Systemic diseases associated with intermediate uveitis

STEVEN A. BOSKOVICH, MD; CAREEN Y. LOWDER, MD, PHD; DAVID M. MEISLER, MD; FRONCIE A. GUTMAN, MD

■ **BACKGROUND** Intermediate uveitis is characterized by vitreal inflammation with associated inflammation of the vitreous base and peripheral anterior retina and choroid. It may be found as an isolated and idiopathic condition or in association with systemic disorders such as multiple sclerosis and sarcoidosis.

■ **OBJECTIVE** To identify the clinical features of intermediate uveitis and assess its association with systemic diseases.

■ **METHODS** Retrospective study of 83 patients presenting with intermediate uveitis between 1970 and 1991.

■ **RESULTS** Evidence of systemic disorders was found in 26 of 83 patients (31.3%). Of these 26 patients, 10 had presumed sarcoidosis, 6 had multiple sclerosis, 2 had isolated optic neuritis, 2 had inflammatory bowel disease, 4 had isolated thyroid abnormalities, and 2 had histories suggestive of Epstein-Barr virus infection. Associated ocular findings included cystoid macular edema, peripheral retinal perivascular sheathing, cataracts, posterior vitreous detachment, fine keratic precipitates, preretinal macular fibrosis, retinal tears, retinal detachment, and optic disc edema.

■ **CONCLUSIONS** Patients with intermediate uveitis may have associated systemic diseases and should have careful follow-up with regular systemic evaluation.

■ INDEX TERMS: UVEITIS, INTERMEDIATE; SARCOIDOSIS; MULTIPLE SCLEROSIS; OPTIC NEURITIS; INFLAMMATORY BOWEL DISEASES; THYROID DISEASES; EPSTEIN-BARR VIRUS ■ CLEVE CLIN J MED 1993; 60:460–465

From the Department of Ophthalmology, The Cleveland Clinic Foundation.

Address reprint requests to C.Y.L., Department of Ophthalmology, A31, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.

THE INTERNATIONAL Uveitis Study Group has proposed the term "intermediate uveitis" to describe ocular inflammation involving the vitreous base and far anterior retina and choroid.[1] The spectrum of clinical findings in intermediate uveitis has included vitreal inflammation, pars plana exudates, peripheral retinal vascular sheathing, and minimal associated anterior segment inflammation. When it has occurred in seemingly healthy individuals, it has been called pars planitis, chronic cyclitis, peripheral uveitis, or basal retinochoroiditis.

The numerous descriptive names used for this condition reflect the lack of an understood pathogenesis.[2] Adding to the confusion about its etiology are reports of intermediate uveitis associated with systemic conditions such as multiple sclerosis, sarcoidosis, inflammatory bowel disease, Lyme disease, Behçet's disease, syphilis, Vogt-Koyanagi-Harada syndrome, Whipple's disease, and amyloidosis.[3–10]

We report the association of systemic disorders with intermediate uveitis in our referral practice,

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document intermediate uveitis as a heralding inflammatory event for underlying diseases, and describe the clinical features of this condition.

PATIENTS AND METHODS

We reviewed the records of 83 patients (42 women and 41 men) at The Cleveland Clinic Foundation who were found to have intermediate uveitis between 1970 and 1991. All patients presented with ocular symptoms or were referred with ocular inflammation. Intermediate uveitis was defined as the presence of vitreal inflammation in one or both eyes with associated inflammatory deposits in the vitreous base or on the pars plana in at least one eye and minimal anterior chamber inflammation. Patients with unilateral and bilateral inflammation were included. Patients were excluded if they had a predominantly posterior uveitis, if they had more than mild anterior chamber reaction, or if the anterior chamber inflammation was granulomatous in appearance on presentation. The average age at which intermediate uveitis was first observed was 23.3 years (range 4 to 54 years). The mean follow-up period after the diagnosis of intermediate uveitis was 5.7 years (ranging up to 21 years).

Associated systemic disorders were identified from the patient history and the laboratory evaluation. The diagnosis of sarcoidosis is usually established by systemic findings with histopathologic and radiologic abnormalities. In the absence of systemic findings, the diagnosis of ocular sarcoidosis is presumptive.[11] The diagnosis of presumed sarcoidosis was based on clinical suspicion and on the findings of anergy and abnormal serum lysozyme or angiotensin-converting enzyme levels; no patients had biopsies to confirm the diagnosis. The diagnosis of multiple sclerosis was based on Poser's classification.[12]

Inflammatory bowel disease was documented by colonoscopy. Thyroid dysfunction was documented by history and need for thyroid replacement therapy. Lyme disease antibody titers were measured in two patients. The most commonly obtained studies in all patients included chest roentgenograms, serologic tests for syphilis, complete blood counts, serum electrolyte levels, liver function tests, the erythrocyte sedimentation rate, and serum angiotensin-converting enzyme and lysozyme levels.

The chronologic order in which the diagnoses of intermediate uveitis and the associated systemic disorders were made was noted. Associated ocular findings in patients with intermediate uveitis were documented.

TABLE 1
SYSTEMIC CONDITIONS ASSOCIATED WITH INTERMEDIATE UVEITIS (N = 26)

	Noted prior to diagnosis	Developed after diagnosis	Total*
Presumed sarcoidosis	1	9	10
Multiple sclerosis	3	3	6
Isolated optic neuritis	1	1	2
Thyroid disease†	5	0	5
Inflammatory bowel disease	1	1	2
Epstein-Barr virus	2	0	2

*Total >26 because one patient had thyroid disease and inflammatory bowel disease
†Graves' disease (2), Hashimoto's thyroiditis (1), unspecified hypothyroidism (2)

RESULTS

Systemic disease associations were noted in 26 of 83 patients (31.3%) with intermediate uveitis (*Table 1*). In these 10 men and 16 women, the mean age at presentation with intermediate uveitis was 24.7 years.

Evidence for presumed sarcoidosis was found in 10 patients (12%). One had sarcoidosis for 2 years before developing intermediate uveitis. In 4 patients, presumed sarcoidosis was diagnosed during the evaluation of the initial episode of intermediate uveitis. The remaining 5 patients were found to have laboratory evidence of presumed sarcoidosis beginning 2.5 to 20 years after intermediate uveitis was first observed. Seven of the 10 patients with presumed sarcoidosis presented with exudation predominantly from the pars plana, 2 presented with vitreous "snowball" opacities without pars plana exudates, and one presented with both. Only 2 of the 10 had peripheral retinal perivascular sheathing noted on initial evaluation, but half eventually demonstrated this on follow-up. Cystoid macular edema developed during the course of evaluation in 5 of the 10 patients.

Multiple sclerosis was associated with intermediate uveitis in six patients (7.2%). Three had clini-

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TABLE 2
ASSOCIATED OCULAR FINDINGS IN INTERMEDIATE UVEITIS

	Idiopathic pars planitis (N=57)	Intermediate uveitis with associations (N=26)
Cystoid macular edema	34 (60%)*	12 (46%)*
Peripheral retinal perivascular sheathing	16 (28%)	14 (54%)
Cataract	15 (26%)	6 (23%)
Posterior vitreous detachment	12 (21%)	7 (27%)
Fine keratic precipitates	10 (18%)	5 (19%)
Preretinal macular fibrosis	8 (14%)	5 (19%)
Retinal tears	4 (7%)	4 (15%)
Retinal detachment or traction	4 (7%)	6 (23%)
Optic disc edema	3 (5%)	5 (19%)

*Total >100% because multiple findings in individual patients are listed separately

cally suspect multiple sclerosis 1 to 8 years before intermediate uveitis was first observed, and three were found to have multiple sclerosis 6 to 15 years after intermediate uveitis was first observed. Two patients with intermediate uveitis were noted to have isolated episodes of optic neuritis without other clinical signs of multiple sclerosis; one episode occurred "several" years prior to the development of intermediate uveitis, the other, 2 months after the diagnosis.

Intermediate uveitis was associated with thyroid disease in two patients with Graves' disease (one of whom also had inflammatory bowel disease and Charcot-Marie-Tooth disease), in one patient with Hashimoto's thyroiditis, and in two patients with unspecified hypothyroidism. All of these thyroid disorders were noted several years before the onset of intermediate uveitis.

Both patients with inflammatory bowel disease had multiple diagnoses. One patient had erythema nodosum 2 years before and Crohn's disease 7 years after the onset of intermediate uveitis. In the other patient, Graves' disease was diagnosed 24 years before the onset of intermediate uveitis, and inflammatory bowel disease was diagnosed 4 years after the onset of intermediate uveitis. This patient also was found to have Charcot-Marie-Tooth disease, a chronic degeneration of peripheral nerves.

One patient reported contracting mononucleosis 6 months before the diagnosis of intermediate uveitis and had a history of hypogammaglobulinemia of 12 years' duration. Another patient with a weakly positive antinuclear antibody titer (1:40) had a history of mononucleosis that began 1 year before the onset of intermediate uveitis.

Fifty-seven of 83 patients had idiopathic pars planitis (31 men and 26 women). Their mean age at presentation was 22.6 years. They either had no identifiable underlying disease or had other systemic diagnoses of uncertain significance including essential hypertension, peptic ulcer disease, nephrolithiasis, hemorrhoids, pilonidal cyst, migraine headache, diabetes mellitus, degenerative osteoarthritis, chronic otitis, polycystic kidneys, hiatal hernia, Gilbert's syndrome, mitral valve prolapse, coronary artery disease, sleep apnea, and atherosclerotic vascular disease. One patient with idiopathic pars planitis had a long-standing history of bronchial asthma.

Nine of the patients with idiopathic pars planitis had abnormal laboratory test results other than those already described. Five of these patients had weakly positive antinuclear antibody titers, three at a dilution of 1:40 (one of these patients had a positive purified protein derivative test for tuberculosis 1 year before the onset of intermediate uveitis), and two at a dilution of 1:80. One of two patients with mildly elevated liver function enzymes had migratory polyarthritis 30 years before the onset of intermediate uveitis. One patient had antibodies against hepatitis core antigen, and one patient had human leukocyte antigen (HLA) HLA-B27.

Associated ocular findings included cystoid macular edema, peripheral retinal perivascular sheathing, cataract, posterior vitreous detachment, fine keratic precipitates, preretinal macular fibrosis, retinal tears, retinal detachment, and optic disc edema. These findings were similar in the patients with and without systemic associations (*Table 2*).

DISCUSSION

This review of a large series of patients presenting with intermediate uveitis reveals the association of systemic conditions in 26 of 83 patients (31.3%). The most common associated disorder in our pa-

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tients was presumed sarcoidosis; its prevalence in our patients (12%) approximates that in other studies (2% and 9.7%) in patients with pars planitis.[8,9] The incidence of intermediate uveitis in patients with known sarcoidosis has been reported to be 4% to 18%.[13–15] One of our patients had sarcoidosis before intermediate uveitis was diagnosed, and two others had laboratory evidence of sarcoidosis on initial evaluation of their intermediate uveitis. However, seven other patients in our series who presented with the clinical findings of intermediate uveitis without other clinical evidence of sarcoidosis subsequently were discovered to have clinical or laboratory evidence of it.

Well-documented associated ocular findings in sarcoidosis have included granulomatous anterior uveitis, iris nodules, iridocyclitis, vitreal inflammation, vitreous snowballs, retinal perivascular sheathing, choroidal granulomas, lacrimal gland involvement, conjunctival nodules, optic nerve granuloma, edema, and neovascularization.[16,17] While all of our patients with presumed sarcoidosis had vitreal inflammation, only three presented with vitreous snowball opacities, and only two presented with peripheral retinal perivascular sheathing. None had other signs of sarcoid ocular disease.

The second most common associated disorder was multiple sclerosis; its prevalence of 7.2% in our series approximates reported rates of 8% and 11%.[8,9] If the two patients with isolated optic neuritis were assumed to have multiple sclerosis, the prevalence of this central nervous system disorder would be 9.6% in our study. No temporal relationship between the onset of the uveitis and the systemic disease was apparent in our patients, as half had intermediate uveitis before signs of multiple sclerosis were manifested, and half developed intermediate uveitis afterward. This lack of temporal relationship has also been reported by others.[3,8,18]

A multitude of studies have reported an incidence of intermediate uveitis in multiple sclerosis ranging between 1% and 27%.[3,4,8,9,14,19] A well-documented associated ocular finding in multiple sclerosis has been peripheral retinal perivascular sheathing.[3,8,9,18,20,21] Similarly, in our study, four of six patients with multiple sclerosis, as well as one patient with optic neuritis, demonstrated peripheral retinal perivascular sheathing. The significance of this finding in multiple sclerosis is not clear. One histopathologic study identified retinal perivascular inflammatory infiltration in multiple sclerosis.[22]

The finding of thyroid disease in patients with intermediate uveitis is of unknown significance. Our three patients with long-standing hypothyroidism may have had Hashimoto's thyroiditis. These patients displayed pars plana exudates and cystoid macular edema. Thyroid microsomal autoantibody titers, which were not obtained, would have helped to confirm this diagnosis. Both of our patients with Graves' disease had pars plana exudates, cystoid macular edema, and vitreoretinal tractional abnormalities as well.

Pars planitis has previously been described in two patients with inflammatory bowel disease, specifically, ulcerative colitis.[6] In contrast, one of our two patients with inflammatory bowel disease had Crohn's disease, and the other had an unspecified inflammatory bowel disease. Both of our patients displayed pars plana exudates, cystoid macular edema, vitreous traction, and retinal tears. One of these patients also displayed peripheral retinal perivascular sheathing.

The association between Epstein-Barr virus infection and intermediate uveitis has been described.[8] Two of our patients described a history suggestive of Epstein-Barr virus infection before the onset of their uveitis. Neither of these patients had confirmatory Epstein-Barr virus titers measured by us. However, serologic studies to prove causality in past or chronic Epstein-Barr virus infections are sometimes difficult to interpret.

No significant systemic disease association could be identified in 57 of the 83 patients. It is possible that idiopathic pars planitis may stand alone as a diagnostic entity. However, it is also possible that in some patients with intermediate uveitis, an underlying systemic disease may not be obvious. The underlying disorder could be subclinical and already exist. For example, oligoclonal bands have been described in a patient with pars planitis without clinical evidence for multiple sclerosis.[23] Possibly, intermediate uveitis may be the harbinger for underlying systemic disease, that is, a systemic disorder may not surface clinically or laboratory test results may not become abnormal until after intermediate uveitis is first observed. In some patients with pars planitis, other signs of associated underlying systemic conditions may never surface clinically. Further, distinguishing between diseases associated with intermediate uveitis may be difficult. For example, central nervous system sarcoidosis may mimic multiple sclerosis by clinical and laboratory evaluation.[24,25]

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Many of the well-recognized diseases associated with intermediate uveitis, such as sarcoidosis and multiple sclerosis, are thought to have an autoimmune basis.[4,16] This is also true of the other systemic disease associations found in this study. For example, primary thyroid gland failure is most commonly caused by autoimmune thyroiditis, and Graves' disease is thought to result from a defective stimulated overproduction of thyroid autoantibodies.[26] Ulcerative colitis is sometimes considered a hypersensitivity reaction associated with circulating antibodies.[6] Despite the possibility that pars planitis may not be pure in etiology and that patients with pars planitis may eventually manifest one of many systemic disorders, investigators have explored a common immunopathogenesis for this group of patients. Evidence for this includes a suggestion of abnormalities in cellular immunity: these patients have increased numbers of CD4 T cells found in the pars planitis "snowbanks" and abnormal ratios of helper T cells to suppressor T cells in aqueous and serum.[5,27] Further, although most investigators have been unable to document an HLA association with pars planitis, one recent study found an increased incidence of the HLA-DR2/DQw1 haplotype in these patients.[28] Interestingly, the DR2 antigen is also found with increased incidence in patients with multiple sclerosis.

This retrospective study is limited by the extent of historical and physical data recorded and laboratory testing information available at the time the patients were evaluated. Possibly, an underlying systemic disease was overlooked because we were unaware of a specific disease association, or confirmatory laboratory studies were not available at that time. For example, Lyme disease has only recently been shown to give rise to clinical findings similar to that found in pars planitis.[29] Further, other diseases not apparent to us now may become apparent with increasing clinical knowledge and laboratory advances in the future. However, our study suggests that patients with intermediate uveitis may have associated systemic disorders and suggests possible avenues of systemic evaluation. Since intermediate uveitis may herald underlying systemic disease, a careful systemic evaluation should be done prior to assigning the diagnosis of pars planitis to a patient with intermediate uveitis. Further, patients with pars planitis should be evaluated periodically for underlying associated systemic conditions.

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