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Step by Step: Identifying and Managing Intermediate Uveitis

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Although uveitis is significantly more common than previously believed, according to a large population-based study,[1] it has been described as the "anatomic diagnosis that causes the most confusion among Ophthalmologists."[2] This issue of *Ophthalmology Rounds* reviews the common etiologies of intermediate uveitis, mainly in the adult population, and presents an approach to its diagnosis and stepwise treatment.

Uveitis is divided into anterior, intermediate, and posterior cases, depending on location of the inflammation. Intermediate uveitis refers to intraocular inflammation of the anterior vitreous, pars plana, and peripheral retina. The term "intermediate uveitis" was introduced in 1987 by the International Uveitis Study Group,[3] and in 2005 the Standardization of Uveitis Nomenclature (SUN) Working Group[4] addressed some ambiguities in the original system. When the vitreous is the major site of inflammation, including cases with peripheral vascular sheathing and macular edema, the term "intermediate uveitis" is used. "Pars planitis" refers to the subset of patients with intermediate uveitis who have "snowbank" or "snowball" formation in the absence of an associated infection or systemic disease (ie, idiopathic).[4] Approximately 75% of patients with intermediate uveitis have pars planitis.

Intermediate uveitis is associated with a bimodal age distribution; it is most commonly identified in children and young adolescents (5-15 years) and in young adults (20-40 years); however, it has been reported in young children and very infrequently in the elderly.[2,5] There is no race or sex predilection for intermediate uveitis. Although uncommon, intermediate uveitis has been reported in families, which suggests that environmental or hereditary factors may predispose individuals to developing the disease. There are also studies linking intermediate uveitis with human leukocyte antigen (HLA) haplotypes. The strongest association is with the HLA–DR15 haplotype, which is also associated with multiple sclerosis (MS). Raja et al[6] found that HLA–DR15 was present in 46.9% patients with pars planitis vs. 23.6% of controls.

In their 2004 population-based (N=731 898) study of the incidence and prevalence of uveitis in Northern California, Gritz and Wong[1] calculated an incidence of 52.4 per 100 000 person-years and a period prevalence over 12 months of 115.3 per 100 000 persons. The results of this largest population-based study of uveitis to date represent a 3-fold increase in incidence compared with previous estimates conducted in the United States. Adding the results of a 20-year population-based study of pars planitis by Donaldson et al, the associated incidence and 12-month prevalence of intermediate uveitis were 1.5-2.1 per 100 000 person-years and 4.0-5.9 per 100 000 persons, respectively.[1,7]

Clinical Features

The most common presenting symptoms of intermediate uveitis are blurred vision and floaters,[2] with pain and photophobia being less common. The onset of inflammation is insidious. In the study by Donaldson et al,[7] 73.9% of patients presented with blurred vision and 60.9% presented with floaters, while pain (6.5%), photophobia (6.5%), and redness (4.3%) comprised the remainder of patient complaints. Bilateral disease occurs in about 70%-80% of presenting patients.

The hallmark of intermediate uveitis is the presence of vitritis.[8] Cells are observed in the vitreous during the slit lamp examination and are always present during active disease. Occasionally, the vitritis is sufficiently dense to obscure the view of the retina. This should be differentiated from a vitreous hemorrhage (VH) that may result from neovascularization at the

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vitreous base or the peripheral retina. Vitreous snowballs refer to white- and yellow-coloured aggregates of inflammatory cells that tend to accumulate in the inferior vitreous. Coalescence of these exudates along the pars plana gives rise to snowbanks, and tends to indicate disease progression (Figure 1). Snowbanks can be discontinuous and can form a fine band along the ora serrata or can extend onto both the peripheral retina and pars plana. These are best observed during scleral depression. In addition, the peripheral retina tends to have vascular abnormalities, particularly sheathing or obliteration of small peripheral venules. Ischemia from retinal phlebitis, in combination with angiogenic stimuli from inflammation, can result in neovascularization along the inferior snowbank in up to 10% of cases.[9] Rarely, peripheral neovascularization may evolve into a vascular cyclitic membrane.[2] Anterior segment inflammation is usually minimal in adults, although it may be more common in children and in patients with intermediate uveitis associated with MS. These patients can develop a granulomatous anterior uveitis with mutton-fat keratic precipitates.

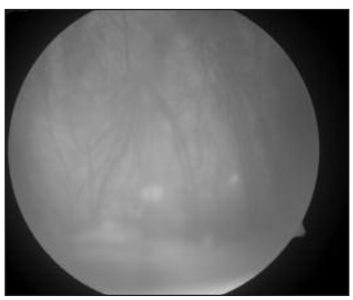
Complications of Intermediate Uveitis

Cystoid macular edema (CME) and cataract formation are the most common causes of intermediate uveitis-associated visual loss, often from chronic inflammation. In a long-term study, Vidovic-Valentincic et al[10] found that 45% of patients progress to CME and 83% to cataracts by 10 years. Cataracts were the most common cause of temporary vision loss, while permanent loss of vision was predominantly the result of CME, secondary to the development of atrophic macular scars. In the same study, less common complications included retinal detachment (10%) and secondary glaucoma (14%). Retinal detachment occurred because of VH and subsequent traction, as well as rhegmatogenous retinal detachment. Glaucoma was related to anterior synechiae, corticosteroids, and seclusio pupillae. Donaldson et al[7] reported epiretinal membranes (ERMs) in 44.4% of patients at 8 years, while 39.6% of subjects had ERMs at 2 years in the study by Raja et al.[6]

The key clinical features found in intermediate uveitis, particularly pars planitis, include the following:[8]

- Bilateral
- Vitreous inflammation
- Snowballs
- Snowbank
- Peripheral vasculitis
- Cystoid macular edema
- Cataracts

Figure 1: "Snowbanks" on funduscopy



Diagnosis

An associated systemic disease can be found in up to one-third of patients with intermediate uveitis.[11] When assessing patients, it is important to take a thorough history and perform a complete physical examination. For example, in a study by Priem et al,[12] the diagnosis of Behçet disease was determined after completing a comprehensive history and physical examination in 6 of the 188 patients with intermediate uveitis.

Intermediate uveitis can also be associated with other systemic diseases, the most common being sarcoidosis and MS. About 23%-26% of patients with sarcoidosis develop intermediate uveitis.[13] In a retrospective 2009 Korean study of biopsy-proven sarcoidosis,[14] 31% of eyes had intermediate uveitis. It has been determined that 7.8%-14.8% of patients with intermediate uveitis/pars planitis develop MS and that 3%-27% of patients with MS develop intermediate uveitis, most commonly bilateral.[13]

Although less common, intraocular lymphoma or "masquerade syndromes" have been associated with uveitis in the elderly.[15] Vitreous cells occurring in sheets are typical for intraocular lymphoma and an examination of the fundus can show subretinal yellow infiltrates through a hazy vitreous.[2] Syphilis, tuberculosis, Lyme disease, toxoplasmosis, toxocariasis, human T-lymphotropic virus Type 1, Epstein-Barr virus, and regional lymphadenitis ("cat-scratch disease") are infectious causes that can present with intermediate uveitis.[13] Before making a diagnosis of pars planitis, one must exclude associated systemic diagnoses. Clues include retinitis, choroiditis, and retinal vasculitis. Table 1 shows the differential diagnoses of intermediate uveitis.

There is no standard panel of tests for intermediate uveitis; however, investigations that cover the main causes are shown in Table 2. These investigations should be guided by the patient's clinical history and physical. The following case study describes a patient presenting with eye symptoms and headaches. The objective of this case study is to stress the importance of diagnosing a systemic disease – in this

Table 1: Differential diagnosis of intermediate uveitis

Noninfectious
- Sarcoidosis
- Multiple sclerosis
- Connective tissue diseases
- Inflammatory bowel disease

Masquerade
- Lymphoma
- Reticulum cell sarcoma

Idiopathic
- Pars planitis

Infectious
- Tuberculosis (TB)
- Syphilis
- Lyme disease
- Peripheral toxocariasis
- Toxoplasmosis
- Whipple disease
- Epstein-Barr virus
- Human T-lymphotropic virus Type 1 (HTLV-1)
- Human immunodeficiency virus

case MS – as an underlying cause of uveitis and describes how appropriate treatment can resolve the condition.

Case Study

A 56-year-old female presents with photophobia, floaters, and an ongoing right-sided headache for 2 months that radiates to both eyes. She denies blurring of vision and scotomas. Her past medical history is significant only for left-sided paresthesias and weakness post-chiropractic manipulation 4 months previously that has since resolved. She is a heavy smoker. The patient is on finasteride, but is taking no ocular medications.

On examination, the patient's visual acuity (VA) is 20/25 in both eyes, with normal reactive pupils and no relative afferent papillary defect. Visual fields by confrontation are full. Intraocular pressure (IOP) is 12 mm Hg in both eyes. Slit lamp examination reveals no conjunctival nodules and a clear cornea with no keratic precipitates. The anterior chamber is deep with 2+ cells per high power field and no flare. There are no iris nodules. Her crystalline lens is clear, with a dusting of pigment. There are a few anterior vitreous cells.

Fundus examination reveals a normal optic nerve with blunted foveal reflex bilaterally. There is periphlebitis inferiorly in the right eye, with normal vessels in the left. There are scattered white spots measuring 50 μm (Figure 2), and retinitis at 7 o'clock in the right eye. There is a pars plana exudate inferiorly in the left eye. A fluorescein angiogram reveals CME in the right eye that is worse than in the left (Figure 3).

The patient is started on prednisolone acetate 1% and ketorolac qid in the right eye. Her work-up includes a complete blood count, erythrocyte sedimentation rate, antinuclear antibodies, rheumatoid factor, cytoplasmic anti-neutrophil cytoplasmic antibody, angiotensin-converting enzyme, Lyme, syphilis serology, chest x-ray, and tuberculin skin test. All are negative except the fluorescent treponemal antibody-absorption test, which is confirmed as false-positive by Western blot assay. The chest x-ray reveals a calcified granuloma at the left apex and compression fractures at T5 and T8.

Because of her recent history of weakness, the patient is referred to the Neurology service and is found to have left upper and lower extremity weakness, left hyperreflexia and a positive Babinski test, and spastic gait with dragging of the left side. Because these findings are suspicious for a lesion of the right hemisphere or cervical spine, the patient undergoes magnetic resonance imaging with gadolinium enhancement. An axial cut of the brain (Figure 4) shows multiple periventricular white matter lesions and, after further work-up, a diagnosis of relapsing-remitting MS is made. The patient's symptoms resolve on prednisolone acetate and topical ketorolac.

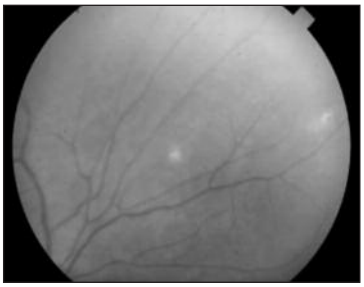
A year later, there is no recurrence of the uveitis and vision is 20/25 in both eyes.

Table 2: Diagnostic screening for intermediate uveitis[7]

- Complete blood count
- Chest x-ray
- Angiotensin-converting enzyme or lysozyme
- Syphilis screen
- TB skin test ± Quantiferon® – TB gold test
- Toxocariasis (ELISA) – if granuloma seen on fundus examination
- Toxoplasmosis (ELISA) or polymerase chain reaction – if aqueous humour or vitreous samples are available
- HTLV-1 (ELISA) – rarely used
- Lyme disease (ELISA) – in endemic regions or if there are systemic symptoms
- MRI of the head – if multiple sclerosis is suspected

ELISA = enzyme-linked immunosorbent assay; MRI = magnetic resonance imaging

Figure 2: White lesion found in the right eye



Management

The first step in determining the treatment course for patients with intermediate uveitis is to exclude the possibility of an underlying systemic disease: infectious, noninfectious, or malignant. Beyond the treatment of an underlying cause, it is critical to exclude infection or malignancy prior to initiating immunosuppressive therapy.[2] The second step is to determine whether therapy is needed. Local therapy is usually indicated if VA is <20/40 or in eyes with snowbanking and extensive neovascularization or vasculitis.[8] Recent opinion is that CME should be treated even if VA is >20/40.[16]

It is also important to assess the spectrum of disease. For instance, in pars planitis, some patients may be asymptomatic and have vitreous cells, vitreous debris, or old snowbanking that does not require treatment. Approximately 75%-90% of patients with pars planitis maintain a visual acuity of 20/40 or better and one-third of patients maintain a normal visual acuity without treatment. In severe cases of pars planitis, disease is aggressive and leads to visual loss secondary to severe CME or RD despite treatment.[6,7]

Figure 3: Cystoid macular edema on fluorescein angiography

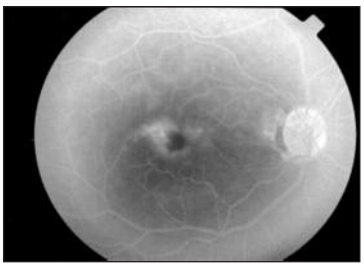
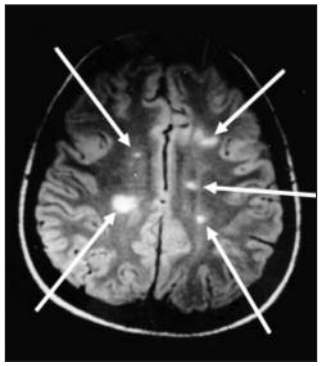


Figure 4: Axial section of MRI of the brain with gadolinium enhancement



Although different regimens are quoted in different publications, the classic "4-step approach," as described by the American Academy of Ophthalmology,[9,17] is perhaps the most reliable framework. The following shows a combination of the classic approach, as well as findings from more recent studies. The basis of treatment depends on disease severity and is summarized below, with a more detailed explanation in Steps 1–4.

- Topical corticosteroids for the initial anterior chamber reaction
- Periocular corticosteroids for vitritis and CME
- Cryoretinopexy for snowbanks with exudative retinal detachment or neovascularization
- Systemic medications (systemic steroids, then immunosuppressives/biological agents) or vitrectomy for refractory cases.

Step 1

Topical steroids such as prednisolone acetate 1% tend to be beneficial for the initial anterior chamber reaction, as well as topical nonsteroidal anti-inflammatories (NSAIDs) for chronic uveitis and CME. Systemic NSAIDs such as diclofenac 75 mg po may be employed for treatment of CME and chronic uveitis.

Step 2

First-line therapy beyond topical medication to reduce inflammation and improve CME is usually periocular corticosteroid injections, routinely using a posterior subtenon route. The most common treatment is triamcinolone acetate at a dose of 40 mg/mL, repeated every 4 weeks until 4 injections have been administered. Beyond 4 weeks, periocular injections may be repeated as needed. If there is no response after 4 weeks or for bilateral cases, it may be necessary to proceed to Step 3. Injections should not exceed 5-6 in one year.

Patients should be aware of the potential complications of periocular depot corticosteroids, particularly ptosis (in about 10%), IOP increases (in 20%-30% of patients at 3 weeks, but maximum at 14 weeks), and cataract formation in the long term. Less common complications of posterior subtenon injections include globe perforation and retrobulbar hemorrhage.

Intravitreal triamcinolone acetonide is also used in noninfectious intermediate uveitis for chronic inflammatory CME in refractory cases. The dose is usually 2-4 mg in 0.05-0.1 mL. Complications include an IOP rise in 30%-43% (1% needing trabeculectomy),[18] cataracts (29%), and the risk of bacterial endophthalmitis (1 in 500 to 1 in 1000).[17] VH is another complication of intravitreal triamcinolone injections. In a retrospective study by Kok et al,[19] intravitreal injections of 4 mg/0.1 mL of triamcinolone acetate resulted in a mean improvement in VA at 4 weeks, and a cessation of the dose of immunosuppressive agents and oral steroids in 54.5% of patients. There was also a mean IOP rise of 10.3 mm Hg, with 43% of patients having an IOP rise of >10 mm Hg and 50% needing antiglaucoma medications; however, no trabeculectomies were required.[19]

Step 3

The next step in patient management involves use of inferior retinal cryotherapy or peripheral retinal laser photocoagulation. Indications for these procedures include CME, intermediate uveitis with or without neovascularization of the vitreous base, and VH. Cryotherapy tends to have an effect in 2-3 weeks with an average duration of efficacy of 3-6 months; however, patient benefit may be as long as 18 months. Devenyi et al[20] reported an improvement in vision and decreased inflammation in 75% of eyes treated with cryopexy that had intermediate uveitis and neovascularization of the vitreous base. There were a few complications, including transient worsening of vitritis (5%), VH (5%), and tractional retinal detachment (7.5%).[21] A small study (10 eyes in 6 patients) by Park et al[22] revealed that peripheral scatter laser photocoagulation was at least as effective as cryotherapy in inducing regression of neovascularization.

The proposed mechanism of action for these methods is obliteration of ischemic tissue leading to regression of neovascularization, as well as a reduction in inflammation due to destruction of the inflammatory stimulus. Cryotherapy is performed by applying a double row of transconjunctival cryopexy using a freeze-thaw technique, approximately 1 o'clock posteriorly to the area of active disease. With laser photocoagulation, burns should be placed confluently in 3-4 rows slightly posterior to the snowbank, extending to the equator posterior to the snowbank on each side. Care should be taken to avoid directly treating the snowbank, as this can lead to contraction of the vitreous base, resulting in secondary retinal tears and, inevitably, rhegmatogenous retinal detachment.

Step 4

Immunosuppressive therapy in the form of systemic corticosteroids is indicated for severe uveitis with or without associated systemic disease. Prednisone is started at 0.5-1 mg/kg/day (roughly 40-80 mg/day), then tapered every 4-6 weeks until a maintenance dose of ≤7.5 mg daily is reached. Intravenous (IV) methylprednisolone can be given as a pulse dose, 250-1000 mg/day IV over 1 hour for 3 days. Adverse events (AEs) associated with systemic cortico-

steroids are well recognized; the most common short-term AEs are increased appetite, elevated blood glucose levels, insomnia, and increased moodiness.[6] Longer-term AEs include osteoporosis, diabetes, and weight gain. Patients should be warned about the uncommon AEs of avascular necrosis of the humeral head. Systemic AEs of IV methylprednisolone include cardiac arrhythmias and psychoses. Long-term ophthalmic AEs include cataracts and glaucoma (similar to the long-term complications of chronic uveitis). Supplemental calcium and vitamin D, as well as a histamine receptor blocker or proton pump inhibitor, should be given to patients on systemic corticosteroid therapy.

In a recent randomized trial comparing pars plana vitrectomy (PPV) with immunomodulatory agents,[23] PPV resulted in better VA with removal of inflammation, as well as relieved vitreoretinal traction (that contributes to CME). The use of PPV or immunosuppressive agents following a trial of corticosteroids is controversial. PPV treats intermediate uveitis by removing inflammatory mediators from the eye and is indicated for persistent VH, dense vitreous debris, ERMs, and neovascularization. This can be combined with a membrane peel in the case of ERMs or lensectomy in the case of cataracts. Stavrou et al[24] performed therapeutic vitrectomy in 43 eyes, resulting in uveitis improvement in 44% and CME resolution in 32.4%. This may reduce the need for long-term immunosuppression. Complications include retinal detachment, recurrent VH, cataracts, and increased IOP.

Immunomodulatory agents are indicated in patients with bilateral disease, nonresponders to long-term periocular corticosteroids, or patients with unacceptable AEs from corticosteroids. This treatment usually requires co-care with Rheumatologists or Internal Medicine specialists to monitor patients for appropriate dosing and to address any adverse events.

Methotrexate is perhaps the most common immunomodulatory drug and tends to work well with few AEs. A 2009 retrospective cohort study[25] revealed that 47.4% of patients with intermediate uveitis had no inflammation at 6 months, and the disease was controlled in 75% at 1 year. AEs such as elevated liver enzymes, nausea, fatigue, as well as more uncommon AEs such as interstitial pneumonitis, stomatitis, and cytopenia did not seem to be an issue once doses were monitored.

Other immunomodulatory drugs reported to be effective include azathioprine[26] (89.8% at 1 year), cyclosporine[27] (51.8% at 1 year), mycophenolate mofetil[28] (76.7% at 1 year), and cyclophosphamide[29] (numbers too small to determine its effect in intermediate uveitis).

Prognosis

The visual prognosis of patients with intermediate uveitis depends on a number of factors. As previously noted, 75% of patients are diagnosed as having idiopathic pars planitis. In this group, 75% of eyes achieve a best-corrected (BC) VA of ≥20/40 at 10 years;[7] similarly 90% achieve a BCVA of ≥20/40 in the better eye at 2 years.[6] Factors associated with a poor prognosis include cataracts, optic neuritis, ERMs, and CME.[6,7]

Recent data have revealed that CME in intermediate uveitis is strongly associated with smoking. Thorne et al[30] found a 4-fold increased risk of CME in intermediate uveitis patients who smoke compared with nonsmokers, while a study by Lin et al[31] revealed an odds ratio of 8.4 in patients with intermediate uveitis and CME compared with an OR of 1.5 for patients with intermediate uveitis alone. Smoking is a modifiable risk factor that should be discussed with all patients with uveitis, especially those diagnosed with intermediate uveitis.

Intermediate Uveitis in the Pediatric Population

The incidence of uveitis in the pediatric population is markedly lower than that in adults, at approximately 30 cases per 100 000. Intermediate uveitis accounts for about 20% of pediatric uveitis,[32] the vast majority being pars planitis. Children typically present with complaints of blurred vision and floaters, but about 25% with intermediate uveitis may present asymptomatically.[33] Children tend to have a worse VA than adults at initial presentation; Guest et al[33] found that this difference was statistically significant at the 2-year follow-up (6/10 versus 6/7; P=0.026), but not at 5 years. The long-term prognosis is good; a retrospective cohort study in 32 patients revealed that 90% had a VA ≥6/20 at 5 years.[34] CME is the most common cause of vision loss (the same as for adults) and papillitis was the most common complication in 60%-75% of patients.[34,35] Topical and periocular steroids are the main treatment modalities. Some authors have found a high rate of remission in pediatric patients with pars planitis treated with vitrectomy. A clear indication for vitrectomy is vitreoretinal traction with retinal detachment.[33,35] Overall, 50% of pediatric patients with pars planitis attain remission at 5 years.[36]

Conclusion

Although intermediate uveitis is not the most common subset of uveitis, it is the "anatomic diagnosis that causes the most confusion among Ophthalmologists."[5] Most cases of intermediate uveitis are pars planitis, but it is important to rule out other causes as treatment of any underlying systemic disease is essential. Clearly, CME, cataracts, and ERMs are the main complications of intermediate uveitis and the cause of decreased vision. Treatment should be individualized based on disease severity, using a stepwise approach. If an underlying systemic condition is found, treatment should be aimed at the systemic condition. Although pars planitis and intermediate uveitis are chronic conditions, with a better understanding of the mechanisms of inflammation and a more targeted treatment approach, better control of this type of uveitis can be achieved, thus decreasing the incidence of complications and improving the prognosis for these patients.

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