INVITED REVIEW

ABSTRACT: Skeletal muscle involvement can occur at all stages of human immunodeficiency virus (HIV) infection, and may represent the first manifestation of the disease. Myopathies in HIV-infected patients are classified as follows: (1) HIV-associated myopathies and related conditions, including HIV polymyositis, inclusion-body myositis, nemaline myopathy, diffuse infiltrative lymphocytosis syndrome (DILS), HIV-wasting syndrome, vasculitic processes, myasthenic syndromes, and chronic fatigue; (2) muscle complications of antiretroviral therapy, including zidovudine and toxic mitochondrial myopathies related to other nucleoside-analogue reverse-transcriptase inhibitors (NRTIs), HIV-associated lipodystrophy syndrome, and immune restoration syndrome related to highly active antiretroviral therapy (HAART); (3) opportunistic infections and tumor infiltrations of skeletal muscle; and (4) rhabdomyolysis. Introduction of HAART has dramatically modified the natural history of HIV disease by controlling viral replication, but, in turn, lengthening of the survival of HIV-infected individuals has been associated with an increasing prevalence of iatrogenic conditions.

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SKELETAL MUSCLE INVOLVEMENT IN HUMAN IMMUNODEFICIENCY VIRUS (HIV)–INFECTED PATIENTS IN THE ERA OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

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Since the initial descriptions of acquired immunodeficiency syndrome (AIDS) in the late 1970s, the history of human immunodeficiency virus (HIV) infection has been profoundly influenced by several major therapeutic advances in developed countries. In the initial phase, prevention and treatment of opportunistic infections was the only way to limit HIV-related morbidity and mortality. Most neuromuscular complications of HIV infection itself and the related immunodeficiency were first recognized during this phase. Introduction of nucleoside-analogue reverse-transcriptase inhibitors (NRTIs) in 1987 was an important step in the fight against AIDS because these drugs were the first ones targeting HIV replication itself. This phase was associated with the emergence of zidovudine (AZT) myopathy.[62] Introduction of protease inhibitors (PIs) in 1996 and so-called highly active antiretroviral therapy (HAART), consisting of a combination of two NRTIs and one or more PIs, dramatically modified the natural history of HIV disease by controlling viral replication. Morbidity, including neurological disorders, and mortality related to HIV infection declined in parallel in countries where these therapies are readily available.[81] In contrast, the HIV/AIDS epidemics continued to expand dramatically in other countries, the worst of the epidemics now being centered in the developing countries of sub-Saharan Africa, Eastern Europe, and Central Asia.[61,73,81] Importantly, in parallel with lengthening of HIV-in-

Abbreviations: CDC, Centers for Disease Control; CK, creatine kinase; CMV, cytomegalovirus; COX, cytochrome *c* oxidase; DILS, diffuse infiltrative lymphocytosis syndrome; EMG, electromyogram; FIV, feline immunodeficiency virus; HAART, highly active antiretroviral therapy; HAM, HTLV-I–associated myelopathy; HHV, human herpesvirus; HIV, human immunodeficiency virus; HMG-CoA, hydroxymethylglutaryl-coenzyme A; HTLV-I, human T-cell lymphotropic virus type I; IBM, inclusion-body myositis; IL, interleukin; IRIS, immune restoration inflammatory syndrome; LBM, lean body mass; MG, myasthenia gravis; MHC, major histocompatibility complex; mt, mitochondrial; nSREBP, nuclear sterol regulatory element binding protein; NRTI, nucleoside-analogue reverse-transcriptase inhibitor; PI, protease inhibitor; PM, polymyositis; SIV, simian immunodeficiency virus; SRV, simian retrovirus; TCR, T-cell receptor; TNF, tumor necrosis factor; TSP, tropical spastic paraparesis

Key words: acquired immunodeficiency syndrome (AIDS); HAART; human immunodeficiency virus (HIV); immune restoration; lipodystrophy; mitochondria; myasthenia; myopathy; polymyositis; rhabdomyolysis; skeletal muscle; vasculitis; wasting; zidovudine

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fected individual survival, HAART was increasingly found to cause a new iatrogenic condition, called the lipodystrophy syndrome.[6,23]

Although the impact of HAART on the prevalence of muscle involvement was not firmly established by epidemiological studies,[92] such an impact seems quite likely in practice, as suggested by the marked decrease of muscle biopsies performed in HIV-infected individuals in French neuromuscular centers since 1998. However, the whole spectrum of previously described muscular complications of HIV infection is still occasionally observed, especially in patients without treatment. Lack of treatment may be due to previously undiagnosed HIV infection, drug withdrawal after an adverse reaction, or unavailability of appropriate therapy for patients originating from developing countries.

Skeletal muscle involvement may occur at all stages of HIV infection and may be classified as follows: (1) HIV-associated myopathies and related conditions; (2) muscle complications of antiretroviral therapy; (3) opportunistic infections and tumor infiltrations of skeletal muscle; and (4) rhabdomyolysis.

HIV-ASSOCIATED MYOPATHY AND RELATED CONDITIONS

HIV Polymyositis. HIV-associated myopathy can occur at any stage of HIV infection[84] and may reveal the underlying infection.[46] The clinical and histopathological features are basically similar to those of polymyositis (PM) in seronegative individuals.[62,80] It is characterized by proximal and often symmetric muscle weakness that develops subacutely, over weeks to months, without cutaneous rash or involvement of the extraocular and facial muscles.[42] Myalgias seem more frequent than in seronegative PM patients.[84] The electromyogram (EMG) typically shows short-duration polyphasic motor unit potentials and abnormal spontaneous activity, but a number of patients have a normal EMG.[84] Serum creatine kinase (CK) levels are more often increased, but without correlation with disease severity.[84]

Muscle biopsy is the definitive test for establishing the diagnosis of PM and excluding other conditions. It typically shows the characteristic triad of scattered necrotic and basophilic fibers, multiple foci of mononuclear inflammatory cells within fascicles, and focal invasion of non-necrotic muscle fibers by inflammatory cells. Most often, the lesions are less well defined and include rare necrotic fibers and inflammatory infiltrates, without a clear focal attack on muscle fibers. Immunohistochemistry is necessary to provide evidence of the polymyositic process. The immunohistological profile of PM includes: (1) endomysial infiltrates of activated $CD8^+$ T cells (Fig. 1A); (2) ubiquitous sarcolemmal expression of MHC class I antigens by muscle fibers (Fig. 1B); and (3) focal invasion of non-necrotic fibers expressing MHC-I by $CD8^+$ T cells, a condition termed "MHC-I/CD8 complex."[43,80,133] The presence of CD8/MHC-I complex at histopathological examination is required to confirm the diagnosis of PM.[43] In addition, histological signs of HIV-associated PM may be intermingled with those of zidovudine myopathy, as discussed in what follows. On the borders of HIV polymyositis, necrotizing myopathies, without inflammation, which may[137] or may not[110] be associated with recurrent myoglobinuria, have been described. Granulomatous myositis with multinucleated giant-cell formation has also been reported in rare HIV-infected individuals.[7,42,59] The significance of multinucleated giant cells is unknown, but their presence is reminiscent of the HIV-associated multinucleated giant cells that have been described in brain[69] and, much more rarely, outside the central nervous system.[68]

Treatment of HIV-associated PM is similar to that of PM in non-HIV patients and remains rather empirical.[43,84] Agents used in the treatment of PM include corticosteroids, azathioprine, methotrexate, cyclophosphamide, cyclosporine, and intravenous immunoglobulins (IVIg). In patients with muscle weakness, prednisone at a dose of 1 mg/kg is usually the first-line drug, but its prolonged administration could favor emergence of opportunistic infections.[84] Pulse intravenous methylprednisolone has been proposed to reduce immunosuppression. Low-dose oral methotrexate (7.5 mg weekly) and azathioprine (150 mg/day) can be used without major adverse effect in HIV-infected patients.[84] Mycophenolate mofetil is a promising, well-tolerated drug,[93] but its place in the treatment of HIV PM needs to be delineated. Nonsteroidal anti-inflammatory drugs may be used with good response in patients without demonstrable evidence of muscle weakness but complaining of myalgias.[84]

From a pathophysiological perspective, elementary mechanisms leading to myofiber injury are the same in both HIV PM and idiopathic/primary PM. MHC-I/CD8 complex assesses the existence of an antigen-directed cytotoxicity mediated by $CD8^+$ cytotoxic T cells.[42,43] This conclusion is supported by the presence of $CD8^+$ cells that initially surround and eventually invade and destroy healthy, nonnecrotic, muscle fibers that aberrantly express MHC-I molecules.[43] In PM, $CD8^+$ T cells were found

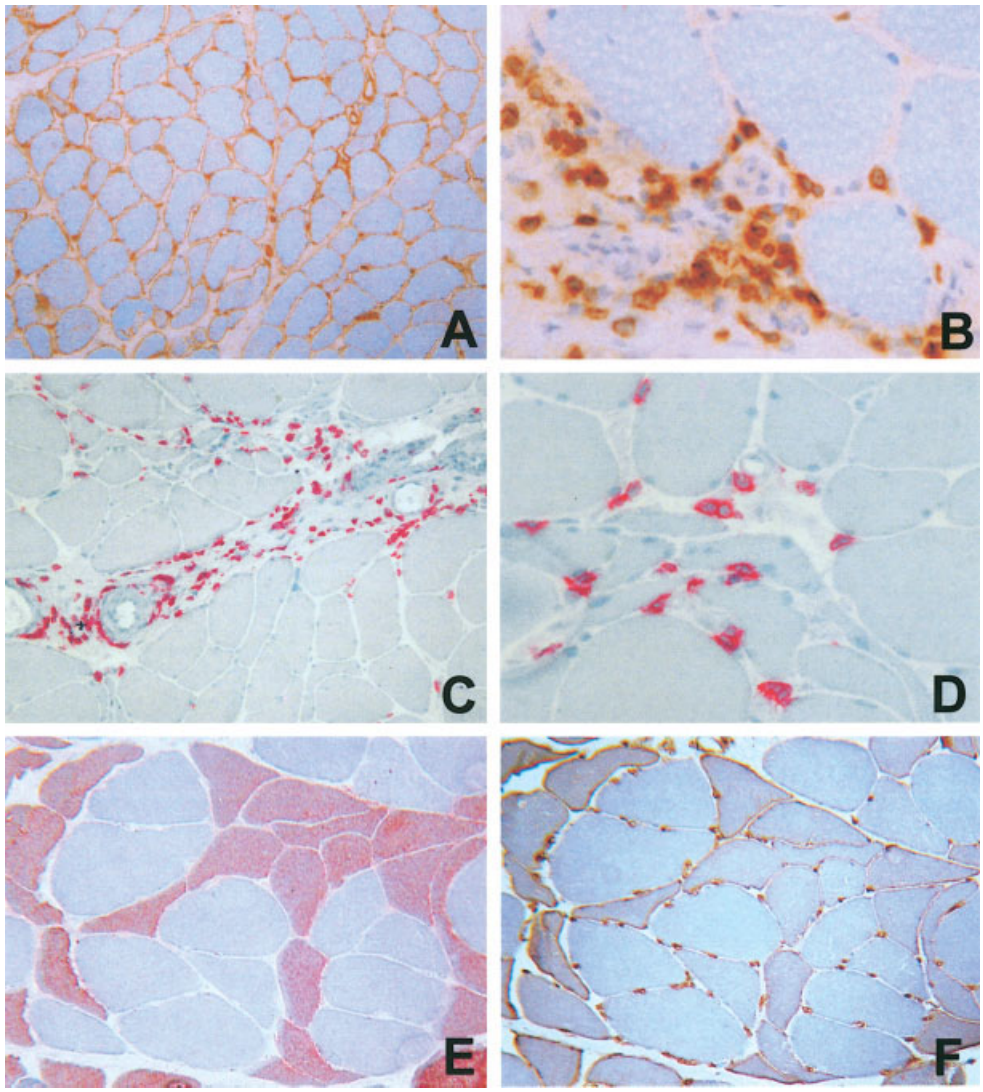

FIGURE 1. (A and **B)** HIV polymyositis. **(A)** Ubiquitous myofiber expression of MHC-I (frozen section, immunoperoxidase stain). **(B)** $CD8^+$ T-cell endomysial infiltration surrounding myofibers (frozen section, immunoperoxidase). **(C** and **D)** Diffuse infiltrative lymphocytosis syndrome (DILS). **(C)** Perivascular and interstitial $CD8^+$ T-cell infiltration (frozen section, APAAP stain). **(D)** Endomysial $CD8^+$ T cells in contact with myofibers (frozen section, APAAP). **(E** and **F)** Wasting syndrome. **(E)** Type 2 fiber atrophy (frozen sections, fast myosin heavy chain, APAAP). **(F)** Abnormal MHC-I expression by atrophic type 2 fibers (frozen sections, immunoperoxidase).

to be clonally expanded in both the circulation and muscle tissue.[15,105] Interestingly, in diseased muscle, clonal expansion is restricted to autoinvasive T cells.[16] When performed, molecular analysis of the T-cell receptor (TCR) CDR3 region of such invasive $CD8^+$ T cells showed the presence of conserved amino acid sequences suggestive of an antigen-driven T-cell expansion[15,16,105]; such an antigen, possibly an autoantigen, remains undetermined. To be effective, $CD8^+$ T-cell–mediated cytotoxicity requires expression of both MHC-I antigens and costimulatory molecules by target cells. Adult myofiber is one of the few cell types that does not constitutively express MHC-I in the normal state, and aberrant widespread MHC-I expression by myofibers is a striking feature of PM. During regeneration, MHC-I is expressed only by myoblasts, and interferon-γ induces MHC-I in regenerating but not mature myofibers.[111] Transgenic mice overexpressing MHC-I in muscle tissue develop an inflammatory myopathy, but their histopathological features seem distinct from those of typical PM.[104] In addition to MHC-I, muscle cells express costimulatory molecules, BB-1 and ICOS (inducible costimulator), and their ligands, CD28/CTLA-4 and LICOS, are upregulated on autoinvasive $CD8^+$ T cells, generating possible cytotoxicity.[17,43] Accordingly, invasive $CD8^+$ T cells contain perforin and granzyme granules located to-

ward the target muscle fibers,[64] with the perforin pathway appearing to be the major cytotoxic effector pathway in PM.[43]

Postnecrosis myofiber regeneration results from activation of myogenic precursor cells residing beneath the muscle-fiber basal lamina, the so-called satellite cells.[76] Once activated, myogenic precursor cells, which are located close to capillaries, initiate monocyte recruitment, and macrophages recruited at the injury site actively remove necrotic debris to facilitate subsequent muscle regeneration.[36] However, in PM, T-cell infiltrates may be an impediment to muscle repair because T-cell–derived cytokine interferon-γ hinders fiber regeneration in addition to upregulating MHC-I expression, and therefore contributes to perpetuation of injury.

The direct role of virus in the HIV-associated PM process remains unclear.[62,84,88] Various retroviruses other than HIV have been associated with PM in humans, monkeys, and cats.[87,101,113] Neither viral replication nor genome has been detected within muscle fibers, except once,[120] whereas HIV sequences and antigens are commonly detected in endomysial macrophages or lymphocytes.[84] Such a discrepancy between the clinical evidence for a pathogenic role for HIV and its absence from the target cells suggests that HIV-associated PM is one of the autoimmune manifestations of HIV infection.[62] Autoimmunity must be considered as a part of HIV-infection immunopathogenesis. Autoimmune diseases are observed mainly in patients with a CD4 cell count of >200. In parallel with the progression of disease and lymphopenia, it may be possible to detect autoantibodies to HLA molecules and other surface markers of CD4 T cells or directed toward a number of regulatory molecules of the immune system.[138] Structural homologies of HIV-1 *env* products to functional molecules involved in the control of self-tolerance could lead to the emergence of autoreactivity, through molecular mimicry mechanisms inducing dysregulation leading to autoimmune response. However, the autoimmune process may also be induced nonspecifically via bystander stimulation.[43] In addition, the restoration of immune competence following highly active antiretroviral therapy (HAART) may favor resurgence of autoimmune diseases.[128,138]

Inclusion-Body Myositis. A myopathy in every respect similar to inclusion-body myositis (IBM) is observed in rare patients infected by HIV-1 or HTLV-1 (human T-cell leukemia virus type 1).[41] Muscle biopsy shows both PM-like endomysial inflammation with MHC-I/CD8 complex and degenerating features including fiber atrophy, red-rimmed vacuoles, amyloid deposits, and eosinophilic inclusions. Retroviral antigens have been detected only on endomysial macrophages but not within the muscle fibers, indicating that retroviruses do not directly infect the muscle but trigger an immune response identical to that occurring in sporadic IBM.[42]

Nemaline Myopathy. A structural myopathy similar to nemaline (rod) myopathy of adult onset has also been described in patients who developed painless, progressive muscle weakness and wasting, and elevated serum CK levels, at an early stage of the disease.[45,50,52,65] Muscle biopsy disclosed prominent, randomly distributed atrophic type 1 fibers with numerous intracytoplasmic rod bodies in the centers of the fibers, corresponding to nemaline rods at electron microscopy. Necrotic fibers and inflammatory infiltrates were usually not found. Some patients had monoclonal gammopathy in association with nemaline myopathy.[45,52,99] Despite the absence of muscle inflammation, positive responses to prednisone therapy have been observed, suggesting an autoimmune mechanism for the myopathy.

Diffuse Infiltrative Lymphocytosis Syndrome. Diffuse infiltrative lymphocytosis syndrome (DILS) is a rare condition in HIV-infected patients, characterized by persistent CD8 hyperlymphocytosis and multivisceral CD8 T-cell infiltration,[82] reflecting a particularly strong host response to HIV infection.[83] DILS usually presents as painless parotid enlargement, accompanied by sicca syndrome in 60% of patients.[115] Extraglandular complications of DILS include facial palsy, peripheral neuropathy, polymyositis, lymphocytic interstitial pneumonitis, renal tubular acidosis, lymphocytic hepatitis, and lymphoma.[102,115] In DILS, muscle lymphocytic infiltration (Fig. 1C and D) is usually found in the setting of peripheral neuropathy,[58,102] but a recent study reported an unexpectedly high prevalence of DILS in HIV-infected patients with inflammatory myopathy.[84] Diagnostic criteria are: (1) HIV infection assessed by enzyme-linked immunoassay and confirmatory Western blot analysis; (2) circulating CD8 hyperlymphocytosis at $>1000/mm^3$; and (3) histological confirmation of CD8 T-cell infiltration in three different organs or tissues.[102] Minor salivary gland biopsy and gallium-67 scintigraphy are of major diagnostic help when DILS is suspected. In particular, patients taking protease inhibitors may develop parotid lipomatosis[107] that gallium scans can distinguish from DILS.[115] Treatment of DILS combines antiretroviral therapy and steroids. Antiretroviral therapy may be effective in

treating glandular swelling, sicca syndrome, and neuropathy.[102,115] Corticosteroids (up to 60 mg/day of prednisone) are effective in treating life-threatening DILS manifestations, particularly lymphocytic interstitial pneumonitis or rapidly progressive neuromuscular complications.[102,115]

HIV-Wasting Syndrome. Cachexia is frequently observed in patients with AIDS, especially in sub-Saharan Africa where it is called "slim disease."[12,70] In Western countries, a condition known as the HIV-wasting syndrome has been defined more precisely by criteria of the Centers for Disease Control (CDC). The syndrome combines involuntary weight loss (>10% of baseline body weight) plus either chronic diarrhea (for 30 days or longer) or chronic weakness and documented fever (for 30 days or longer), in the absence of a concurrent illness or condition other than HIV infection that could explain the findings. Weight loss and decreased lean body mass (LBM) are independent predictors of increased mortality and morbidity in HIV-infected patients.[70] Although surveillance data by the CDC suggest that incidence of new wasting has declined in proportion to opportunistic infections, there is accumulating evidence that loss of weight and LBM is common in HIV-infected patients, even in populations with widespread access to HAART.[70]

Classic wasting with generalized weight loss must be clinically distinguished from changes in fat distribution, also termed lipodystrophy. Wasting may be more likely to occur in the context of virological or immunological failure, infection, diarrhea, or anorexia, unlike the lipodystrophy that occurs in patients with robust responses to antiretroviral therapy. It is also critical to distinguish wasting syndrome from the rapid weight loss often observed in lactic acidosis.[70]

In patients with HIV-wasting syndrome, muscle biopsy may show diffuse atrophy, or type II atrophy (Fig. 1E and F), mild neurogenic atrophy, or thick-filament loss, without conspicuous inflammation, as in cachectic myopathies of other causes.[12,100] In a few patients classified as having wasting syndrome, muscle biopsy may disclose inflammatory changes including PM, necrotizing arteritis, and microvasculitis.[100] Among a variety of possible causes of HIV-wasting syndrome, one attractive hypothesis involves the proinflammatory cytokines interleukin (IL)-1β and tumor necrosis factor (TNF)-α, two molecules abundantly produced by HIV-infected monocytes/macrophages, which can induce cachexia in animal models.[11] The ubiquitin–ATP-dependent proteolytic system was shown to be activated in muscle from cachectic AIDS patients, possibly in response to changes in circulating cytokines, and this could be at the origin of skeletal muscle wasting.[90] Another mechanism involves increased expression of the negative regulator of skeletal muscle growth myostatin.[66]

Vasculitic Processes. A wide range of inflammatory vascular diseases including necrotizing vasculitis, resembling polyarteritis nodosa, Henoch–Schönlein purpura, hypersensitivity vasculitis, cryoglobulinemic vasculitis, and mononuclear small-vessel vasculitis, may occur in HIV-infected individuals.[57] Vascular inflammation appears to be multifactorial and may result from HIV-induced immunological abnormalities and exposure to a variety of xenoantigens such as HIV itself,[60] other infectious agents, and drugs. Vasculitis may seldom present as a genuine acquired myopathy with proximal limb weakness, increased serum CK levels, and myopathic EMG.[53] However, muscle necrotizing vasculitis is most often observed in patients with peripheral neuropathy.[19] Vasculitic neuropathy usually presents as a distal symmetric polyneuropathy with weight loss, myalgias, weakness, and leg tenderness, and less often as asymmetric polyneuropathy or true mononeuropathy multiplex.[57] In case of necrotizing vasculitis, disease course is usually monophasic without relapses and remissions.[19] Treatment of HIV-related vasculitis is not clearly defined, but usually combines antiretroviral drugs and immunomodulatory agents, including intravenous immunoglobulins. Corticosteroids may be extremely effective. Cytotoxic agents commonly used in the treatment of arteritis are regarded as contraindicated in immunocompromised patients. So, by analogy with hepatitis B–related polyarteritis nodosa, a strategy combining antiviral treatments and plasma exchanges has been proposed. This strategy seems effective and does not jeopardize the outcome of AIDS, as could occur with cytotoxic agents.[71]

On the fringe of clinically overt full-blown vasculitis, changes restricted to the microcirculation, including microvasculitis, noninflammatory microangiopathy, and perivascular iron-pigment deposits, are commonly observed in muscle biopsies from HIV-infected patients.[61] Microvascular inflammation is mainly found at the level of postcapillary venules. It may be asymptomatic, and is probably more pronounced at early stages of the disease.[35] Hemosiderin deposits may also be observed in the lower limbs, particularly at advanced stages of HIV infection.[61] The finding is not specific and it may be observed in other immunological disorders, in diabetes mellitus, or in infection by hepatitis C virus.

Myasthenic Syndromes and Chronic Fatigue. Myasthenia gravis (MG) has been reported very occasionally in HIV-infected patients, most often at early stages of disease, and can be the presenting manifestation.[5,130,134] The diagnosis is assessed by the edrophonium test and electrophysiological study. HIV-associated MG is not always associated with positive detection of antibodies to acetylcholine receptors. In addition, it tends to occur as a transient phenomenon, fading with immunodepression.[5] Treatment of HIV-associated MG is based on antiretroviral drugs, combined, if necessary, with pyridostigmine, prednisone, or intravenous immunoglobulin.[5,129] A unique case of MG occurring 3 weeks after introduction of ritonavir has been reported, suggesting that this drug should be avoided in HIV-infected MG patients.[117]

In addition, positive detection of circulating antibodies to acetylcholine receptors in patients with HIV-associated chronic fatigue could represent a predictive factor for a positive response to pyridostigmine therapy, in spite of the absence of definite myasthenia.[41] More generally, fatigue is a commonly reported symptom in HIV-infected patients that may correlate positively with clinical AIDS, depression, and anemia, but not with viral load or $CD4^+$ cell count.[130]

MUSCLE COMPLICATION OF ANTIRETROVIRAL THERAPY

Zidovudine and Other NRTI Myopathies. Antiretroviral drugs mainly include NRTIs: zidovudine (AZT), stavudine (d4T), didanosine (ddI), zalcidabine (ddC), and lamivudine (3TC); non–nucleoside-analogue reverse-transcriptase inhibitors (NNRTIs; nevirapine, delaviridine, efavirenz); and protease inhibitors (PIs; saquinavir, ritonavir, indinavir, nelfinavir, amprenavir). Nucleoside analogues act in their triphosphorylated form through competition with the natural substrates of both HIV reverse transcriptase and γDNA polymerase, an enzyme involved in mitochondrial DNA (mtDNA) replication.[6,8,13,89] Some NRTIs, such as zidovudine, stavudine, and fialuridine, are preferentially phosphorylated in replicating cells; others, such as didanosine, zalcidabine, and lamivudine, are replicated in resting cells.[47] Phosphorylation of each NRTI may be selectively achieved by definite cellular thymidine-kinase isoforms, the expression of which could vary from one tissue to another, thus possibly explaining the remarkable tissue selectivity of NRTI-induced tissue toxicity.[89] Until now, zidovudine has been the main NRTI causing a mitochondrial myopathy in HIV-infected patients.[23]

Zidovudine myopathy is a reversible toxic mitochondrial myopathy occurring in patients who have received high cumulative doses of the drug.[44,96] Clinically, it mimics HIV-associated PM. Histologically, it is characterized by the presence of "AZT fibers," a term coined by Dalakas to designate atrophic ragged-red fibers with marked myofibrillar alterations, including thick myofilament loss and cytoplasmic-body formation (Fig. 2).[28,31,44,67,96] All currently available tests for the detection of mitochondrial diseases are positive in patients with zidovudine myopathy, among them: (1) respiratory chain dysfunction assessed by biochemical assays on muscle homogenates[96]; (2) partial deficiency in cytochrome *c* oxidase (COX) activity (complex IV of the respiratory chain) assessed by histoenzymology (Fig. 2C and D)[31,32]; and (3) a high lactate:pyruvate ratio in blood.[33] Patients with zidovudine myopathy consistently show marked depletion of their mtDNA ("mtDNA-depleting myopathy").[3] Muscle mtDNA depletion in zidovudine-treated HIV-infected patients was found to be more marked in patients who had either weakness, myalgia, increased serum CK levels, or ragged-red fibers.[26]

Several lines of evidence have confirmed that AZT induces mitochondrial dysfunction. First, experimentally, it was shown that AZT affects the oxidation–phosphorylation coupling and the activity of complex I and III of the respiratory chain of muscle mitochondria.[85] Second, exposure of cultured human myotubes to AZT induces destructive changes in the mitochondria.[122] Third, in vivo ^{31}P-magnetic resonance spectroscopy showed that AZT decreases the maximal work output and the maximal rate of muscle ATP synthesis in treated patients.[126] Oxidative stress occurs in tissues of HIV-infected patients. Micronutrient deficiencies have long been recognized in HIV infection and involve vitamins and trace elements such as zinc, iron, and selenium. Selenium is a component of glutathione peroxidase, an enzyme having a major function in the removal of reactive oxygen species from cells and tissues. Selenium-deficient patients can develop a congestive cardiomyopathy or skeletal muscle involvement, manifested by pain and proximal weakness.[29] Muscle involvement in HIV-infected patients is associated with marked selenium deficiency.[30] In the case of zidovudine administration, selenium deficiency could potentiate the mitochondrial toxicity of zidovudine by allowing an increased formation of reactive oxygen species. Accordingly, dietary supplements with antioxidant vitamins C and E at supranu-

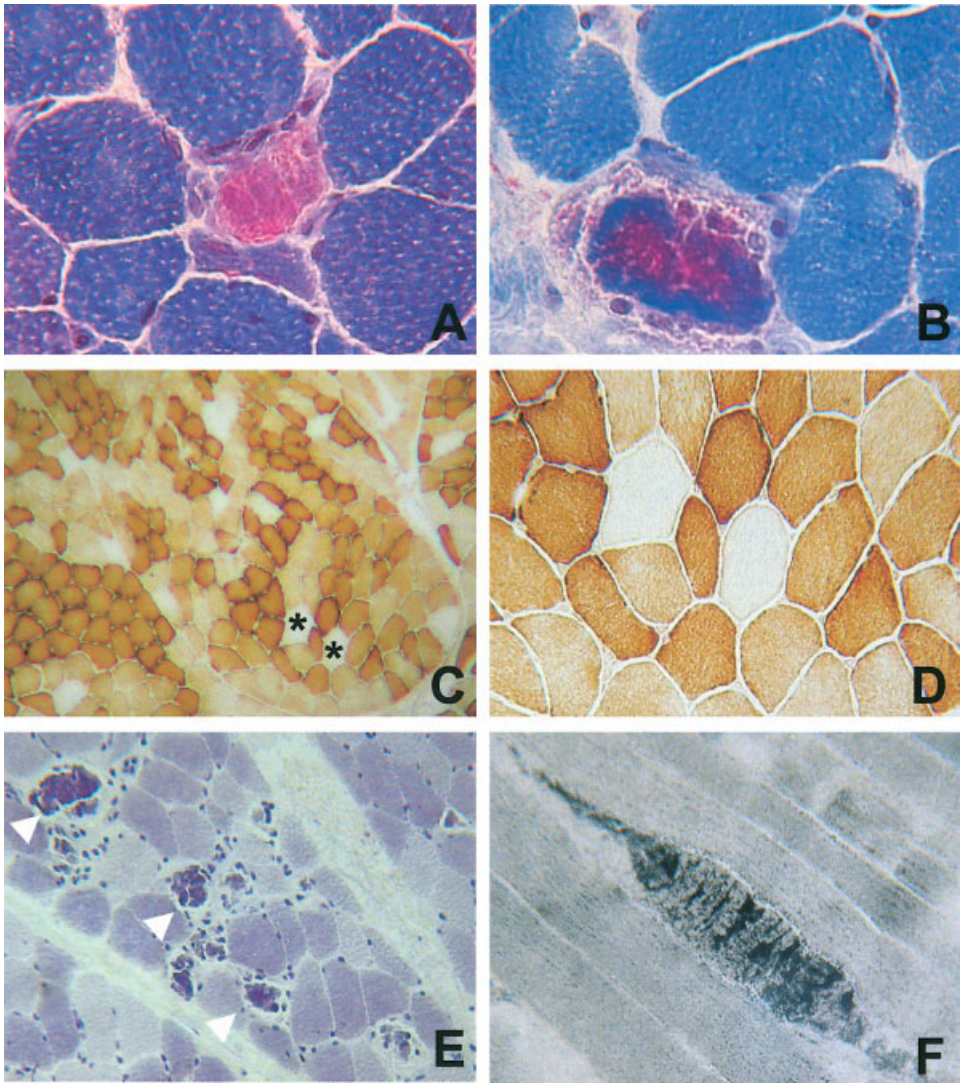

FIGURE 2. AZT myopathy. **(A** and **B)** Ragged-red fibers (AZT fibers) showing marked myofibrillar alterations (frozen sections, Masson trichrome stain). **(C)** Partial deficiency in cytochrome *c* oxidase (COX) activity. **(D)** At higher magnification, two COX-negative fibers [asterisk in **(C)**] showing normal appearance (frozen section, COX). **(E)** Myofilamentous degradation in AZT fibers (arrowheads) (frozen sections, ATPase 10.4). **(F)** Increased succinate dehydrogenase (SDH) activity indicating mitochondrial accumulation (frozen section, SDH).

tritional doses have been proposed to protect skeletal muscle mitochondria against oxidative damage caused by AZT.[48]

The validity of zidovudine myopathy has been disputed repeatedly.[123,124,136] Ragged-red fibers may be rare in some patients and they usually combine mitochondrial accumulation with myofibrillar loss, which may hinder their recognition. In addition, in a number of patients, mitochondrial changes are mixed with inflammatory changes, and, on some occasions, the polymyositic process overwhelms zidovudine myopathy. Muscle biopsy from patients with muscle symptoms receiving zidovudine may show no abnormality and may lack the typical features of zidovudine myopathy if one excludes partial COX deficiency. Such a deficiency is constantly observed in our experience and represents a valuable sign in young patients.[32]

In addition, myopathologic abnormalities very similar to those observed in zidovudine myopathy have been reported in a patient treated with ribavirin and interferon-α.[4]

Lactic Acidosis, Hepatic Steatosis, and Myopathy. A life-threatening syndrome with severe hepatic steatosis, lactic acidosis, pancreatitis, and mitochondrial myopathy with lipid accumulation, resembling Reye's syndrome, has been described in patients

taking stavudine in association with another nucleoside analogue and a PI.[20,23,42,98] Early detection of this syndrome may be ensured by close monitoring of liver and muscle enzymes in serum and lactate level in blood,[42] and fatty infiltration of liver can be detected by computed tomography.[98] Selective inhibition of DNA polymerase-γ by nucleoside analogues leads to depletion of mtDNA and impairment of oxidative phosphorylation, and could be at the origin of this syndrome.[98] Recently, it was shown that mtDNA depletion could be detected in patients with symptomatic nucleoside-related hyperlactatemia by evaluating the ratio of mitochondrial to nuclear DNA in peripheral blood lymphocytes.[40] In addition, in patients followed longitudinally, the decline in mitochondrial DNA preceded the increase in venous lactate levels,[40] suggesting that this procedure may be appropriate for monitoring patients receiving HAART.

HIV-Associated Lipodystrophy Syndrome. A syndrome called HIV-associated lipodystrophy syndrome has been recognized on an increasing basis since 1998 in HIV-1–infected individuals, usually treated with HAART.[25] The syndrome consists of a combination of metabolic abnormalities (hyperlipidemia and insulin resistance) and morphological changes (central fat accumulation and peripheral fat atrophy).[18] At least one physical abnormality is detected in about 50% of patients after 12–18 months of therapy.[24] Lipodystrophy is independent of plasma HIV load.[24] Although duration of antiretroviral therapy is a recognized risk factor, lipodystrophy can occur in recently infected patients receiving HAART.[97] When muscle biopsy is performed for a reason unrelated to lipodystrophy, it may show various degrees of lipid accumulation, indicating disturbances of lipid metabolism. Increased lipid content in muscle may be detected by ^{1}H-magnetic resonance spectroscopy[55] and computed tomography.[132] The picture of lipodystrophy as a multifactorial condition is emerging. It is likely that PIs cause fat accumulation (increased visceral abdominal fat, breast hypertrophy, and buffalo hump), hyperlipidemia (increased total cholesterol and triglycerides), and insulin resistance (increased circulating levels of insulin and C-peptide, glucose intolerance/type 2 diabetes mellitus), whereas NRTIs contribute to lipoatrophy, possibly with HIV infection itself, and to other manifestations often described in affected patients, including lactic acidemia, fatty liver, weight loss, nausea, and fatigue.[15,18,20,24,25,79,103,106]

The mechanisms of PI-induced metabolic abnormalities are complex.[79] First, PIs inhibit proteases that degrade transcription factors crucially involved in lipid homeostasis, called nuclear sterol regulatory element binding proteins (nSREBPs). Subsequent accumulation of these factors results in increased fatty acid and cholesterol hepatic biosynthesis, and decreased leptin expression in adipose tissue at the origin of both lipodystrophy and insulin resistance. Second, PIs also suppress proteasome-mediated breakdown of apolipoprotein B, which results in overproduction of triglyceride-rich lipoproteins. Third, in addition, PIs directly inhibit GLUT-4, a glucose transporter that mediates insulin-stimulated cellular uptake of glucose, in fat and muscle, thus directly contributing to insulin resistance.[103,106] Although firm conclusions regarding mechanisms of the clinical syndrome are still lacking, resemblance between HAART-related lipodystrophy and multiple symmetrical lipomatosis syndrome (Launois–Bensaude or Madelung's syndrome), which is associated with mtDNA point mutations or deletions impairing COX activity,[20] suggests that NRTIs add their mitochondrial toxic effects to PI-induced metabolic disturbances.

HAART-Related Immune Restoration Inflammatory Syndrome. Immunodeficient HIV patients treated by HAART may develop paradoxical inflammatory responses due to the reconstitution of the previously incompetent specific immunity, a phenomenon termed immune restoration inflammatory syndrome (IRIS).[128] HAART-related IRIS encompasses: (1) overt infectious inflammatory processes secondary to silent opportunistic pathogens, including tuberculosis and other nontuberculosis mycobacterial infections, cytomegalovirus (CMV) retinitis, and herpes zoster and herpes simplex reactivation; (2) human herpesvirus (HHV)-8–associated diseases, including Castleman's disease and Kaposi's sarcoma; and (3) noninfectious inflammatory diseases, including autoimmune diseases, allergic reactions, sarcoidosis, and induction of atherogenic chronic inflammation.[116,128] Muscle involvement in the setting of IRIS consists of polymyositis,[22,121] which may masquerade as antiretroviral toxicity.[114] Although there have been few reported cases, muscle biopsy findings and treatment of IRIS polymyositis seem similar to those of classic HIV polymyositis (Fig. 3A–D). The risk of developing IRIS seems linked to various putative risk factors: (1) duration of immunodeficiency; (2) extent of immunodeficiency; (3) velocity and extent of immune reconstitution; (4) specific pattern of immune reconstitution under HAART, including immune reconstitution without complete suppression of HIV replication, high levels of circulating CD8 T cells, persisting polyclonal hyper-

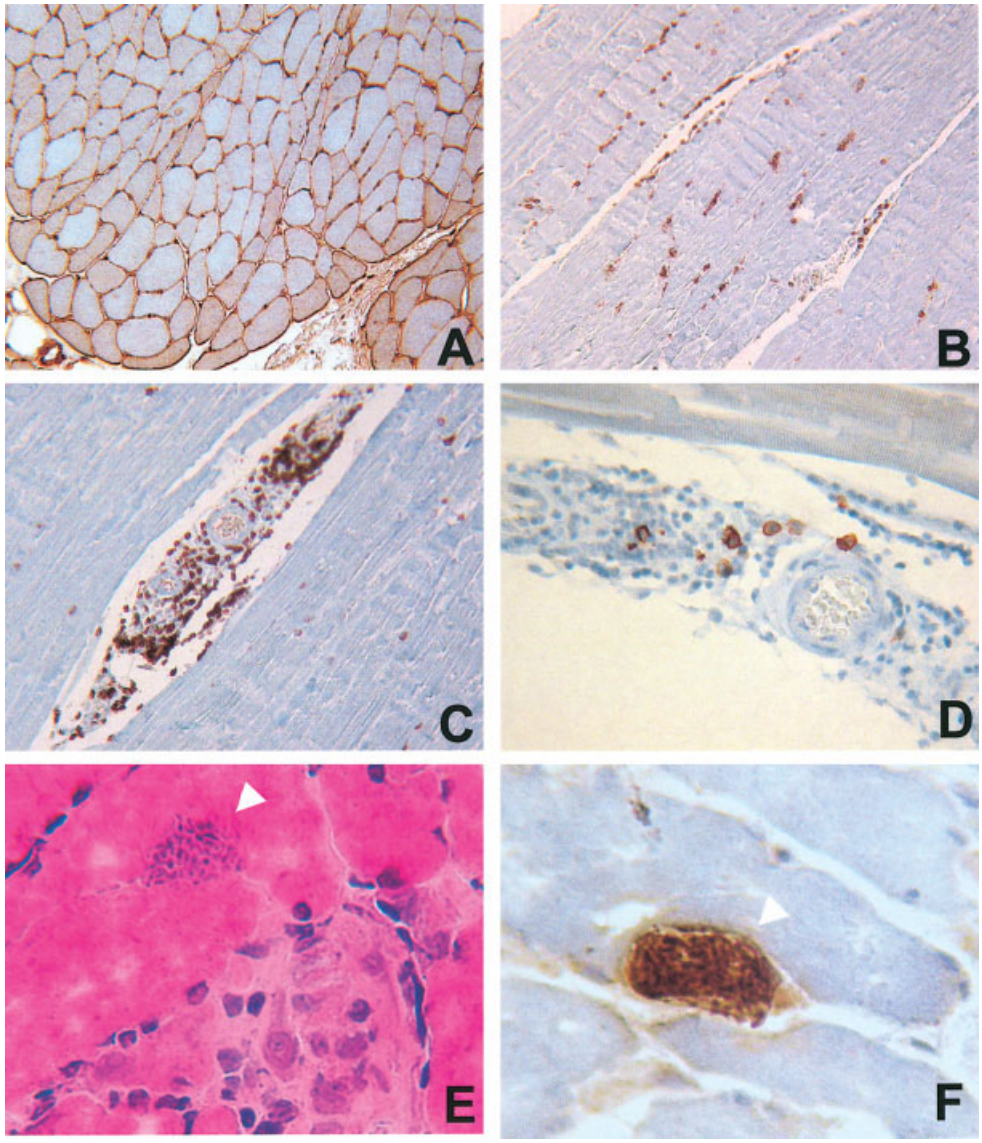

FIGURE 3. (A–D) Muscle involvement during immune restoration syndrome. **(A)** Ubiquitous myofiber expression of MHC-I (frozen section, immunoperoxidase stain). **(B)** Scattered $CD8^+$ T cells in endomysium (paraffin section, immunoperoxidase). **(C** and **D)** Perivascular mononuclear cell infiltration with numerous $CD8^+$ T-cells **(C)** and rare $CD138^+$ plasma cells **(D)** (paraffin sections, immunoperoxidase). **(E** and **F)** Muscle toxoplasmosis. **(E)** A collection of bradyzoites (arrowhead) in a muscle fiber (frozen section, haematoxylin–eosin stain). **(F)** Immunodetection of bradyzoites (arrowhead) within a cyst by using an anti–*Toxoplasma gondii* antibody (frozen sections, immunoperoxidase).

gammaglobulinemia, increase in (CMV-) specific IgG antibodies, development of specific delayed-type hypersensitivity, and high levels of IL-6 and soluble IL-6 receptor; and (5) genetic susceptibility, including distinct HLA haplotypes and polymorphism in TNF-α, IL-6, and IL-12 genes.[128]

OPPORTUNISTIC INFECTIONS AND TUMORS OF MUSCLE

Opportunistic infections of the skeletal muscle are seldom recognized. They mainly include focal pyogenic infection (so-called pyomyositis), usually due to *Staphylococcus aureus*,[10] but infections by CMV, *Cryptococcus neoformans*, *Mycobacterium avium intracellulare*, microsporidiosis, and *Toxoplasma gondii* have been also reported.[62] Muscle toxoplasmosis is found in profoundly immunodepressed patients, typically presenting with a painful subacute myopathy and concurrent multivisceral toxoplasmosis.[56,112] *Toxoplasma* cysts are mainly observed in muscle fibers at muscle biopsy, and identification of cysts as *Toxoplasma* may be easier by using specific antibodies or

electron microscopy (Fig. 3E and F). A PM-like process of unknown significance is usually associated with muscle toxoplasmosis.[112] Treatment is based on a combination of drugs acting synergistically against *T. gondii*, pyrimethamine, and sulfadiazine or trisulfapyrimidines.

Extranodal non-Hodgkin's lymphoma is frequently observed in AIDS, but rarely involves muscle. Muscle involvement in non-Hodgkin's malignant lymphoma may be the presenting manifestation and become apparent by a rapidly growing muscle mass associated with fever.[38] Typically, histopathological examination shows a lymphomatous proliferation destroying the muscle tissue, and invading the fascia and subcutaneous tissue. Magnetic resonance imaging is useful in distinguishing muscle lymphoma from other causes of limb swelling in patients with AIDS, including pyomyositis, deep vein thrombosis, focal onset of polymyositis, and even muscle involvement by Kaposi's sarcoma.[9,59,72,127]

RHABDOMYOLYSIS

Rhabdomyolysis/myoglobinuria is defined by acute myofiber injury leading to release of cellular components into the blood and urine. Rhabdomyolysis is associated with myalgias, weakness, and edema, and by a marked increase of blood CK and myoglobin levels. A urinary myoglobin level of >250 μg/ml results in cola-colored urine.[119] Rhabdomyolysis can occur at all stages of HIV infection and may be separated into three groups: (1) HIV-associated rhabdomyolysis, including rhabdomyolysis in primary HIV infection, recurrent rhabdomyolysis, and isolated rhabdomyolysis; (2) drug-induced rhabdomyolysis; and (3) rhabdomyolysis at the end stage of AIDS, associated or not with opportunistic infections of muscle.[34] Drugs implicated in rhabdomyolysis in HIV patients include didanosine, lamivudine, trimethoprim–sulfamethoxazole, ritonavir, and indinavir.[2,14,34,95,125] In addition, PIs may increase the concentrations of most hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins),[39] and treatment of PI-related hyperlipidemia by statins seems associated with an increased risk of rhabdomyolysis.[1,27,37,39,75,91,94]

HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE I (HTLV-I) MYOSITIS

Various other retroviruses, such as HTLV-I in humans, simian immunodeficiency virus (SIV) and simian retrovirus (SRV) type I in monkeys, and feline immunodeficiency virus (FIV) in cats, may cause inflammatory muscle involvement.[42] HTLV-I–infected individuals may develop various neurological disorders, including HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP), motor neuron disease, peripheral neuropathy, polymyositis, and IBM.[41,49,54,63,74,86,139] Muscle involvement in HTLV-I–infected patients may occur alone or in association with HAM/TSP.[51,135] HTLV-I–related muscle involvement closely resembles that encountered in HIV patients. HTLV-I PM has a more insidious presentation, a more protracted course, and a poorer response to steroids than seronegative PM.[63] In addition, some patients develop a chronic myopathy corresponding to IBM with proximal and distal weakness and the characteristic histological features at muscle biopsy.[41,108] Mechanisms leading to muscle involvement during HTLV-I infection seem comparable to those implicated in HIV myopathy. Endomysial cells are mainly $CD8^+$ cytotoxic cells, surrounding and invading non-necrotic MHC-I–positive fibers. Molecular analysis has shown muscle-infiltrating T cells consisting of predominantly locally expanded clones.[118] This suggests a T-cell–mediated MHC-I–restricted cytotoxic process, similar to that described for HIV PM.[42] Viral genome may be seen in muscle tissue from patients with HTLV-I PM,[21,54,77,131] with localization of viral antigens in muscle-infiltrating $CD4^+$ lymphocytes.[78] A recent study showed the presence of both perforin-positive $CD8^+$ T cells directed toward the dominant Tax antigen and tax mRNA–positive mononuclear cells in muscle tissue from an HTLV-I–infected patient with IBM.[109] This strongly supports the cytotoxic immune reaction model for the pathogenesis of HTLV-I–associated inflammatory myopathy.[109]

CONCLUSION

Skeletal muscle involvement in HIV-infected patients varies according to both immunological status and antiretroviral therapy. So far, the influence of HAART on muscle complications of HIV infection has not been accurately evaluated. HIV-wasting syndrome and opportunistic muscle infections are still encountered in untreated patients, particularly in migrants or in underprivileged sections of the population. In contrast, treated patients may develop inflammatory myopathy related to immune restoration or drug-induced muscle involvement. Physicians must be aware that HAART has modified but not erased muscle complications of HIV infection, and that increased life expectancy of treated patients may favor emergence of iatrogenic disorders.

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