Case Report

Sarcoid-Associated Bilateral Multifocal Choroiditis Secondary to Adalimumab

Carl Stanley Wilkins[1], Kristen Taylor Ashourian[2], Ethan Kyle Sobol[1], Matthew Fink[3], Brian Saltzman[4], Steven Teich[4]

[1]Department of Ophthalmology, New York Eye and Ear Infirmary of Mount Sinai, New York, NY, USA, [2]Department of Ophthalmology, Stroger Eye Clinic/Cook County Health, Chicago, IL, USA, [3]Department of Neurology, Weill Cornell Medicine, Cornell University, New York, NY, USA, [4]Icahn School of Medicine at Mount Sinai, New York, NY, USA

Abstract

Purpose: To report a rare paradoxical development of systemic sarcoidosis in a patient taking adalimumab manifesting as multifocal choroidal infiltrates and seventh nerve palsy.

Methods: This was a single patient case report.

Results: A 30-year-old man with a history of psoriatic arthritis on adalimumab presented with intermittent fevers and headaches. Initial infectious serology and initial ophthalmic examination were within normal limits. Over the next month, he developed a seventh nerve palsy, unilateral decreased visual acuity, and bilateral multifocal choroidal infiltrates. The patient was diagnosed with systemic sarcoidosis secondary to tumor necrosis factor alpha (TNFα) inhibitor use after a hilar lymph node biopsy. Upon treatment with high-dose oral corticosteroids, the patient's symptoms and choroidal lesions significantly improved.

Conclusion: This case report illustrates a rare presentation of ocular, neurologic, and systemic sarcoidosis presenting as a bilateral multifocal choroiditis and seventh nerve paresis in a patient treated with adalimumab. We highlight the importance of obtaining an ophthalmic evaluation in the management of this rare adverse effect of TNFα inhibitors.

Keywords: Adalimumab, Drug reaction, Multifocal choroiditis, Sarcoidosis, Tumor necrosis factor alpha inhibitor, Uveitis

Address for correspondence: Carl Stanley Wilkins, New York Eye and Ear Infirmary Retina Center, 310 East 14th Street, New York, NY, USA.
E-mail: Carl.Wilkins@mountsinai.org
Submitted: 13-Oct-2020; **Revised:** 24-Dec-2020; **Accepted:** 04-Feb-2021; **Published:** 05-Jul-2021

Introduction

Tumor necrosis factor alpha (TNFα) inhibitors are biologic agents that are commonly used in the treatment of many rheumatologic and autoimmune diseases including sarcoidosis. Adalimumab (Humira, AbbVie Ltd.) is a Food and Drug Administration-approved humanized monoclonal antibody to TNFα that inhibits both soluble and transmembrane moieties, thereby inhibiting multiple downstream proinflammatory pathways.[1]

The adverse effects of anti-TNFα agents have been well described in the literature and most frequently include risk of infection, malignancy, demyelinating disorders, and cardiovascular disease.[2] Interestingly, there have been several cases reported of paradoxical sarcoid granulomatous reactions developing after the initiation of TNFα inhibitor therapy. We describe pulmonary, neurologic, and ocular sarcoidosis associated with adalimumab therapy, first manifesting as bilateral multifocal choroidal infiltrates detected on ophthalmologic examination.

Case Report

A 30-year-old man with a medical history significant for

Access this article online

Quick Response Code:

Website: www.jcurrophthalmol.org

DOI: 10.4103/2452-2325.312161

How to cite this article: Wilkins CS, Ashourian KT, Sobol EK, Fink M, Saltzman B, Teich S. Sarcoid-associated bilateral multifocal choroiditis secondary to adalimumab. J Curr Ophthalmol 2021;33:205-8.

psoriatic arthritis, hereditary spherocytosis, and cutaneous herpes zoster infection presented to an infectious disease specialist with intermittent fevers and headaches over the course of 2 weeks. He had also reported an unintentional 10-pound weight loss over the last 9 months. For the last 6 years, the patient was receiving adalimumab for psoriatic arthritis with adequate suppression.

The patient discontinued adalimumab and underwent an extensive workup for an infectious etiology. Serologies for syphilis, Lyme, and toxoplasmosis were negative, chest X-ray was normal, and an ophthalmic examination was within normal limits. Laboratory studies showed an erythrocyte sedimentation rate of 2 mm/h and a C-reactive protein of 0.4 mg/L. Complete blood count and comprehensive metabolic profile were normal, except for elevations in bilirubin, lactate dehydrogenase, and reticulocyte count, consistent with hereditary spherocytosis. The patient was given a trial of doxycycline 200 mg twice daily and valacyclovir 1 g three times daily for 2 weeks and restarted on adalimumab.

The patient traveled to Mexico and returned 1 month later with complaints of worsening headache, left facial paresis, ageusia, and persistent fever. Examination revealed a visual acuity of 20/20 in the right eye (OD) and 20/50 in the left eye (OS) and a left seventh nerve paresis. Anterior segment examination was significant only for exposure keratopathy OS without anterior chamber cell or flare in either eye. Funduscopic examination now showed dozens of multifocal 100–200 micron-sized circular creamy, yellow-white choroidal infiltrates disseminated throughout the fundus of each eye. There was no vitritis, vasculitis, or optic nerve edema [Figure 1a and b]. Optical coherence tomography revealed the choroidal lesions to be hyporeflective and showed no macular cysts or thickening. Enhanced depth imaging was unavailable. Given the patient's history of immunosuppressive therapy and travel to Mexico, he was admitted for urgent evaluation for suspected fungal or mycobacterial meningitis, as well as possible lymphoma. Serum testing for Lyme, syphilis, tuberculosis (TB), and West Nile virus was negative. Comprehensive metabolic panel and complete blood count testing were within normal limits. Cerebrospinal fluid examination was similarly negative for organisms including cryptococcal antigen but revealed 8 white blood cells (91% lymphocytes) and normal chemistries.

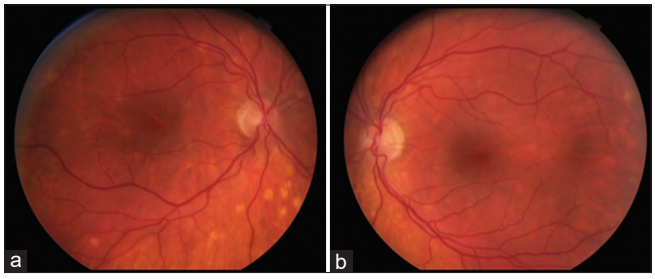

Figure 1: (a and b) Color fundus photograph of the right (a) and left (b) eyes demonstrating diffuse, well-circumscribed, round, yellow-white choroidal lesions in the posterior pole representing multifocal choroiditis

Magnetic resonance imaging of the brain and orbits revealed enhancement of the left facial nerve. Due to concerns for possible lymphoma, a chest computed tomography (CT) was performed, which demonstrated mediastinal lymphadenopathy. Histopathology of a transbronchial hilar lymph node biopsy showed noncaseating granulomatous inflammation without organisms, consistent with sarcoidosis. Special stains for mycobacterial and fungal organisms were negative. At this time, a diagnosis of sarcoid granulomatosis secondary to TNFα inhibitor use was made. Treatment with 40 mg daily of oral prednisone was initiated with resolution of the patient's fever, headache, and left facial paresis.

Funduscopic examination 1 month after his admission and completion of a 2-week course of prednisone revealed the choroidal lesions to be more sharply demarcated, paler, and partly regressed from prior examination. Follow-up fluorescein angiography demonstrated diffuse, multifocal, hypofluorescent choroidal lesions without late staining, and no macular edema or vascular leakage [Figure 2a and b]. Rheumatologic evaluation with possible initiation of alternative immunosuppressive therapy was planned.

Discussion

We describe a case of multifocal choroiditis with neurologic and pulmonary sarcoidosis developing in a patient treated with the TNFα inhibitor, adalimumab. Our patient presented with constitutional symptoms which prompted suspicion for an infectious etiology, given his chronic immunosuppression and recent travel to a TB-endemic area. The development of bilateral disseminated multifocal choroidal lesions with a seventh nerve palsy and worsening systemic symptoms in a patient on a TNFα inhibitor heightened suspicion of infection, especially a fungal or mycobacterial etiology. Chest radiography was normal; however, a chest CT was performed due to high suspicion, and hilar lymphadenopathy was seen. A subsequent endobronchial lymph node biopsy confirmed sarcoidosis, and the patient improved upon initiation of oral corticosteroids. Lymphoma and birdshot chorioretinopathy (BSC) are important masquerades for sarcoid-associated choroiditis;

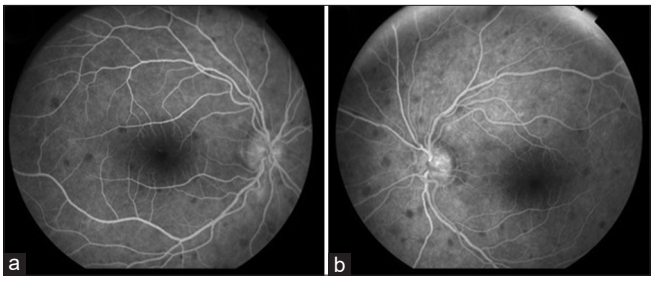

Figure 2: (a and b) Mid-phase fluorescein angiography of the right (a) and left (b) eyes demonstrating many areas of well-circumscribed hypofluroescence in the posterior pole due to blockage from the choroidal lesions, including more numerous lesions in the macula than seen on ophthalmoscopy. There is notable absence of optic nerve edema, macular edema, or vascular leakage

however, workup for lymphoma was negative and retinal imaging and examination did not support a diagnosis of BSC. Of interest, in this case, the sarcoidosis progressed to choroidal and neurologic involvement despite the cessation of adalimumab, suggesting that, once the sarcoid reaction develops, discontinuation of the TNFα inhibitor may not prevent the inflammatory reaction from advancing.

Although adalimumab may be used itself as a treatment for sarcoidosis, it is also associated with the paradoxical development of sarcoidosis in patients being treated for other autoimmune disorders. TNFα inhibitor-associated sarcoidosis is a rare occurrence estimated to occur in 0.04% of patients on these agents.[3] This immune response has been rarely associated with all classes of anti-TNFα, suggesting that the reaction occurs primarily due to dysregulation of the inflammatory cytokines.[4] One review of the literature found that the most commonly reported inciting agent for paradoxical sarcoidosis was etanercept in 59% of cases, followed by adalimumab (23%) and infliximab (18%). Regarding uveitis, this review found that only 12/90 (13%) reports of paradoxical sarcoid reactions included intraocular inflammation.[5] A recent review also indicates that etanercept is the agent most associated with paradoxical reaction, frequently in patients with concomitant spondyloarthritis.[6] To our knowledge, this is the first report of diffuse multifocal choroidal infiltrates in this setting.

Though rare, isolated descriptions of TNFα inhibitor-associated sarcoid uveitis exist with manifestations in all subtypes of uveitis.[7] The mean time from TNFα inhibitors initiation to development of sarcoid-like granulomatosis is thought to be 18 months (range 1–51).[3] Though this patient was on adalimumab for roughly 6 years, his rheumatologist stopped and re-started the medication while undergoing initial workup for infection, and therefore, this reaction developed in our patient a little more than 4 weeks after initiation. There are two prior reports of panuveitis that resolved with cessation of biologic therapy and initiation of high-dose oral steroids, like the course of our patient. The chorioretinal lesions in these cases, however, were restricted to the periphery.[8,9] Another report of panuveitis was shown to partially resolve upon cessation of etanercept and completely resolve 10 months later after initiation of adalimumab.[10] Interestingly, a similar report of response after switch from adalimumab to etanercept led to regression of bilateral anterior uveitis.[3] These case reports suggest variable, patient-dependent immunogenicity to these agents related to a "class–effect" among various medications with anti-TNFα activity. One case of intermediate uveitis resolved with cessation of etanercept and initiation of the antimetabolite methotrexate.[11] Our patient presented with obvious warning signs of systemic disease, which lead to highest suspicion of sarcoidosis, including unilateral facial nerve palsy. Only one case has been published to date of uveitis and facial nerve palsy in this context, and those authors reported resolution of anterior uveitis and systemic disease with cessation of the agent and initiation of high-dose corticosteroids and methotrexate.[12] Based upon this case and other prior reports, patient-dependent–isolated cessation of treatment with adjuvant oral steroids, switching immunosuppression within the same class, or switching to an anti-metabolite medication are all reasonable options.

Ultimately, this case report demonstrates the importance of ophthalmic examination among patients with systemic disease and highlights the importance of including sarcoidosis in the differential diagnosis of multifocal choroiditis in patients treated with TNFα inhibitors. Conclusive evidence of the etiology of this paradoxical reaction is not yet available, and we may only make a putative hypothesis of an immune dysregulation among a select subset of patients. In addition, this case shows that the granulomatous lesions can regress with cessation of the TNFα inhibitor and the initiation of corticosteroid treatment. As the use of biologic agents increases, the incidence of adverse effects and secondary syndromes may also increase, and ophthalmologists should play an important role in the early diagnosis and management of these potentially fatal conditions.

Ethics approval and consent to participate

Patient was consented and all pictures are anonymous in compliance with HIPAA standards. This report is in compliance with the Declaration of Helsinki.

Consent for publication

Patient was consented for publication of images and case description.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Lis K, Kuzawińska O, Bałkowiec-Iskra E. Tumor necrosis factor inhibitors – State of knowledge. Arch Med Sci 2014;10:1175-85.
2. Ramos-Casals M, Brito-Zerón P, Muñoz S, Soria N, Galiana D, Bertolaccini L, *et al*. Autoimmune diseases induced by TNF-targeted therapies: Analysis of 233 cases. Medicine (Baltimore) 2007;86:242-51.
3. Daïen CI, Monnier A, Claudepierre P, Constantin A, Eschard JP, Houvenagel E, *et al*. Sarcoid-like granulomatosis in patients treated with tumor necrosis factor blockers: 10 cases. Rheumatology (Oxford) 2009;48:883-6.
4. Massara A, Cavazzini L, Corte RL, Trotta F. Sarcoidosis appearing during anti-tumor necrosis factor α therapy: A new "Class Effect" paradoxical phenomenon. Two case reports and literature review. Sem Arthritis Rheum 2010;39:313-9.
5. Decock A, Van Assche G, Vermeire S, Wuyts W, Ferrante M.

Sarcoidosis-like lesions: Another Paradoxical Reaction to Anti-TNF Therapy? J Crohns Colitis 2017;11:378-83.
6. Nicolela Susanna F, Pavesio C. A review of ocular adverse events of biological anti-TNF drugs. J Ophthalmic Inflamm Infect 2020;10:11.
7. Cunningham ET Jr., Pasadhika S, Suhler EB, Zierhut M. Drug-induced inflammation in patients on TNFα inhibitors. Ocul Immunol Inflamm 2012;20:2-5.
8. Seve P, Varron L, Broussolle C, Denis P, Kodjikian L. Sarcoid-related uveitis occurring during adalimumab therapy. Ocul Immunol Inflamm 2012;20:59-60.
9. Moisseiev E, Shulman S. Certolizumab-induced uveitis: A case report and review of the literature. Case Rep Ophthalmol 2014;5:54-9.
10. Dragnev D, Barr D, Kulshrestha M, Shanmugalingam S. Sarcoid panuveitis associated with etanercept treatment, resolving with adalimumab. BMJ Case Rep 2013;2013:bcr2013200552.
11. Fonollosa A, Artaraz J, Les I, Martinez-Berriotxoa A, Izquierdo JP, Lopez AS, *et al*. Sarcoid intermediate uveitis following etanercept treatment: A case report and review of the literature. Ocul Immunol Inflamm 2012;20:44-8.
12. Durel CA, Feurer E, Pialat JB, Berthoux E, Chapurlat RD, Confavreux CB. Etanercept may induce neurosarcoidosis in a patient treated for rheumatoid arthritis. BMC Neurol 2013;13:212.