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Case Report

CASE REPORT

Acute motor axonal neuropathy in a patient with prolonged CD4 depletion due to HIV: a local variant of macrophage activation syndrome?

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Abstract

Acute inflammatory demyelinating polyneuropathy or Guillain-Barré syndrome is well recognized as a presenting feature of human immunodeficiency virus (HIV) seroconversion and, to a lesser extent, as a complication of HIV infection, particularly immune reconstitution. Acute motor axonal neuropathy (AMAN) is much rarer in this setting. A case is presented of acute motor neuropathy, with features most consistent with AMAN in the setting of congenital HIV and prolonged non-compliance with antiretroviral treatment. The case throws new light on the pathogenesis of this condition. Macrophage activation is proposed as fundamental; the patient was predisposed by HIV as well as the use of granulocyte colony-stimulating factor and AMAN was then precipitated by a bacterial infection.

INTRODUCTION

Acute inflammatory demyelinating polyneuropathy (AIDP) has long been associated with human immunodeficiency virus (HIV). Presentation, treatment and outcomes are similar to those in patients without HIV, although colony-stimulating factor (CSF) pleocytosis is more common and the initial presentation may be more severe with and take longer to resolve [1]. Screening for HIV is advised in those with AIDP in endemic areas. Cases have been reported as occurring as part of the immune reconstitution syndrome, including in children with congenitally acquired HIV.

There are only four recorded cases of AMAN occurring in a patient with HIV. These are summarized in Table 1. Based on cases to date, it had been suggested that AMAN occurs before the stage of profound immune suppression; the current case makes this highly unlikely.

CASE REPORT

A 22-year-old lady with congenitally acquired HIV presented with generalized weakness and numbness of the body for almost 2 weeks. She had been discharged from another institution 2 weeks before following the treatment of an episode of pyelonephritis. Blood cultures grew *Escherichia coli*, and she underwent a 14-day course of treatment with ciprofloxacin. Two days after discharge she noted tingling and numbness affecting the hands and legs. Later that day, her legs gave way while she was standing at a bus stop. These symptoms progressed to the point where she was not able to support herself sitting up and had needed to move in with her partner for help with her activities of daily living.

She had been repeatedly non-compliant with HAART for her HIV, which was multidrug resistant. She had been taking filgrastim [a granulocyte colony-stimulating factor (G-CSF) analogue] for neutopenia. Her last CD4 count prior to admission was 3

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Table 1: Reported cases of HIV and AMAN

Case	HIV	Stage	CD4 count	Recent infection	Reference
1	Acquired	New	150	No	[2]
2	Unknown	Chronic	440	No	[3]
3	Unknown	Chronic	350	No	
4	Congenital	Chronic	540	Dysentery	[4]
Current	Congenital	Chronic	5	*E. coli* pyelonephritis	

Table 2: Nerve conduction studies

	Velocity (m/s)	Amplitude (mV)	Latency (ms)
L median nerve	50 (>48)		
L peroneal	38 (>50)	2.1 (>2.5)	
R peroneal motor		0.3 (>2.5)	10.4 (<5.5)
R tibial motor		4.3 (>2.9)	6.2 (<6.0)
L tibial motor		4.4 (>2.9)	6.7 (<6.0)
L superficial peroneal sensory			3.8 (<2.4)
F waves			
L median			25 (<31)
L&R peroneal			Absent
R tibial			52 (<58)
L ulnar			29 (<31)

Figures in parentheses show reference values.
Findings are typical of a predominantly axonal neuropathy.

months ago and was 1/μl. On this admission, it was 5. It had always been <10 since she had first attended here 21 months prior to this. She had a prior episode of *Pneumocystis* pneumonia. aged 17.

Her initial examination showed generalized weakness, particularly proximally and particularly of the legs. Reflexes were initially preserved, but were absent even with reinforcement 10 days later. There were no sensory signs. She had mild fine nystagmus in all directions of gaze. No ophthalmoplegia or ataxia was present.

Her initial complete blood count, coagulation profile, comprehensive metabolic profile, Mg^{2+}, lactate, CK, B12 and TSH were all normal apart from her hemoglobin/hematocrit of 10 g/deciliter/29% which was normocytic. Her lumbar puncture showed a protein of 95 mg/dl with no cells and normal glucose. MRI of the spine with contrast showed diffuse, symmetric enhancement of multiple ventral nerve roots.

Nerve conduction studies performed 1 week after admission are summarized in Table 2. These show diffuse motor neuropathy in the legs, with no involvement of the arms or of sensory nerves. The only evidence of demyelination was in the right peroneal nerve. While this does not meet the formal criteria for AMAN as proposed by the Guillain-Barré Syndrome Trial Group, the pattern is in keeping with this rather than AIDP [5]. Electomyography showed increased spontaneous activity and decreased motor unit amplitudes in the legs.

She was given a 5-day course of intravenous immunoglobulin (ivIg). There was no initial sign of clinical improvement and she was discharged to rehabilitation. We were unable to contact her for follow-up in our clinic as planned.

DISCUSSION

The CD4 count reported here is the lowest reported for a patient with an acute motor neuropathy. The neuropathy is all the more striking in that it is predominantly axonal.

In the largest series of patients with HIV and AIDP, 10 in total, the two lowest CD4 counts at time of presentation were 55 and 118/μl [6]. Another series of six patients showed the lowest CD4 count to be 46.

What light does this throw on pathophysiology? The key event here appears to be macrophage activation, precipitated by a recent infection and with the use of G-CSF as a predisposing factor.

While it is already recognized that patients with HIV can develop AIDP at any stage of the disease process, our patient provides evidence that the same is true for AMAN. Furthermore, the precipitating event does not appear to be solely the result of a *change* in CD4 levels. Varying levels (and changes in levels) of CD4 at the time of diagnosis suggest that these cells are not crucial to the pathogenesis. CD4 depletion in animal models has been shown to result in other organ-specific autoimmune conditions, although not AIDP or AMAN [7].

Both AIDP and AMAN are thought to be mediated by activated macrophages, targeting either the myelin sheaths or the nodes of Ranvier, respectively [8]. Macrophages become 'classically activated' following the stimulus of IFN-γ (primarily); local tissue destruction results. Macrophages serve as a reservoir for HIV and its intracellular presence allows them to 'auto-activate', in part by secreting IFN-γ in response to viral protein gp120 exposure [9].

Widespread systemic mobilization is known as 'macrophage activation syndrome' (MAS). This often follows infection in immunosupressed patients and is characterized by an increase in circulating IFN-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF). One case has been reported as occurring in a patient with HIV following infection with *Nocardia*, also with a low CD4 count (53/μl) [10].

If AMAN and AIDP are organ-specific variants of MAS, then markers of this process should be elevated and could be measured in such patients (IFN-γ is available commercially and may be expected to fall with resolution of the neuropathy). Confirmation would provide a rationale for use of steroids in addition to ivIg. There are also reports of dramatic benefit from the use of anakinra (a recombinant IL-1 receptor antagonist) in MAS; monocyte–granulocyte apheresis is another therapeutic possibility. Given the rarity of this condition, treatments will necessarily continue to be individualized.

CONFLICT OF INTEREST STATEMENT

None declared.

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