

BRIEF REVIEW

Uveitis in the elderly—is it easy to identify the masquerade?

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Uveitis tends to occur in working age adults and is a major cause of visual loss in this age group.¹ It does however occur both in childhood and in the elderly, and considerably less information is available regarding these two groups, particularly the latter. Regardless, in all age groups, it is necessary to accurately diagnose the form of uveitis, and to detect any underlying or associated systemic problems. Management is guided by the significant features of a patient's history, the signs present within the eye, and the results of relevant investigations.² While the causes of uveitis are legion, most are immune mediated, requiring the patient's immune system to mount and perpetuate an immune response, irrespective of the initiating stimulus.³ It is known that the aging immune system is less able to respond to foreign antigens and that autoimmune antibody production rises. Overall, however, it is believed that the incidence of true immune mediated uveitis declines in the elderly. Infectious endophthalmitis, particularly that arising after surgery, and lymphoma both occur at higher frequency in the elderly. These constitute the masquerade syndromes.

In this review, information available on the types of uveitis found in the elderly is presented, along with data on the aging immune system. Specific information is given on the causes of the masquerade syndromes, and an approach to clinical management is suggested.

Epidemiology and incidence of uveitis in the elderly

In most published series, there is a decline in the incidence of uveitis presenting in patients over the age of 65 years. Uveitis starting in the younger age groups may still be active in the older patient, although in many the disease has become quiescent.

Very few studies address the epidemiology of uveitis in the elderly per se, and still fewer provide useful data regarding patterns of presentation and the likely diagnoses in this age group. Since many forms of uveitis are recurrent, or low grade chronic, the distinction between new and recurrent disease is difficult. Documentation of recurrent uveitis of course reflects prevalence, not incidence, and is of little help to the clinician when presented with new onset disease. In 1962 in north east USA, there was an overall incidence of uveitis of 17 per 100 000 population.⁴ Categorised by age, there was a peak rate of nearly 30/100 000 in the 24–44 year age group, which declined to 14/100 000 in the population over 65 years. Classified by aetiology, and no doubt reflecting the prevalence of tuberculosis in the 1940s and 1950s, seven out of 33 diagnostic categories were defined as some expression of tuberculosis. Other 'uveitic' diagnoses included angioid streaks, drusen, phthisis bulbi, and vitreous opacities. No neoplastic conditions were identified. In 1982, in Ohio, USA, of 1820 patients referred to a uveitis clinic, 337 (16%) were over 50 years old,⁵ but only 229 of these elderly patients were found to have uveitis. However,

in their 'non-uveitic group', one had a leukaemic infiltrate and three had inflammatory disease (vitritis, optic neuritis, and temporal arteritis). The most common causes of posterior uveitis were found to be presumed ocular histoplasmosis, toxoplasmosis, and tuberculosis. Idiopathic iridocyclitis and iritis represented most cases of anterior disease, while all five cases of panuveitis were sympathetic ophthalmia. Although these data reflect new referrals to the uveitis clinic, some patients could remember similar episodes of eye disease in the preceding 10, 20, or 30 years making interpretation of these data difficult.

More recently, in 1994, uveitis in 94 patients over the age of 60 was reported.⁶ Although this series excluded patients presenting with ocular lymphoma, it did demonstrate a statistically significant rise in the incidence of idiopathic panuveitis, herpes zoster uveitis, uveitis associated with scleritis, and granulomatous anterior uveitis, whereas a significant reduction was found in the incidence of intermediate uveitis, HLA-B27 associated anterior uveitis, pars planitis, and non-granulomatous anterior uveitis. The authors reported no cases of Reiter's syndrome, Posner-Schlossman disease, Behçet's disease, Vogt-Kayanagi-Harada disease, or toxoplasmosis in their elderly group.

In 1994,⁷ uveitis in 71 patients over the age of 60 years was described. This series excluded patients with uveitis secondary to exogenous infection, and those arising postsurgically. Endogenous infections such as herpes zoster, bacteraemia, or fungaemia were included, as were patients with a new diagnoses of lymphoma. Sixty two per cent of patients had anterior segment disease, two thirds of which were acute. Thirty eight per cent had disease involving other parts of the uvea; panuveitis was the largest subgroup. Correlation with systemic disease was specifically assessed, and the highest associations were with insulin dependent diabetes mellitus, hypothyroidism, Crohn's disease, and sarcoidosis. Interestingly, despite the reported increase in systemic and ocular lymphoma with age,⁸ no case of lymphoma was found in this series.

In 1996,⁹ of 712 patients with uveitis, the largest group, 217, had an associated systemic condition, especially HLA-B27 related disease. After this, 192 patients had uncategorised idiopathic uveitis; 183 were idiopathic but categorised; 116 were associated with infection; and nine were induced by intraocular lens implantation. Stratified by age and sex herpes zoster ophthalmicus, arthritis associated uveitis, and idiopathic panuveitis typically presented in women with an average age of 50 or more. Among men, herpes zoster ophthalmicus alone presented with an average age over 50.

In another recent study,¹⁰ of the patients with uveitis presenting to a tertiary centre, and substratified by age over 50 years, anterior segment inflammation was most probably due to herpetic keratouveitis and intraocular lens

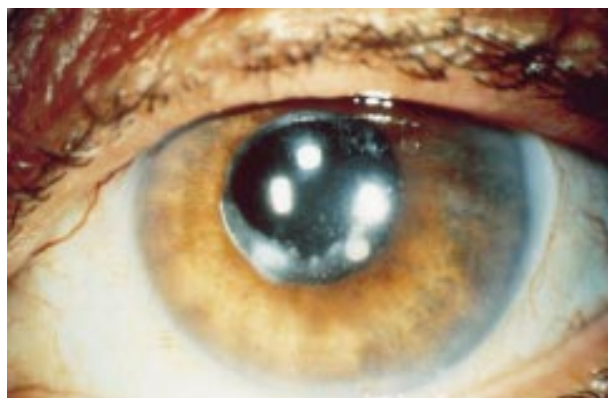


Figure 1 Classic appearance of *Propionibacterium acnes* endophthalmitis.

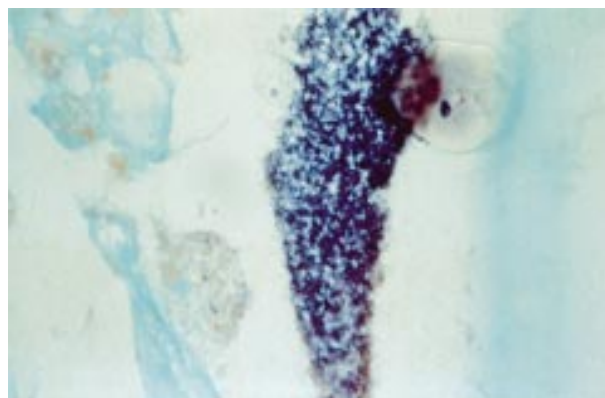


Figure 2 *Propionibacterium acnes* seen on specimen of posterior capsule.

induced persistent uveitis, while panuveitis was most commonly associated with rheumatoid arthritis.

It is evident that a variety of well recognised immune mediated uveitides can present in both the young and elderly patient. However, among the elderly, some disorders such as idiopathic pars planitis do not occur, while idiopathic anterior uveitis of all types, and idiopathic panuveitis are described frequently. *Toxoplasma chorioretinitis* is very uncommon, while uveitis following herpes zoster ophthalmicus is frequent.

The immune system in the older patient

Uveitis is thought in most instances to be immune mediated, and autoimmunity may play a major role.² With age, the immune system is known to change, and it is well recognised that the immune response to exogenous antigens, often infectious, declines with age. Concurrently, there is a marked rise in the production of antibodies directed against self antigens,^{11–13} typically of the IgG class, with a decrease of the IgM response. Specific autoantibodies include rheumatoid factor, antinuclear antibodies (ANA), anti-double stranded DNA, anti-single stranded DNA, antithyroid antibodies,¹⁴ anticollagen antibodies,¹⁵ and anticardiolipin antibodies. Interestingly, while autoantibody production is known to rise, it is not necessarily associated with disease, and the peak period for onset of autoimmune disease seems to be in early to mid adult life.¹⁶ It is currently estimated that 10–15% of healthy elderly individuals have raised circulating autoantibodies, yet only 5% suffer some form of autoimmune disease.^{14, 16} Suggested mechanisms for the rise in autoantibody response may include repeated or prolonged insult by endogenous antigens, molecular mimicry with exogenous antigens, or decreased production/function of suppressor cells.¹⁶

Uveitis, particularly affecting the posterior segment, is thought to be T cell mediated.¹⁷ The T cell lymphocyte population has also been found to change with age^{18, 19} and the proportion of helper and suppressor T cells, as well as their subgroups, has also been found to be different in the aged.²⁰ In general, T cell dependent responses decline with age.^{21, 22} Some studies tend to suggest that this occurs especially in the population over 80 years of age, and may be related to general health.

It is clear that some components of the integrity and function of the immune system change with age. It is therefore possible for an elderly patient to mount an immune response which may, or may not, be different from that seen in younger patients. An elderly patient may present with an acute immune mediated uveitis in exactly the same way as a younger patient does: whether this reflects a sinister underlying cause is for the clinician to determine.

The masquerade syndrome

The term 'masquerade' is used to describe the uveitides which are not immune mediated in the usual way, but which have an underlying primary cause. It is the underlying cause which requires treatment, not only the uveitis per se.²³ Uveitis can be a component of an ocular disorder which, when treated, will result in resolution of the uveitis—but treatment for the uveitis will not be effective for the underlying problem. For example, uveitis can be a feature of rhegmatogenous retinal detachment and herpes simplex keratitis, both of which require specific treatment. When this is successfully achieved, the uveitis will no longer be present. Detailed ocular examination is of paramount importance in the management of any patient with uveitis.

The two underlying disorders for which the term masquerade is most commonly used are intraocular infection and intraocular lymphoma. Both can appear to be a chronic panuveitis with little in the way of other signs. Acute endophthalmitis occurs within a few days after surgery and is usually recognised, but delayed onset endophthalmitis may occur weeks or months after the surgery, and can be much more difficult to diagnose. Aqueous and vitreous sampling may not yield viable organisms which can be grown on laboratory media, and the inflammation may be partially suppressed by corticosteroids. Patients with intraocular lymphoma may be perfectly well with no systemic or neurological symptoms and signs, and few other ocular signs except cells, predominantly in the vitreous, with some in the anterior chamber. Vitreous sampling may not yield enough cells for the diagnosis to be confidently established, and the vitritis may be steroid sensitive, at least initially.

Delayed postoperative endophthalmitis

The two most common ophthalmic procedures performed in the aging population are cataract extraction and trabeculectomy. In the acute postoperative period, there is often a high index of suspicion that the inflammation may have an infective cause. Cases of recurrent low grade postoperative uveitis have an estimated incidence of 0.5 in 1000 cases,²⁴ and for these, the infective aetiology can be overlooked. Late onset endophthalmitis is characterised by a delayed onset of weeks to months, a stuttering course with exacerbation and remission, and transient steroid responsiveness. It may present with mild pain, granulomatous uveitis with vitritis, capsular thickening (Fig 1), and an eventual decrease in visual acuity.^{24, 25} Several organisms have been isolated from eyes with late onset, low grade inflammation. *Propionibacterium acnes*^{24–27} and coagulase negative staphylococcal species²⁸ are found in the majority of the cases. Other micro-organisms include

Achromobacter,²⁹ *Cephalosporium*,³⁰ *Mycobacterium chelonae*,³¹ and *Nocardia asteroides*.³² These organisms are often of low virulence and become sequestered within the lens capsule (Fig 2).

There is a significantly reduced oxygen tension in the anterior chamber of aphakic and pseudophakic eyes compared with cataractous eyes,³³ ideal conditions for growth of anaerobic organisms. Although *P. acnes* has been reported after intracapsular surgery,²⁶ it has become more common with extracapsular techniques. The presence of an intraocular lens significantly increases the risk of endophthalmitis compared with intracapsular extraction without lens implantation.³⁴ Late onset endophthalmitis may also occur following trabeculectomy, especially if adjunctive 5-fluorouracil or mitomycin are used.³⁵ This is typically due to *Haemophilus* species, or nutrient variant streptococci. Confirmation of the diagnosis requires culture of both aqueous and vitreous, samples of which should be promptly inoculated into appropriate media and placed in incubators that allow for growth of both aerobic and anaerobic bacteria. Cultures should be maintained for at least 2 weeks as it may take this long to observe growth of certain anaerobic species such as *P. acnes*. Often however both aqueous and vitreous samples are sterile, and confirmation of the diagnosis waits until further specimens are taken, usually from the posterior capsule or intraocular lens.

Other causes of intraocular inflammation after surgery

Not all signs of inflammation in the postoperative period are the result of infection. Subacute postoperative inflammation following cataract extraction can result from retained lenticular material,³⁶ or as a reaction to foreign material used in the manufacture of intraocular lenses. Some patients with rheumatoid arthritis were found to have persistent sterile inflammation postoperatively which correlated with their titre of rheumatoid factor³⁷ and, of course, patients with pre-existing uveitis can reactivate after surgery.

Ocular lymphoma

Ocular lymphoma is of greater concern as it can lead to death if untreated. Several types of lymphoma can involve the eye and mimic uveitis. Ocular involvement in Hodgkin's lymphoma is relatively rare and usually occurs late in the course of the disease.³⁸ The ocular manifestations of Hodgkin's lymphoma include iritis, retinal periphlebitis, and chorioretinitis with associated vitritis.^{39,40} Two clinically distinct forms of non-Hodgkin's lymphoma more frequently involve the eye—non-Hodgkin's lymphoma of the CNS and systemic non-Hodgkin's lymphoma with metastases to the eye.²³ The majority of these are of B cell origin. Although T cell lymphoma represents about 20% of all non-Hodgkin's lymphoma in Europe,⁴¹ ophthalmic involvement is rare, with only a small number of cases reported, about half in association with mycosis fungoides. Other T cell lymphomas are associated with T cell lymphotropic virus type 1 (HTLV-1),^{42,43} and systemic involvement is common.

Patients with systemic non-Hodgkin's lymphoma are usually unwell and the diagnosis is rarely difficult. In contrast, patients with CNS lymphoma often produce a diagnostic problem, and the incidence of intraocular and CNS lymphoma is on the increase in both immunocompetent and immunocompromised patients.⁴⁴ Classically, patients present in their fifth to seventh decade with a refractory 'uveitis' associated with vitritis and vitreal opacities. Intraocular lymphoma may however present in a variety of

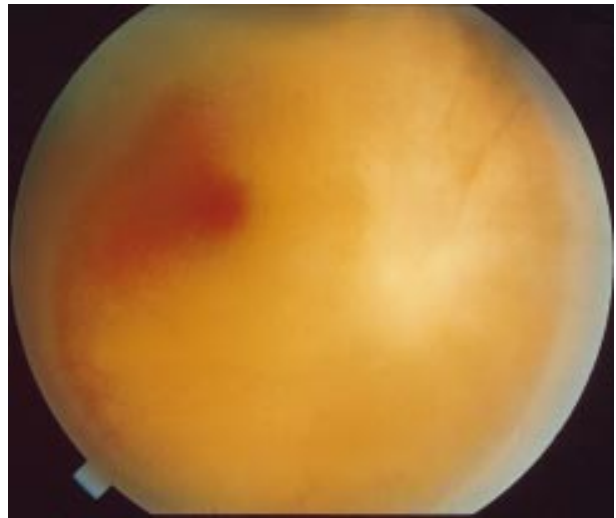


Figure 3 Vitritis in patient with intraocular lymphoma.

different ways, and may mimic necrotising viral retinopathies, toxoplasmosis, the vasculitis of sarcoid, the subretinal lesions of infectious choroiditis, and the panuveitis syndromes.

Diagnosis of intraocular lymphoma can be very difficult as the clinical features are non-specific, and there are often no associated systemic signs. Peripheral blood, bone marrow cytology, and cellular morphology are usually normal and therefore unhelpful.^{45,46} Imaging of the CNS has been used to delineate the presence and extent of CNS involvement, but this is unreliable as many cases with established intraocular or early CNS involvement have normal computed tomography and magnetic resonance imaging. If a mass is visualised, the exact nature of the mass (for example, intracranial abscess, metastases, or lymphoma) cannot always be absolutely determined.^{45,46}

Ocular examination can be helpful in establishing a diagnosis of intraocular lymphoma, but marked variation exists in the degree of vitreous cellularity and retinal lesions may or may not be found. Siegel *et al*, in their series of patients with intraocular lymphoma, found that although all patients had vitritis (Fig 3), only 50% showed intraretinal and/or subretinal lesions and only 21% had anterior uveitis.⁴⁵ Even in the presence of retinal lesions, biopsy is hazardous, may miss the lesion, and if successful will only yield a small number of cells. Delayed or lack of response to steroid treatment has in the past been assumed to be indicative of malignancy. However, in intraocular disease, both chronic inflammation and that secondary to malignancy may respond positively to steroid treatment, at least initially. Steroid responsiveness therefore cannot be used as a means of differentiation.

Vitritis is the only universal finding in lymphoma, but traditional methods of histology and cytology (Fig 4) may be unreliable as the cellular response in the vitreous is often sparse, and the number of abnormal cells obtained inadequate to confirm monoclonality, the hallmark of the malignant process.⁴⁷ In many cases, only inflammatory cells are seen. This makes the distinction between chronic uveitis and malignancy induced inflammation very difficult.^{48,49} Rarely, lymphomas can arise in the setting of previous chronic inflammation or after immunosuppression such as for organ transplantation.^{50,51}

Other ocular malignancies

Uveal melanoma and choroidal metastases can present with symptoms and signs of uveitis. In some series, ocular metastases are recognised in up to half of patients before a

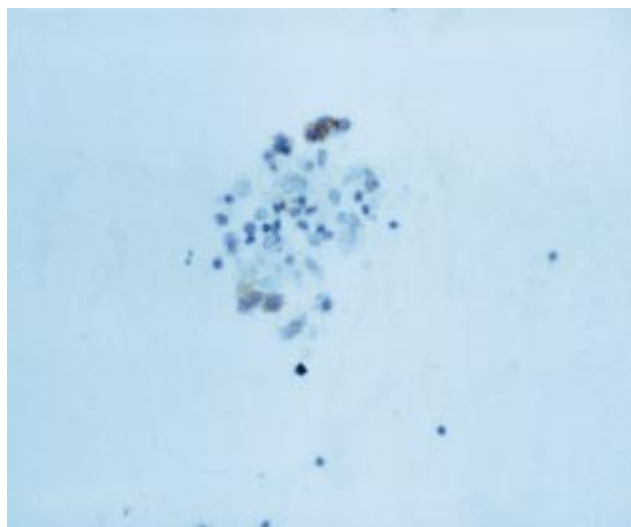


Figure 4 B cells stained with anti-CD20 monoclonal antibody found on vitreous aspirate.

diagnosis of malignancy is made.⁵² Renal and lung carcinomas are most likely to manifest with ocular secondaries. Although breast carcinomas frequently metastasise to the eye, in more than 90% of cases the primary lesion is known at the time of the diagnosis.

Paraneoplastic syndromes have been described in patients of all ages, and, because of the increased incidence of malignancy in the elderly, the incidence of paraneoplasia probably increases with age. Included among these are CAR (cancer associated retinopathy), MAR (melanoma associated retinopathy), LEMS (Lambert-Eaton myasthenic syndrome), and PCD (paraneoplastic cerebellar degeneration). Lung, colon, breast, bladder, uterine, prostate, salivary glands, and melanocytic tumours are associated with CAR and MAR.⁵³⁻⁵⁸ In these conditions, although rare, patients can present with vasculitis,⁵⁴⁻⁵⁷ vitritis, and iridocyclitis.⁵⁴

Suggested clinical approach to elderly patients with uveitis

All patients presenting with uveitis must be asked about known systemic disorders, past or present, with specific questions aimed to identify major systemic problems. As with any type of uveitis, a thorough ocular examination is vital to ensure that the type of uveitis can be accurately diagnosed. This is very important so that further questioning of the patient, and investigations, can be appropriately targeted.

Anterior uveitis alone can be divided into those which are acute and severe, such as occurs in patients who are HLA-B27 positive, or chronic and of variable intensity, such as occurs with sarcoidosis, Fuchs' heterochromic cyclitis, or following herpes zoster ophthalmicus (HZO). The clinical features of these in the elderly are typically the same as in younger patients except that in HZO, patients do not always notice skin vesicles, which may be very few. In both age groups, the cornea is usually anaesthetic. Any patient who has intraocular surgery and who presents with a uveitis which they did not have before surgery must be considered to have an underlying infection. As the organism may be sequestered between the lens and the capsule, it may be difficult both to detect it and to eradicate it. It may be necessary to undertake a partial capsulectomy and put the capsular pieces into culture, and to perform aqueous and vitreous sampling. Intracameral antibiotics are given and often complete removal of the lens and capsule may be necessary to settle the eye.⁵⁹⁻⁶⁰ The use of sys-

temic steroids tends to complicate the judgment of the clinical response and may delay further treatment as the eye may initially settle but reactivate when the dose is reduced. Systemic steroids may be used to finally quieten the eye when the infection has been eradicated with local antibiotics and capsule, plus or minus IOL, removal.⁶¹⁻⁶³

Patients with posterior segment inflammation may have well defined clinical syndromes such as bird shot choroidopathy or sympathetic ophthalmia. The problem is with the patient who has vitritis with little else. These are the ones in whom an underlying lymphoma needs to be eliminated. At present this can be very difficult. Systemic investigations tend to be normal but tests such as a full blood count, liver function tests, and chest x ray should be undertaken. Computerised tomography of the brain may reveal CNS foci, but more often is normal. A vitreous biopsy would seem to be the definitive investigation but, as indicated, may be misleading even when a large sample is taken. Most patients do not have retinal lesions but if they do, these lesions can be biopsied and may allow the diagnosis to be made. Vitreous biopsy may be helpful because T cells and macrophages are more common in the immune mediated disorders than in lymphoma, where B cells predominate. Repeat biopsy may be necessary.

If all investigations are negative and the patient has sight reducing disease, systemic steroids may be used, and the response monitored very carefully. As stated above, however, lymphoma associated uveitis may be steroid responsive, at least initially. New diagnostic techniques offer promise for the future, both for infection⁶⁴ and lymphoma,⁶⁵⁻⁶⁶ but remain to be further developed. In the meantime, we must continue to use conventional diagnostic tests despite their relatively high failure rate. In the future, with a better understanding of the immune mechanisms of eye disease, and more effective ways to distinguish infective, malignant, and autoimmune cellular proliferations, it may be possible to ensure optimal management of the elderly patient with uveitis.

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