

Perspectives

Microcysts in the Inner Nuclear Layer, a Nonspecific SD-OCT Sign of Cystoid Macular Edema

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Recently, many authors have propagated the notion that a specific form of “microcystic macular edema” occurs in patients with optic neuritis and optic atrophy of various etiology and is due to retrograde synaptic degeneration. The finding is isolated to the inner nuclear layer on spectral-domain optical coherence tomography in most cases, and is present in a parafoveal, circumferential, and central macular distribution. This perspective critically reviews the evidence and suggests that inner nuclear layer cystoid changes are an early and nonspecific indicator of typical cystoid macular edema of any cause, and that the finding is likely not a distinct entity.

Keywords: cystoid macular edema, inner nuclear layer cysts, microcystic macular edema, optic neuropathy

Recently, multiple authors¹⁻⁷ have reported microcystic changes in the central macula of multiple sclerosis (MS) and optic neuropathy of various etiologies, predominantly involving the inner nuclear layer (INL). These cystoid changes are common to many retinal and optic nerve diseases, and are a final common spectral-domain optical coherence tomography (SD-OCT) finding in diseases of various etiologies.⁸ Isolated INL cystoid changes in the absence of outer plexiform morphology have been reported in a subset of these processes^{6,9,10}; however, many significant questions remain regarding these findings. Additionally, “cystic” indicates that the spaces are true cysts, with an epithelial lining. Because this is not the case, the term “cystoid” is more accurate terminology.

Balk et al.⁹ report a single patient with cystoid change in their cohort of MS patients and go on to report “glare” and recurrent isolated optic neuritis in this patient. However, there is no mention of a slit-lamp examination, scleral indentation, or fluorescein angiography. Barboni et al.⁵ state that optic atrophy appears necessary, but not sufficient for INL cystoid changes, and proposed vitreous traction as a second factor that contributes to INL changes. They do report the lack of angiographic leakage in 10 patients with INL cystoid changes, but fail to report other important clinical variables, such as lens status and ophthalmoscopy. These considerations become exceedingly important when interpreting the SD-OCT appearance of cystoid macular edema from any cause. The Figure illustrates the appearance of early, treated, and subclinical cystoid macular edema (CME) that is isolated to the INL and appears similar to the INL cystoid changes reported in MS and optic atrophy, and also resembles our recently reported⁹ delayed-onset INL cystoid change following internal limiting membrane peeling. In fact, the INL is the location of many early inflammatory and tractional cystoid spaces,⁸ and this morphology is often seen before, on resolution of, or in conjunction with an outer plexiform morphology, the most widely recognized of these being typical pseudophakic CME, or Irvine-Gass syndrome. Furthermore, with the advent of wide-

field fluorescein angiography, we have been consistently surprised at the degree of peripheral chorioretinal and vascular pathology that is often missed by other examination or imaging techniques.

Barboni et al.⁵ and Lujan et al.¹¹ consider vitreous traction as a potential important contributing factor to INL cystoid changes in optic atrophy, and epimacular membranes (EMM) and vitreomacular traction often demonstrate isolated INL cystoid changes (Fig.); therefore, retinal traction is sufficient to cause INL spaces in the absence of any primary neuronal or inflammatory pathology. Importantly, however, tractional cystoid spaces typically exhibit inner retinal contour elevations and fluorescein angiographic leakage, which are presumably absent from the reported cases. Clearly, the parafoveal region contains a posterior vitreous cortex attachment, which is demonstrated in the Lujan et al.¹¹ article; however, there is no reason to suspect that this is not physiologic (i.e., there is no tractional inner retinal contour change, no vitreoschisis, and no epimacular membrane). Further, the cystoid changes are limited to the parafovea, which is well known to contain unique structural features that make it a common location for cystoid changes. This includes Henle fibers, or obliquely oriented foveolar cone axons emanating from the central foveal depression. Certainly many disorders include retinal thickening with isolated INL cystoid changes in the absence of vitreous traction (e.g., CME). Additionally, firm hyaloidal attachments occur at many additional locations, including the peripapillary and additional perivascular regions, which lack INL cystoid in the reported cases. Although it seems unlikely that vitreous traction, by the standard definition, is present in reported cases of retrograde synaptic degeneration,^{5,11} cell loss combined with a normal vitreofoveal attachment may have led to a balance of forces that, combined with the lack of structural support provided by previous INL cells, has led to cystoid spaces more prominent in the region of vitreofoveal adherence. Therefore, a combined degenerative and tractional hypothe-

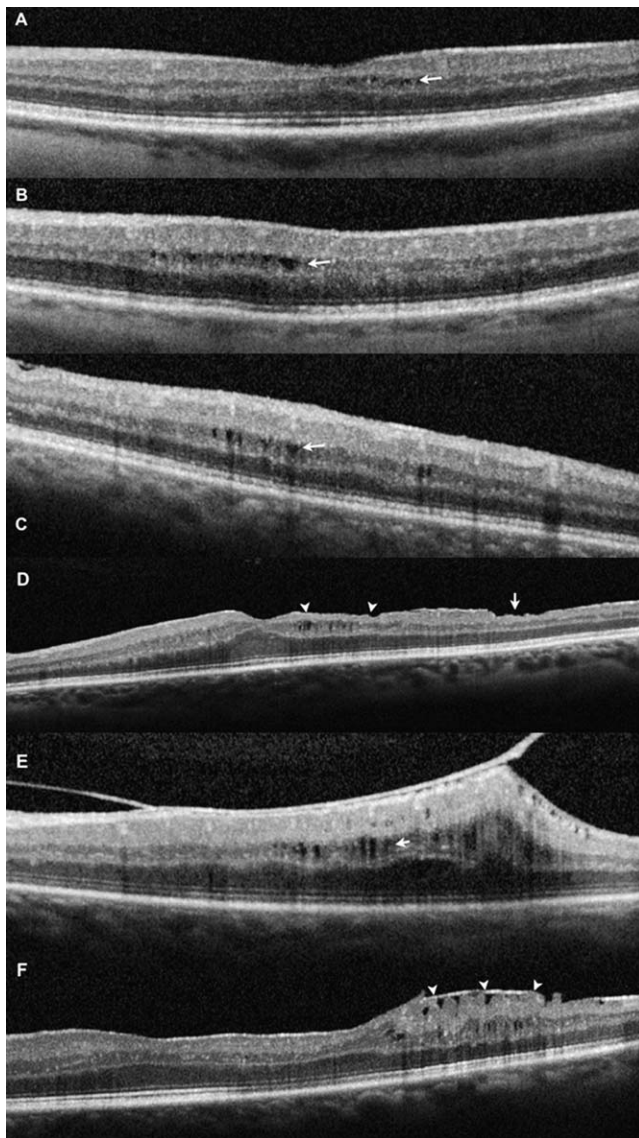


FIGURE. Typical cystoid retinal spaces of various etiology limited to the INL. (A) Inner nuclear layer microcysts in the phakic fellow eye of a patient with resolved pseudophakic cystoid macular edema. (B) Early pseudophakic cystoid macular edema limited to the INL; this finding resolved without treatment over a 3-month period. (C) Inner nuclear layer cystoid changes in this 28-year-old female with a history of MS and optic neuritis; the finding resolved with topical glucocorticoids and nonsteroidal anti-inflammatories over 6 weeks. (D) Nerve fiber layer defects in the location of forceps grasp sites (*arrowhead*); INL cystoid changes limited to one quadrant of the parafoveal region beneath a grasp site (*arrow*), but absent from some areas of NFL trauma (*arrowhead*). (E) Vitreomacular traction with cystoid spaces limited to the INL (*arrow*). (F) Extrafoveal epimacular membrane (*arrowheads*) with isolated INL cystoid changes limited to the region of epimacular membrane.

sis^{5,11} appears plausible. It is also possible that subclinical CME is present, which would be a more simple explanation.

The concept of retrograde trans-synaptic degeneration leading to isolated INL cystoid changes is plausible and a potentially interesting feature of optic neuropathies, including optic neuritis, optic atrophy, and compressive optic neuropathies. In contrast to the report by Green,⁷ in fact INL cystoid changes have been seen in glaucomatous optic neuropathy,

and have recently been formally reported.¹² However, many glaucoma patients (as well as many otherwise healthy patients) also have had cataract extraction, and are on prostaglandin analogs for IOP control. These factors are also both well-known causes of CME, which commonly involves the INL.⁸ Our report of delayed-onset INL cystoid changes¹⁰ was unique to previously observed INL cystoid changes for several reasons. First, the cystoid spaces were always absent in the reported cases before EMM removal and internal limiting membrane (ILM) peeling. The findings appeared at least several weeks after surgery, and displayed no angiographic leakage. Since that report, we have demonstrated no improvement in these cystoid spaces with topical or periocular glucocorticoids (six cases), topical carbonic anhydrase inhibitors (five cases), and topical nonsteroidals (eight cases), and have observed only mild worsening in all cases, which are distinct features from typical CME. As illustrated in the Figure, these cystoid changes are focal (not circumfoveal) and often correspond to areas deep to obvious nerve fiber layer (NFL) defects from forceps grasp sites. Interestingly, however, even with the most delicate techniques and ILM forceps, many obvious NFL defects are seen postoperatively, with little, if any, visual consequence. Delayed-onset INL cystoid changes, however, are exceedingly rare (roughly 1%), indicating that additional factors besides mechanical trauma are important in the development of these findings. We have hypothesized that the appearance results from Müller cell dropout, which may occur from physical trauma (ILM peeling or NFL grasp sites). The fact that INL cystoid changes are only rarely seen may result from a critical stretch or mechanical trauma threshold for which cell loss occurs in a subset of epimacular membranes, and therefore may represent the severity of the underlying EMM and the quantity of shear force required for membrane removal. This is consistent with recent experimental evidence that Müller cells are particularly pliable and respond with a spectrum of intracellular responses to various levels of mechanical stretch.¹³ Müller cell trauma and dropout would likely result in loss of additional INL cell types, which is consistent with our observation that the INL cysts tend to enlarge slightly over time, but do not appear to migrate laterally.

As SD-OCT becomes increasingly incorporated into clinical practice, it is likely that these findings will continue to be more important and our understanding of structural alterations in various retinal disease states will continue to expand. Were one to convincingly prove the concept of retrograde trans-synaptic degeneration as a cause of INL cystoid changes, one might try to demonstrate localized INL changes corresponding to a specific neural lesion on magnetic resonance imaging and support this finding with perimetry. If cell dropout is the etiology, then this finding should be focal, not limited to the parafovea, should occasionally also be present peripherally (as seen by peripheral OCT), should lack angiographic leakage, should correspond to a visual pathway lesion, and should occur at a reasonable time-course following upstream tissue injury. A lack of a response to cessation of medications involved in CME, topical or periocular glucocorticoids, and nonsteroidal anti-inflammatories also should be demonstrated. Currently, it is not at all clear that the reported cases of INL cysts are not simply CME from any of the many reported causes, including MS-related uveitis, pseudophakia, and medications.

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