Spontaneous resolution of a case of anti-retroviral treatment-naïve HIV-associated polymyositis

Venkat R, Jawad ASM, Chikanza IC

Department of Rheumatology, The Royal London Hospital Whitechapel London E1 4DG UK

Corresponding author: *Dr R Venkat. Email: vrreddy113@gmail.com*

Abstract

Autoimmune Rheumatic Diseases (ARD) have been described in individuals with Human Immunodeficiency Virus (HIV) infection. However, the incidence of ARD in individuals with HIV has evolved since the introduction of Highly Active Anti Retroviral Therapy (HAART) for the treatment of HIV. Clinicians face a therapeutic dilemma regarding the use of potent immunosuppressants when managing ARD in individuals with HIV infection. The disease activity of ARD varies during the natural course of HIV infection and its treatment with HAART. The outcomes of some ARDs may be better in individuals with HIV when compared with individuals without HIV. Here we report the first case of spontaneous resolution of HIV-Associated Polymyositis (HAM) presenting with profound proximal muscle weakness occurring in a treatment-naïve patient with HIV and discuss the possible treatment options of HAM based on evidence from the literature.

Keywords: HIV, Polymyositis, HIV-associated myositis, HAART, Highly Active Antiretroviral Treatment and anti-retroviral drugs

Introduction

Autoimmune polymyositis is a chronic condition that affects muscles and vital organs such as lungs and heart. However, polymyositis may be caused by infections with bacteria or viruses. Polymyositis (PM) may resolve with successful treatment of bacterial infection whereas the course of PM in the context of viral infections such as Human Immunodeficiency Virus (HIV) is usually chronic, probably because the virus persists in the host. The course of PM in an individual may undulate consequent to a continual change in the host's immune system toward containing the HIV. Therefore, a better understanding of the dynamics of the host's immune system in the course of HIV infection would be of clinical relevance to guide the use of immunosuppression to control PM. To this end, we present a case of spontaneous resolution of a case of HIV-associated anti-retroviral treatment naïve PM. We show that with careful monitoring during an initial presentation allowed us to cautiously withhold immunosuppression and introduce anti-retroviral treatment. We discuss the pathways of Immunopathogenesis of HIV-associated PM and highlight that immunosuppression may be withheld for HIV-associated PM.

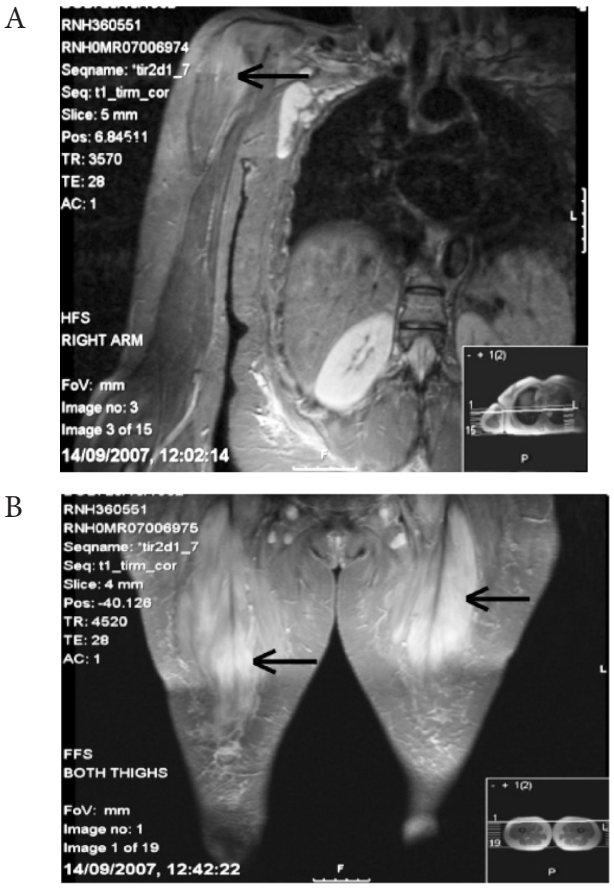
Case Report

A 44-year-old Nigerian lady presented with an acute history of generalised weakness, painful legs and joint pains. She found it difficult to manage routine daily activities due to severe weakness of arms and legs. She could no longer carry on working as a domestic cleaner. There was no preceding history of intercurrent illness. She had no respiratory, cardiovascular or gastrointestinal or any neurological symptoms. There was no history of smoking, alcohol or other drug abuse. Past medical history included hypertension and uterine fibroids. Five months prior to her presentation she was diagnosed with HIV-I infection (asymptomatic). Her CD4 count was greater than 280 (reference range 500-1600) cells/mm^3 and CD8 count was 1280 (reference range 375-1100) cells/mm^3. She had not needed any antiretroviral treatment. There was no family history of autoimmune diseases. On examination, she looked generally unwell. She was afebrile and had non-tender cervical, axillary and inguinal lymphadenopathy. There was no evidence of any rash, parotid enlargement, mouth ulcers or hair loss. There was no joint swelling or tenderness. There was erythema and oedema of both upper and lower limbs. The proximal muscles of upper and lower limbs were also tender and weak with their power limited to 3/5. Sensation, muscle tone and reflexes were normal. Respiratory and cardiovascular examination was unremarkable.

Initial blood tests revealed a Creatinine Kinase (CK) level of >90,000

IU/L. Erythrocyte sedimentation rate was 44 mm/hour and C reactive protein was 22g/L (normal <5). Full blood count, urea, electrolytes, thyroid function tests, chest X-ray, electrocardiogram, spirometry and echocardiography were normal. Antinuclear antibody, extractable nuclear antibody and anti Jo-1 antibody were negative. Hepatitis serology was negative. Urine dipstick analysis was normal. Electromyography revealed subtle evidence of myopathy but no evidence of neuropathy. MRI findings revealed widespread patchy hyperintense lesions affecting the proximal muscles of both upper and lower limbs indicative of active PM (Figure 1).

Figure 1: Active proximal myositis detected by magnetic resonance imaging. T1 weighted image of the right upper limb showing patchy areas of hyperintense signal in the deltoid, supraspinatus (black arrow) (A). T1 weighted MRI of lower limbs showing patchy areas of hyperintense signal (black arrow) (B)



Whilst waiting for the results of the muscle biopsy, she received physiotherapy and her power gradually improved in both upper and lower limbs to 4/5. A MRI-guided targeted muscle biopsy was performed after 2 weeks. The histological features of which were diagnostic of autoimmune polymyositis. There was evidence of CD8+ T cell and macrophage infiltration surrounding the MHC-I- expressing muscle fibres, similar to that in seronegative myopathies. Clusters of CD3+ and CD8 +ve T lymphocytes were also seen in the endomysium and around blood vessels. Few CD20 +ve lymphocytes were also seen perivascularly. Further, there were regenerating muscle fibres and some atrophic fibres but no features to suggest drug induced or nemaline rod myopathy. No inclusion bodies were seen.

Highly Active Antiretroviral Treatment (HAART) with a combination of abacavir and limuvidine was initiated. Under close monitoring including 6-hourly spirometry, immunosuppressive therapy was judiciously withheld. Within three weeks of the onset of symptoms, she was able to carry on with her daily activities. On further review, at five weeks from the onset of symptoms, her power continued to improve and CK levels normalised, at 146 IU/L. She has continued to be asymptomatic on follow up at 72 months since the initial presentation.

Discussion

This case report illustrates that spontaneous remission can occur in HIV-Associated Myositis (HAM), even in individuals with profound weakness and HAART therapy may aid in sustaining remission.

ARD in an HIV-infected individual: The outcomes for individuals with HIV infection have remarkably improved, since the introduction of anti-retroviral drugs in 1987 and HAART in 1996[1]. However, HAART therapy is associated with the occurrence of IRIS and an increase in certain Autoimmune Rheumatic Diseases (ARD)[2]. Factors related to HIV such as the viral load and genotype, and the susceptibility of the infected individual to develop ARD such as HLA B27 positivity, determine the outcomes of HIV-associated ARD. For example, the estimated risk of developing Reiter's syndrome in HIV infected individuals is many fold (up to 140) higher than in seronegative population and the risk is linked with HLA B27 positivity[3]. This estimate was prior to the introduction of HAART and could be lower, since the introduction of HAART in 1996[4]. ARDs occurring in individuals with HIV and their relationship to HAART are summarised in Table 1.

Table 1: Common ARD associated with HIV and their relation to HAART

Condition	Comments	Relation to HAART	Reference
Polymyositis		Occurs de novo or exacerbates	(2)
Dermatomyositis		?	(48)
Reiter's syndrome	Up to 140 fold higher, HLA B27 linked susceptibility	Risk reduced	(3), (4)
Rheumatoid Arthritis		Tends to improve	
Spondyloarthropathy		Tends to improve	(2)
DILS	CD8+ T cell infiltration of tissues	Improves	(2)
Antiphospholipid syndrome/ antibodies	Positive antibodies high, however, clinical syndrome is rare		
Autoimmune thrombocytopenia	Up to 40% estimated	Improves with HAART	(49)
SLE	Extremely rare	Occurs de novo or exacerbates	(2)
TTP	Very rare	Tends to improve	(50)
Vasculitis		Occurs de novo	

HAM may be the presenting manifestation of HIV infection[5]. Rarely, the manifestations can be severe with life-threatening myocardial and oesophageal involvement[6]. Antisynthetase syndrome with positive anti-Jo 1 antibodies and pulmonary fibrosis has also been reported[7]. HAM has been reported to result in myoglobinuric renal failure[8], although myoglobinuria could occur even in the absence of muscle inflammation[9]. The creatine kinase levels in HAM could be normal[10] or modestly elevated (two fold increase above normal) and almost four fold lower than the CK levels in autoimmune polymyositis[11]. Although, radionuclide scan has been used as non-invasive diagnostic modality in the diagnosis of HAM[12], MRI-guided muscle biopsy demonstrating characteristic Immunohistochemical changes in the affected muscle remains the investigation of choice to diagnose HAM.

The effect of HAART on the prevalence and prognosis of HAM: Since the first report of PM in a patient with Acquired Immunodeficiency Syndrome (AIDS) in 1986[13], several independent groups have confirmed PM in HIV as a distinct condition, HIV-associated (HAM)[14-17]. The estimated prevalence of polymyositis in HIV varies from 2-7%[15,18]. Since the introduction of HAART, a study of 888 individuals from 1995 to 2006 estimated the overall prevalence of rheumatic manifestation in HIV infection is approximately 9%, only one patient in this cohort was diagnosed with polymyositis and there were no cases of seronegative spondyloarthritis or Sjogren's syndrome[4]. PM has been reported to occur during immune restoration with HAART therapy[19,20]. The prevalence of HAM was found to be higher in symptomatic individuals not previously treated with HAART[21]. As in the case of most ARDs, a higher prevalence was noted in women and younger individuals[11]. A possible explanation for the observed discrepancy in the estimated prevalence rate of HAM in various studies is the introduction of HAART for the treatment of HIV. Taken together, the difference in the estimated prevalence of HAM between studies undertaken prior to and following the introduction of HAART suggest that HAART treatment influences the development of clinically evident HAM. HAART therapy reduces the viral load and consequently, the disease activity of HAM. Further, asymptomatic individuals or those with milder symptoms may not seek specific medical attention and remain undiagnosed.

Immunopathogenesis

What factors regulate the outcome in HAM? HIV infection activates both cellular[22] and humoral immune response; the latter is indicated by the presence of hypergammaglobulinemia[23,24]. The net effect of these responses determines the timing and the severity of ARD. Both the viral load and its sensitivity to HAART therapy determine the outcome of HIV infection. It has been suggested that the natural course of HIV infection and its response to HAART could be represented as stages of the infection. For example, Zandman-Goddard *et al*.[25] suggest that the occurrence of ARD in HIV relates to the stage of infection and the viral load.

Defective classic apoptosis of T cells in the muscle: HIV has a predilection to infect CD4+ T cells inducing their activation and apoptosis[26]. Rawson *et al*[27] proposed that the dendritic cells phagocytose T cell apoptotic material and process it in their proteasome where caspases break down the proteins into peptides (self antigens), which are then coupled with MHC before presenting to the effector cells. This hypothesis is supported by the observed correlation between the T cell-apoptotic load and the number of autoreactive CD8+ T cells. With effective therapy using HAART, the apoptotic load is reduced

which results in decreased number of autoreactive CD8+ T cells. In contrast in HAM, there is differential lack of T cell apoptosis (predominantly CD8+ T cells) in the neuromuscular tissues when compared with lymph nodes[28]. The mechanisms that underlie this differential anti-apoptotic T cell survival are not clearly understood. However, there is some indirect evidence that suggests an increased expression of classic anti-apoptotic proteins and the up-regulation of the Fas/Fas ligand system in HIV[29].

Myocytes act as antigen presenting cells and sustain local inflammation: The striking histological similarities between HAM and PM suggest that HIV inflicts widespread muscle inflammation using the same immune effector pathway as PM. However, the precise mechanism by which this immune response is triggered remains undefined. Based on the histological findings demonstrating the presence of effector cells around the site of muscle damage, it has been suggested that HIV virus could infiltrate myocytes. The infected myocytes act as non-professional antigen presenting cells and recruit immune effector cells, which amplify the immune effector response at the site. Using *in situ* polymerase chain reaction-amplification Seidman *et al*[30] have detected the presence of HIV nucleic acids in the muscle fibres of individuals with HAM. However, another group found fewer CD4+ cells in muscle biopsies from 19 individuals with HAM when compared with five individuals with seronegative PM. Further, they detected the presence of HIV antigens (p24, gp 120 and gp41) in the interstitial mononuclear cells but not in the muscle fibres. There was no quantitative difference in B cells, natural killer cells, interleukin-2 receptor positive cells or macrophages[31]. Another study found evidence of HIV antigen (gp41) in muscle macrophages[32]. However, other groups have not been able to demonstrate the presence of HIV in myocytes using *in situ* hybridisation[16] and polymerase chain reaction[33]. Based on this, the authors concluded that it is not likely that HIV virus infects or replicates in myocytes. Similarly, in the case of PM in individuals with HTLV-I infection the histological features are indistinguishable from autoimmune PM[34], where it has not been possible to detect the HTLV-I in the affected myocytes[35] . Further, HIV infection and hepatitis C infection may coexist, and myositis in this context may present with atypical multinodular polymyositis[36]. Thus the data on direct infiltration of myocytes by HIV remains contentious. Alternatively, this conflicting evidence could be due to a limitation of the technique used for the detection of the virus and does not exclude a transient infection of myocytes.

Role of cytokines and toll-like receptors: Proinflammatory cytokines are thought to play a key role in sustaining a state of chronic inflammation in PM. Several cytokines have been implicated to play a functional role. Evidence from immunohistochemical study of damaged muscle fibres implicates a functional role for Tnf-alpha. Further, the expression of endothelial cell adhesion molecules (ICAM-1) and LFA-1 (the main counter-receptor for ICAM-1) on effector cells such as monocytes and lymphocytes is up-regulated[37]. In the presence of IFN-γ, the muscle fibers up regulate TLR-3, which renders the muscle fibers more receptive to stimulation by viral ds-RNA. Furthermore, there is up regulation of NKG2D-ligand on myoblasts, which attract counter-receptor bearing effector cells such as NK cells, cytotoxic CD8 T lymphocytes and macrophages[38]. Thus, direct infiltration is not essential to initiate the self-sustaining inflammatory.

Differential diagnosis: Individuals infected with HIV are susceptible to myositis from HIV, its treatment with anti-retroviral drugs, autoimmune, inflammatory and infective causes (Table 2).

Table 2: Muscle involvement in HIV

Differential diagnosis for myositis in HIV
Infective
Bacterial (*staphylococcus*)
Tuberculosis
Toxoplasmosis
Pyomyositis
Autoimmune
Polymyositis
Dermatomyositis
DILS
Miscellaneous
Drug induced myopathy
Non infective necrotising myopathy
HIV myopathy/ wasting disorder

Anti-retroviral drugs and HAM: Anti-retroviral drugs such as Zidovudine (AZT) affect the mitochondria resulting in myopathy[39]. It is difficult but important to distinguish ARV-induced myositis from HAM[40].

Non-autoimmune polymyositis associated with HIV: Diffuse Infiltrative Lymphocytosis *(DILS)* is a multisystem inflammatory condition occurring in individuals with HIV, characterised by persistent CD8 T lymphocyte infiltration of the involved organs. Polymyositis as a manifestation of DILS is a distinct entity, histological features may be very similar to autoimmune polymyositis, but can be differentiated on electron microscopy[41]. A study of 35 individuals with DILS from a cohort of 4,100 HIV-infected subjects found biopsy-proven evidence of polymyositis in four individuals[42].

Infections: Reduced number of T cells, common in HIV infection or from other causes, increases the host's susceptibility to opportunistic infections. Infections of the muscle or pyomyositis may mimic polymyositis. Toxoplasmosis is one such infection to be considered in the differential diagnosis[43]. *Staphylococcal polymyositis* may complicate HIV infection[44]. HIV infected individuals are susceptible to tuberculosis, which can cause tuberculous polymyositis[45]. Both MRI and CT scans can be used to diagnose range of muscle/soft tissue

involvement including polymyositis, pyomyositis and necrotising fasciitis associated with HIV[46].

Treatment: Available evidence appears to suggest that HAM usually runs a milder course[18]. Standard immunosuppressants used to treat PM have all been used for the treatment of HAM and appear to be effective[18]. HAM has also been effectively treated with intravenous immunoglobulins[47]. Our patient with HAM who presented with profound weakness the symptoms resolved spontaneously over a 3-4 week period. She has tolerated the introduction of HAART initiated at this time and remains asymptomatic at 36 months since diagnosis. In conclusion, HIV-associated myositis may resolve spontaneously and HAART may be used for sustaining remission.

References

1. Goldenberg DM, Stein R, Leonard JP, Steinfeld SD, Dorner T, Burmester GR. B cell therapy with the anti-CD22 monoclonal antibody epratuzumab: comment on the editorial by St. Clair and Tedder. *Arthritis Rheumat*. 2006;**54(**7):2344; author reply-5. Epub 2006/06/28.
2. Nguyen BY, Reveille JD. Rheumatic manifestations associated with HIV in the highly active antiretroviral therapy era. *Current Opinion in Rheumatology*. 2009;**21**(4):404-10. Epub 2009/05/16.
3. McGaha TL, Chen Y, Ravishankar B, van Rooijen N, Karlsson MC. Marginal zone macrophages suppress innate and adaptive immunity to apoptotic cells in the spleen. *Blood*. 2011;**117**(20):5403-12. Epub 2011/03/30.
4. Yao Q, Frank M, Glynn M, Altman RD. Rheumatic manifestations in HIV-1 infected in-patients and literature review. *Clin Exper Rheumatol*. 2008;**26**(5):799-806. Epub 2008/11/27.
5. Marcum J. HIV infection presenting as polymyositis. *Delaware Med J*. 1995;**67**(3):185. Epub 1995/03/01.
6. Lateef A, Lahiri M, Teng GG, Vasoo S. Use of rituximab in the treatment of refractory systemic lupus erythematosus: Singapore experience. *Lupus*. 2010;**19**(6):765-70. Epub 2010/02/02.
7. Salliot C, Escaut L, Minoui P, Minozzi C, Coumbaras J, Vittecoq D. [Anti-Jo1 antibodies syndrome in an HIV-infected patient]. *Annales de medecine interne*. 2002;**153**(3):209-10. Epub 2002/09/10. Syndrome des anticorps anti-Jo1 chez un patient infecte par le VIH.
8. Eustace S, McEnif N, Rastegar J, Roizental M, Costello P. Acute HIV polymyositis with complicating myoglobinuric renal failure: CT appearance. *J Computer Ass Tomography*. 1995;**19**(2):321-3. Epub 1995/03/01.
9. Younger DS, Hays AP, Uncini A, Lange DJ, Lovelace RE, DiMauro S. Recurrent myoglobinuria and HIV seropositivity: incidental or pathogenic association? *Muscle & Nerve*. 1989;**12**(10):842-843. Epub 1989/10/01.
10. Kenyon C, Pillay K, Heckmann JM. Beware of 'normal' creatine kinase levels in HIV-associated polymyositis. *South Afr Med J* = Suid-Afrikaanse tydskrif vir geneeskunde. 2010;**100**(3):156-7. Epub 2010/05/13.
11. Heckmann JM, Pillay K, Hearn AP, Kenyon C. Polymyositis in African HIV-infected subjects. *Neuromuscular disorders* 2010;**20**(11):735-739. Epub 2010/07/16.
12. Scott JA, Palmer EL, Fischman AJ. HIV-associated myositis detected by radionuclide bone scanning. *Nuclear Medicine*: official publication, Society of Nuclear Med. 1989;**30**(4):556-558. Epub 1989/04/01.
13. Dalakas MC, Pezeshkpour GH, Gravell M, Sever JL. Polymyositis associated with AIDS retrovirus. *J Amer Med Ass*. 1986;**256**(17):2381-2383. Epub 1986/11/07.
14. Macdermott EJ, Adams A, Lehman TJ. Systemic lupus erythematosus in children: current and emerging therapies. *Lupus*. 2007;**16**(8):677-683. Epub 2007/08/23.
15. Rigal D, Bendali-Ahcene S, Monier JC, Mohana K, Fournel C. Identification of canine T lymphocytes by membrane receptor to peanut agglutinin: T-lymphocyte identification in dogs with lupus-like syndrome. *Amer J Vet Res*. 1983;**44**(9):1782-1785. Epub 1983/09/01.
16. Simpson DM, Bender AN. Human immunodeficiency virus-associated myopathy: analysis of 11 patients. *Annals Neurol*. 1988;**24**(1):79-84. Epub 1988/07/01.
17. Marolda M, De Mercato R, Camporeale FS, Carandente M, Noce S, Cioffi M, *et al.* Myopathy associated with AIDS. *Italian J Neurol Sci*. 1989;**10**(4):423-427. Epub 1989/08/01.
18. Johnson RW, Williams FM, Kazi S, Dimachkie MM, Reveille JD. Human immunodeficiency virus-associated polymyositis: a longitudinal study of outcome. *Arthritis Rheumatism*. 2003;**49**(2):172-178. Epub 2003/04/11.
19. Joseph A, Brasington R, Kahl L, Ranganathan P, Cheng TP, Atkinson J. Immunologic rheumatic disorders. *J Allergy Clin Immunol*. 2010;**125** (Suppl 2):S204-215. Epub 2010/03/05.
20. Calza L, Manfredi R, Colangeli V, Freo E, Chiodo F. Polymyositis associated with HIV infection during immune restoration induced by highly active anti-retroviral therapy. *Clin Exper Rheumatol*. 2004;**22**(5):651-652. Epub 2004/10/16.
21. Masanes F, Pedrol E, Grau JM, Coll-Vinent B, Casademont J, Miro O, *et al*. Symptomatic myopathies in HIV-1 infected patients untreated with antiretroviral agents--a clinico-pathological study of 30 consecutive patients. *Clinical Neuropath*. 1996;**15**(4):221-225. Epub 1996/07/01.

22. Cohen SB. B-cell depletion for rheumatic diseases: where are we? *Medscape General Med*. 2005;**7**(2):72. Epub 2005/12/22.
23. Hasegawa M. [B lymphocyte]. Nihon Rinsho Men'eki Gakkai kaishi. *Japanese J Clin Immunol*. 2005;**28**(5):300-308. Epub 2005/11/09.
24. Marks SD, Patey S, Brogan PA, Hasson N, Pilkington C, Woo P, *et al*. B lymphocyte depletion therapy in children with refractory systemic lupus erythematosus. *Arthritis Rheumatism*. 2005;**52**(10):3168-3174. Epub 2005/10/04.
25. Zandman-Goddard G, Shoenfeld Y. HIV and autoimmunity. *Autoimmunity Reviews*. 2002;**1**(6):329-337. Epub 2003/07/10.
26. Gougeon ML, Lecoeur H, Dulioust A, Enouf MG, Crouvoiser M, Goujard C, *et al.* Programmed cell death in peripheral lymphocytes from HIV-infected persons: increased susceptibility to apoptosis of CD4 and CD8 T cells correlates with lymphocyte activation and with disease progression. *J Immunol.* 1996;**156**(9):3509-3520. Epub 1996/05/01.
27. Sabugo F, Llanos C, Soto L, Gutierrez J, Cuchacovich M. [Rituximab (anti-CD20 monoclonal antibody) for refractory systemic lupus erythematosus: report of one case]. *Revista medica de Chile.* 2005;**133**(6):681-4. Epub 2005/08/03. Uso del rituximab(anticuerpo monoclonal anti-CD20) en lupus eritematoso sistemico refractario a tratamiento: Caso clinico.
28. Schneider C, Dalakas MC, Toyka KV, Said G, Hartung HP, Gold R. T-cell apoptosis in inflammatory neuromuscular disorders associated with human immunodeficiency virus infection. *Archives Neurology*. 1999;**56**(1):79-83. Epub 1999/01/29.
29. Vattemi G, Tonin P, Filosto M, Spagnolo M, Rizzuto N, Tomelleri G. T-cell anti-apoptotic mechanisms in inflammatory myopathies. *J Neuroimmunology*. 2000;**111**(1-2):146-151. Epub 2000/11/07.
30. Seidman R, Peress NS, Nuovo GJ. In situ detection of polymerase chain reaction-amplified HIV-1 nucleic acids in skeletal muscle in patients with myopathy. *Modern pathology* : an official journal of the United States and Canadian Academy of Pathology, Inc. 1994;**7**(3):369-375. Epub 1994/04/01.
31. Illa I, Nath A, Dalakas M. Immunocytochemical and virological characteristics of HIV-associated inflammatory myopathies: similarities with seronegative polymyositis. *Annals Neurology*. 1991**;29**(5):474-481. Epub 1991/05/01.
32. Chad DA, Smith TW, Blumenfeld A, Fairchild PG, DeGirolami U. Human immunodeficiency virus (HIV)-associated myopathy: immunocytochemical identification of an HIV antigen (gp 41) in muscle macrophages. *Annals Neurol*. 1990;**28**(4):579-582. Epub 1990/10/01.
33. Leon-Monzon M, Lamperth L, Dalakas MC. Search for HIV proviral DNA and amplified sequences in the muscle biopsies of patients with HIV polymyositis. *Muscle & Nerve*. 1993;**16**(4):408-413. Epub 1993/04/01.
34. Tucci M, Ciavarella S, Strippoli S, Dammacco F, Silvestris F. Oversecretion of cytokines and chemokines in lupus nephritis is regulated by intraparenchymal dendritic cells: a review. *Annals of The New York Academy of Sciences*. 2009;**1173**:449-457. Epub 2009/09/18.
35. Higuchi I, Nerenberg M, Yoshimine K, Yoshida M, Fukunaga H, Tajima K, *et al*. Failure to detect HTLV-I by in situ hybridization in the biopsied muscles of viral carriers with polymyositis. *Muscle & Nerve*. 1992;**15**(1):43-47. Epub 1992/01/01.
36. Richardson SJ, Lopez F, Rojas S, Cho S, Holodniy M, Herndier B, *et al*. Multinodular polymyositis in a patient with human immunodeficiency and hepatitis C virus coinfection. *Muscle & Nerve*. 2001;**24**(3):433-437. Epub 2001/05/16.
37. Carota A, Pizzolato GP, Redard M, Gailloud P, Grau GE. Adhesion molecules in HIV-related and idiopathic polymyositis: immunohistochemical studies. *Clin Neuropath*. 1997;**16**(6):312-318. Epub 1997/12/24.
38. Schreiner B, Voss J, Wischhusen J, Dombrowski Y, Steinle A, Lochmuller H, *et al.* Expression of toll-like receptors by human muscle cells in vitro and in vivo: TLR3 is highly expressed in inflammatory and HIV myopathies, mediates IL-8 release and up-regulation of NKG2D-ligands. *The FASEB J* : official publication of the Federation of American Societies for Experimental Biology. 2006;**20**(1):118-120. Epub 2005/11/19.
39. Gherardi RK, Florea-Strat A, Fromont G, Poron F, Sabourin JC, Authier J. Cytokine expression in the muscle of HIV-infected patients: evidence for interleukin-1 alpha accumulation in mitochondria of AZT fibers. *Annals Neurol.* 1994;**36**(5):752-758. Epub 1994/11/01.
40. Walsh K, Kaye K, Demaerschalk B, Stewart S, Crukley J, Hammond R. AZT myopathy and HIV-1 polymyositis: one disease or two? *The Canadian J Neurological Sci.* Le journal canadien des sciences neurologiques. 2002;**29**(4):390-393. Epub 2002/12/05.
41. Attarian S, Mallecourt C, Donnet A, Pouget J, Pellisser JF. Myositis in infiltrative lymphocytosis syndrome: clinicopathological observations and treatment. *Neuromuscular Disorders*. 2004;**14**(11):740-743. Epub 2004/10/16.
42. Kazi S, Cohen PR, Williams F, Schempp R, Reveille JD. The diffuse infiltrative lymphocytosis syndrome. Clinical and immunogenetic features in 35 patients. *AIDS.* 1996;**10**(4):385-391. Epub 1996/04/01.
43. Plonquet A, Bassez G, Authier FJ, Dray JM, Farcet JP, Gherardi RK. Toxoplasmic myositis as a presenting manifestation of idiopathic CD4 lymphocytopenia. *Muscle & Nerve*. 2003;**27**(6):761-765. Epub 2003/05/27.

44. Lenert P, Yasuda K, Busconi L, Nelson P, Fleenor C, Ratnabalasuriar RS, *et al.* DNA-like class R inhibitory oligonucleotides (INH-ODNs) preferentially block autoantigen-induced B-cell and dendritic cell activation in vitro and autoantibody production in lupus-prone MRL-Fas(lpr/lpr) mice in vivo. *Arthritis Res & Therapy*. 2009;**11**(3):R79. Epub 2009/05/30.
45. Pouchot J, Vinceneux P, Barge J, Laparre F, Boussougant Y, Michon C. Tuberculous polymyositis in HIV infection. *American J Med*. 1990;**89**(2):250-251. Epub 1990/08/01.
46. Nakou M, Katsikas G, Sidiropoulos P, Bertsias G, Papadimitraki E, Raptopoulou A, *et al*. Rituximab therapy reduces activated B cells in both the peripheral blood and bone marrow of patients with rheumatoid arthritis: depletion of memory B cells correlates with clinical response. *Arthritis Res Therapy*. 2009;**11**(4):R131. Epub 2009/09/01.
47. Viard JP, Vittecoq D, Lacroix C, Bach JF. Response of HIV-1-associated polymyositis to intravenous immunoglobulin. *Amer J Med*. 1992;**92**(5):580-581. Epub 1992/05/01.
48. Carroll MB, Holmes R. Dermatomyositis and HIV infection: case report and review of the literature. *Rheumatol Intern*. 2011; **31**(5):673-679. Epub 2009/10/27.
49. Huang Z, Fu B, Zheng SG, Li X, Sun R, Tian Z, *et al*. Involvement of CD226+ NK cells in immunopathogenesis of systemic lupus erythematosus. *J Immunol*. 2011;**186**(6):3421-3431. Epub 2011/02/08.
50. Hart D, Sayer R, Miller R, Edwards S, Kelly A, Baglin T, *et al.* Human immunodeficiency virus associated thrombotic thrombocytopenic purpura--favourable outcome with plasma exchange and prompt initiation of highly active antiretroviral therapy. *Brit J Haematol*. 2011;**153**(4):515-519. Epub 2011/03/12.