after 2 anti-VEGF injections.

Conclusion

The detection of i-CNV is very challenging due to the difficulties of visualizing the lesion among inflammatory lesions, pigmentation, significant background fundus scarring, visually significant cataract, poorly dilating pupil, media haze due to vitritis, cystoid macular edema. OCTA in conjunction with FA, ICGA, and OCT can help in improved detection of CNV lesions, especially in cases of inconclusive conventional imaging. Anti-VEGF agents are usually employed as the first-line agents for treating i-CNV keeping in mind that the inflammation needs to be controlled for the best outcome and reduction of recurrences. No prospective randomized studies exist to compare their use with other modalities of therapy which could probably be due to the low incidence of inflammatory CNV. The ideal therapeutic goal should include timely detection and treatment of inflammatory CNVM besides effective eradication of inflammation.

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