Cystoid Macular Edema

Disease

The American Academy of Ophthalmology Preferred Practice Patterns defines Cystoid Macular Edema (CME) as retinal thickening of the macula due to a disruption of the normal blood-retinal barrier; this causes leakage from the perifoveal retinal capillaries and accumulation of fluid within the intracellular spaces of the retina, primarily in the outer plexiform layer [1]. Visual loss occurs from retinal thickening and fluid collection that distorts the architecture of the photoreceptors. CME is a leading cause of central vision loss in the developed world [2].

Pathophysiology

A delicate exchange of homeostatic mechanisms is in place with the vitreous, retina, retinal pigment epithelium (RPE), and choroid receiving their circulation through the retinal and choroidal vasculature.

A variety of risk factors may disrupt the normal interactions affecting the retinal environment. There is an intrinsic balance amongst the osmotic force, hydrostatic force, capillary permeability, and tissue compliance that occur within the vasculature [3][4]. Specifically, the capillary filtration rate should equal the rate of fluid removal from extracellular retinal tissue, such as glial and RPE cells. Once these forces are disrupted an imbalance occurs and accumulation of fluid is seen in cystoid spaces within the inner layers of the retina, most commonly the outer plexiform layer (OPL). The OPL is more prone to fluid collection due to the watershed area that exists between the retinal and choroidal circulation, especially within the central retina due to its anatomical avascular zone [5]. Accumulation of the fluid commonly occurs in the Henle's fiber layer causing the classic petaloid pattern.

Specifically, a common factor that can cause CME is vitreomacular traction (VMT). VMT can cause stress at the Muller cell end-feet, exerting tractional forces and contributing to the release of inflammatory factors such as basic fibroblastic grown factor (bFGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF). This results in blood-retinal barrier breakdown from separation of the retina and RPE, lysis of muller cells, leakage and edema [6][7][8][9]. However, typically CME associated with VMT does not demonstrate leak on FFA.

Diagnosis

Signs

Using slit lamp or direct/indirect ophthalmoscopy, clinically significant foveal edema and retinal thickening more than 300 μm can be seen as a loss of foveal reflex; this is better visualized using

green light to outline the cystic spaces. Subclinical foveal edema is described as edema less than 300 µm and is better seen through retinal imaging [10]. Vitritis and optic nerve head swelling can also be seen in clinical examination.

Symptoms

Symptoms include decrease in visual acuity that is associated with retinal edema, loss of contrast sensitivity and color vision, metamorphopsia that can be demonstrated on Amsler grid, micropsia, and central scotoma. Leakage on fluorescein angiography does not seem to correlate with a decrease in visual acuity [11].

Risk Factors

DEPRIVENS is a common mnemonic for risk factors that cause leakage on FA [12][13][14][15][16].

Diabetes	Diabetic macular edema (DME) is associated with leakage from microaneurysms and retinal capillaries causing circinate rings of hard exudates or lipoprotein deposits. Early Treatment Diabetic Retinopathy Study (ETDRS) defines clinically significant macular edema as: ● Any retinal thickening within 500 µm of the foveal center. ● Hard exudates within 500 µm of the foveal center that are associated with adjacent retinal thickening (which may lie more than 500 µm from the foveal center). ● An area of retinal thickening at least 1 disc area in size, any part of which is located within 1 disc area of the foveal center. [17]
Epinephrine	One study indicated that 28% of aphakic eyes treated with epinephrine drops vs 13% of untreated aphakic eyes developed CME [18]. Resolution of CME occurred with cessation of epinephrine drops.
Pars Planitis/Uveitis	In pars planitis, there is accumulation of T-cell inflammatory mediators such as interferon-gamma, interleukin-2, interleukin-10, and tumor necrosis factor-α that has been associated with CME [19].
Retinitis Pigmentosa (RP)	The CME may not leak in RP. Usually responds to topical dorzolamide or systemic acetazolamide. Rarely, CME due to RP with intermediate uveitis is seen, which responds well to posterior subtenon triamcinolone acetonide or oral steroid.[20][21]

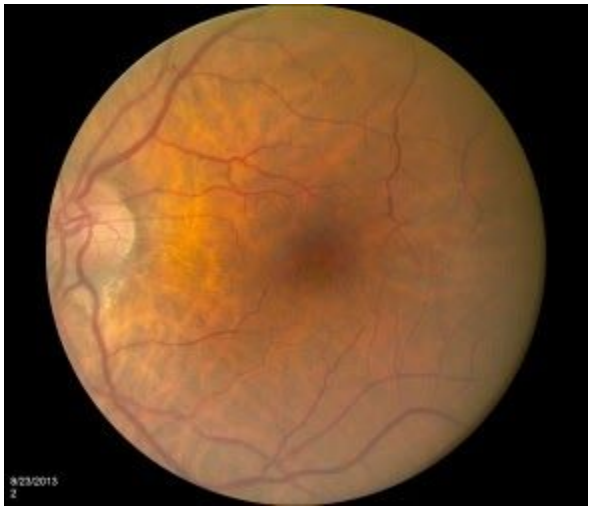
Irvine-Gass	Irvine-Gass is an inflammatory process occurring in up to 20% of cataract extraction with intraocular lens. 1% of these have a clinically significant decrease in visual acuity; in more complicated surgeries, such as those in which there is violation of the posterior capsule, this figure can reach 20%. CME usually occurs up to 6-10 weeks postoperatively. 95% of CME due to Irvine-Gass has been shown to resolve spontaneously within 6 months [22][23][24][25].
Vein Occlusion	Both central retinal vein occlusion/CRVO and branch retinal vein occlusion may cause CME which usually responds well to anti-VEGF agents.
E2-prostaglandin	E2-prostaglandins cause disruption of the tight junctions of the retinal capillaries.
Nicotinic acid and Niacin	Blurry vision associated with CME has been reported in doses greater than 1.5g/day [26].
Surgery	Various types of surgery can induce inflammation and alter the retinal blood flow. Treatment of CME prior to undergoing any procedures listed below can prevent the acceleration or persistence of pre-existing edema [27]. • Pars plana vitrectomy (PPV) • Laser photocoagulation • Cryopexy • Glaucoma procedures

CME **that does not demonstrate leakage on FA include:**

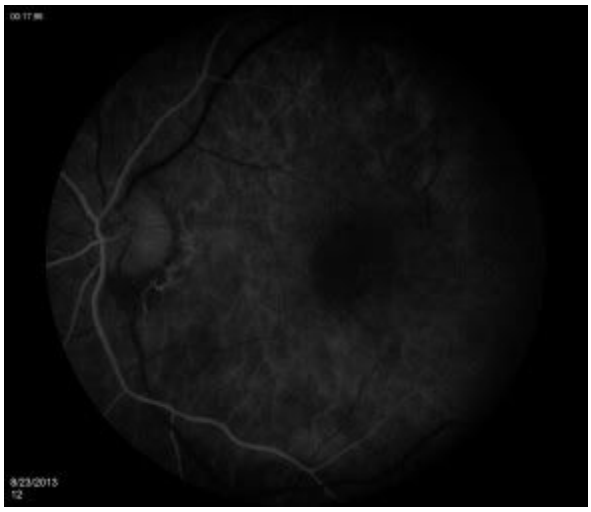
- Juvenile retinoschisis
- Goldmann-Favre disease
- Certain types of RP
- Nicotinic Acid maculopathy
- Phototoxicity
- Antimicrotubule agents

Imaging

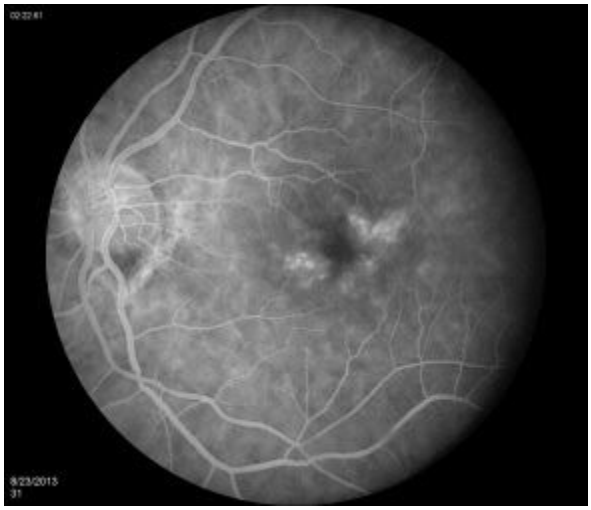
Color Fundus Photography (CFP) depicts intraretinal cysts within the foveal region of the macula in Henle's layer in a honey comb pattern (Figure 1).



Fluorescein Angiography (FA) studies the circulation of the retina and choroid. In the early phase of FA, capillary dilation in the perifoveal region is appreciated (Figure 2).

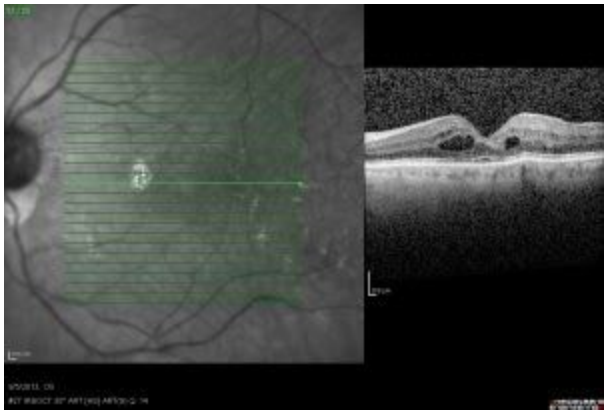


In the late phase (may take 5-15 minutes) of FA, leakage into the cystoid spaces is distributed radially in Henle's layer forming the classic petaloid leakage pattern or expansile dot appearance (Figure 3).



FFA can also show late staining of the optic disc (especially in intermediate uveitis, Irvine Gass syndrome, Birdshot chorioretinopathy) . If leakage is elsewhere, such as in the peripheral retina or near the optic nerve, the appearance looks more honeycomb-like [10][28][29].

Optical Coherence Tomography (OCT) objectively obtains cross-sectional, high-resolution images of the retina. In CME, OCT can be diagnostic through measurement of the retinal thickening with depiction of the intraretinal cystic areas of low reflectivity in OPL [30][31] (Figure 4).



OCT can depict the mechanical forces induced by vitreomacular interface abnormalities, such as VMT or epiretinal membrane (ERM), via a hyperreflective band on the inner surface of the retina [32][33]. In severe CME, subfoveal fluid may be evident on OCT.

Autofluorescence (AF) depicts the health of the RPE and intraretinal cysts appear as hyperautofluorescent.

Retinal Thickness Analyzer (RTA) generates a wide 3D map of the retina.

Management

General treatment

Therapeutic approaches, whether medical or surgical, in treating CME are dependent on the underlying etiology. Most cases are self-limiting within 3-4 months. If CME persists then medical or surgical therapy is warranted.

Medical therapy [24]

NSAIDS – Topical or systemic indomethacin inhibits cyclooxygenase enzyme that decreases the production of prostaglandins. Ketorolac tromethamine 0.5%, indomethacin 1%, nepafenac 0.1%, bromfenac 0.07%, and diclofenac 1% are used postoperatively for aphakic or pseudophakic CME [34][35].

Corticosteroids – Topical, periocular, systemic, intravitreal injection or implant corticosteroids inhibit phospholipase A2 that consequently inhibits prostaglandin and leukotriene production. Steroids specifically help in uveitic macular edema. Intravitreal triamcinolone reduces fluid accumulation by stimulating endogenous adenosine signaling in Muller cells and decreasing VEGF production [36][37]. There are currently four corticosteroid-based intravitreal implants: dexamethasone biodegradable implant, helical triamcinolone acetonide implant, fluocinolone acetonide implant, and an injectible version of the fluocinolone acetonide implant. Well-known side effects of steroid injection include glaucoma and cataract formation [38]. Triamcinolone acetonide can be given through various routes in CME- intravitreal, subtenon, peribulbar/trans-septal/orbital floor.

Carbonic anhydrase inhibitors (CAIs) – CAIs alter the polarity of the ionic transport systems in the RPE moving fluid away from the intracellular spaces [39]. CAIs are helpful in paclitaxel and docetaxel induced CME [40][41] and RP induced CME [42].

Anti-VEGF agents – Pegaptanib (anti-VEGF 165 RNA aptamer), ranibizumab (antibody fragment), and bevacizumab (full antibody) act by decreasing vascular permeability from disrupted endothelial cells. Marked reduction in retinal thickness and fluid accumulation has been noted in various studies with a significant improvement in visual acuity with minimal side effects [43][44][45][46][47].

Pharmacologic vitreolysis agents – Chondroitinase, dispase, hyaluronidase, plasmin, and microplasmin induce a posterior vitreous detachment to relieve CME from VMT [48][49][50][51]. Microplasmin is currently the agent that shows greatest promise with its stability, patient tolerance, and ease of storage and administration. Phase II trial has shown that a 125 µg dose repeated three times released VMT in 58% of patients one month after injection [52][53][54]. Phase IIb trial has shown that intravitreal injection of 125 µg seven days prior to vitrectomy resolved VMT in 28% of patients [55]. Phase III trial has shown that intravitreal injection of 125 µg for treatment of VMT associated with subjective visual dysfunction showed improvement of the adhesion [56].

Surgery

PPV can help to relieve macula edema due to tractional or nontractional components, especially when refractory to medical therapy. The Vitrectomy-Aphakic-Cystoid Macular Edema Study, a prospective, multicenter study of patients with chronic aphakic CME, showed statistically significant improvement in visual outcomes following vitrectomy [57].

Tractional components can be addressed by releasing the posterior hyaloid in VMT or conducting an internal limiting membrane peel of an ERM. Specifically, PPV for the tractional component of VMT

causing CME secondary to diabetes has been shown to improve macular edema in 80-92% of patients [58][59]. Harbour et al. demonstrated that vitrectomy done on vitreous incarceration in the anterior segment and pseudophakic macular edema resulted in improvement in visual acuity in all patients [60]. Though internal limiting membrane peeling in CME secondary to diabetes, central retinal vein occlusion (CRVO), uveitic macular edema, and RP has shown anatomical improvement, visual acuity results are inconclusive [61][62][63][64][65][66][67][68][69][70][71][72]. Neodymium yttrium aluminum garnet (Nd:YAG) laser can also help to relieve tractional components, such as vitreous adhesions to iris.

Nontractional components are addressed by theoretically clearing the inflammatory factors when undergoing PPV [73][74]. However, one study has shown that high vitreous levels of VEGF in CRVO patients correlated with less improvement in visual acuity after vitrectomy, suggesting that high VEGF levels may be associated with ischemia and permanent photoreceptor damage [75]. However, one study showed an increase in VEGF levels in branch retinal vein occlusion (BRVO) patients correlated with an improvement in visual acuity after vitrectomy [76]. Furthermore, studies have shown that oxygen in the posterior segment and the rate of oxygen exchange in the vitreal cavity is increased after PPV [77][78][79][80][81][82]. Specifically, PPV for nontractional components causing CME secondary to diabetes and uveitic macular edema has resulted in inconclusive data on improvement in visual acuity [83][84][85][86][87][88]. Pendergast et al. demonstrated that vitrectomy in pseudophakic CME without any tractional component showed an improvement in visual acuity [89].

Side effects of vitrectomy include cataract, retinal detachment, vitreous hemorrhage, and a rise in intraocular pressure.

Prognosis

CME is usually self-limiting and spontaneously resolves within 3-4 months. Depending on the etiology, resolution of the edema may be helped via medical or surgical options. If the edema is chronic (more than 6-9 months) permanent damage to the photoreceptors with retinal thinning and fibrosis can occur

Additional Resources

- Porter D, Vemulakonda GA. Macular Edema. American Academy of Ophthalmology. EyeSmart® Eye health. https://www.aao.org/eye-health/diseases/macular-edema-5. Accessed March 18, 2019.

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