Lens-Induced Uveitis

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Core Messages

- Intraocular inflammation due to lens protein exposure.
- Phacoantigenic ("phacotoxic") uveitis represents mild to moderate non-granulomatous anterior uveitis that usually presents subacutely.
- Phacoanaphylactic endophthalmitis produces an acute, severe granulomatous inflammation involving both the anterior and posterior segments but does not produce the same degree of pain as infectious endophthalmitis.
- May elevate IOP due to collection of inflammatory debris or lens particles within the trabecular meshwork.

89.1 Definition

Lens-induced uveitis (LIU), which is synonymous with lens-associated uveitis (LAU), has been traditionally thought to result from immune reactivity directed at lens proteins following disruption of the lens capsule, resulting in the production of intraocular inflammation. Capsular disruption may be spontaneous, traumatic, or surgical in nature.

The severity and location of inflammation associated with this condition can vary and has led to the creation of several terms to define

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"distinct" LIU conditions. Phacoantigenic (formerly phacotoxic) uveitis comprises a mild to moderate inflammatory reaction to lens protein, while phacoanaphylactic endophthalmitis represents severe LIU. The incidence of these entities is unknown.

89.2 Manifestations

89.2.1 General Disease

This disorder is limited to the eye.

89.2.2 Ocular Disease

The presentation of LIU can be quite heterogeneous. The time of onset following capsular disruption, severity of symptoms, degree of inflammation, and location of inflammation can all vary widely. The clinician should carefully elicit any history of recent intraocular surgery and ocular trauma. The severity of symptoms will be determined by the degree of inflammation present and include eye pain or discomfort, redness, irritation, blurry vision, and photophobia. Headache may also be present due to ciliary body spasm or rapidly evolving ocular hypertension. Careful examination should be performed at the slit lamp, and any suggestion of capsular disruption—such as capsular wrinkling in the case of a mature lens or capsular rent from trauma or intraocular surgery—should be noted. Detailed inspection should be conducted for retained lens fragments following cataract surgery. If none are clearly visible, gonioscopy should be performed to ensure that there are no occult lens chips within the angle.

In cases of less severe LIU, previously termed phacoantigenic uveitis, the patient may experience mild to moderate photophobia and diminution of vision. Slit-lamp biomicroscopy will reveal a nongranulomatous uveitis with mild cell and flare present in the anterior chamber. Rarely, vitreous cells may be found. In an obvious case, a disrupted lens capsule, opacified lens material, and hypopyon can be seen. If uveitis persists for a long period of time, posterior synechiae may form.

Phacoanaphylactic endophthalmitis, representing the severe form of LIU, is a panophthalmitis that produces significant vision loss and inflammation. A granulomatous uveitis is seen clinically, manifesting with "mutton-fat" keratic precipitates, a vigorous anterior chamber reaction with hypopyon, posterior synechiae, and vitreous cells.

Although the optic nerve, choroid, and retina are usually unaffected in LIU, retinal vasculitis affecting both the arterioles and venules has been reported to occur. In this particular case, the vasculitis was localized to the area immediately surrounding a fragment of retained lens lying on the retina [1]. LIU has also been reported to occur following Nd:YAG capsulotomy [9].

89.3 Etiology and Pathogenesis

LIU was thought to occur following exposure of lens protein to the immune system. It was believed that the crystalline lens was an immune-privileged site; therefore, the generation of an inflammatory response required compromise of the anterior capsule, be it from natural capsule and lens maturation, trauma, or intraocular surgery. Once disruption of the capsule occurred, lens antigen could trigger an immune response and produce intraocular inflammation.

Work by Rahi and associates on an experimental model of LAU indicated that animals are tolerant to heterologous gamma-crystallins and an immune response can only be generated when using either complete or incomplete Freund's adjuvant [12]. When using homologous lens antigen, immunofluorescence and immunoperoxidase methods indicated an IgG-mediated response; however, other classes of immunoglobulins could not be excluded [11]. Immunoglobulins of the IgG class were also associated with experimental LAU in an autologous lens protein model, but like in the heterologous model, other classes could not be excluded [13]. These reports indicate that lens protein is antigenic and that autoimmunity is possible and might play a role in LAU but also suggest that lens tolerance is possible under normal conditions. Interestingly, earlier work in experimental LAU suggested a greater role for humoral rather than cellular response in autoimmunity;

however, a more recent report indicated a greater cellular immunity component [3, 7].

Although the exact mechanism by which the immune system produces LAU is unclear, work by Marak on experimental LAU has demonstrated that lens capsule rupture is required to produce the granulomatous inflammation that is similar to human disease [8]. The histopathologic findings of granulomatous LAU were not seen in rat eyes that had no capsular disruption. In work by Gelderman and associates, alphaB-crystallin knockout mice were subjected to thermal cautery to the cornea, treatment with lipopolysaccharide (LPS) injection, sodium iodate, irradiation, or capsulotomy [2]. Only those mice with capsulotomy developed inflammation in the treated eye; the fellow eye remained quiet.

From both a clinical and pathologic standpoint, LAU is a spectrum. In severe LAU, or phacoanaphylactic endophthalmitis, a variety of cell types are present including PMN leukocytes, and both macrophages and giant cells engorged with phagocytosed lens material. The PMNs and mononuclear phagocytes invade the lens, and both giant cells and PMNs can be found surrounding the lens or lens fragments, within the iris, and within pupillary membranes that often form (Fig. 89.1) [6]. The classic description includes three zones of inflammation centered around the lens: neutrophils invading the lens

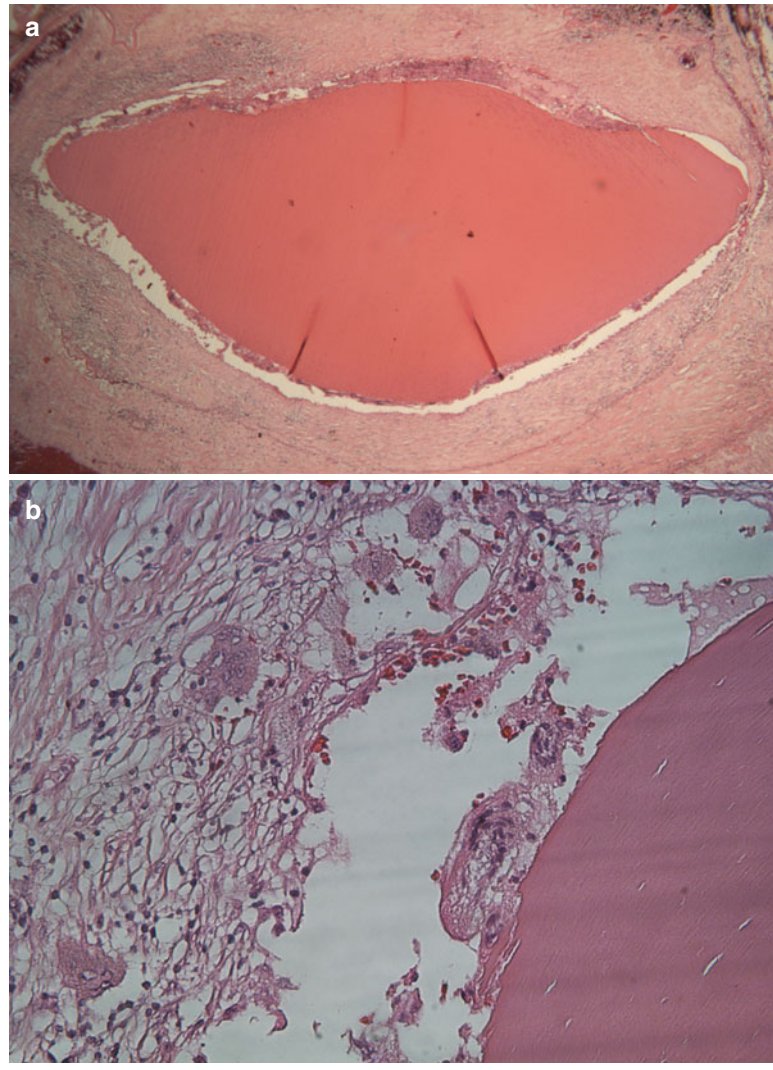

Fig. 89.1 Phacoanaphylactic endophthalmitis. (**a**) An intense inflammatory reaction is noted to surround the crystalline lens consisting of polymorphonuclear leukocytes (hematoxylin and eosin, 100×). (**b**) Note the presence of giant cells adjacent to the lens seen under higher magnification (hematoxylin and eosin, 400×) (Images courtesy of Narsing A. Rao, M.D.)

material (inner); monocytes, macrophages, epithelioid cells, and/or giant cells surrounding a lens capsule disruption (middle zone); and fibrotic or granulation tissue infiltrated with nongranulomatous inflammation and plasma cells (outer zone).

Less severe cases include the phacotoxic response and lens-associated glaucoma. In the phacotoxic response, histopathologic examination has revealed an immune response localized primarily to the anterior chamber [5]. Characteristics of this form of LIU include copious plasma cells within the iris, lens material in the anterior chamber and/or anterior vitreous, and eosinophilic macrophages engorged from phagocytosed lens material. A polymorphonuclear cell response occurs; however, a mononuclear cellular infiltrate predominates. In phacolytic glaucoma, lens protein leaks through a macroscopically intact capsule and is phagocytosed by macrophages. Subsequently, these macrophages block the trabecular meshwork, thereby obstructing aqueous outflow, resulting in ocular hypertension.

89.4 Diagnosis

Despite the fact that LIU is a well-known entity, it still remains under-recognized and often goes undiagnosed. The medical and ophthalmic history and a thorough examination remain the best means by which this condition can be identified and properly treated. Patients who are poor historians often make this a challenging diagnosis; thus, the clinician's index of suspicion should remain high in those cases involving traumatic injuries or ocular surgical intervention. In mild to moderate cases, the area of lens capsule rupture or retained lens particle may be seen, allowing for the simple diagnosis of LIU; however, in cases simulating endophthalmitis, B-scan ultrasonography may be helpful in visualizing a posteriorly located lens fragment.

Fine-needle aspiration of the anterior chamber has also been suggested as an additional means to support the diagnosis, though its utility has not been well established [4, 10].

89.5 Differential Diagnosis

Because LIU is a spectrum of disease, the presentation may be somewhat heterogeneous. Mild to moderate cases can produce anterior chamber reactions with varying degrees of cyclitis that may resemble the uveitis associated with trauma, HLA-B27 disease, and autoimmune conditions. More severe disease may mimic infectious endophthalmitis or sympathetic ophthalmia (Table 89.1).

Distinguishing severe LIU, or phacoanaphylactic endophthalmitis, from infectious endophthalmitis can be challenging. Both conditions may present with a vigorous anterior chamber reaction including keratic precipitates, dense cell and flare, hypopyon, and fibrinous membranes. Care must be taken to evaluate the posterior vitreous; copious vitreous cells is more closely associated with infectious disease. Additionally, the patient with infectious endophthalmitis will often experience more pain than one with severe LIU. If the view to the vitreous is obscured by corneal edema or other opacities, evaluation by B-scan ultrasonography is quite helpful; a hyperechogenic mass in the posterior segment may represent a lens fragment leading to the diagnosis of LIU. Interestingly, cases of *Propionibacterium acnes* infection are more likely to mimic mild to moderate cases of LIU, and care must be taken to examine the lens implant and/or remnant capsule for a white plaque that has been described in such cases.

Fortunately, sympathetic ophthalmia (SO) is quite rare. While LIU is usually a unilateral process, SO is typically a bilateral condition with inflammation beginning in the traumatized eye followed by a "sympathetic" response in the fellow eye.

89.6 Treatment

Cases of LIU can be "cured" with removal of the inciting lens antigen. In cases in which the lens is essentially intact but the anterior capsule is torn, careful cataract extraction by either phacoemulsification, extracapsular, or intracapsular technique can be employed. If LIU developed following cataract extraction, care should be taken to

Table 89.1 Differential diagnoses for lens-induced uveitis

	LIU	SO	*P. acnes* endophthalmitis	HLA-B27-associated uveitis	JIA	FUS	HSV/VZV iridocyclitis	Syphilitic uveitis	TB uveitis	UGH	PSS
Laterality	Unilateral	Bilateral	Unilateral	Alternating	Bilateral	Unilateral	Unilateral	May be bilateral	May be bilateral	Unilateral	Unilateral
Affected segment	Anterior	Anterior and posterior	Anterior and posterior	Anterior	Anterior	Anterior	Anterior	Anterior and posterior	Anterior and posterior	Anterior	Anterior
Etiology	Capsular injury	Penetrating trauma and subsequent uveal antigen sensitization	*P. acnes*, after ECCE	Autoimmune	Autoimmune	Unknown, prob. rubella	HSV or VZV	*T. pallidum*	*Mycobact. tuberculosis*	Mechanical irritation of the iris	Unknown, probably CMV
Course	Lens removal curative	Chronic, recurrent	Indolent, need to rule out other postoperative infectious etiologies	Acute, recurrent	Recurrent, indolent	Chronic, insidious	Acute, recurrent	Treatable disease	Treatable disease	Acute or chronic, may require IOL removal	Acute, recurrent
Diagnosis	Visualization of lens fragment	History of trauma	Characteristic plaques in capsular bag, time course	HLA-B27+-associated spondyloar-thropathies	Quiet eye, pauci- or polyarticular presentation, ANA+	Clinical diagnosis	Prior or concurrent corneal/external disease, iris atrophy with TI	Positive titers for *T. Pallidum*	Presumed diagnosis with positive CXR/CT and/or tuberculin testing	Rule out other infectious/autoimmune etiologies; presence of AC-IOL or PC-IOL	Elevated IOP, clinical exam, diagnosis of exclusion

LIU lens-induced uveitis, *SO* sympathetic ophthalmia, *P. acnes Propionibacterium acnes*, *JIA* juvenile idiopathic arthritis, *FUS* Fuchs' uveitis syndrome, *HSV* herpes simplex virus, *VZV* varicella zoster virus, *T. pallidum Treponema pallidum*, *TB* tuberculosis, *UGH* uveitis-glaucoma-hyphema syndrome, *ECCE* extracapsular cataract extraction, *IOL* intraocular lens, *CXR* chest X-ray, *AC* anterior chamber, *PC* posterior chamber, *PSS* Posner-Schlossman syndrome, *TI* transillumination

remove the remaining fragments. For those cases associated with dislocated lens material to the vitreous cavity, pars plana vitrectomy with phacofragmentation is required. In any event, removal of the lens material will result in resolution of the immune response.

The use of topical corticosteroids and cycloplegics may be considered to aid in reduction of inflammation and patient comfort. Additionally, patients may have elevated intraocular pressure which may need management with antiglaucoma medications tailored to the severity of patient symptoms and the degree of ocular hypertension.

89.7 Prognosis

If diagnosed and treated in a timely fashion, LIU has a favorable prognosis; however, if the inciting lens antigen is not removed and the inflammation persists, complications of chronic uveitis can be observed. Corneal edema and glaucoma may develop and both pupillary and cyclitic membranes may form. Retinal detachment and cystoid macular edema may also limit vision. Hypotony can result in phthisis and the eye may become blind and painful with the eventual need for enucleation.

Take-Home Pearls

- A history of trauma or ocular surgery can often be elicited.
- Medical/ophthalmic history and a thorough examination can lead to early diagnosis and treatment.
- Do perform gonioscopy to evaluate for occult lens fragments in the angle.
- Removal of the lens or lens fragment(s) is "curative."
- Failure to diagnose and properly treat LIU may lead to profound vision loss and/or phthisis bulbi.

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