CASE REPORT

Adalimumab and Non-Arteritic Anterior Ischaemic Optic Neuropathy: A Case Report

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ABSTRACT

Sequential anterior ischaemic optic neuropathy was observed in a patient treated with a tumour necrosis factor α (TNF) inhibitor, adalimumab, for ankylosing spondylitis. He developed decreased visual acuity in the right eye after 17 months of treatment. Findings showed right optic disc oedema with haemorrhages and visual field defect. Adalimumab was discontinued and vision stabilised. After restarting adalimumab, he developed optic neuropathy in the left eye. Findings showed optic disc oedema, with haemorrhages and visual field changes in the left eye. Adalimumab may be associated with optic neuropathy; providers prescribing TNF inhibitors should be aware of optic neuropathy as a potential complication.

Keywords: Adalimumab, anterior ischaemic optic neuropathy, drugs, optic nerve, pharmacology

INTRODUCTION

We describe a case of sequential non-arteritic anterior ischaemic optic neuropathy (NAAION) associated with adalimumab use for treatment of ankylosing spondylitis. One of the features most suggestive of a link between the AION and the adalimumab was a second eye event of AION upon re-challenge with the drug. Although the aetiology of NAAION is multifactorial, this patient lacked many of the commonly associated risk factors, such as hypertension, diabetes, cardiovascular disease, and major blood loss. Thus, it is likely that adalimumab played a role in development of ischaemic optic neuropathy.

CASE REPORT

A 65-year-old Caucasian male had been treated for 17 months with adalimumab 40 mg subcutaneously every 2 weeks for human leukocyte antigen (HLA)-B27-positive ankylosing spondylitis. He presented with a sudden, painless decrease of vision in his right

eye upon awakening in early November 2011. Five days after onset of his symptoms, he was found to have right optic nerve head oedema and started on oral prednisone 60 mg once daily (qd). His visual acuity was 20/50 OD and 20/20 OS. Cup-to-disc ratio in his left eye was 0.1. He had a right relative afferent pupillary defect and an abnormal Humphrey visual field (HVF).

The patient's anterior segment examination was normal. He had optic nerve oedema of his right eye, with venous congestion and a superior nerve fibre layer flame haemorrhage. His adalimumab was stopped, and further workup was initiated, because of concern for optic neuritis. Other medical problems included hyperlipidaemia, obstructive sleep apnoea treated with continuous positive airway pressure (CPAP), with which the patient was compliant, benign prostatic hypertrophy, and bilateral hearing loss. Medications included prednisone (new), methotrexate, terazosin (taken in the morning daily for many years), sulindac, calcium, and simvastatin.

Laboratory workup demonstrated normal erythrocyte sedimentation rate (ESR), dilute Russell viper

venom time (DRVVT), factor V Leiden, lupus anti-coagulant, reptilase time, thrombin, and partial thromboplastin time (PTT). Testing for *Bartonella*, Lyme disease, and hepatitis C was negative. Protein S total antigen and total protein C were elevated. Magnetic resonance imaging (MRI) of the orbits showed normal optic nerves and optic radiations without enhancement, but also showed focal FLAIR (fluid attenuation inversion recovery) hyperintensity of the left cuneus and a small heterogeneous enhancing area of the right parotid space. He continued all of his other medications, including the newly prescribed prednisone.

A neuro-ophthalmologist evaluated him in December 2011. At this examination, his best-corrected visual acuity was 20/30 eccentrically OD and 20/20 OS. Colour testing was 10/10 with Ishihara plates, and stereovision was reduced. Pupillary examination revealed a 0.6 log unit relative afferent pupillary defect in the right eye. Extraocular motility was full and painless bilaterally. Intraocular pressures were normal bilaterally. Visual fields were full to confrontation except for the inferotemporal quadrant of the right eye and stable inferior arcuate defect on HVF. Anterior segment examination was normal bilaterally. Dilated fundusoscopic examination revealed stage II optic nerve oedema of the right eye, with a small superior flame-shaped haemorrhage and hard exudates in the nasal macula. Lattice degeneration was present peripherally in both eyes. His cup-to-disc ratio was 0.1 in the both eyes. Full neurologic examination was normal. Optical coherence tomography (OCT) of the macula demonstrated hard exudates but no retinal oedema or other abnormal architecture; the exudates were attributed to his optic nerve swelling. He was diagnosed with anterior ischaemic optic neuropathy, started on daily aspirin, and advised that he could restart his adalimumab, since there was no evidence of demyelinating optic neuritis. In addition, he was asked to have his CPAP readjusted. A fasting lipid panel revealed elevated lipoprotein A, low-density lipoprotein (LDL), and triglycerides, and his primary care physician was notified about these findings. He was tapered off oral steroids by January 2012 and restarted on adalimumab toward the end of January 2012.

At neuro-ophthalmology follow-up in February 2012, the patient's best-corrected visual acuity was 20/25 on the right and 20/15 on the left with normal colour vision and stereopsis of 8/9 circles. His right relative afferent pupillary defect had decreased from 0.6 to 0.3 log units with neutral density filters. The optic nerve oedema in his right eye had resolved, and the left eye was still normal. His HVF had a stable inferior arcuate defect with mild superior depression OD (Figure 1). He reported a pressure sensation that lasted for a week in both eyes after each

adalimumab injection, consistent in presentation since starting the medication, that would resolve spontaneously. Consequently, he was seen in clinic for an intraocular pressure (IOP) check 4 days after his most recent adalimumab injection; his IOP was found to be normal.

In mid-March 2012, the patient noticed sudden and painless loss of vision in his left eye upon awakening. The next day, his uncorrected visual acuity was 20/25 OD and 20/30 OS. His IOP was normal, and his pupillary examination was normal. On dilated examination, pallor of the optic nerve was present in the right eye and new disc oedema was present in the left eye. His adalimumab was stopped and prednisone restarted. He was reminded to take terazosin in the morning only, which he had been doing since the first event. One week later, during a return visit to the neuro-ophthalmologist, the patient's uncorrected visual acuity was 20/30 OD and 20/70 OS. On pupillary examination he was found to have a 0.3 log unit relative afferent pupillary defect in the left eye. Ishihara colour plates were 12/13 OD and 9/13 OS. HVF showed a persistent inferotemporal defect OD and a new superior arcuate and inferotemporal defect OS (Figure 2). His complete blood count (CBC), C-reactive protein (CRP), and ESR were again normal. Prednisone was tapered. He was continued on daily aspirin and asked to remain off adalimumab. Twenty-four-hour blood pressure monitoring showed a mean nocturnal blood pressure of 110/60 mmHg, but a low nocturnal pressure of 86/52 mmHg. He had no change of his vision on follow-up examination. Based on the 24-hour blood pressure monitoring, his terazosin was stopped and he was changed to tamsulosin in April 2012.

DISCUSSION

Adalimumab is a recombinant human monoclonal antibody that blocks the interaction between tumour necrosis factor α (TNF α) cytokines and receptors. In 2006 adalimumab was approved by the US Food and Drug Administration (FDA) for ankylosing spondylitis, a form of chronic inflammatory arthritis that causes functional impairment, diminished quality of life, and considerable socioeconomic burden.¹ TNF-inhibitor therapy is central to the management of this disorder, since it is the only FDA-approved class of anti-rheumatic drugs consistently shown to have good effects on axial ankylosing spondylitis in patients with inadequate responses to non-steroidal anti-inflammatory drugs.²

The most common ocular manifestation of ankylosing spondylitis is acute anterior uveitis, which is experienced by up to 40% of patients.³ TNF inhibition is known to decrease the frequency of uveitis flares.^{1,4} With adalimumab, the rate of anterior uveitis flare

FIGURE 1 Humphrey Visual Field of the right eye, showing inferior arcuate defect 1 month after vision loss.

FIGURE 2 Humphrey Visual Field of the left eye showing new inferior and superior arcuate defects, cecocentral scotoma, and enlarged physiologic blind spot.

decreased from 64.8/100 patient-years before treatment to 28.9/100 patient-years with treatment ($p < 0.001$), and additional studies evaluating TNF-inhibitor therapy for uveitis are underway.⁵ Optic neuritis and optic neuropathy have been associated with ankylosing spondylitis in several case reports, and concurrent uveitis was typically present.^{4,6,7}

TNF inhibitors are associated with optic neuritis, demyelination, toxic optic neuropathy, and multiple sclerosis.^{4,5,8–12} As a result, potential ocular adverse events of TNF inhibitors must be assessed as the role of TNF inhibition for refractory uveitis is better defined. Specifically, adalimumab has been associated with one case of presumed anterior toxic optic neuropathy, since there was no enhancement of the nerve on MRI and visual function returned with discontinuation of the drug.^{9,10} Approximately 21 cases of optic neuritis associated with TNF inhibitors exist in the literature.^{4,10} Three cases of toxic anterior optic neuropathy associated with infliximab have been documented.¹¹

NAAION is the leading cause of sudden optic nerve-related vision loss. Although NAAION is typically unilateral, 15–20% of patients experience bilateral NAAION. Its aetiology is not clearly understood, and currently there is no effective treatment.¹² However, aspirin has been shown to decrease the incidence of second eye involvement from 35% to 13%.¹³

In this report we describe a case of bilateral anterior ischaemic optic neuropathy associated with adalimumab. This patient's vision loss was painless and abrupt, with minimal recovery, arguing against optic neuritis. There was no enhancement of the optic nerve on MRI, which is a common finding in demyelinating neuritis. The sequential occurrence and the pattern of visual field loss were not typical of a toxic optic neuropathy. He was started on methotrexate shortly before the vision loss. Four cases of toxic optic neuropathy due to methotrexate have been reported; one was found to be secondary to abnormal folate metabolism,^{14,15} but all displayed central and cecentral defects suggestive of toxic rather than ischaemic optic neuropathy. This patient did not have any systemic symptoms suggestive of Giant Cell Arteritis. His ESR, CRP, and CBC were checked monthly by rheumatologists and were normal. If the aetiology of his vision loss were a malignant process, CBC and MRI abnormalities likely would have been observed, and his clinical course typically would have been progressive.

The patient's risk factors for NAION included hyperlipidaemia, crowded disc, obstructive sleep apnoea, and possibly terazosin use. A retrospective study documented only a marginal increase in the risk of ischaemic optic neuropathy with concurrent

phosphodiesterase type 5 (PDE5) inhibitors and alpha blockers. Alpha blockers alone have not been associated specifically with optic neuropathy in the literature, but may lower blood pressure.¹⁶ Although terazosin was not a new medication to this patient, and he had no symptoms of hypotension, he did have an episode of nocturnal hypotension on 24-hour blood pressure (BP) monitoring while still on terazosin. He did not have a history of hypertension, diabetes, cardiovascular disease, or major blood loss, which also are risk factors for NAAION.

This case could represent sequential NAAION, which might have occurred without adalimumab. Second eye involvement occurred in 14.7% of patients in the Ischaemic Optic Neuropathy Decompression Trial (IONDT) over 5 years.¹⁷ However, the recurrence after re-challenge with this medication raises the possibility that adalimumab played a role in the pathogenesis of the events. It is possible that this medication could have stimulated a vasculitis that resulted in ischaemia of the optic nerve, as has been reported in another case.¹⁸ Clinicians should be alert to the possibility of TNF α inhibitors playing a role in a variety of optic neuropathies.

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