

Intermediate Uveitis: Its Relationship with Multiple Sclerosis and Unique Management Considerations

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Abstract

This case report demonstrates the appropriate diagnosis and management of intermediate uveitis associated with multiple sclerosis. Though uveitis is not the most common ocular inflammatory sign in multiple sclerosis, a careful case history and evaluation should be conducted in patients with intermediate uveitis to rule out multiple sclerosis. This is especially important prior to the initiation of TNF-alpha inhibitors in cases of recalcitrant uveitis. Eye care providers must know how to screen for multiple sclerosis in patients with intermediate uveitis and the appropriate management.

KEYWORDS:

Multiple sclerosis, uveitis, TNF-alpha inhibitors

INTRODUCTION

Intermediate uveitis and multiple sclerosis (MS) are immune-mediated conditions that affect millions of people worldwide. Intermediate uveitis, also known as pars planitis, has been shown to be associated with MS.^{1,2} Understanding this association is critical as early diagnosis and treatment of MS may decrease the incidences of relapse and progression.³ Also, TNF-alpha inhibitors, which are often used to treat recalcitrant uveitis, are known to promote the progression of demyelinating disease.^{4,5} The following case demonstrates the appropriate diagnosis and management of MS-associated uveitis and reports its defining signs and symptoms.

CASE REPORT

A 36-year-old Caucasian male presented with symptomatic floaters. He had a history of chronic, bilateral, non-infectious intermediate uveitis starting at the age of 32. His prior work-up included QuantiFERON gold (QFT), fluorescent treponemal antibody absorption (FTA-ABS), rapid plasma reagin (RPR), angiotensin-converting enzyme (ACE), and a chest x-ray, which were all negative. The patient had previously failed to respond to methotrexate and mycophenolate mofetil, and was currently managed with 5 mg of oral prednisone daily. His uncorrected visual acuity was reduced to 20/50+ in the right eye and 20/40 in the left eye without improvement on pinhole. His pupils were equal, round and reactive to light, without afferent pupillary defects. He had no extraocular motility restrictions, his confrontation visual fields were full, and his intraocular pressures were 19 and 17 mmHg in the right and left eyes, respectively. Slit lamp examination revealed trace injection of the bulbar conjunctiva, fine keratic precipitates, 2+ cell and 1+ flare bilaterally. The dilated fundus exam showed 2+ posterior subcapsular cataracts (PSC) in both eyes, 2+ vitreous haze with inferior snowballs in the right eye and 0.5+ vitreous haze in the left. Optic nerve cup-to-disc ratios were 0.2 and 0.3 in the right and left eyes. After treatment options were discussed with the patient, the decision was made to trial the TNF-alpha inhibitor adalimumab. The patient was referred to a neurology clinic to rule out

demyelinating disease. In the interim, he was treated with prednisone 20 mg daily PO and prednisolone acetate was prescribed three times a day OU. The topical steroid was prescribed at a reduced dose due to a history of steroid-response ocular hypertension.

During his neurology examination, the patient disclosed repeated episodes of left arm numbness. A T2-weighted MRI of the brain with FLAIR image processing revealed four hyperintense foci in the supratentorial region. Analysis of the cerebrospinal fluid demonstrated oligoclonal bands. The patient was diagnosed with MS and started on dimethyl fumarate. Due to the concern that the adalimumab recommended to treat his uveitis could adversely affect the course of his MS disease, his future uveitis treatment plan was limited to topical, local and systemic steroids with close monitoring.

DISCUSSION

Intermediate uveitis is defined by the Standardization of Uveitis Nomenclature (SUN) working group as inflammation occurring primarily in the vitreous.⁶ Clinical signs include vitreous cells, haze, inflammatory aggregates known as snowballs, and exudates along the inferior pars plana known as snowbanks. Less commonly, peripheral vascular sheathing may be present. Intermediate uveitis can lead to many sight-threatening complications including cataracts, glaucoma and cystoid macular edema.^{2,7}

Multiple sclerosis is an inflammatory autoimmune disease characterized by plaques in the white and gray matter in the central nervous system.^{3,4} The disease can affect both the afferent and efferent pathways of the visual system, and can cause inflammation in multiple tissues within the eye.⁸ The most common ocular manifestations of MS are optic neuritis, internuclear ophthalmoplegia and, less frequently, uveitis.^{9,10} Ocular manifestations are thought to occur because the central nervous system and the eye have the same embryologic origins.¹¹ The co-expression of antigens present in both the uvea and the central nervous system sensitizes the eye to inflammation following an immune-mediated inflammatory event in the CNS.¹² A genetic predisposition to uveitis-associated MS has also been hypothesized.¹³

A diagnosis of MS carries a 10-fold increased risk of developing uveitis, as intraocular inflammation is seen in 0.82-9.33% of MS patients.^{11,14} Conversely, MS is diagnosed in 1.03-3% of individuals with all types of uveitis.^{1,2,11} However, when we consider specifically at patients with intermediate uveitis, the incidence of MS is significantly higher (8-12%).² The typical presentation of ocular inflammation associated with MS is a chronic, bilateral, intermediate uveitis. Bilateral granulomatous anterior uveitis and retinal vasculitis occur less frequently.^{1,12,15} Other factors that increase the chance of diagnosis of MS in intermediate uveitis patients include female gender, age over 25 years, and increased latitude.² The onset of uveitis can precede the onset of MS in 49-78% of cases.^{12,15,16} Though intermediate uveitis is rare, when encountered, MS should be ruled out.² Patients diagnosed with intermediate uveitis should be made aware of systemic MS symptoms such as numbness, tingling or weakness of limbs, tremors, or unsteady gait. Questions regarding their presence should be included in all follow-up examinations.^{3,8} Positive symptoms warrant investigation with neuro-imaging and referral to neurology for further evaluation.¹⁷

UVEITIS TREATMENT

The treatment of non-infectious uveitis involves a step-wise approach, advancing to sequentially more aggressive therapies as necessary.^{18,19} Clinicians must select the appropriate level of treatment by considering age, disease type and severity, medical and social history, and barriers to treatment.¹⁹

Corticosteroids are the typical first step in the management of intermediate uveitis as they provide robust control of inflammation. Their mechanism of action creates a rapid, widespread response by binding intracellular glucocorticoid receptors, leading to the inhibition of all cytokine transcription. However, this nonspecific inhibition also produces many adverse side effects which make steroids unsuitable for long-term treatment. These include, but are not limited to, elevated intraocular pressure, glaucoma, cataracts, and, specific to oral steroids, increased fracture risk and adrenal suppression.¹⁸⁻²⁰

Systemic immunomodulatory therapy is the next level of treatment available. Uveitis, regardless of anatomic location, often cannot be controlled by reasonable doses of topical or systemic steroids. Immunomodulatory therapy has been shown to be safe and effective at controlling intraocular inflammation and reducing exposure to the harmful side effects of high-dose or long-term treatment with steroids.^{20,21} The three main categories of immunomodulatory

therapy are antimetabolites, T-cell inhibitors, and alkylating agents. Antimetabolites are often used as a first-line therapy and include methotrexate, mycophenolate and azathioprine. These medications work by inhibiting various steps of DNA synthesis in T and B-cells. T-cell inhibitors and alkylating agents are used less frequently for uveitis due to poor side effect profiles.¹⁸⁻²⁰

Biologics, such as monoclonal antibodies (usually with a -mab suffix), are the final stage of treatment for non-infectious uveitis and include adalimumab and infliximab. These drugs target tumor necrosis factor alpha (TNF-alpha), a cytokine with pleiotropic effects important to maintaining homeostasis.^{22,23} TNF-alpha has also been shown to be involved in intraocular inflammatory disease. The most commonly used biologic is adalimumab, which was approved to treat noninfectious intermediate, posterior, and panuveitis in 2016.^{18,24} Since then, it has been used extensively for severe and recalcitrant cases of noninfectious uveitis. Adalimumab is effective in both reducing active inflammation and delaying the recurrence of uveitis flares, allowing steroids to be tapered or discontinued. The medication is typically given as a subcutaneous injection every two weeks and can be used alone or in conjunction with other immunomodulatory therapies.^{25,26}

Higher levels of TNF-alpha present in the cerebral spinal fluid have been associated with progressive MS disease states and severity.^{22,27,28} Historically, this provided a rationale for treating MS patients with TNF-alpha inhibitors. However, preliminary studies of these drugs were terminated prematurely because MS patients experienced exacerbation of gadolinium-enhancing lesions and symptoms after receiving TNF-alpha inhibitor treatment.^{4,5} These adverse effects are not specific to a single TNF-alpha inhibitor, and appear to be shared by all drugs in the class.²⁹

The pleiotropic effects of TNF-alpha are achieved via two bioactive forms of TNF: soluble TNF and transmembrane TNF. Soluble TNF interacts with a receptor that has a death domain and causes systemic inflammatory effects. Transmembrane TNF interacts with a receptor that activates genes important for homeostasis and resolution of inflammation.^{22,23} At this time, TNF-alpha inhibitors are not selective for soluble and transmembrane TNF, but rather inhibit the actions of both.²⁷ Though the pathogenesis of central and peripheral neuropathies is unknown, a more holistic view of the role of TNF-alpha may help to explain the growing number of reported cases of demyelinating disease associated with TNF-alpha inhibitors.^{23,30} Prior to initiating TNF-alpha inhibitors for treatment of intermediate uveitis, a diagnosis of MS should be excluded since these medications are implicated in the progression of demyelinating disease.^{4,5} Neuroimaging should be performed to screen for demyelinating lesions and positive findings again warrant further investigation by neurology.

TAKE HOME POINTS

A diagnosis of MS is associated with significant changes in quality of life, healthcare costs, and morbidity. Patients with intermediate uveitis carry an increased risk of an MS diagnosis compared to the general population. MS-associated uveitis is most often intermediate, bilateral and chronic. The risk of an MS diagnosis increases for intermediate uveitis patients who are female, over the age of 25 and have bilateral disease. A diagnosis of intermediate uveitis should prompt further investigation of MS symptoms, particularly because the onset of uveitis can precede the onset of MS. Clinicians should also review MS symptoms at follow-up examinations. Positive findings necessitate brain imaging with possible referral to neurology pending outcomes. TNF-alpha inhibitors are used to treat recalcitrant uveitis. It is recommended that patients be screened for demyelinating disease before initiating TNF-alpha inhibitors. ●

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Figure 1: MRI scan with gadolinium infusion T2 with FLAIR transverse section. Periventricular hyperintense ovoid lesion perpendicular to ventricles.

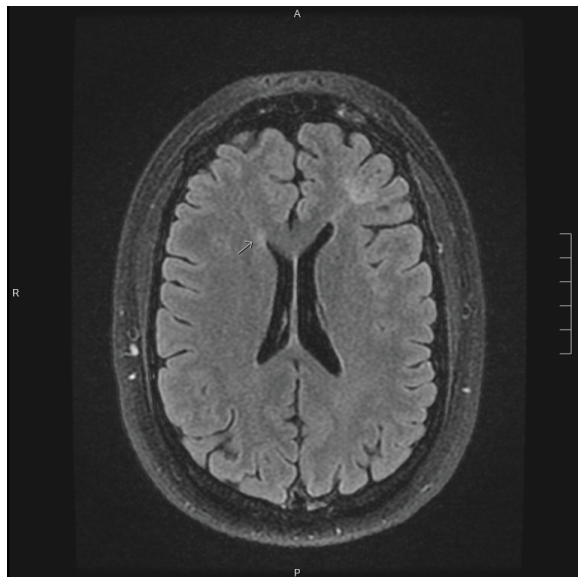
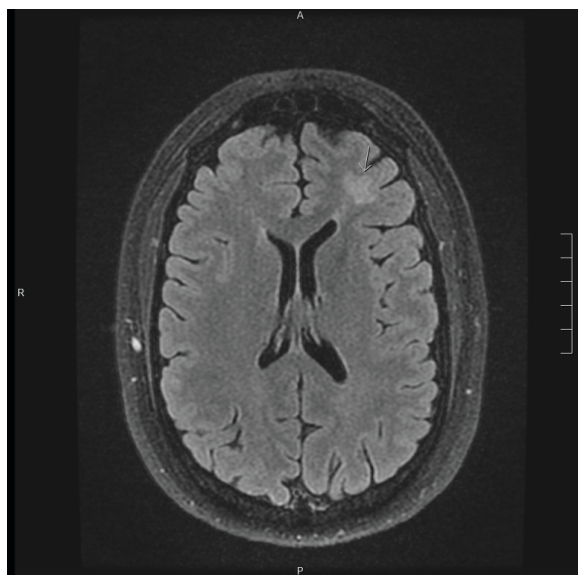


Figure 2: MRI scan with gadolinium infusion T2 with FLAIR transverse section. Large juxtacortical ovoid lesion. Lesions in different locations fulfill the MS diagnostic criteria of separation in space.



REFERENCES

1. Zein G, Berta A, Foster CS. Multiple sclerosis-associated uveitis. *Ocul Immunol Inflamm*. 2004;12(2):137–42. doi: 10.1080/0927394049089534
2. Gordon LK, Goldstein DA. Gender and uveitis in patients with multiple sclerosis. *J Ophthalmol*. 2014;2014:565262. doi:10.1155/2014/565262
3. Ghasemi N, Razavi S, Nikzad E. Multiple Sclerosis: Pathogenesis, Symptoms, Diagnoses and Cell-Based Therapy. *Cell J*. 2017;19(1):1-10. doi.org/10.22074/cellj.2016.4867.
4. TNF neutralization in MS: Results of a randomized, placebo-controlled multicenter study. The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. *Neurology*. 1999;53(3):457–65.
5. van Oosten BW, Barkhof F, Truyen L, et al. Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2. *Neurology*. 1996;47(6):1531–4. doi: 10.1212/wnl.47.6.1531
6. Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of Uveitis Nomenclature for Reporting Clinical Data. Results of the First International Workshop. *Am J Ophthalmol*. 2005;140(3):509–16. doi: 10.1016/j.ajo.2005.03.057.
7. Sancho L, Kramer M, Koriati A, et al. Complications in Intermediate Uveitis: Prevalence, Time of Onset, and Effects on Vision in Short-Term and Long-Term Follow-Up. *Ocul Immunol Inflamm*. 2019;27(3):447–55. doi: 10.1080/09273948.2017.1420203.
8. Chen L, Gordon LK. Ocular manifestations of multiple sclerosis. *Curr Opin Ophthalmol*. 2005;16(5):315–20. doi: 10.1097/OI.icu.0000179804.49842.e2.
9. Hickman SJ, Raoof N, McLean RJ, et al. Vision and multiple sclerosis. *Mult Scler Relat Disord*. 2014 Jan;3(1):3-16. doi: 10.1016/j.msard.2013.04.004.
10. Balcer LJ, Miller DH, Reingold SC, et al. Vision and vision-related outcome measures in multiple sclerosis. *Brain*. 2015;138(1):11–27. doi: 10.1093/brain/awu335.
11. Olsen TG, Frederiksen J. The association between multiple sclerosis and uveitis. *Surv Ophthalmol*. 2017;62(1):89–95. doi: 10.1016/j.survophthal.2016.07.002.
12. Messenger W, Hildebrandt L, Mackensen F, et al. Characterisation of uveitis in association with multiple sclerosis. *Br J Ophthalmol*. 2015;99(2):205–9. doi: 10.1136/bjophthalmol-2014-305518.
13. de-la-Torre A, Silva-Aldana CT, Muñoz-Ortiz J, et al. Uveitis and Multiple Sclerosis: Potential Common Causal Mutations. *Mol Neurobiol*. 2019; 56(12):8008–8017. doi: 10.1007/s12035-019-1630-2.
14. Karara AM, Macky TA, Sharawy MH. Pattern of Uveitis in an Egyptian Population with Multiple Sclerosis: A Hospital-Based Study. *Ophthalmic Res*. 2013;49(1):25–9. doi: 10.1159/000341735.
15. Shugaiv E, Tüzün E, Kürtüncü M, et al. Uveitis as a prognostic factor in multiple sclerosis. *Mult Scler*. 2015;21(1):105–7. doi: 10.1177/1352458514539782.
16. Jouve L, Benrabah R, Héron E, et al. Multiple Sclerosis-related Uveitis: Does MS Treatment Affect Uveitis Course? *Ocul Immunol Inflamm*. 2017;25(3):302–7. doi: 10.3109/09273948.2015.1125508.
17. Petrushkin H, Kidd D, Pavesio C. Intermediate uveitis and multiple sclerosis: to scan or not to scan. *Br J Ophthalmol*. 2015;99(12):1591–3. doi: 10.1016/s0002-9394(00)00659-0.
18. Rosenbaum JT, Bodaghi B, Couto C, et al. New observations and emerging ideas in diagnosis and management of non-infectious uveitis: A review. *Semin Arthritis Rheum*. 2019 Dec;49(3):438–45. doi: 10.1016/j.semarthrit.2019.06.004.
19. Lee K, Bajwa A, Freitas-Neto CA, et al. A comprehensive review and update on the non-biologic treatment of adult noninfectious uveitis: part I. *Expert Opin Pharmacother*. 2014;15(15):2141–54. doi: 10.1517/14656566.2014.948417.
20. Jabs DA, Rosenbaum JT, Foster CS, et al. Guidelines for the Use of Immunosuppressive Drugs in Patients With Ocular Inflammatory Disorders: Recommendations of an Expert Panel. *Am J Ophthalmol*. 2000;130(4):492–513. doi: 10.1016/s0002-9394(00)00659-0.
21. Galor A, Jabs DA, Leder HA, et al. Comparison of Antimetabolite Drugs as Corticosteroid-Sparing Therapy for Noninfectious Ocular Inflammation. *Ophthalmology*. 2008;115(10):1826–32. doi: 10.1016/j.ophtha.2008.04.026.
22. Kemanetzoglou E, Andreadou E. CNS Demyelination with TNF-Blockers. *Curr Neurol Neurosci Rep*. 2017;17(4):36. doi: 10.1007/s11910-017-0742-1.
23. Probert L. TNF and its receptors in the CNS: The essential, the desirable and the deleterious effects. *Neuroscience*. 2015;302:2–22. doi: 10.1016/j.neuroscience.2015.06.038.
24. Jaffe GJ, Dick AD, Brézín AP, et al. Adalimumab in Patients with Active Noninfectious Uveitis. *N Engl J Med*. 2016;375(10):932–43. doi: 10.1056/NEJMoa1509852.
25. Nguyen QD, Merrill PT, Jaffe GJ, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10050):1183–92. doi: 10.1016/S0140-6736(16)31339-3.
26. Suhler EB, Adán A, Brézín AP, et al. Safety and Efficacy of Adalimumab in Patients with Noninfectious Uveitis in an Ongoing Open-Label Study: VISUAL III. *Ophthalmology*. 2018;125(7):1075–87. doi: 10.1016/j.ophtha.2017.12.039.
27. Stübgen J-P. Tumor necrosis factor- α antagonists and neuropathy. *Muscle Nerve*. 2008;37(3):281–92. doi: 10.1007/978-981-32-9636-7_23.
28. Sharief MK, Hentges R. Association between Tumor Necrosis Factor- α and Disease Progression in Patients with Multiple Sclerosis. *N Engl J Med*. 1991;325(7):467–72. doi: 10.1056/NEJM199108153250704.
29. Theibich A, Dreyer L, Magyari M, et al. Demyelinating neurological disease after treatment with tumor necrosis factor alpha-inhibiting agents in a rheumatological outpatient clinic: description of six cases. *Clin Rheumatol*. 2014;33(5):719–23. doi: 10.1007/s10067-013-2419-8.
30. Cordero-Coma M, Sobrin L. Anti-tumor necrosis factor- α therapy in uveitis. *Surv Ophthalmol*. 2015;60(6):575–89. doi: 10.1016/j.survophthal.2015.06.004.