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CASE REPORT

Relapsing-remitting Optic Neuropathy in an HIV-infected Patient: Secondary Auto-immune Optic Neuropathy or Infectious Optic Neuropathy? A Case Report and Review of the Literature

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ABSTRACT

It can be challenging to disentangle human immunodeficiency virus (HIV)-related infectious optic neuropathy and secondary triggered auto-immune disease when an HIV positive patient presents with vision loss. We report a 44-year-old untreated HIV positive Congolese woman who presented with two episodes of vision loss associated with pain in first her left eye and then her right eye and was diagnosed with a relapsing optic neuropathy. A correlation was observed between the clinical activity and cerebrospinal fluid viral load, CD4-count in the blood and magnetic resonance imaging signs of blood – optic nerve barrier breakdown. CD4 cell counts and viral loads are great clinical features to identify the type of acute optic neuropathy since differential diagnosis between an infectious optic neuropathy or an auto-immune induced optic neuropathy such as neuromyelitis optica spectrum disorder or immune reconstitution inflammatory syndrome can be puzzling.

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Introduction

Optic neuropathy in human immunodeficiency virus (HIV)-infected patients can be secondary to different pathophysiologies and can mimic optic neuritis (ON), commonly associated with multiple sclerosis (MS).[1,2] Para-infectious optic neuropathy is one of the aetiologies described in HIV patients as well as the neuromyelitis optica spectrum disorder (NMOSD), a recently recognised entity of which an association with HIV infection has been reported.[3] Additionally, HIV itself may be directly responsible for the optic neuropathy but the pathophysiology of this has not yet been fully elucidated. The differential diagnosis should be carefully considered in HIV positive patients since the evolution, treatment, and functional prognosis differ.

Case report

A 44-year-old Congolese female patient who had lived in Belgium for more than 20 years presented to the Emergency Department with a 48 hour history of subacute visual loss in the left eye associated with pain on eye movement in that eye. She did not complain of diplopia, headaches, fever or vertigo. She had had untreated HIV infection for the last 7 years. Clinical examination confirmed light perception (LP) in the nasal quadrant of the left eye with a marked relative afferent pupillary deficit (RAPD). The anterior segment was normal but she had grade 1 optic nerve oedema (Figure 1). The remainder of the posterior segment examination was unremarkable. She had normal eye motility but eye movements were painful with the left eye. She had a large concentric visual field defect in the left eye. The visual evoked potentials (VEP) were severely delayed in the left eye. The standard neurological examination was normal.

Comprehensive blood screening was performed including infectious serologies (Treponema pallidum, hepatitis B and C viruses, cytomegalovirus (CMV), Herpes zoster virus, Rubella, Toxoplasmosis, and QuantiFERON-TB) and auto-immune markers (anti-aquaporin 4, anti-

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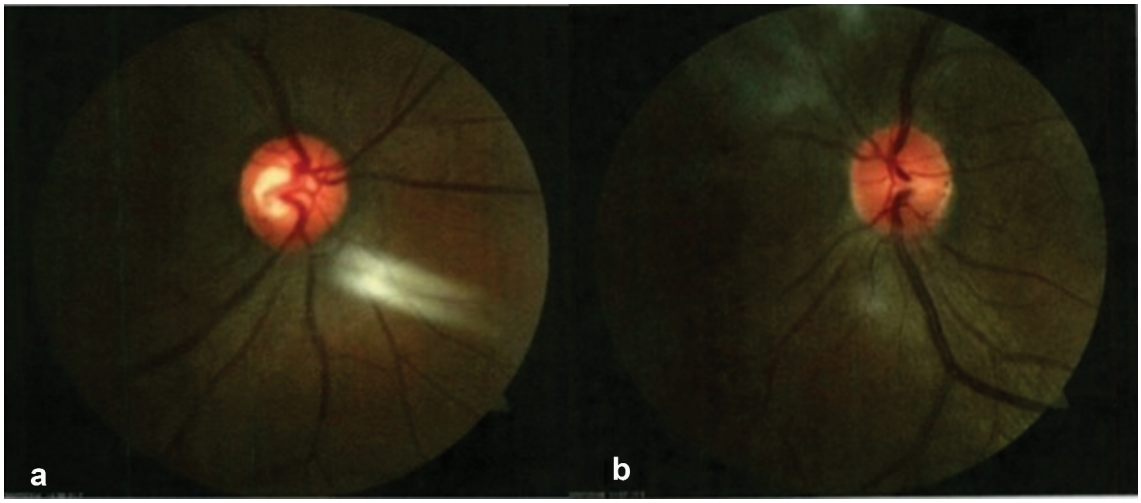

Figure 1. Fundus photographs at the first presentation. (a) Normal right fundus. (b) Absence of the cup and grade 1 oedema of the left optic nerve head.

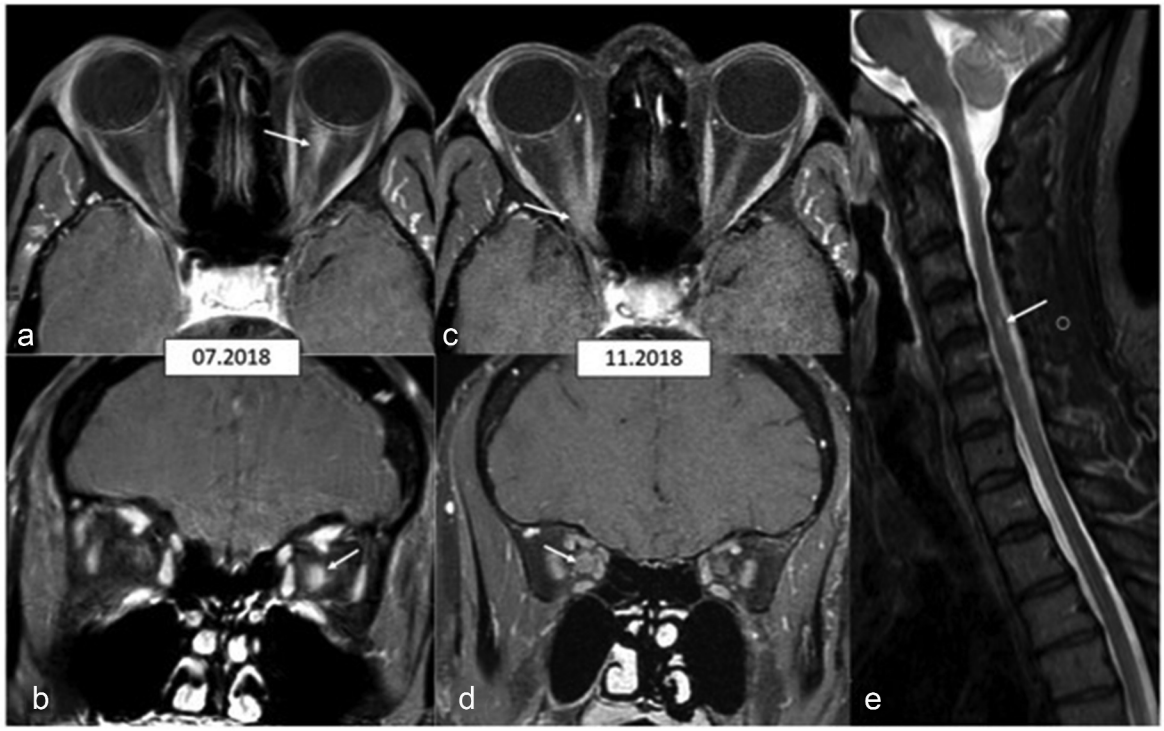

Figure 2. Magnetic resonance imaging. (a) Axial contrast-enhanced (CE) T1-weighted image with fat suppression (FS) at the initial presentation showing abnormal enhancement of the retrobulbar segment of the left optic nerve (arrowed). (b) Coronal CE T1-weighted image with FS at the same time as (A) confirming swelling and enhancement of the left optic nerve (arrowed). (c) Axial CE T1-weighted image with FS at the second presentation revealing swelling and abnormal enhancement of the intra-orbital segment of the right optic nerve (arrowed). (d) Coronal CE T1-weighted image with FS at the same time as (c) confirming swelling and enhancement of the right optic nerve (arrowed). (e) Sagittal T2-weighted image of the cervical spine revealing a non-specific small focus of abnormal signal intensity at the C4/5 level (arrowed).

myelin oligodendrocyte glycoprotein, anti-nuclear antibody, anti-saccharomyces cerevisiae antibody, anti-neutrophil cytoplasmic antibody, rheumatoid factor, C3, and C4), which were negative as were angiotensin conversion enzyme (26 nmol/mL/min; normal range: 12–66 nmol/mL/min) and serum lysozyme (8.3 mg/mL; normal range: 9.6–17.1 mg/mL) tests. Chest radiography and

(^{18}F) fluorodeoxyglucose positron emission tomography revealed no lesions of sarcoidosis or other systemic inflammatory diseases. A high HIV viral load (VL) (112,028 copies/ml) and a low T-lymphocyte count with a low CD4 count (111/μL) were found in the blood. A lumbar puncture revealed a cerebrospinal fluid (CSF) total cell count of 27/μL (78% lymphocytes), an HIV VL of 47,017 copies/ml, a raised IgG level (20.2 g/L), a raised protein level (105 mg/dl), and a normal CSF glucose level (51 mg/dL, compared with a blood glucose level of 81 mg/dL). The opening pressure was 17 cmCSF. Oligoclonal bands were positive in the CSF without any corresponding bands in the serum. The polymerase chain reaction on CSF was negative for Escherichia coli, Haemophilus influenza, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae, CMV, Enterovirus, Herpes simplex virus (HSV)-1, HSV-2, Herpes zoster virus, human herpesvirus 6, Human parechovirus and Cryptococcus neoformans/gattii.

Magnetic resonance imaging (MRI) showed focal swelling and contrast-enhancement of the retrobulbar segment of the left optic nerve (Figure 2a,b). Spine MRI revealed a non-specific and non-enhancing T2 hyperintense lesion in the cervical spinal cord (Figure 2e). The remainder of the central nervous system (CNS) imaging work-up was unremarkable.

The clinical presentation and comprehensive work-up were considered compatible with an optic neuritis secondary to HIV infection. We initiated concomitantly 5 day bolus therapy (intravenous methylprednisolone 1 g daily) with standard anti-retroviral treatment (ART) (dolutegravir and emtricitabine/tenofovir alafenamide), anti-fungal and antibacterial prophylaxis (cotrimoxazole) since her CD4 cell count was < 200/μL.

Subsequent monitoring of her HIV VL and CD4 count confirmed the effectiveness of the ART as her VL dropped to become undetectable and her CD4 count improved. After treatment, she recovered to 60/60 visual acuity with the left eye together with normalisation of the visual field in spite of left optic nerve atrophy seen on MRI.

Four months later she re-presented with a similar clinical presentation in the right eye, although it was painless this time. She had stopped taking her ART after 2 months. LP only was detected in the nasal quadrant of the right eye and there was a marked RAPD in that eye. The anterior and posterior segments were normal. The eye motility was complete and painless. The visual field demonstrated a large concentric defect in the right eye. Systemic and neurological examination was unremarkable.

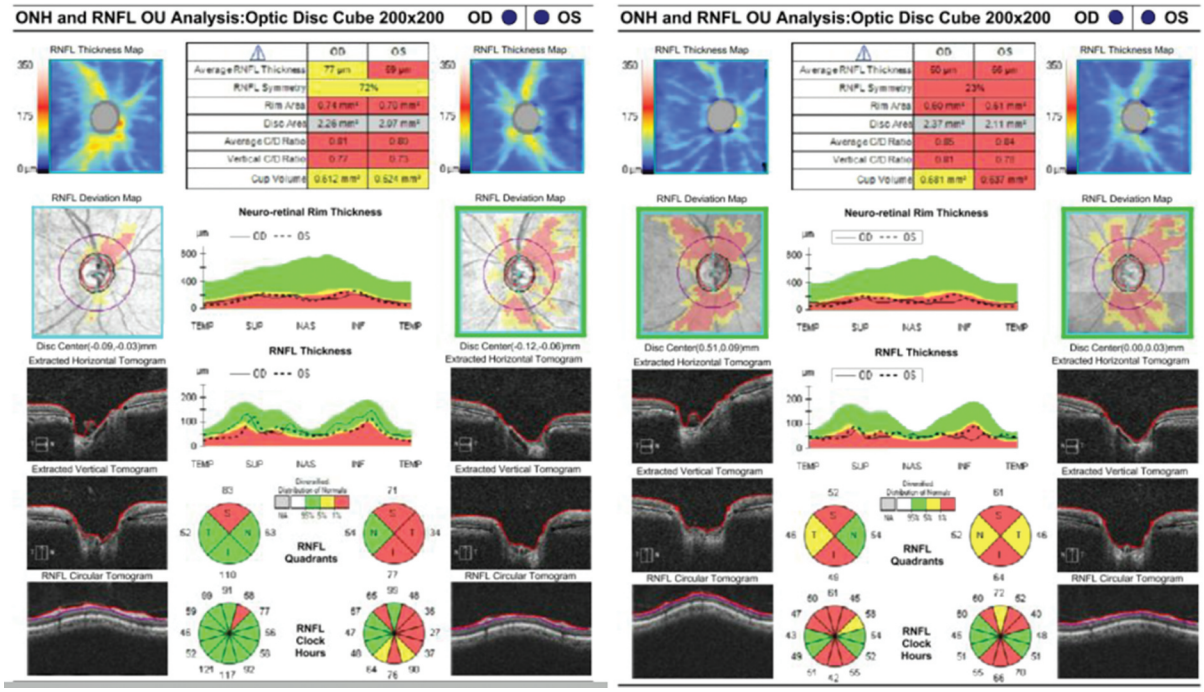

Figure 3. Optical coherence tomography of the retinal nerve fibre layer (RNFL). Left: 3 months after the second presentation showing bilateral RNFL thinning. Right: 15 months after the second presentation confirming worsening of the bilateral atrophy.

As expected, blood testing revealed a very low CD4 count (11/μL). Another lumbar puncture was performed with an opening pressure of 15 cmCSF. The CSF total cell count was 37/μL (87% lymphocytes), the HIV VL was 8400 copies/mL, the IgG level was raised at 20.2 g/L, the protein level was raised at 78 mg/dL and the CSF glucose level was normal at 60 mg/dL (blood glucose level was 82 mg/dL). An MRI revealed disappearance of the left optic nerve enhancement seen previously but new swelling and abnormal enhancement of the intraorbital segment of the right optic nerve (Figure 2c,d) .

We initiated the same treatment less than 24 hours after the onset of vision loss in the right eye, but this time she did not make any significant recovery. The final vision with the right eye was hand motion perception compared with 60/60 with the left eye. The time course of this clinical relapse again matched with the HIV biological activity. Three months later, optical coherence tomography (OCT) confirmed severe bilateral retinal nerve fibre layer thinning, that progressed as shown on an OCT performed 15 months after the second event (Figure 3).

Discussion

Atypical ON and NMOSD in HIV

In case of atypical presentation of ON in HIV patients, various aetiologies should be excluded, especially inflammatory (NMOSD, sarcoidosis, chronic relapsing inflammatory neuropathy) and infectious Syphilis (syphilis, Bartonella, tuberculosis, West Nile virus, Borrelia, Herpes zoster and simplex viruses) causes.[4,5] In this particular population, seronegative cases of syphilis have been described in the literature and new recommendations suggest baseline venereal disease research laboratory (VDRL) screening and follow-up at 3 months to rule out the possibility of false-negative results.[6] HIV-infected patients who have secondary opportunist infectious optic neuropathies usually have low CD4 counts and high VLs.[7]

Regarding inflammation, NMOSD must be excluded. Clinical characteristics include core clinical features (lesions in the optic nerve, spinal cord, area postrema of the dorsal medulla, brainstem, diencephalon or cerebrum), specific MRI findings (posterior optic nerve and optic chiasm lesions, long spinal cord lesions and the absence of typical MS lesions)[8] and the presence of anti-aquaporin 4 antibodies. The association between HIV-infection and NMOSD has recently been recognised as a specific entity.[3]

Considering the atypical presentation, especially the second event, the untreated and active HIV infection, and the dramatic clinical response to ART and corticosteroids, we diagnosed recurrent auto-immune optic neuropathies linked to untreated HIV. Despite similarities with NMOSD, our patient did not match all the clinical criteria for seronegative NMOSD. Isoelectric focusing and subsequent immunoblotting showed clonally restricted IgG in our patient's CSF, with a type 2 pattern of oligoclonal bands, related to local, intrathecal synthesis of IgG, supporting the diagnosis of an inflammatory disease of the CNS, extending from immune to infectious pathologies. In our case, recurrences were systematically associated with high HIV activity and thus potentially reactivations of auto-immune dysfunction.

ON and HIV aetiology

Direct damage of CNS tissue due to the HIV has already been described and the combination with auto-immune response is becoming more recognised. Mechanisms by which HIV induces primary optic neuropathy remain to be clarified but a few theories have been proposed and will be discussed here.

Degeneration in the optic nerve may be mediated by HIV-infected macrophages rather than by direct viral infection of neurons. Axonal degeneration due to HIV at the level of the optic nerve can occur independently of retinal infection.[9]

Sadun et al. suggested that optic nerve degeneration may be mediated by HIV-infected macrophages.[9] Since viral particles have never been detected in optic nerve axons, the current hypothesis favours an immune-mediated mechanism to explain cell loss.

Virus-infected macrophages release cytokines, particularly tumour necrosis factor-α which plays

a major role in HIV-induced neuronal apoptosis, leading to optic nerve degeneration. The same mechanism seems to cause a transverse (short segment) partial myelopathy at seroconversion and a vacuolar myelopathy, which could explain the lesion in our patient in the cervical spinal cord. If present, this could confuse even more the initial differential diagnosis between seronegative NMOSD and optic neuropathy secondary to HIV infection. Longitudinal extensive transverse myelitis is not usually described after seroconversion and therefore could be a key diagnostic feature in the distinction from seronegative NMOSD.[3,10]

Two main theories stand out regarding the physiopathology of optic neuropathy in HIV: the coexistence of a hyperactive state of the immune system and allogeneic immune reaction by virus proteins. Both could trigger auto-immune disease.

The first theory is the well-known immune reconstitution inflammatory syndrome (IRIS). IRIS occurs during the early immune recovery period with ART and after a prolonged and profound immunosuppressed state. IRIS is frequently associated with opportunistic infections such as due to Cryptococcus neoformans, Mycobacterium tuberculosis, and John Cunningham virus.[6] It results from a pathological host response that occurs when the immune system is restored following commencement of ART. The quick rise of the CD4 cell count that ensues dysregulates T-cell balance and leads to an exuberant inflammatory response. It has been associated with lupus-like disease, thyroid disease, sarcoidosis, and numerous other auto-immune conditions.[11] The highly active auto-immune state is probably responsible for optic neuropathies being initially misdiagnosed as having an infectious cause or being due to MS.[11] In these cases, increased CD4 counts and undetectable HIV VLs following ART commencement are key findings and are highly suggestive of ON secondary to IRIS syndrome.[6]

The second theory postulates that as the CD4 blood count drops and the VL rises, an allogeneic immune reaction occurs, triggered by the virus proteins gp120, Taf and Nef. This also triggers several auto-immune diseases in the infected organism with impaired response against other antigens.[12] Studies have suggested that early immune ageing occurs as a result of the constant antigen burden causing persistent immune activation.[13]

In situations of visual loss with untreated HIV without secondary infectious disorders, we suggest starting ART with high doses of steroids and close biological, serological and clinical follow-up. This treatment combination probably is effective in the initial phases when axonal degeneration has still not set in. Studies have suggested that much of the optic nerve failure is due to a reversible dysfunction of the optic nerve neurons rather than their death.[14] Therefore, this treatment should be initiated promptly.[3,14]

First, the unusual delay between the HIV infection and optic neuropathy events (7 years), as well as the absence of meningitis, led us towards secondary auto-immune disease triggering the optic neuropathies in our patient, although we could not prove it. Further immune markers are needed to develop this theory. The low CD4 count, high VL, the dramatic improvement observed after treatment of the first episode, as well as the absence of NMOSD diagnostic criteria led us to a diagnosis of a primary HIV optic neuropathy. The absence of improvement after the second episode, which started after cessation of ART, support the hypothesis of progressive degeneration of optic nerve fibres.

Indeed, results suggest that a low CD4 nadir may be associated with widespread neural injury in the frontal and temporal regions of the brain.[15] This feature could explain optic nerve atrophy as a result of chronic low CD4 counts in HIV infection.

The close relationship between HIV and secondary triggered auto-immune disease needs to be kept in mind. Some of those pathologies could explain optic neuropathies but few clinical cases have been reported and some cases of seronegative NMOSD have probably been overlooked. It is important to recognise this clinical presentation as specific therapies are available.

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