Post-traumatic Uveitis and Post-operative Inflammation

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Scott M. Barb

Traumatic Uveitis

Etiology

Trauma to the globe and its contents can occur in many forms including chemical, radiation, electrical, blunt force, and penetrating or perforating injury with and without intraocular foreign body. The mechanism for which ocular trauma leads to uveitis in most cases is thought to be related to disruption of the microvasculature within the uveal tissue leading to infiltration of leukocytes and other pro-inflammatory mediators into the tissue or chamber [1, 2]. There is growing belief that those with autoimmune disease and other inflammatory disorders may be predisposed to an increased risk or degree of inflammation than the normal population after ocular trauma [3, 4].

Epidemiology

The overall incidence of uveitis as a whole is reported to be 52.4/100,000 person/years with a prevalence of 115.3/100,000 persons [5]. In most epidemiological studies of uveitis, traumatic uveitis is excluded from analysis with other exogenous causes. However, in evaluations of large groups of patients with uveitis, nonsurgical traumatic uveitis appeared to represent around 0.5–4.8 % of the population with most cases presenting as anterior uveitis [2, 6, 7].

Over 2.4 million eye injuries are reported to occur annually in the United States alone and the overwhelming majority are in male patients [8]. Large studies evaluating eye injuries due to all mechanisms show that isolated traumatic uveitis is seen in around 0.5 % of cases [9]. However, uveitis often presents in the context of multiple other concomitant injuries and has been much more prevalent in studies looking specifically at severe injuries and those conducted in other parts of the world. It is possible that many cases of traumatic uveitis are overlooked due to concurrent hyphema or other more significant visually threatening injury.

In a study of electrical-burn patients, 9 % of patients were shown to have unilateral iritis [10]. Studies evaluating blunt traumatic injury to the eye demonstrate the rate of uveitis to be as high as 10 % [11]. The incidence of uveitis is not well defined in penetrating or perforating eye injury. However, there is certainly an increased likelihood of ocular inflammation and infection with the presence of an intraocular foreign body [12–14]. Perhaps, more concerning is this increased risk of infection in open globe injury. The risk of

S.M. Barb (✉)
Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114, USA
e-mail: scott_barb@meei.harvard.edu

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endophthalmitis in open globe injury is estimated to range from 3.3 to 30 % and increase to 1.3–61 % in those with intraocular foreign bodies [15, 16]. Epidemiological information regarding the other mechanisms of injury discussed above remains limited.

Clinical Presentation

History and physical examination of the face and eye often give clues to the type of trauma a patient has sustained. The patient will often give a history of work (metal, construction, house), assault, sports/motor vehicle injury, or fall that help the examiner understand the mechanism and force of injury.

Clinical Signs

Lacerations, ecchymoses, and edema of the surrounding face and eyelids often coincide with blunt or penetrating trauma. Orbital fractures are often commonly seen in blunt force injury involving the eye [17]. Burns of the surrounding adnexal structures often give clues to the type of burn a patient has endured.

However, slit lamp examination of the eye is always necessary to know the extent of ocular damage sustained by injury. Burns of the conjunctiva and cornea may be seen with or without fluorescein staining in chemical and electrical burns. Corneal and conjunctival abrasions may occur in the setting of both blunt and penetrating trauma. Corneal and conjunctival lacerations often occur in the setting of penetrating or sharp injury. Hyperemia of the conjunctiva and increased tearing/discharge are commonly seen in all types of injury involving the conjunctiva and cornea. Microhyphema or hyphema are often seen with blunt ocular trauma but may also be seen in penetrating trauma. Anterior chamber inflammation (flare, cell, or cell and flare) may often be seen with or without accompanying pigmented cell. Damage to the angle structures (angle recession or cyclodialysis) occurs more commonly with blunt trauma [18, 19]. Zonular damage and lens dislocation can be seen in both blunt and penetrating trauma. Vitreous hemorrhage and traumatic posterior vitreous detachment may occur in the setting of blunt and penetrating trauma. Retinal commotio or tears as well as choroidal rupture may also be seen in the setting of significant blunt trauma [20].

Open globe injury may occur with direct blunt rupture or penetrating/perforating trauma to the eye. Inspection should always be paid for intraocular foreign body especially in the setting of penetrating ocular injury. The severity of inflammation and toxicity seen with foreign bodies depends on the substance with severe toxicity typically seen in iron, copper, and vegetable matter, mild inflammation in nickel, aluminum, and zinc, and minimal to no inflammation with inert substances such as gold, glass, plastic, and stone [21, 22].

Clinical Symptoms

Patients often experience a number of clinical symptoms in the setting of traumatic uveitis. Most common among these symptoms is general discomfort, which can be seen with any type of trauma. Photophobia is also quite common especially in the setting of corneal disruption or anterior chamber reaction (pigmented or non-pigmented cell). Flashes and floaters may be experienced in the setting of vitreous hemorrhage, posterior vitreous detachment, and acute retinal break. And of course, blurred vision may occur in the setting of all traumas involving the eye.

Diagnosis

The diagnosis of ocular inflammation after trauma is often determined by history and physical examination along with the presence of inflammatory non-pigmented cells in the anterior chamber or vitreous cavity. Ancillary testing is often not necessary unless view to the fundus is limited by cataract or vitreous hemorrhage or there is concern for ruptured globe, intraocular foreign body, or orbital fracture. In these cases, B scan ultrasonography or CT scan may be indicated to determine the extent or cause of inflammation and ocular damage [23, 24].

Treatment

Treatment is directed at removing the cause of inflammation, treating the inflammation itself, and preventing any side effects related to prolonged inflammation. In the cases of radiation, electrical, and most blunt injuries, the inflammatory stimuli are typically removed at time of presentation and thus anti-inflammatory topical medication such as prednisolone may be started and titrated to the degree of inflammation present. In addition, topical cycloplegics such as cyclopentolate are often used to prevent long-term side effects of prolonged inflammation such as formation of synechiae and to reduce photophobia.

For those cases involving chemical injury, the eye must be irrigated to achieve a physiologic pH with careful examination to remove any chemical particulate matter. In these cases there are often significant corneal or conjunctival epithelial defects and the balance of treating inflammation and allowing appropriate healing of the defects must be weighed when deciding to start topical steroids [25, 26].

Finally, the main goal of treatment in cases of penetrating or perforating intraocular injury with and without intraocular foreign body is to close the eye and remove any intraocular foreign body [27]. Post-operatively, these patients are often started on topical steroid and cycloplegic medication to help control the acute inflammatory reaction and eventually tapered off while under close observation for rebound inflammation. These patients must be followed regularly given the increased risk for endophthalmitis and sympathetic ophthalmia [28].

Prognosis

The long-term outcomes of patients with isolated traumatic anterior uveitis or iritis are often excellent. However, visual outcomes may be limited by concurrent injury to other parts of the eye. In the case of blunt injury, there is a possibility of retinal and optic nerve injury or eventual cataract formation, which may limit vision [20, 29]. In addition, significant blunt injury can also result in open globe injury. Chemical injury may result in corneal scarring obstructing the visual axis [26]. Electrical and radiation injury may result in the development of cataract [30]. Finally, penetrating or perforating open globe injury limits vision in a number of ways depending on the extent of ocular injury, the presence of an intraocular foreign body, time to primary closure, presenting visual acuity, and risk of infection [31–33].

Surgical Trauma and Post-operative Inflammation

Etiology

Inflammation in the setting of surgery is a common phenomenon and a normal/expected response to the tissue trauma induced by the surgical intervention. All ophthalmic procedures including even the most standard such as cataract surgery, vitreoretinal surgery, lasers, and injections often result in post-operative inflammation.

Cataract Surgery

There have been major advances in the field of cataract surgery over the last few decades with a continued shift to small clear corneal incisions and phacoemulsification. The goal of this shift is to improve surgical times and outcomes, which includes minimizing energy usage and tissue damage to lessen post-operative inflammation and resultant side effects [34–36].

Anterior chamber inflammation, as demonstrated by the presence of cell and flare, is common after cataract surgery. Other than the surgery itself, there are a number of etiologies that may cause more severe or prolonged ocular inflammation. These include surgical complications, malpositioned intraocular lens implants, retained nuclear material, reactivated uveitis, endophthalmitis, uveitis–glaucoma–hyphema (UGH) syndrome, and retained foreign body or toxic solution in the anterior chamber [37–41].

Patients who developed more significant post-operative inflammation are at greater risk of

cystoid macular edema, glaucoma, and compromising a technically successful surgical procedure. Patients who develop post-operative macular edema are often asymptomatic aside from blurry vision. The diagnosis is often established by imaging studies such as optical coherence tomography and fluorescein angiography [42].

Studies suggest that clinical CME related to post-operative inflammation can be seen in as many as 1–2 % of all uncomplicated cataract surgeries [43]. However, the rate of CME is higher in complicated surgical cases and those with pre-existing diabetic retinopathy and uveitis [44]. A ruptured posterior capsule increases the risk of CME to 10–20 % and retained nuclear fragment increases the risk to as much as 29 % [45, 46].

The pathophysiological mechanism for post-operative inflammation resulting in CME is related to the production of prostaglandin analogs and other pro-inflammatory molecules leading to the increased permeability of retinal vessels [47].

Although most cases of post-operative inflammation respond very well to topical therapy, there are resistant cases that require periocular, systemic, or intravitreal (injection or implant) steroids. In fact, infrequently, vitrectomy may aid in relieving vitreous adhesions and reduce vitreomacular traction leading to macular edema [48–51]. Additional treatment goals of post-operative inflammation due to a specific source other than the surgery itself include fragment removal in cases of retained nuclear material, treatment of infection in endophthalmitis, improved or more intense perioperative control of previously existing uveitis, and repositioning or lens exchange of the intraocular lens in cases of UGH syndrome [39, 40, 52–54].

Vitreoretinal Surgery

Similar to cataract surgery, cystoid macular edema (CME) can occur in the post-operative setting of vitreoretinal surgery. The mechanism for CME related to post-operative inflammation in vitreoretinal surgery is similar to that of cataract surgery described above [55].

However, the incidence of CME related to post-operative inflammation alone is difficult to discern since many of these patients have existing CME or cause for CME at the time of surgery including diabetic retinopathy, vein occlusion, and retinal traction. Perhaps, the most effective way to evaluate the incidence of CME due to post-operative inflammation alone is in a subset of patients undergoing vitrectomy for a benign condition such as floaters with a low likelihood of pre-operative CME. Studies evaluating these patients have shown CME in as many as 5.5 % of cases but many reports show no patients developing CME [56–58]. The incidence of CME is higher in patients undergoing vitreoretinal surgery of longer duration with more instrumentation including laser or tamponade agent [59, 60]. In addition, patients undergoing cataract surgery after vitrectomy are at an increased risk of post-operative CME as high as 26 % [61]. However, it is difficult to attribute the degree of CME due to post-operative inflammation alone since many of these patients undergoing more significant surgery often have pre-existing CME.

The diagnosis of CME after vitreoretinal surgery is mostly reliant on clinical exam and OCT. Treatment paradigms are similar to cataract surgery with evidence suggesting the combined use of topical steroid and NSAID achieves the best visual outcomes and resolution of CME [43]. In addition, it is common for patients to receive periocular or intravitreal steroids at the time of surgery especially in patients with pre-existing uveitis [62, 63].

Similar to cataract surgery, there are other causes for more extensive and prolonged post-operative inflammation after vitrectomy including retained tamponade agent, endophthalmitis, pre-existing uveitis, and sympathetic ophthalmia [64, 65]. The incidence of endophthalmitis and sympathetic ophthalmia after vitrectomy is quite low and estimated to be 0.07 % and 0.015–0.125 %, respectively [66–68]. Despite this increased risk for sympathetic ophthalmia, the number of reported cases of sympathetic ophthalmia after vitrectomy is quite small especially with sutureless 23- and 25-gage technique.

However, the role of vitrectomy in the setting of uveitis and post-operative inflammation must not be forgotten. In cases of retained dropped nuclear fragments, endophthalmitis, or uveitic diagnostic dilemmas, vitrectomy is often crucial for diagnosis and treatment [69–71].

Lasers

Mild inflammation after anterior and posterior segment laser is quite common [72, 73]. The mechanism of inflammation is similar to other surgical interventions as a result of alterations in the blood–eye barrier and production of pro-inflammatory cytokines from the laser-induced tissue damage [74, 75].

These patients typically present with anterior chamber or vitreous cell and have minimal to no discomfort. The diagnosis is often made from slit lamp exam alone. The inflammation typically peaks within the first few days post procedure. The treatment for post-operative inflammation is typically observation versus topical steroid depending on the extent of inflammation. Patients often have a quick response to these medications with minimal need for long-term use [73].

Clinically evident anterior chamber inflammation is present in 23 % of patients with primary open angle glaucoma after undergoing argon laser trabeculoplasty (ALT). This incidence is much higher in patients with pseudoexfoliation and pigmentary glaucoma [73]. As the use of selective laser trabeculoplasty (SLT) has become more common, the incidence and degree of inflammation after laser trabeculoplasty has decreased dramatically. This is likely due to the reduced tissue damage and overall energy use in SLT [76]. In fact, some studies have shown little to no clinical inflammation in eyes treated with SLT [77].

The use of cyclophotocoagulation is becoming more common for advanced or refractory glaucoma. Mild inflammation is expected given the targeted destruction of uveal tissue that occurs during this procedure. However, clinically significant inflammation is rare even in patients with inflammatory glaucoma especially with the targeted use of endocyclophotocoagulation [78, 79]. However, sympathetic ophthalmia has been rarely reported after cyclophotocoagulation [80].

Laser peripheral iridotomy (LPI) is one of the most common anterior segment laser procedures. Mild anterior chamber inflammation is often inevitable. Those with pre-existing uveitis or darkly pigmented irides are more prone to this inflammation and this has a direct impact on the rate of maintained patency of the iridotomy [81]. Iridotomies are commonly created using YAG laser or a combination of argon and YAG laser. YAG laser typically results in less inflammation due to the overall reduction in total energy used. Periprocedural topical steroids are often used but are of questionable proven benefit. LPI has been rarely shown to lead to recurrence of herpetic keratouveitis in several patients [82].

Posterior capsular opacification (PCO) occurs in nearly 33 % of pseudophakic patients after 5 years. Prolonged post-operative inflammation after cataract surgery appears to be a possible risk factor for PCO [83]. Studies have shown an increased risk of PCO in uveitic patients undergoing cataract surgery but this finding is confounded by the younger age of most of these patients [84]. Minimal inflammation is expected after YAG capsulotomy, but CME related to inflammation has been shown to occur in as many as 1 % [85]. Persistent inflammation (>6 months) in the anterior chamber and vitreous has been shown to occur in 0.4 and 0.7 % of patients after YAG capsulotomy, respectively [86]. This is often responsive to topical steroids. However, the more significant impact of mild inflammation is IOP rise after capsulotomy. This is often treated or prevented with use of a periprocedural IOP-lowering medication such as apraclonidine [87]. Interestingly, a noted but rare complication of YAG capsulotomy is the release of sequestered capsular bacterial organisms leading to severe inflammation and endophthalmitis [88].

Focal laser and panretinal photocoagulation (PRP) remain the most commonly used posterior segment lasers despite the increasing use of intravitreal anti-VEGF therapy. Retinal laser burns are known to incite inflammatory activity by disrupting the immune privilege of the eye

and increasing the permeability of the blood–aqueous barrier [89]. In fact, PRP has been shown to increase pro-inflammatory cytokines in proliferative diabetic patients and actually temporarily worsen macular edema as a result [90, 91]. Aqueous flare has been reported to persist as long as 90 days after routine PRP in patients with diabetes [92]. Despite this fact, topical anti-inflammatory medications are not routinely used after focal laser or PRP.

Intravitreal Injections

The use of intravitreal injections has increased dramatically in the last decade due to the proven efficacy of anti-VEGF (vascular endothelial growth factor) medications in diabetic retinopathy and macular edema related to neovascular age-related macular degeneration (AMD) and retinal vein occlusion (RVO) [93, 94].

Inflammation in the setting of intravitreal injection can occur in the form of a sterile reaction or infectious endophthalmitis. Sterile endophthalmitis is defined as any acute intraocular inflammation without infection that resolves without antibiotic treatment. The incidence of sterile endophthalmitis after injection is reported to be between 0.033 and 2.9 % [95–97]. However, the incidence of infectious endophthalmitis appeared to also vary slightly by technique and was reported to be between 0.0075 and 0.2 % [98, 99].

The etiology of a sterile inflammatory reaction due to intravitreal injection of anti-VEGF agents remains unclear. Several theories have been proposed such as improper storage protocol, increased immune response after repeated injections, and endotoxin contamination during production. Despite clusters of these sterile reactions being explained by improper storage or production, the sporadic incidence cannot be fully accounted for by these mechanisms [100]. The increased immune response theory provides an intriguing explanation since repeated injections are often necessary for many patients. However, studies have shown that history of prior injections or inflammation does not increase the risk of future sterile reaction or worsening of current inflammation [96, 97].

It may be difficult to differentiate between sterile and infectious endophthalmitis but diagnostic clues are often available in the clinical presentation. Sterile endophthalmitis usually presents slightly earlier after injection (<1 day to 1 week) [101, 102]. The sterile group often presents with complaints of blurred vision and floaters. Also there is usually less severe anterior chamber and vitreous reaction as well as less pain [103, 104]. Typically, the duration of inflammation is also shorter in sterile endophthalmitis (2–10 weeks) but this difference is unreliable given that duration of infectious endophthalmitis is highly variable with treatment [96, 102].

Management varies quite markedly and includes topical medications, intravitreal antibiotics, and even vitrectomy. Comparisons between patients believed to have sterile endophthalmitis show similar results between each of these modalities of treatment in respect to duration of inflammation [100, 105]. However, this data is of uncertain value as those with more significant inflammation typically receive more aggressive treatment confounding outcomes. Therefore, many studies suggest that it is reasonable to maintain a low threshold for vitreous tap and inject of antibiotics especially with significant pain and inflammation [102]. Perhaps, the greatest difference between these two groups is prognosis with the sterile group often returning to baseline visual acuity regardless of treatment and the infectious group often having significantly reduced visual acuity.

Despite the relatively small risk of inflammation related to intravitreal injection, it must not be forgotten that intravitreal injections are used to treat ocular inflammatory conditions or the consequences of inflammation. This includes the use of steroid implants to treat uveitis and refractory macular edema [106, 107].

Conclusion

Multiple mechanisms of injury can lead to intraocular inflammation. The greater the associated tissue trauma is usually correlated with a

more robust ocular inflammatory response. The most commonly employed treatment for the majority of these cases is topical corticosteroids.

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