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REVIEW ARTICLE

Concomitant diagnosis of multiple sclerosis and human immunodeficiency virus (HIV) infection: case report and the review of literature

Assunta Trinchillo[1] · Antonio Luca Spiezia[1] · Antonio Carotenuto[1] · Enrico Tedeschi[2] · Giuseppe Servillo[1] · Carmine Iacovazzi[1] · Francesco Borrelli[3] · Giovanni Di Filippo[3] · Vincenzo Brescia Morra[1] · Roberta Lanzillo[1]

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Abstract

Background To date, few cases of multiple sclerosis (MS) patients with concomitant Human Immunodeficiency Virus (HIV) infection have been described. However, none of the previously described cases has been treated with Natalizumab, probably due to the increasing risk of progressive multifocal leukoencephalopathy (PML).

Case We report the case of a patient concomitantly diagnosed for HIV infection and MS treated with combined antiretroviral therapy (cART) and Natalizumab for 19 months, without clinical or radiological MS activity.

Conclusions Our case might suggest considering Natalizumab in patients with concomitant HIV infection, especially for those with significant disease activity requiring a high efficacy disease modifying treatment.

Keywords Multiple sclerosis · Natalizumab · HIV

Introduction

Patients with human immunodeficiency virus (HIV) infection may develop acquired immunodeficiency syndrome (AIDS). Usually, 40% and 70% of these patients may also present with concomitant neurological symptoms [1].

Progressive multifocal leukoencephalopathy (PML) is one of the most fatal neurological affections in AIDS patients, and it is usually related to JC virus opportunistic infections. Besides AIDS, PML can also occur in multiple sclerosis (MS) patients treated with Natalizumab or other immunosuppressive treatments [2].

The association between HIV infection and MS has been rarely described, probably because of their different etiopathogenetic mechanisms—the CD4 T cells overactivation in MS and the suppression of the same cell population in HIV infection.

HIV infection can shift to AIDS usually when CD4 count is under 200 cells/mm^3. At this stage, a number of potentially life-threatening infections and illnesses can occur because of the immune suppression, and a treatment with drugs which may decrease further the cell count could increase the risk of AIDS and its complications (such as PML) in HIV patients. Therefore, physicians tend to avoid them, even if a MS is concomitantly diagnosed.

In this paper, we describe the case of a patient, who was diagnosed concomitantly for MS and HIV and was treated with Natalizumab with a follow-up up to 19 months. We also reviewed available cases of patients presenting with both conditions, illustrating the radiological features and the various treatments proposed.

Case

A 34-year-old man experienced in December 2020 a sudden loss of visual acuity in the left eye associated with pain during ocular movements.

✉ Assunta Trinchillo
assuntatrinchillo94@gmail.com

[1] Department of Neurosciences, Reproductive Sciences and Odontostomatology, "Federico II" University, Naples, Italy

[2] Department of Advanced Biomedical Sciences, "Federico II" University, Naples, Italy

[3] Infectious Diseases Unit, "Federico II" University, Naples, Italy

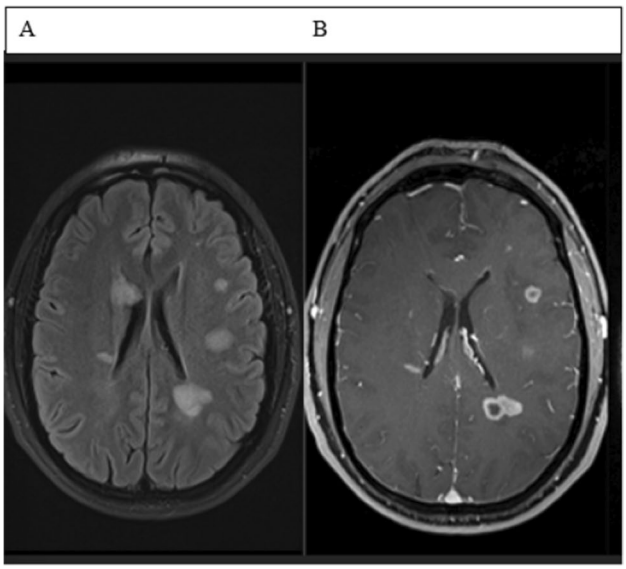

Fig. 1 **A**MRI-FLAIR axial slice showing periventricular and subcortical whitematter lesions. **B** Contrast-enhancement T1-weighted scan showing multiple activelesions

At HIV-screening on serum, a viral load (HIV-RNA 20,914 copies/mL) associated with mild decrease of CD4-lymphocites (CD4 354 cells/μL) was detected.

Therefore, plasma-exchange therapy was immediately interrupted, and the patient received the diagnosis of "retrobulbar HIV-related optical neuritis."

Then, he was referred to the HIV disease center of our university hospital, where combination antiretroviral therapy (cART) with Abacavir/Lamivudine/Dolutegravir (ABC/3TC/DTG) in single-tablet regimen (STR) was started and undetectable HIV-RNA was achieved in about 4 months. Nevertheless, only 2 weeks after cART start, symptoms exacerbated, and visual acuity decreased in both eyes. The patient was therefore referred to our MS Center.

At clinical examination, visual acuity disturbances and urinary urgency were detected—functional status score (FSS): visual system 4 (visual acuity 3/10); sphincterial system 2; expanded disability status scale (EDSS) as therefore 3.5. Patient underwent a new MRI scan showing a new contrast uptake at the left optical nerve (Fig. 2A–C).

Another steroid bolus was prescribed (1 g methylprednisolone i.v. daily for 5 days), with partial improvement.

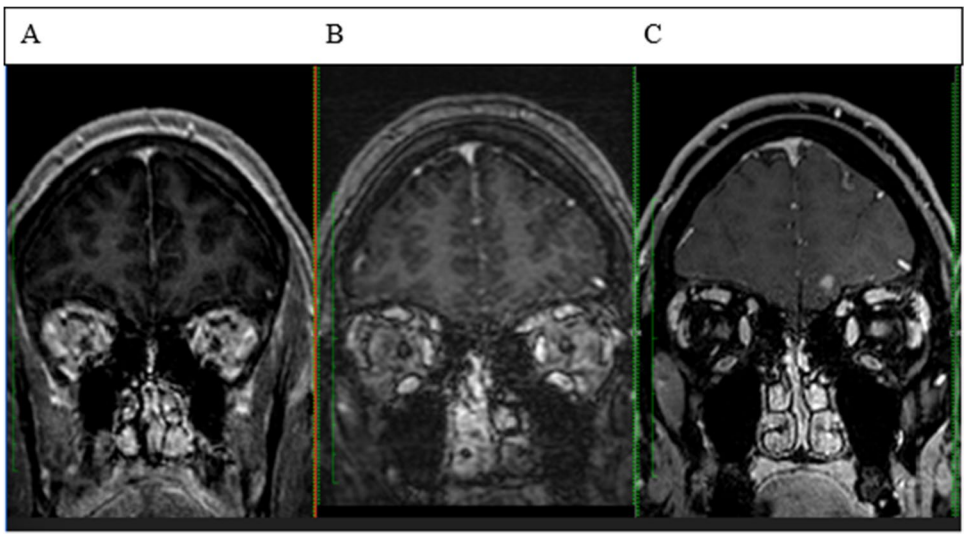

Fig. 2 T1-weighted coronal slices at the orbital level **A**, **B**were performed at the onset of symptoms, **C**instead was performed 2 weeks after the patient started cART and showed anew contrast-enhancing lesion in the left optic nerve. **A** and **B** were performedwithout fat-suppression, whereas **C**was made with fat-suppression; therefore, a lesion at the optic nerves waseasier to detect

The cerebrospinal fluid (CSF) analysis showed normal values of glucose, proteins, leucocytes count, and a "mirror" oligoclonal bands pattern in serum and CSF was found. Meningitis-encephalitis film array panel resulted unremarkable. The patient underwent a brain MRI scan, showing a high load of periventricular and subcortical lesions, and 2 larger contrast-enhancing lesions located in the left retrotrigonal white matter and in the subcortical white matter of the frontal operculum (Fig. 1A, B).

Suspecting an inflammatory-demyelinating disease, a steroid therapy was started with no improvement; therefore, patient underwent plasma-exchange therapy.

Moreover, we decided to search anti-AQ4 and anti-MOG antibodies on serum, using indirect immunofluorescence and a home-made method/cell-based essay respectively. Both resulted negative.

Finally, we made definite diagnosis of relapsing remitting MS and, after examining anti-JC virus antibody presence (titer 0.71) and having discussed therapeutic options with HIV disease center specialists, we started therapy with Natalizumab.

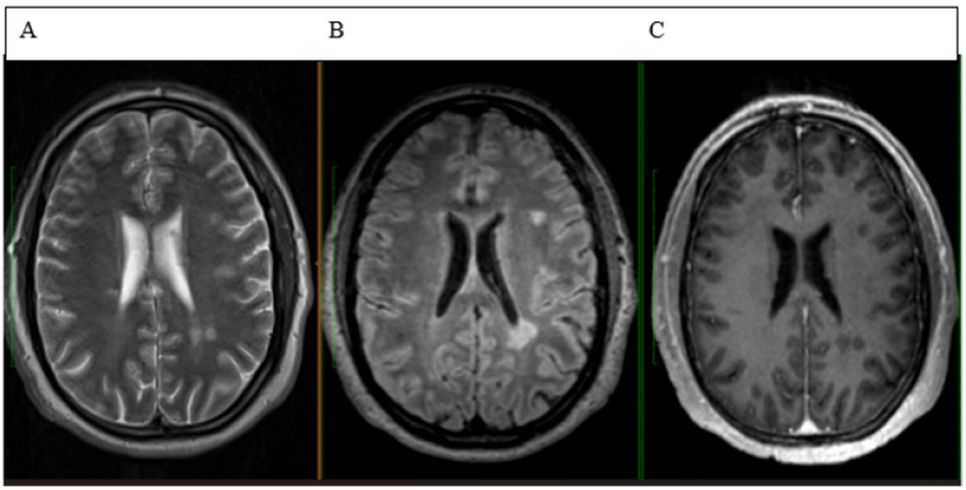

Fig. 3 **A** T2, **B** FLAIR, **C** contrast-enhancedT1 showing reduction of lesions after 2 months from the start of thetreatment with Natalizumab, without any contrast uptake

He performed another MRI after 2 months from treatment start, showing a slight volume reduction of the previous T2 lesions and of contrast uptake (Fig. 3A–C).

Treatment with Natalizumab—associated to cART—was continued up to 19 months and he did not present neither any relapses nor new MRI lesions.

During Natalizumab treatment, other 2 MRI scans were performed.

A first MRI, at the seventh month of treatment, showed a further reduction of T2 lesions volume, while there were no more lesions with contrast enhancement in T1.

After 12 months, another brain MRI revealed a black hole in the left peritrigonal area, without other changes. Concomitantly, the patient presented visual recovery (visual FSS improved from 4 to 3, with a visual acuity of 5/10) and the urinary urgency resolved. The final EDSS was 2.

Despite good clinical and radiological outcomes, Natalizumab was discontinued after 19 infusions because of PML risk (JCV antibody titer was 1.03) and, after discussion with HIV Center specialists, treatment with Ocrelizumab was started.

At the last clinical examination (4 months after Ocrelizumab start), he presented a stable visual acuity and a slight reduction of the strength at the right lower limb (FSS: visual: 3 pyramidal: 2, EDSS 2.5). His $CD4^+$ cell count reached 788 cells/μL and he kept an undetectable viral load. The last MRI did not reveal significant changes.

Methods

Reports of patients with MS associated with HIV infection were collected through a literature review conducted using the Medline database, covering the period between the year 2010 and 2021. Keywords were the following: ("Human Immunodeficiency Virus" AND/OR "HIV") AND ("multiple sclerosis" AND/OR "MS" AND/OR "demyelinating disease"), ("acquired immune deficiency syndrome" AND/OR "AIDS") AND ("multiple sclerosis" AND/OR "MS" AND/OR "demyelinating disease").

We only selected those papers reporting clinical cases with complete clinical-radiological features.

Results

We identified 6 case reports and collected MRI findings and several treatments proposed (Table 1).

Onset of diseases was never concomitant except in one case [3].

In most cases, a combination of cART and MS therapy was initiated. Immunosuppressive therapy has never been started. Natalizumab was indeed withdrew in one case, after the patient received the HIV infection diagnosis, then it was restarted and withdrew again, therefore a real efficacy of the drug could not be assessed [4].

Outcomes are different and they are usually stable. Speculations on the efficacy of the cART in controlling MS symptoms have been done [3]; nevertheless, there is not enough evidence to confirm them.

Discussion

To date, literature on concomitant HIV infection and MS is still poor.

A Danish record-linked database showed indeed a lower risk of MS in HIV treated patients, with a rate ratio of developing MS in people with HIV, relative to those without HIV, of 38% (95% CI 0.15 to 0.79) [5].

Nevertheless, we found some interesting cases in literature, since all patients described were treated with cART mainly—which seems to control also the demyelinating disease [3]—sometimes associated with immune modulators

Table 1 A review of the analyzed literature and our unreported case

Ref	Age	Sex	MRI	Treatment
Skarlis 2017	36	M	multifocal white matter lesions	Efavirenz/emricitabine/tenofovir + disproxil fumarate
Anand 2018	47	F	multiple lesions in the periventricular and juxtacortical white matter with contrast enhancement of the right optic nerve	Dolutegravir/emricitabine/tenofovir + glatiramer acetate
Chalkley 2014	32	M	hyperintense lesions of the left frontal lobe and the right brachium pontis with contrast enhancement of the former	Non specified antiretroviral therapy + interferon B1a
Chin 2015	30	F	spinal cord with multiple lesions	No cART + non specified immune modulator
Delgado 2014	45	M	longitudinally extensive thoracic transverse myelitis that showed enhancement. symmetric lesions bilaterally in the cerebral and middle cerebellar peduncles with heterogeneous enhancement	Ritonavir/atazanavir/abacavir/lamivudine
Mainardi 2020	35	F	multipile enhancing supratentorial lesions	Tenofovir/alafenamide/emtricitabine/rilpivirine + glatiramer acetate
OUR CASE	34	M	Multiple non-enhancing lesions and contrast uptake in the left peri trigonal area and in the left optic nerve	Abacavir/Lamivudine/Dolutegravir + Natalizumab

(first-line therapies), even if patients needed stronger treatments.

We may speculate that generally MS experts preferred to avoid immune suppressant drugs because of the increasing risk of opportunistic infections and PML. In one case, Natalizumab was indeed suspended when HIV was discovered.

Despite the previous reports, we started treating our patient with Natalizumab with his consent after thorough information.

This drug is a recombinant humanized IgG4κ monoclonal antibody indicated as first-line monotherapy for patients affected by highly active forms of relapsing–remitting MS (rrMS) or as second line, when the first line therapies either give suboptimal response or have to be interrupted because of adverse events [6, 7].

Generally, accepted criteria which indicate to physicians the best time to start with this drug are (i) two or more relapses in the first year of first-line treatment, (ii) a severe relapse with functional impairment, (iii) FSS and/or EDSS change > 1 point after a recovery from relapse, and (iv) enlarging lesions on MRI [7].

As we mentioned before, the most serious complication of the use of Natalizumab is related to an increased risk of developing PML—between 1/100 and 1/10,000—especially in those patients with time of exposure to Natalizumab ≥ 12 months, positive JCV antibody status, and previous use of immunosuppressants [8].

Moreover, HIV infection is the first cause of PML, which cannot be prevented with cART because it can also occur in the context of an ART-induced immune reconstitution inflammatory syndrome (IRIS) [9].

Despite the doubled risk, we opted to treat our patient with Natalizumab for different reasons.

Firstly, his highly active MS phenotype and the increase of MRI lesions in a short time, which are two of the mentioned criteria for starting a "second line" therapy [7].

In addition, the worsening of MS symptoms after the start of the cART predicted for a high susceptibility to IRIS, which would have risked compromising the future of the anti-retroviral therapy. In order to prevent that complication, we decided for a high efficacy drug with rapid and sustained reduction in disease activity such as Natalizumab [10].

Moreover, our patient's severe visual deficit was another driver of choice for Natalizumab, following the report of a patient who had increased her visual acuity after 10 infusions [11] and the described drug's efficacy in reducing visual loss [12].

However, in order to reduce PML risk, we monitored JCV titer monthly and MRI every 6 months, since it was previously demonstrated that not only JCV positivity but also JCV antibody titer is meaningful to stratify patients according to PML risk.

Following the continuous monitoring, we found a sudden increase of anti-JCV titer. This exposed the patient to a greater risk of PML (0.3 over 1000). Hence, we decided to stop natalizumab treatment, especially given the concomitant HIV infection status. Differently from natalizumab, ocrelizumab treatment is safer with regards to PML as only sporadic cases have been described so far in ocrelizumab-treated MS patients not previously treated with other disease modifying treatment with increased PML risk [13–15].

Conclusions

This case report describes the first patient who has been treated with Natalizumab—without any interruptions—for MS despite the diagnosis of HIV infection.

Our patient recovered under the radiological and clinical point of view, and he did not experience any complications related to the treatment. Therefore, we want to highlight that clinical and imaging findings should always guide physicians in the decision-making process.

Our case shows that the use of a second-line therapy such as Natalizumab in severe MS phenotypes may be a feasible option, even in presence of concomitant HIV infection.

To avoid a treatment because of possible adverse events, increasing the risk of clinical worsening should not be considered a right choice, whereas if physicians monitor the patient with a scrupulous follow-up, the benefits of a treatment are likely to outweigh the possible drawbacks.

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Data Availability The data that support the findings of this study are available on request from the corresponding author, [AT]. The data are not publicly available due to information that could compromise the privacy of the patient.

Declarations

Research involving human participants and/or animals Manuscript has compliance with standards of research involving animals. Manuscript has compliance with standards of research involving humans as subjects.

Conflict of interest The authors declare no conflict of interest.

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