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Case Report

Optic Atrophy Occurring with Anti-Tumor Necrosis Factor Alpha Therapy: A Case Report

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Abstract

Ocular involvement related to treatment with tumor necrosis factor alpha inhibitors is a rare adverse effect that may lead to irreversible outcomes. We illustrate through this report a case of optic atrophy under Etanercept in a patient with spondyloarthritis. The diagnosis was suspected due to visual acuity impairment, and was confirmed by ophthalmological examination. Although the TNF-blockers were discontinued and corticosteroids were administered, the follow-up examination did not reveal any improvement in visual acuity. This is a potential serious complication of TNF inhibitors that rheumatologists should recognize when monitoring patients with rheumatic diseases.

Keywords: TNF Inhibitors, Etanercept, Optic Atrophy, Optic Neuritis, Optic Neuropathy, Spondyloarthritis.

INTRODUCTION

Tumor necrosis factor alpha inhibitors (TNFi) have revolutionized the treatment of inflammatory rheumatic diseases (IRD) including rheumatoid arthritis (RA) and spondyloarthritis (SpA). Although they are highly effective against these diseases, it has been shown that they can be associated with several adverse events, such as infections, autoimmunity, and neurological events [1].

In this article, we will focus on ocular side effects through a clinical case that illustrates the relationship between TNFi agents and optic atrophy in a patient with SpA.

CASE REPORT

This is a 50-year-old female patient with no significant past medical history who was diagnosed with axial non-radiographic and peripheral SpA in 2013. She was refractory to nonsteroidal anti-inflammatory drugs (NSAIDs), and different classes of conventional synthetic disease-modifying antirheumatic drugs (CsDMARDS): salazopyrine (3 g/d) and methotrexate (20 mg/d). She was then treated with infliximab at a dose of 5 mg/kg at zero, two, six and then every eight weeks with clinical and biological remission. Four years later, she presented a therapeutic escape from infliximab with anti-infliximab antibodies at a rate of 80.520 ng/ml and a residual concentration of 0.69 ug/d. Then, the patient received etanercept at a dose of 50 mg/week with a favourable clinical and biological response.

In September 2020, she consulted for eye redness with decreased visual acuity. Ophthalmological examination did not reveal anterior uveitis, and examination of the posterior segment did not find vasculitis. An optic coherence tomography was therefore performed, and confirmed clearly the presence of bilateral optic atrophy with decrease in peripapillary nerves fibres and ganglion cells. Etiologically, and according to the ophthalmologist, SpA only affects the anterior segment of the eye, and can only affect the optic nerve by contiguousness in case of anterior uveitis, which is not the case in our patient. It can therefore be either optic atrophy as part of a connective tissue disease, a demyelinating pathology, or secondary to drug toxicity. Immunological tests were negative. Magnetic resonance imaging (MRI) brain was without abnormalities. Given the negative etiological investigation, there was a strong suggestion of an iatrogenic origin for this optic atrophy which is likely attributed to TNFi treatment.

Our decision was to discontinue TNFi. The patient received a corticosteroid bolus and a switch to an anti-interleukin 17 (anti-IL17) was decided with regular

monitoring by ophthalmologists. No improvement in visual acuity was observed over two-year of follow up.

DISCUSSION

This paper illustrates a case report of optic atrophy occurring during treatment with TNFi in a patient with spondyloarthritis.

Optic atrophy is defined by degeneration of ganglion cell axons from the retina to the lateral geniculate body. Etiologies of optic atrophy are diverse, encompassing conditions such as compressive optic neuropathy, hereditary and traumatic optic neuropathies, toxic and nutritional optic neuropathies, and retrobulbar neuritis occurring secondarily to multiple sclerosis (Table 1) [1].

Table 1: Optic Atrophy etiologies

Hereditary optic neuropathy	**Lerver hereditary optic atrophy (LHOA)** **Dominant optic atrophy or Kjer disease**
Ischemic optic neuropathy	Anterior ischemic optic neuropathy (NOIA) Aetiologies: Horton, Atherosclerosis
Inflammatory optic neuropathy	Demyelinating disease Inflammatory disease: Systemic Lupus Infectious diseases
Post traumatic optic neuropathy	Head or maxillofacial trauma
Compressive optic neuropathy	benign intracranial hypertension Intra- orbital process
Metabolic and toxic optic neuropathy	Smoking, Alcoholism Deficiency: Vitamin B1, B6, B12, nicotinic acid Drugs: TNF alpha inhibitors,….

Establishing a causal link between an adverse event and medication administration can present challenges. In our patient, all causes of optic atrophy such as infections, traumatism, compressive and immunological causes, have been eliminated on the basis of clinical, biological and radiological arguments. Given the timing link between the occurrence of visual acuity impairment and treatment with TNFi, and the presence of similar cases in the literature, optic atrophy resulting from a potential iatrogenic optic neuropathy was suspected.

The association of TNFi agents and optic neuropathy has been reported in the past 13 years ago. Two types are possible according to the literature; retrobulbar optic neuritis demyelinating and bilateral anterior toxic optic neuropathy.

- **Retrobulbar Optical Neuritis:**

Retrobulbar optic neuritis (NORB) is a demyelinating condition of the optic nerve. It's considered to be the inaugural sign of multiple sclerosis (MS) in 38% of cases. Several pathophysiological hypotheses have been proposed to explain the demyelinating action of anti-TNF alpha, but none has undergone extensive validation [2]:

- TNF-alpha which is involved in the inflammatory demyelination process cannot be suppressed by TNFi due to their inability to cross the blood-brain barrier. This theory may explain why TNFi are ineffective in multiple sclerosis.
- TNFi can reduce IL-10 levels and elevate IL-12 levels, resulting in a profile similar to that of multiple sclerosis.
- Finally, TNFi may unmask an underlying latent infection which could potentially lead to demyelination.

Demyelinating neuropathies resulting from TNFi were mainly linked to infliximab and Etanercept and were typically detected within the first year of treatment. Some cases appeared in the 30th month, and the longest period was 49 months [3].

Unilateral decrease in visual acuity is the typical clinical feature, occasionally accompanied by eye pain. Bilateral forms of this condition have also been reported. MRI reveals hypersignal STIR of the optic nerve, and visual evoked potentials is consistent with demyelinating bilateral optic neuropathy with prolonged latency. Hyposignals related to demyelinating lesions are sometimes demonstrated in brain MRI [4, 5].

Regression can occur spontaneously after stopping TNFi agents or after intravenous corticosteroid administration [4, 5]. However, some cases have been reported as irreversible [4].

Given the variability in clinical presentation and response to treatment, the exact relationship between TNFi agents and optic neuropathy remains controversial. And some authors suggest that this demyelination may be related to other predisposing factors or a toxic process. [4].

- **Anterior Toxic Optic Neuropathy:**

Being rare, we have identified only a few cases of patients with anterior toxic optic neuropathy on TNFi treatment [table 2].

Table 2: Cases of anterior toxic optic neuropathy reported in the literature:

Case	Age (years)	Gender	Disease treated	Anti-TNF agent	Dose and Duration of Therapy	Therapeutic management	Outcomes
1 [6]	54	Male	Rheumatoid arthritis	Infliximab	3 mg/Kg 3 months	Steroids	Vision did not recover.
2 [6]	62	Female	Rheumatoid arthritis	Infliximab	3 mg/Kg 5 months	Steroids	Vision did not recover.
3 [6]	54	Male	Rheumatoid arthritis	Infliximab	3 mg/Kg	infliximab was immediately discontinued	Vision did not recover
4 [7]	68	Male	Crohn disease	Infliximab	3 mg/Kg 2 months	infliximab was immediately discontinued and IV methylprednisolone 1 g/day for 3 days	Vision did not recover
5 [8]	60	Female	Rheumatoid arthritis	Adalimumab	40 mg/ 14 days 6 months	infliximab was immediately discontinued	Visual acuity recovered slowly
6 [9]	62	Male	Psoriatic arthritis	Golimumab	50 mg/ month 3 months	Golimumab discontinued	Vision recovered

This entity was first described by ten Tusscher and al [6], in 3 patients aged 54 to 62 years treated with infliximab, considering the possibility of a cumulative toxic dose. A similar case was also reported by Jane W and others in 2010 [7]. In the 4 patients, a decrease in visual acuity was objectified after the third infusion. The diagnosis of anterior toxic optic neuropathy was made after excluding a demyelinating or hereditary cause: normal brain MRI, normal inflammatory and immunologic tests, normal cerebrospinal fluid analysis, visual evoked potential without abnormalities, and visual field deficits suggesting a toxic rather than ischemic mechanism of this anterior optic neuropathy. Visual acuity did not improve despite discontinuation of treatment and administration of bolus methylprednisolone.

In addition to infliximab, cases associated with Adalimumab and Golimumab have been reported [8, 9], with regression after corticosteroid therapy and discontinuation of biologic treatment.

It is important to be aware of the possibility of bilateral anterior toxic optic neuropathy in addition to retrobulbar optic neuritis in patients who experience sudden onset of visual loss while being treated with TNFi More data are needed to establish the histopathogenetic mechanism of this entity.

In our case report, considering the lack of evidence pointing towards a demyelinating disease, toxic optic neuropathy is the most likely diagnosis.

Currently, data are insufficient to make conclusions about managing optic neuropathies resulting from TNFi treatment, and valid consensus is needed. Simsek *et al.*, have suggested an algorithm based on a strict ophthalmologic and neurological evaluations for those patients [10]. If optic neuropathy is diagnosed, additional investigations may be recommended. The treatment with anti-TNF should be discontinued and steroid treatment should be implemented.

CONCLUSION

Despite the benefit of TNFi therapy, side effects can arise. Our clinical case is about an optic atrophy during Etanercept treatment. Thus, we recommend a lot of vigilance in prescribing TNFi and we suggest that patients being treated with this biologic agent should be strictly monitored ophthalmologically and neurologically. Furthermore, large-scale studies are necessary in order to establish definitive conclusions and validated consensus regarding the management of this rare and severe adverse event.

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REFERENCES

1. Sadun, A. A., & Wang, M. Y. (2011). Abnormalities of the optic disc. *Handbook of clinical neurology*, *102*, 117-157.
2. Kemanetzoglou, E., & Andreadou, E. (2017). CNS demyelination with TNF-α blockers. *Current neurology and neuroscience reports*, *17*, 1-15.
3. Yokoyama, W., Takada, K., Miyasaka, N., & Kohsaka, H. (2014). Myelitis and optic neuritis induced by a long course of etanercept in a patient with rheumatoid arthritis. *Case Reports*, *2014*, bcr2014205779.
4. de Frutos-Lezaun, M., Bidaguren, A., de la Riva, P., Meneses, C. F., & Olascoaga, J. (2017). Bilateral retrobulbar optic neuropathy associated with Golimumab. *Clinical Neuropharmacology*, *40*(3), 149-151.
5. Chung, J. H., Van Stavern, G. P., Frohman, L. P., & Turbin, R. E. (2006). Adalimumab-associated optic neuritis. *Journal of the neurological sciences*, *244*(1-2), 133-136.
6. ten Tusscher, M. P., Jacobs, P. J., Busch, M. J., de Graaf, L., & Diemont, W. L. (2003). Bilateral anterior toxic optic neuropathy and the use of infliximab. *Bmj*, *326*(7389), 579.
7. Chan, J. W., & Castellanos, A. (2010). Infliximab and anterior optic neuropathy: case report and review of the literature. *Graefe's archive for clinical and experimental ophthalmology*, *248*, 283-287.
8. Von Jagow, B., & Kohnen, T. (2008). Anterior optic neuropathy associated with adalimumab. *Ophthalmologica*, *222*(4), 292-294.
9. Chang, J. R., & Miller, N. R. (2014). Bilateral Optic Neuropathy Associated with the Tumor Necrosis Factor–Alpha Inhibitor Golimumab. *Journal of Neuro-Ophthalmology*, *34*(4), 336-339.
10. Simsek, I., Erdem, H., Pay, S., Sobaci, G., & Dinc, A. (2007). Optic neuritis occurring with anti-tumour necrosis factor α therapy. *Annals of the rheumatic diseases*, *66*(9), 1255-1258.