

Guillain Barré syndrome in an HIV-1-infected patient after the beginning of combined antiretroviral therapy: an immune reconstitution inflammatory syndrome?

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SUMMARY

HIV-1-associated Guillain-Barré syndrome (hGBS) is an ascendant progressive polyradiculoneuropathy described throughout the course of the viral disease, mainly associated with the acute retroviral syndrome. HGBS is occasionally described in severely immunocompromised subjects in the context of the immune reconstitution inflammatory syndrome. The case described occurred soon after the start of a combined antiretroviral treatment in an HIV-1 infected patient with ulcerative colitis in the absence of severe immunosuppression. This manifestation may be interpreted as an uncommon appearance of an immune reconstitution syndrome in the presence of a predisposing autoimmune pathology.

KEY WORDS: Guillain-Barré syndrome, HIV-1, HAART, IRIS.

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INTRODUCTION

Guillain-Barré syndrome (GBS) is an ascendant progressive polyradiculoneuropathy characterized by a rapidly evolving symmetrical limb weakness, loss of tendon reflexes, absent or mild sensory signs, and a variable autonomic dysfunction (Dua *et al.*, 2010). GBS can appear with different pathological subtypes, the most common in the western world is an acute inflammatory demyelinating polyradiculoneuropathy (Asbury *et al.*, 1969; Prineas, 1972). Other variants described are an acute motor axonal neuropathy frequently observed in Asia and Japan, an acute motor and sensory axonal neuropathy, and the Miller-Fisher syndrome

characterized by acute ophthalmoplegia, ataxia, and areflexia (McKhann *et al.*, 1991; Griffin *et al.*, 1996).

GBS commonly occurs a few days or weeks after respiratory or gastrointestinal infections. *Campylobacter jejuni* and *Cytomegalovirus* (CMV) constitute the main bacterial and viral triggers (Singer *et al.*, 2010). *Epstein-Barr* virus (EBV), *Mycoplasma pneumoniae*, and human immunodeficiency virus type 1 (HIV-1) have also been associated with GBS, whereas *parvovirus* B19 (B19V) is rarely cited as a causative agent (Bucher Praz *et al.*, 2012). The diagnostic approach is based on clinical, laboratory, and electrophysiological criteria. Progressive motor weakness and areflexia are the main requirements for diagnosis. Cerebrospinal fluid (CSF) analysis is the only laboratory criterion: examination of CSF shows increased proteins and normal or slightly increased cellularity. HIV-1 concomitant GBS (hGBS) is described throughout the course of the viral disease, but more frequently associated with the acute retroviral

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syndrome (Howlett *et al.*, 1996; Thornton *et al.*, 1991). However, hGBS has also been described during the chronic phase of HIV-1 infection, as an immune reconstitution inflammatory syndrome (IRIS), a clinical picture occurring in severely immunocompromised patients after the beginning of combined antiretroviral therapy (cART) (Piliro *et al.*, 2003; Zaffiri *et al.*, 2013). Although hGBS generally has a favourable outcome, a rapid worsening of clinical conditions with respiratory failure has been reported (Pontali *et al.* 2011). According to the literature, both plasmapheresis and intravenous immunoglobulins (IVIg) have been successfully used (Berger *et al.*, 1997).

Here we describe a case of Guillain-Barré syndrome occurring a few months after the beginning of cART, in a chronically HIV-1 infected patient without severe immunosuppression, affected by an inflammatory bowel disease.

CASE REPORT

A 36-year-old man-who-have-sex-with-men with a two-year history of HIV-1 infection reached our outpatient clinic on July 2012. According to the CDC classification, he belonged to B1 Group, showing a CD4+ T cell count 775 cells/ μ l and plasma HIV-1 RNA load 178,000 copies/mL. In 2006, he was diagnosed with ulcerative colitis, currently clinically silent. He resulted CMV IgG and *Toxoplasma gondii* IgG positive; no report of opportunistic infections, diabetes or alcoholism were highlighted. His neurologic clinical history was negative. In May 2012, he was histologically diagnosed with human papillomavirus (HPV) infection-related anal warts and low grade squamous intraepithelial lesions (LSIL). In November 2012, an immune-virological examination showed CD4+ T cells 545/ μ l and HIV-1 RNA 212.000 copies/mL and a tenofovir-difumarate (TDF)/emtricitabine (FTC)-fixed dose plus ritonavir-boosted darunavir (DRV/r 800/100 mg QD)-based cART was started. Two months later, he complained of rapidly progressing weakness, bilateral lower limb paresthesias, and partial inability to ambulate. He showed at that time CD4+ T cells 517/ μ l (17%) and HIV-1 RNA load 116 copies/mL. A few weeks before the onset of symptoms

he reported fever, gastrointestinal discomfort, joint pain, dorsal and lumbar muscular tenderness, treated with anti-inflammatory drugs (acetaminophen). No vaccines were administered before symptom onset.

The patient was promptly hospitalized. Neurologic examination on admission showed a bilateral reduction of muscle strength in the lower limbs and hyporeflexia, without signs of autonomic dysfunction. Meningeal signs were absent. A brain CT scan performed during the acute phase of the disease resulted negative for focal densitometric abnormalities in encephalic tissues, with absence of bleeding. A lumbar puncture was done. Biochemical CSF analysis showed: clear liquor with Pandy's reaction positive, no leucocytes, erythrocytes, or atypical cells, total proteins 97 mg/dl (normal value 15-55); glucose 29 mg/dl (normal value 50-70). CSF bacterioscopic examination and microbiological cultures resulted negative. Detection of neurotropic viruses (EBV, CMV, VZV, HSV 1 and 2, and JC virus) by a real-time polymerase chain reaction (RT-PCR) was negative (Nanogen, Inc., CA, USA). HIV-1 RNA CSF level resulted negative (<37 copies/mL) as was HHV-6 detection. Complete blood count, metabolic parameters, inflammatory indexes such as erythrocyte sedimentation rate (ESR), C-reactive protein (PCR), anti-streptolysin O titre, coagulation study, urine analysis, and serum electrophoresis were all within the normal ranges. *Treponema pallidum*, hepatitis B and C serologies were negative, as well as stool cultures and *Campylobacter jejuni* and *Mycoplasma pneumonia* serologies. An extensive plasmatic viral panel performed with PCR (CMV-DNA, EBV-DNA, and VZV-DNA) was negative.

Electro-neuro-myography showed widespread damage to the nerve myelin, highly suggestive for the presence of a demyelinating polyradiculoneuropathy. Brain and spinal cord MR imaging resulted negative for focal lesions of the grey and white matter; but a bilateral diffuse mild atrophy of the hemispheric cortex was present, reasonably attributable to HIV-1 infection. Patient was diagnosed with GBS and treated with high-dose IVIGs (400 mg/kg/die for 5 days) with a rapid clinical improvement. During hospitalization no corticosteroids were administered and no cART discontinuation allowed.

At the three month follow-up evaluation the patient showed a complete remission of the neurological symptoms. Blood analyses show CD4+ T cell count 825 cells/ μ l (17%) and HIV-1 RNA load <37 copies/mL. Antiretroviral therapy remained unchanged. The appearance of IgM and IgG auto-antibodies against myelin gangliosides GM1-GM2, GMD1a, and GMD1b was documented two months after hGBS onset, whereas their search resulted negative in plasma samples taken before the onset of the neurologic symptoms.

DISCUSSION

Neurologic complications are present at all stages of HIV-1 infection (Geraci, 2001). Antiretroviral agents may be responsible for neurologic disorders, usually such as distal symmetric peripheral neuropathy. GBS is an acute or sub-acute peripheral polyneuropathy characterized by symmetrical muscle weakness. Genetic, infectious, metabolic, and toxic factors have been hypothesized as GBS triggers. Recent findings have demonstrated that anti-ganglioside antibodies may play an important role in the pathogenesis of GBS and Fisher syndrome (FS). The anti-GM1 antibodies are likely to damage peripheral nerves through complement activation with dysfunction of voltage-gated sodium channels. Some anti-ganglioside antibodies may cause dysfunction of voltage-gated calcium channels without complement activation. Clustered epitopes of ganglioside complexes (GSCs) consisting of two gangliosides can be targeted by serum antibodies in GBS and FS. Anti-GD1a/GD1b complex antibodies are associated with severe GBS (Hughes *et al.*, 2005).

HGBS occurs early in HIV-1 infection, often as an acute neurologic manifestation at the seroconversion time, generally in the presence of high CD4+ T cell counts. It has been hypothesized that hGBS recognizes as eliciting causes the direct action of neurotropic HIV-1 strains on the peripheral nerves, the involvement of autoimmune mechanisms (i.e. the presence of auto-antibodies against myelin), and the immune dysregulation related to the viral infection (Nishijima *et al.*, 2011). However, hGBS

has also been described as an IRIS in advanced HIV-1 infected subjects. Effective cART has been associated with several different immune reconstitution illnesses (Howlet *et al.*, 1996; Hassan *et al.*, 2000) that generally occur in the first 3–6 months after the initiation of antiretroviral therapy and represent an anomalous host immune response to an opportunistic pathogen (Berger *et al.*, 1987; Brannagan *et al.*, 2003; Piliro *et al.*, 2003). In accordance with different IRIS definitions, this syndrome is an ‘unmasking’ or paradoxical worsening of a pre-existing infection, in the presence of a decrease of HIV-1 RNA loads, more than 1 \log_{10} copies/mL in the first 3 months of cART. Generally, IRIS is characterized by a rapid recovery of T-cell immunity in response to pre-existing antigens from infectious opportunistic agents, that leads to a worsening of clinical symptoms (Tsang *et al.*, 2010). The pathogenetic mechanisms involved in IRIS development could depend on a combination of three aspects:

- 1) degree of immune restoration following cART;
- 2) underlying antigenic burden;
- 3) host genetic susceptibility.

Our case presents some peculiar aspects with respect to the majority of those described during HIV-1 infection to date:

- a) it occurred during the chronic phase of the infection in association with a precipitous decrease in the virus load following the start of cART, consistent with an IRIS diagnosis;
- b) hGBS onset occurred in the absence of severe immune suppression;
- c) the patient had a pre-existing imbalanced immune system as he suffered from an autoimmune disease (ulcerative colitis).

We can hypothesize that in our patient hGBS onset may be the consequence of an IRIS and that the three factors previously reported have all contributed in different ways to triggering the neurologic disease. In fact, hGBS onset was strictly related to a dramatic decrease of virus load that fell from 212,000 to 116 copies/mL after two months of cART (close to a 3 \log_{10} decay from pre-therapy values), and a rapid initial reduction in HIV-1 RNA levels within 90 days after starting cART has been proposed as a risk factor for IRIS (Muller *et al.*, 2010). Despite the apparent initial absence of a con-

sistent immune recovery in terms of CD4+ T cell rise, an increased risk of IRIS development linked to the redistribution of memory CD4+ T lymphocytes may be hypothesized as a response to the cART-driven drop in HIV-1 RNA levels (Shelburne *et al.*, 2006). The restoration of immune system functionality may have determined an immune-mediated inflammatory response to his peripheral nervous system causing a rapidly progressive motor neuropathy. Finally, both in IRIS and hGBS pathogenesis an important role is played by the host genetic susceptibility, and our patient was previously diagnosed with ulcerative colitis, an inflammatory bowel disease that could predispose him to an altered mucosal absorption, also including microbial translocation. It was previously demonstrated that in the development of hGBS a central role is exerted by autoimmune phenomena. However, we cannot consider a contribution of the molecular mimicry between *Campylobacter jejuni* epitopes of the wall lipo-oligosaccharides and the nerve gangliosides in the reactivation of T cell immunity, due to the absence of infections by neurotropic viruses and intestinal pathogens. Moreover, the detection of anti-ganglioside antibodies, despite their pivotal role in other variants of GBS, could not play a direct role in the present case since they may simply represent an epiphenomenon during IRIS.

In conclusion, according to the pathogenetic mechanisms involved in IRIS onset, we can assume that in our patient a significant virologic response to cART in the presence of predisposing factors probably led to an aberrant immune attack against his peripheral nervous system, triggering hGBS onset and eliciting the development of the anti-gangliosides auto-antibodies.

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