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Allergic and immunologic disorders of the eye

Leonard Bielory, MD, *** and Larry P. Frohman, MD**** Newark, N.J.

ANATOMY: CONJUNCTIVA, LENS, CORNEA, UVEAL TRACT, RETINA, AND OPTIC NERVE

The eye is involved in the entire spectrum of immunologic hypersensitivity reactions, including mast cell, cytotoxic antibody, CICs, and cell-mediated reactions (Table I).¹⁻⁶ The eye, like the skin, is unique in immediately alerting the patient of any dysfunction. The eye is also distinctive in that it permits the direct in vivo visualization of ongoing immunologic processes. Examples of such immunologic processes include the appearance of corneal immune rings reflecting CIC deposition analogous to precipitins in Ouchterlony plates, the development of the Khoudahoust line reflecting lymphocyte migration into the rejecting corneal allograft, and the detection of floaters reflect-

Abbreviations used

CIC:	Circulating immune complexes
AC:	Allergic conjunctivitis
VKC:	Vernal keratoconjunctivitis
AKC:	Atopic keratoconjunctivitis
GPC:	Giant papillary conjunctivitis
WG:	Wegener's granulomatosis
TA:	Temporal arteritis
HSV:	Hypersensitivity vasculitis
KD:	Kawasaki's disease
BD:	Behçet's disease
CS:	Cogan's syndrome
PAN:	Polyarteritis nodosa
ESR:	Erythrocyte sedimentation rate
SLE:	Systemic lupus erythematosus

From the Departments of *Medicine, **Ophthalmology, and ***Neurosciences, University of Medicine and Dentistry, New Jersey Medical School, Newark, N.J.

Reprint requests: Leonard Bielory, MD, Director, Division of Allergy and Immunology, Department of Medicine, UMDNJ-New Jersey Medical School, 185 South Orange Ave., MSB E-583, Newark, NJ 07130-2714.

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ing "floating" lymphocytes that have migrated into the inflamed uvea comparable to the migration of cells into a Boyden chamber.

The eye is essentially constructed of four layers that are commonly involved in immunologic reactions: (1) the tear fluid and the conjunctiva, providing the primary barrier of the eye against environmental aeroal-

TABLE I. Hypersensitivity reactions of the eye

Category	Recognition component	Soluble mediators	Time course	Cellular response	Clinical example
IgE/mast cell	IgE	Leukotrienes Arachadonates Histamine	Seconds	Eosinophils	AC
			Minutes	Neutrophils Basophils Late phase Eosinophils Lymphocytes	Anaphylaxis AKC VKC
Cytotoxic antibody	IgG	Complement	Hours	Neutrophils	Mooren's ulcer
	IgM		Days	Macrophages	Pemphigus Pemphigoid
Immune complex	IgG	Complement	Hours	Neutrophils	Serum-sickness
	IgM		Days	Eosinophils Lymphocytes	uveitis Corneal immune rings Lens-induced uveitis Behçet's syndrome Vasculitis
Delayed hypersensitivity	T-Cells	Lymphokines Monokines	Days	Lymphocytes	Corneal allograft
	Monocytes		Weeks	Monocytes Eosinophils Basophils	rejection Sympathetic ophthalmia Sarcoid-induced uveitis Vogt-Koyanagi-Hara- da's syndrome

lergens, chemicals, and infectious agents, (2) the collagenous sclera predominately involved in rheumatic (connective tissue) disorders, (3) the highly vascular uvea, primarily involved in inflammatory reactions associated with CIC and cell-mediated hypersensitivity reactions, and (4) the retina, functionally an extension of the central nervous system (Table II).¹⁻⁵ However, mast cell-mediated reactions (e.g., periorbital edema and conjunctivitis) predominate as the most common hypersensitivity responses of the eye caused by the presence of a large number of ocular-associated mast cells.^{2, 3, 6}

The ocular globe has no recognized lymphatic supply but has a unique lymphovascular modification, the uvea (Fig. 1). The uvea comprises a continuous layer of iris, ciliary body, and choroid, with a characteristic highly vascular architecture (blood flow rate of 1.5 L/100 gm of tissue per minute). The ciliary body is the production site of the aqueous humor and is similar to other structures that produce a "filtrate," for example, the renal glomerulus (urine) and the choroid plexus (cerebrospinal fluid) in its tendency toward being a target site for the deposition of CIC.^{7, 8}

Tear fluid is the initial immunologic barrier to the environment. Tears contain a large amount of im-

munologically active proteins and mediators, including secretory IgA, IgG, lactoferrin, lysozyme, histamine, prostaglandins, ceruloplasmin, complement, and cytokines, with a notable paucity of cellular components.⁹⁻¹⁴

In addition, the conjunctival tissue surrounding the globe provides a supplementary barrier to the environment with its rich supply of mucosa-associated lymphoid tissue and mast cells.¹⁵⁻¹⁸ Subepithelial accumulations of lymphoid tissue forming papillary hypertrophy ("cobblestoning") are uncommon in healthy conjunctiva but are a prominent feature in inflammatory and allergic conjunctival conditions affecting the conjunctiva, for example, VKC, AKC, and GPC.^{1-6, 18} In these areas of papillary hypertrophy, there are elongated microvilli with microplacoids and medium-sized lymphocytes, but plasma cells are noticeably absent. The conjunctiva contains a large population of chymase-negative–tryptase-positive mast cells that produce large quantities of leukotriene C₄ similar to that of mucosal-type mast cells found in the bronchial and gastrointestinal-associated lymphoid tissue. However, when the conjunctiva becomes involved in a chronic inflammatory process, there is an increase in the chymase-positive–tryptase-positive mast cells, whereas T cells tend to populate the sub-

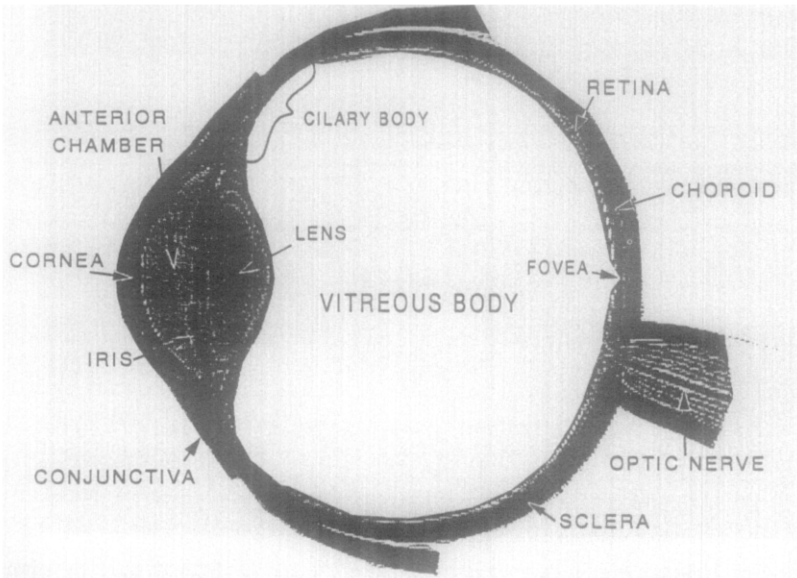


FIG. 1. Anatomic cross section of the eye with its major structures involved in allergic and immunologic reactions.

mucosa and the B cells to populate the lacrimal glands.^{15, 16} The eye has additional unique immunologic properties, as reflected by the avascularity of the cornea resulting in its ability to support allogeneic grafts with minimal immunomodulation.¹⁹ However, the cornea can express major histocompatibility complex antigens, resulting in corneal allograft rejection.²⁰⁻²²

MAST CELL-MEDIATED DISORDERS
Conjunctivitis

Acute conjunctivitis is an inflammatory reaction that is most commonly caused by infection (viruses and bacteria) or IgE-mast cell-mediated reactions. The differential features in conjunctivitis include the type of discharge (clear, viral or allergic; purulent, bacterial), cell type (mononuclear, viral; polymorphonuclear, bacterial; mixed with eosinophils, allergic), lid swelling (mild, viral; moderate, bacterial; allergic, severe), node involvement (predominantly in viral conjunctivitis), and pruritus (allergic, most intense).

AC

AC, originally described in 1863 as “rose fever,” is not an allergy to “roses” but reflects that the eyes appear to be one of the most sensitive targets for grass aeroallergens occurring in the spring and fall (“Indian summer”). Because of the direct exposure of the ocular mucosal surfaces to the environment, mast cell- and IgE-mediated reactions are the most common hypersensitivity responses of the eye. The

TABLE II. Immunologic involvement of various anatomic portions of the eye

Ocular structure	Immunologic disorder
Eyelids	Atopic dermatitis Contact dermatitis
Conjunctiva	Conjunctivitis Allergic Vernal Atopic Giant papillary Pemphigoid and pemphigus Sjögren's syndrome Sarcoid
Cornea	Corneal graft rejection Amyloid
Extraocular muscles	Myasthenia gravis Orbital pseudotumor Graves' ophthalmopathy
Sclera	Scleritis Episcleritis
Lens	Phacogenic uveitis
Uvea	Uveitis Iritis Choroiditis Vasculitis
Retina	Vasculitis
Optic nerve	Optic neuritis Vasculitis

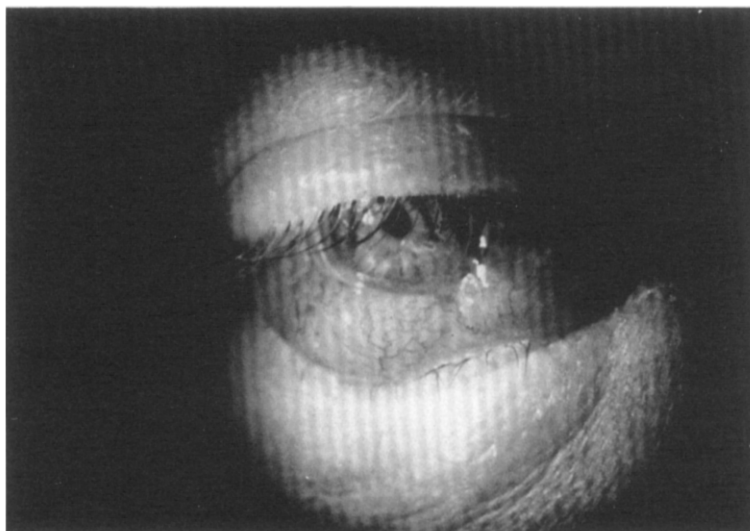


FIG. 2. Chemosis, reflected by edema of the conjunctiva forming swelling around the cornea, is observed in patients with anaphylaxis or in patients having a localized ocular allergic reaction.

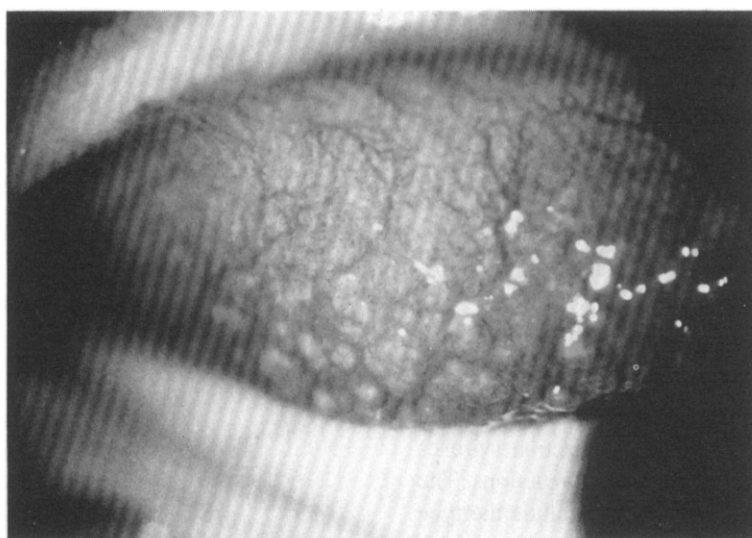


FIG. 3. GPC in patient using contact lens. Note early development of the round papilla in the center of palpebral conjunctival surfaces. Papillary hypertrophy is also observed in patients with VKC and AKC.

conjunctiva, a common site for periorbital angioedema, contains the largest number of ocular-associated mast cells. The classic conjunctival symptoms of itching, tearing, and burning may also include corneal symptoms of photophobia and blurring of vision. Clinical signs of AC include milky, pale-pink conjunctiva with vascular congestion that may progress to conjunctival swelling (chemosis) (Fig. 2).^{23,24} A white exudate may form during the acute state that becomes stringy in the chronic form. Tear fluid has been found

to contain a small amount of eosinophils and histamine.²⁵ Perennial AC is similar to AC, but is less common and occurs without seasonal preference; perennial allergens, such as the house dust mite, may provoke this dyscrasia.

VKC

An entity commonly confused with AC is VKC. As the name implies, it commonly begins in the spring (Greek, vernal) and was originally described by Hor-

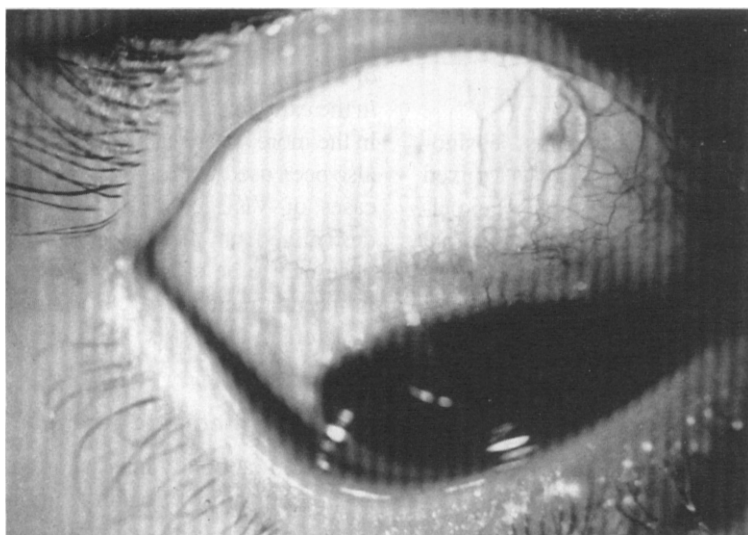


FIG. 4. Perilimbal infiltrates, that is, growths noted on conjunctival surface reflect chronic inflammatory process around iris that can be observed in patients using contact lens with VKC or AKC.

ner in 1880 as "Easter's gift." It commonly appears in young male subjects and peaks at puberty, after which, it is equally distributed among the sexes.^{26, 27} VKC dissipates by the third decade of life. Histopathologically, this condition is characterized by the "cobblestone" appearance of the conjunctiva (Fig. 3), an area infiltrated with eosinophils, degranulated mast cells, basophils, lymphocytes, and macrophages, supporting the hypothesis that VKC is a combined mast cell-IgE- and lymphocyte-mediated hypersensitivity reaction.

VKC commonly begins in the spring. Symptoms include intense pruritus exacerbated by time, exposure to wind, dust, bright light, hot weather, or physical exertion associated with sweating. Corneal involvement is common with photophobia, foreign-body sensation, lacrimation, and Charcot-Leyden crystal-infiltrated corneal ulcers. Signs include conjunctival hyperemia with papillary hypertrophy ("cobblestoning") reaching 7 to 8 mm in diameter on the superior tarsal plate, a thin copious milk-white fibrinous secretion composed of eosinophils, epithelial cells, and Charcot-Leyden granules, limbal or conjunctival "yellowish-white points" (Horner's points or Trantas' dots) that are cysts filled with degenerating eosinophils and epithelial cells, an extra lower eyelid crease (Dennie's line), gelatinous hypertrophy of the limbus (Fig. 4), or pseudomembrane formation of the upper lid when it is everted and exposed to heat (Maxwell-Lyons sign). Tears contain histamine, major basic protein, Charcot-Leyden crystals, basophils, IgE and IgG specific for ragweed pollen, and eosinophils (90% of

cases).²⁸ The specific IgE found in tears does not correlate to the patients' immediate skin test results.²⁹

AKC

AKC is mediated by a mixture of mast cell/IgE and lymphocytic interactions, as reflected by infiltrations of basophils, eosinophils, plasma cells, and lymphocytes within the "cobblestoned" lower palpebral tissue (Fig. 3). A familial history for atopy is common. Symptoms include itching, burning, and tearing. Signs include pale conjunctiva and limbal infiltration (Horner's points or Trantas' dots). Tears may have IgE, eosinophils, and mononuclear cells with a paucity of basophils and mast cells. Other abnormalities include increased histamine release, eosinophilia, and elevated serum IgE.³⁰

Corneal ulceration and scarring and keratoconus may occur in patients with AKC. Keratoconus is a slowly progressive ectasia of the cornea that usually is bilateral. The conical shape of the cornea commonly causes major changes in the refractive power of the eye and is often associated with frequent alteration in eyeglass prescriptions. Cataracts may be observed, both as a sequelae of prolonged topical corticosteroid therapy and as a feature of AKC. An unusual feature of AKC cataracts is that they involve the anterior, most portion of the lens, and may evolve rapidly into complete opacification within 6 months.³¹ Similarly, glaucoma may be observed as a steroid complication.³² Many patients may develop secondary staphylococcal blepharitis.³³ In addition to the characteristic cutaneous changes of atopic dermatitis, patients may

have other atopic conditions, for example, asthma, urticaria, and rhinitis.

GPC

Conjunctival infiltration with basophils, eosinophils, plasma cells, and lymphocytes suggests a mixed mast cell- and lymphocyte-mediated process associated with a variety of foreign bodies on the external ocular surface, for example, the continued use of contact lenses.^{34, 35} Thimerosal (a preservative), the contact lens polymer, and proteinaceous deposits on the surface of the lens have been implicated as possible causes of GPC.^{36, 37} There is an increase of symptoms during spring pollen season. Symptoms include itching, burning, and tearing. Signs include a white or clear exudate on awakening that chronically becomes thick and stringy, and the patient may develop Trantas' dots, limbal infiltration, and bulbar conjunctival hyperemia and edema. Cobblestoning has been described with the use of contact lens (5% to 10% of wearers of soft lens and 3% to 4% of wearers of hard contact lens) (Fig. 3). A recent study revealed that tryptase was found in tears of patients with GPC compared with that in tears of normal control subjects and may provide an early marker for this disease.³⁸

Treatment of AC

Mast cells appear to be the key cell in several of the inflammatory reactions of the eye (vide supra). Environmental, systemic, and topical approaches are used to control ocular inflammation, prevent relapses, and restore visual acuity. Antihistamines are used systemically or topically with a potent vasoconstrictor to provide immediate relief of the common symptoms of AC but are usually of minimal use in AKC or VKC.³⁹ Topical steroids are extremely useful in the treatment of all forms of conjunctivitis but are associated with glaucoma, cataract formation, and infections of the conjunctiva and cornea.³² In VKC, frequent applications of a topical corticosteroid are beneficial, supplemented by small oral doses in the more recalcitrant cases. If topical steroids are used for more than a few weeks, intraocular pressure must be routinely monitored. Cromolyn sodium solution is a useful adjunctive therapy in AC, providing relief within 1 to 2 weeks, and has been used successfully in some patients with AKC or VKC.^{40, 41} Acetylcysteine in a 5% to 10% solution has been recommended for the removal of the sticky mucus discharge.³ Immunotherapy with grass pollens and other antigens have been reported in studies to be an adjunctive treatment modality for patients with AC and some patients with VKC.^{42, 43} Thin, highly hydrated, extended wear ("bandage") contact lenses have also been used as a physical barrier to protect the cornea from the me-

chanical disruption caused by the cobblestoned papillae. Treatment for GPC involves stopping the use of contact lenses, initiating the use of topical cromolyn in the early stages of GPC, and cyclosporine treatment in the more severe cases.^{44, 45} Topical cyclosporine has also been used with success in some of the more severe cases of VKC or AKC. Recently, a 5-amino acid derivative from the Fc receptor of IgE has been demonstrated to be effective in controlled human studies in the treatment of AC, blocking the development of hyperemia, chemosis, and itching up to 4 hours after treatment.⁴⁶

Antibody-mediated reactions

Antigen-antibody interactions affecting the eye can be in the form of circulating antibody attacking fixed ocular antigen (e.g., pemphigus and pemphigoid) or in the deposition of CIC (e.g., vasculitis).

CICs depositing within the cornea can be observed as a "precipitin" line (ocular Auer reaction). These infiltrates occur in several forms of CIC-associated disorders, for example, WG, SLE, PAN, and TA. The inflammation caused by the localized deposition of CIC can lead to corneal ulceration (e.g., Mooren's ulcer), limbal and scleral inflammation (e.g., iritis and scleritis), and vasculitis. In scleritis, the collagen undergoes fibrinoid necrosis with an abnormal deposition of mucopolysaccharides, and commonly becomes granulomatous. Autoimmune disorders affecting the eye include rheumatoid arthritis, Sjögren's syndrome, ankylosing spondylitis, and SLE (Table III). The classic autoimmune disease associated with CIC affecting the eye is SLE.⁴⁷ Principal ocular manifestations are retinal "cotton-wool" patches in which CICs deposit in the capillaries of the nerve fiber layer and flame-shaped hemorrhages.^{48, 49} Occasionally, papilledema, secondary to raised intracranial pressure induced by pseudotumor cerebri, is observed.⁵⁰⁻⁵²

Pemphigoid

Pemphigoid of the eye (cicatricial pemphigoid) has a similar histopathologic picture to "bullous pemphigoid" of the skin. The desmosomal attachments between epithelial cells are lysed. IgG and IgA deposits at the basement membrane have been detected in 80% of patients.⁵³ When the subepidermal blister ruptures, an overgrowth of fibrous tissue occurs, leading to severe corneal damage, dry eyes, neovascularization with fibrosis, and subsequent loss of vision.⁵⁴ In the eye, the denuded conjunctival epithelium leads to adhesions (symblepharons) that can obliterate the mechanical closing of the eyelids and the mucus-producing goblet cells, leading to excessive drying of the eyes, subsequent corneal opacification, and blindness. Similarly, pemphigus vulgaris is mediated by

TABLE III. Ocular complications of autoimmune disorders

Disease	Ocular manifestations	Laboratory findings
Rheumatoid arthritis	Keratoconjunctivitis sicca Scleritis Scleromalacia perforans	RF ESR CIC HLA-DR4
Sjögren's syndrome	Keratoconjunctivitis sicca Scleritis	RF CIC ANA SS-A SS-B
Ankylosing spondylitis	Anterior uveitis	HLA-B27 Sacroiliitis
Behçet's syndrome	Conjunctivitis Anterior uveitis Retinal vasculitis Retinochoroiditis Optic nerve papillitis Ophthalmoplegia	Acute-phase reactants HLA-Bw51 CIC
SLE	Keratoconjunctivitis sicca Cotton-wool spots Scleritis Retinal vasculitis	ANA (ds-DNA, Sm) HLA-DR3 CIC Antiphospholipid antibody
Giant cell arteritis	Ischemic optic neuropathy Central retinal artery occlusion Diplopia Amaurosis fugax	ESR Acute-Phase reactants TA

ANA, Antinuclear antibody; RF, rheumatoid factor; SS-A, SS-B, antibodies to nuclear antigens (Ro, La).

complement-fixing IgG to intercellular cement substance—producing acantholysis and intraepithelial blisters all over the body, including the skin, mouth, and eyes. Lesions of the eye commonly involve the conjunctiva. The bursting of the bulla are painful but usually heal without sequela.

Mooren's ulcer

This corneal ulcer is a chronically progressive, marginal, nonpurulent lesion that is similar to ulcers observed in patients with other forms of vasculitis, for example, WG and PAN. The ulcer is due to the necrosis occurring at the sclerocorneal junction with a large number of neutrophils, lymphocytes, and eosinophils (Fig. 5). Immunoreactant deposition, including complement and IgG, have been found in the corneal epithelium.^{55, 56}

WG

WG is a granulomatous necrotizing vasculitis, whose hallmark is the predilection of both the upper and lower respiratory tracts, often in association with

glomerulonephritis. The typical age of onset is 20 to 50 years, with 60% of cases occurring in male subjects. The systemic nature of the disease is reflected in the involvement of the lung (about 100% with multiple bilateral infiltrates or thin-walled cavities), paranasal sinuses (91%), the kidney (85% with glomerular sclerosis), the joints (67%), the nose or nasopharynx (64%, classically with a saddle-nose deformity), the eye (60%), and the skin (45%). The presenting symptoms can be quite vague and nonspecific, with pulmonary infiltrates (71%), sinusitis (67%), joint pains (44%), fever (34%), and ocular involvement (18%) being the most common symptoms^{57, 58} (Table IV). Episcleritis and scleritis, marginal corneal ulceration (Fig. 5), and granulomatous uveitis are the typical anterior signs. As granulomatous lesions of the sinus and orbit are not uncommon, proptosis may be a presenting sign. Inflammation of the choriocapillaris, retinal vasculitis, and optic neuritis occur, as does cranial neuropathy with diplopia.^{59, 60} When WG occurs in children, it tends to have an even greater predilection for ocular involvement, most commonly



FIG. 5. Mooren's ulcer is a chronically progressive corneal ulceration at junction of cornea and sclera. Observed in patients with vasculitis, for example, WG and PAN. Large accumulation of neutrophils, lymphocytes, and eosinophils are found in biopsy specimens of these lesions.

as orbital pseudotumor, but may also present as scleritis.^{61, 62}

Tissue diagnosis, especially open lung biopsy, is the "gold standard." Recently, a new serologic assay, the antineutrophil cytoplasmic antibodies, has been demonstrated to be extremely sensitive and specific for the necrotizing vasculitides.⁶³⁻⁶⁷ Other useful tests are the ESR, CIC, and chest and sinus radiographs.

Diffuse WG was previously a uniformly lethal disease, with a mean untreated survival time of 5 months and a 2-year mortality of 90%. WG was really the first great success of immunosuppressive agents in vasculitis, with prednisone (1 mg/kg/day) in combination with low-dose cyclophosphamide (2 mg/kg/day) inducing remission in 90% of patients.⁵⁸

Giant cell arteritides

Giant cell arteritis includes TA and Takayasu's arteritis. Next to HSV, TA is the most common vasculitis. Although it is rare in subjects younger than the age of 55 years, it occurs in nearly 1% of all subjects who reach the age of 80 years. There is a slight female predominance affecting all races.^{68, 69}

TA was first described by Hutchinson⁷⁰ in 1890, who described patients with painful red streaks in the temple who could no longer wear hats. He called this entity "thrombotic arteritis." The first pathology of a temporal artery biopsy specimen was reported by Hor-

ton et al. in 1932.⁷¹ The association of blindness with TA was first described by Jennings in 1938,⁷² although the term "ischemic optic neuropathy" did not come into use until 1966.⁷²

Although TA is largely a disease of the cranial arteries, it is associated with systemic vasculitis, including coronary arteries that has been associated with fatalities with aortitis or cerebral or coronary involvement.⁷³ Its systemic features include headache (60%), usually described as boring and increased by cold, a tender temporal artery (55%), polymyalgia rheumatica (50%), manifested by stiffness, aching, and frank pain in the muscles of the neck, shoulder, and pelvis, and fever (43%). Jaw claudication (36%), probably the only pathognomonic sign, is a crampy pain that gets worse as one chews and improves with rest. This is due to a true ischemia of the masseter muscles from facial artery involvement.^{69, 74}

The ocular hallmark of TA is ischemic optic neuropathy presenting as loss of vision in 16% of cases, although more than one third (36%) will eventually lose vision. The ischemia is primarily due to the occlusion of the ciliary arteries supplying the optic nerve head, although some cases of central retinal artery occlusion are not rare. Once one eye is involved, the risk of developing bilateral blindness has been estimated to be 25% to 50%.^{75, 76} Although visual loss is equated as *the* ocular manifestation of TA, amaurosis fugax and diplopia can be the presenting signs of TA as often as is visual loss (i.e., 16% and 12%, respectively). Blindness is preceded by constitutional symptoms (e.g., fever, malaise, depression, and anorexia) for a mean duration of 3 to 4 months.⁶⁹

The key laboratory test is the ESR, although it need not be elevated to make the diagnosis of TA. Marked elevation in the ESR is said to be observed in 95% of proven cases of TA by biopsy specimen; yet a normal ESR should never prevent a diagnosis from being made.⁷⁷⁻⁸⁰ One study reported that 10% of patients with TA had an ESR of <50 mm/hr.⁸¹ An iron replacement-resistant normochromic-normocytic anemia (or hypochromic-microcytic) is observed in 15% to 30% of patients that respond to corticosteroid therapy.⁶⁹ Nonetheless, because of the well-known side effects of prolonged steroid therapy in this population (i.e., 25% of treated patients with TA will develop symptomatic vertebral fractures), pathologic confirmation of the clinical diagnosis is preferable before committing the patient to a year of steroid therapy.

The classic pathology of active arteritis involving the presence of Langerhan's "giant cells" is not a consistent feature, with nonspecific inflammation with

TABLE IV. Ocular systemic manifestations of the major vasculitides

Vasculitic syndrome	Vessels involved	Organs involved	Ocular findings
Necrotizing	Small- and medium-sized arteries and veins	Kidneys Liver Viscera Spares lungs	Sjögren's syndrome Necrotizing sclerokeratitis Iridocyclitis Retinal vasculitis Central retinal artery occlusion Exophthalmos Diplopia
Granulomatous	Medium- and small-sized arteries and veins	Lung Skin Viscera Cardiac Renal	Amaurosis fugax Marginal corneal ulcer Conjunctival amyloid Uveitis Ischemic optic neuropathy Retinal infarction
Giant cell arteritis	Large- and medium-sized arteries	Blood vessels Cardiac	Amaurosis fugax Ischemic optic neuropathy Central retinal artery occlusion
Hypersensitivity	Venules Arterioles Capillaries	Skin Renal Musculoskeletal	Hemorrhage Conjunctivitis Retinal occlusion Uveitis

mixed cellular infiltrate (polymorphonuclear leukocytes, lymphocytes, and eosinophils) being more common (Figs. 6 and 7). Active arteritis is not necessary to make the diagnosis of TA; healed arteritis with intimal fibrosis or fragmentation may be observed, although an elastin stain to optimally demonstrate this finding is needed. It cannot be reliably predicted from the clinical picture whether a given patient will have pathology of active or healed arteritis. In clinical cases of TA, 83% will have a positive biopsy specimen. It takes 7 to 8 weeks of steroid therapy to lose the active pathologic features; yet the pathology of healed arteritis persists indefinitely. The ideal section is 4 to 6 cm long, and skip lesions, which in an old study were reported to be as high as 25%, are now believed to be extremely rare if the tissue is properly sectioned.⁸²

Therapy is primarily aimed at preventing contralateral visual loss and cerebral and cardiac complications of the disorder. The usual regimen is to begin oral prednisone (1.5 to 2 mg/kg/day), to maintain this dose for about 4 weeks, and to begin tapering based largely on the patient's constitutional symptoms. The prednisone may be tapered to the smallest daily maintenance dose that suppresses these symp-

toms and then may be maintained for a minimum of 12 months of therapy. If no constitutional signs remain at this point, the patient may be weaned from the steroids. The use of "megadose" (e.g., 1 to 3 gm of daily intravenous methylprednisolone), especially in hyperacute visual loss or in the event of infarction of the second optic nerve, has been suggested.^{83, 84}

HSV

HSV is a group of disorders characterized by small vessel involvement. The skin is the most commonly affected organ, being involved in virtually 100% of cases. Histologically, the classic finding of "palpable purpura" consists of leukocytoclastic and lymphohistiocytic vasculitis. Other clinical manifestations include fevers/malaise (100%), arthralgia/myalgia (67%), abdominal cramps/nausea (67%), and headaches (57%).⁸⁵ Ocular involvement, beyond cutaneous lesions of the eyelids, is quite rare and includes iritis, papilledema, and blurring of vision, as well as bilateral fibrinous uveitis.⁸⁵⁻⁸⁷ There are studies of visual changes associated with administration of a variety of medications and with vasculitis.⁸⁸ Useful laboratory tests include the ESR, CIC, complement, and tissue biopsy specimen.

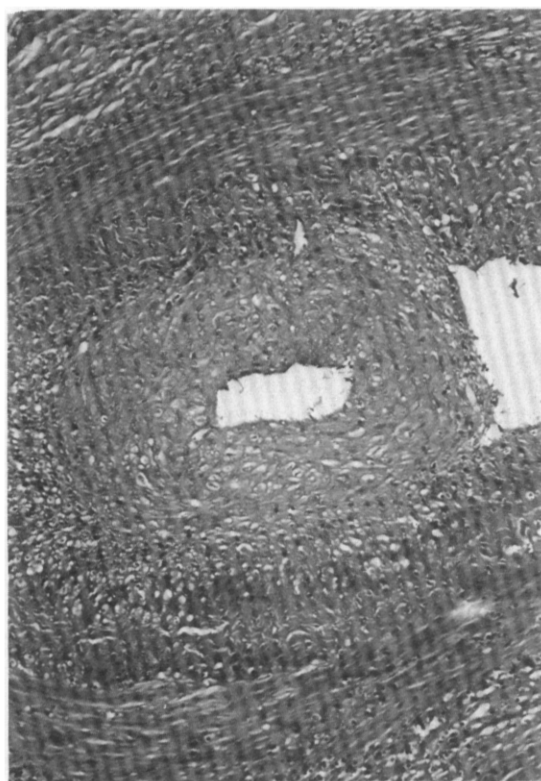


FIG. 6. Temporal artery biopsy specimen with routine histologic hematoxylin and eosin stain reveals extensive inflammation of temporal artery. Giant cells or granulomas are not present in every histopathologic cut. Evidence of perivascular round-cell infiltrate, occlusion of the artery, fibrinoid necrosis, and early granulomatous changes are present. (Original magnification $\times 100$.)

KD

KD, also known as mucocutaneous lymph node syndrome, is an acute exanthematous illness that is almost exclusively a disease of children, with 50% of cases occurring predominantly in male subjects younger than the age of 2 years and with an increased incidence in individuals of Japanese ancestry. Five of six criteria must be present for diagnosis: (1) fever, (2) bilateral conjunctival injection, (3) upper respiratory tract mucous membrane changes, (4) skin and nail changes, (5) maculopapular cutaneous eruption, and (6) cervical lymphadenopathy. The disease may occur in cyclic epidemics, and the current theory is that an infectious agent (*Rickettsia*-like organism has been demonstrated on electron microscopy) causes a hypersensitivity response. Although most cases of KD are benign and self-limited, 2% of the patients experience sudden cardiac death from coronary artery vasculitis leading to aneurysmal dilatation and subsequent myocardial infarction.⁸⁹⁻⁹¹

The most typical ocular finding is bilateral nonex-

udative conjunctival vasodilatation, typically involving the bulbar conjunctiva. Anterior, mild, bilateral, and symmetric uveitis is observed in 70% of patients. Superficial punctate keratitis is observed in 12%. Choroiditis has been reported (and pathologically demonstrated) in a case of infantile periarteritis nodosa, which may be indistinguishable from KD.⁹² On magnetic resonance imaging of the brain, deep white-matter lesions, typical of the vasculopathic lesions of systemic vasculitis, as opposed to the periventricular lesions more classic of multiple sclerosis, have been observed.^{91, 93} Laboratory evaluation is nonspecific, with an elevated ESR, sterile pyuria, leukocytosis, and thrombocytosis with a demonstrable hypercoagulable state. Ultimately, the diagnosis is one of exclusion, but a high index of suspicion is required to initiate treatment with intravenous gammaglobulin and aspirin to prevent the late development of cardiac complications.

BD

BD, first described in 1937 by a Turkish dermatologist, is a clinicopathologic entity characterized by recurrent bouts of oral, nasal, and genital mucosal ulcers, in association with a predominant *venular* vasculitis involving any organ, coupled with a uveitis. Most patients present with the incomplete form of the disease; that is, they do not have all the clinical features at the same time (e.g., retinal vasculitis and mouth ulcers, but no genital ulcers). There is a link to HLA B5/B51, especially when ocular disease is present (Table V). It is an occlusive retinal vasculitis affecting arteries and veins at its principal sites, but it also includes other portions of the highly vascular uveal tract (e.g., hypopyon, iritis, and choroiditis). Although serum immunoglobulins, CIC, and neutrophil chemotaxis are increased, there is no laboratory test that will definitively confirm the diagnosis of BD. Headaches are observed in 50% of the patients; 28% have other neurologic involvement with frequent reports of meningoencephalitis.^{94, 95} The magnetic resonance imaging scan of the brain may reveal deep demyelinating lesions similar to that of KD.^{93, 96} Once the eye is involved, 50% of the subjects are blind in less than 5 years.⁹⁶ Uveitis is observed in 70% of cases with the most classic ocular sign, the sterile hypopyon, observed in the minority of cases (Fig. 8). Perivascular sheathing has been reported, as have branch and central venous and arterial occlusions.^{94, 96-98} Pseudotumor cerebri, presumably caused by cerebral venous thrombophlebitis, is not uncommon.⁹⁹⁻¹⁰² The role of the reportedly increased incidence of antiphospholipid antibodies in these patients is not clear.¹⁰³

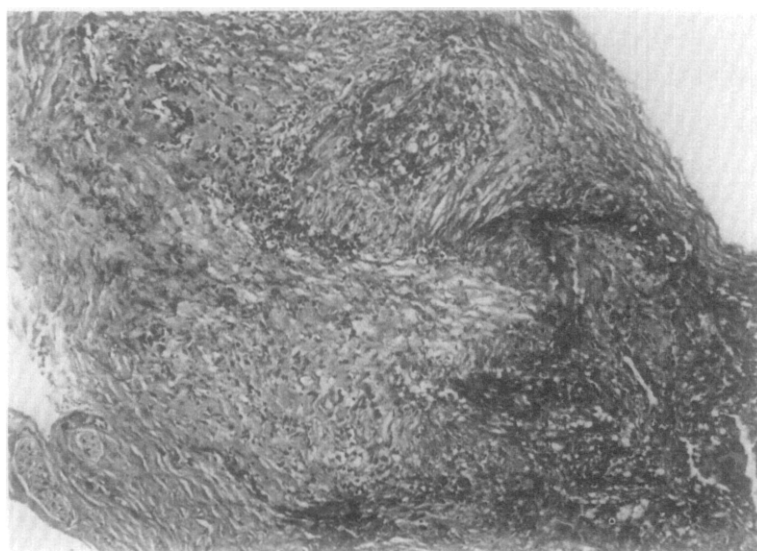


FIG. 7. Temporal artery biopsy specimen with elastin stain reveals disruption and duplication of internal elastic lamina around temporal artery. Stain is picked up by internal elastic lamina as *discontinuous black line*. Vascular portion of artery is obliterated. (Original magnification $\times 100$.)

TABLE V. HLA antigens in diseases with ocular manifestations

Disease	HLA antigen	Relative risk
Anterior uveitis	B27	10.4
Ankylosing spondylitis	B27	87.4
Reiter's syndrome	B27	37
Behçet's syndrome	B5/Bw51	6.1
Multiple sclerosis	DR2	4.1
Sjögren's syndrome	DR3	9.7
Pemphigus	DR4	14.4

CS

CS is an uncommon inflammatory disorder of the eyes and ears. Classically, CS is a nonleucitic interstitial keratitis in association with Menière's-like attacks of vertigo, tinnitus, or hearing loss, often with otic pain. Systemic, nonotic/ocular symptoms of fever (26%) and arthralgia/myalgia (21%) are more unusual in CS than in the other vasculitides.¹⁰⁴ Other "nonclassic" ocular forms have been described that include sub-epithelial peripheral corneal stromal infiltrates, episcleritis, scleritis, orbital pseudotumor, uveitis, conjunctivitis, papillitis, and retinal vasculitis.¹⁰⁴⁻⁵

That CS is an autoimmune disease is supported by such evidence as demonstration of antibodies against inner ear and corneal tissue, cellular immune response to inner ear antigens, pathologic demonstration of lymphocytic and plasma cell infiltrate in the cornea

and inner ear, and cell-mediated immunity against corneal antigens.¹⁰⁶ CS may be an isolated entity or, in 10% of cases, it may be a feature of the systemic necrotizing vasculitides, especially PAN, often with aortic insufficiency and proximal aortitis.¹⁰⁷⁻¹¹⁰ For this reason, echocardiography is part of the evaluation of CS. The "nonclassic" eye signs are associated with both an increased risk of severe visual loss (27% of these patients) and of a more widespread systemic vasculitis (21%).¹⁰⁴

Laboratory evaluation is often not fruitful, and this remains a clinical diagnosis of exclusion. Elevated ESR, leukocytosis with neutrophilia, thrombocytosis, and anemia are observed. Without therapy, 60% of patients will sustain severe hearing loss; with steroid treatment beginning within 2 weeks of onset, 80% will preserve their hearing.¹¹¹



FIG. 8. Inflammatory changes of anterior chamber of eye (portion in front of iris), anterior uveitis, may cause variety of opacifications of cornea, such as hypopyon (pus in anterior chamber that layers out in lower portion of the anterior chamber) or precipitates on inner surface of cornea. These two entities can be differentiated since fluid (pus) level of hypopyon will shift with position, whereas corneal precipitates do not. Young patient with sarcoid, uveitis, and corneal precipitates.

Uveitis

Uveitis (affecting the iris, ciliary body, and choroid) represents the preeminent immune ocular disorder and is the clinical expression of many hypersensitivity reactions induced by both CIC and cell-mediated hypersensitivity reactions.¹¹⁶ The uveal tract usually contains a sparse collection of B- and T-lymphocytes, mast cells, and fibroblasts. During a chronic inflammatory reaction involving the choroid, plasma cells, phagocytes, and T and B cells aggregate, forming pseudolymphoid follicles or granulomas with some cells entering the aqueous humor of the anterior chamber. Specific uveal antigens, primarily the soluble "S antigen" (molecular weight, 55 kd) and opsin retinal proteins (e.g., rhodopsin and interphotoreceptor retinoid-binding protein), can induce an autoimmune uveoretinitis as well as an autoimmune pinealitis.¹¹²⁻¹¹⁵

Uveitis may be anatomically classified as anterior (iritis or iridocyclitis), intermediate (cyclitis or peripheral uveitis), posterior (choroiditis with retinitis), and diffuse (iritis plus intermediate uveitis plus chorioretinitis).¹¹⁷ The symptoms and signs include ocular pallor, photophobia, conjunctival injection, visual impairment, and black floating spots. The major signs in anterior uveitis are pupillary miosis and perilimbal flush, which is a peculiar injection observed adjacent to the limbus and can be easily confused as "conjunctivitis." Severe pain, photophobia, and blurred

vision occur in cases of acute iritis or iridocyclitis. Vitreal cells and cellular aggregates are characteristic of intermediate uveitis and can be observed with the direct ophthalmoscope. Cells (inflammatory leukocytes in anterior chamber), flare (proteins in the aqueous) and keratic precipitates (clumps of inflammatory cells), deposited on the corneal endothelium (Fig. 8), and exudates with membranes covering the ciliary body can be visualized with the slit lamp and indirect ophthalmoscopy. Posterior uveitis commonly presents with inflammatory cells in the vitreous, retinal vasculitis, and secondary macular edema that threatens vision. Anterior uveitis is often linked to the HLA-B27 genotype and systemic immunologic disorders, for example, ankylosing spondylitis (sacroiliitis), Reiter's syndrome, infections, for example *Klebsiella* bowel infections (caused by molecular mimicry), brucellosis, syphilis, and tuberculosis, as well as HLA-B5, Bw22, A29, and D5 genotypes (Table V).¹¹⁸

Sarcoidosis is one of the more commonly associated systemic diseases associated with any type of anterior, intermediate, posterior, or diffuse uveitis.^{119, 120} The noncaseating granulomas may appear as "mutton-fat precipitates," obstructive glaucoma, Busacca, or Koeppe nodules in the iris, or sheathing of vessels, often periphlebitis ("candle-wax drippings"). The ocular inflammatory response may occur independently of any evidence of systemic involvement.

Diagnostic tests for ocular sarcoidosis may include chest x-ray, angiotensin-converting enzyme, serum lysozyme, gallium scan, and anergy panel.^{117, 121} The delayed hypersensitivity skin tests (anergy panel) are placed in conjunction with several other antigens (e.g., *Candida*, mumps, and *Trichophyton*) to determine the presence of "anergy" that is commonly observed in patients with sarcoid. Other serologic tests that are often helpful are hepatic transaminases and a complete blood cell count for bone marrow involvement. Definitive diagnosis, as in systemic sarcoidosis, is made by biopsy of any involved organ that commonly includes lung, liver, and bone marrow. Biopsy of clinically involved conjunctiva and lacrimal gland is commonly used. A recent study found that 2% of all patients with uveitis had evidence of systemic sarcoidosis at time of presentation, and an additional 2.8% of patients with uveitis followed for 8 years will develop subsequent extraocular sarcoidosis.¹²⁰ Other granulomatous processes involving the eye include tuberculosis and histoplasmosis that may occur months to years after the primary infection.

Treatment of uveitis usually includes the local use of corticosteroids (topical drops and periocular retrobulbar depot injection or systemic), mydriatic/cycloplegic drops, as well as systemic immunomodulation.¹²²

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