Chapter 2

HIV-Associated Vasculopathy

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Abstract

HIV vasculopathy is a wide range of clinical spectrum related to HIV infection. Increasing longevity of HIV-infected individuals secondary to antiretroviral therapy advancements has resulted in increasing the number of patients with HIV-related vasculopathy. Clinicians need to be aware of the different types of HIV vasculopathy to be able to diagnose and manage the pathology and improve patient care.

Keywords: HIV vasculopathy, vascular disease, carotid disease, aortic aneurysm, peripheral arterial disease, cerebral vasculopathy

1. Introduction

Human immunodeficiency virus (HIV) reduces the immunity of a body, making it vulnerable to opportunistic diseases. HIV was first reported in the USA in 1981, in young homosexual men. The young men were said to have severe opportunistic infections [1]. Two years later the virus was labeled as HIV and acquired immune deficiency syndrome (AIDS), if advanced [2]. A patient is diagnosed with AIDS when their immune system is significantly low, and their CD4 count is <200 cells/μl. The areas most affected with HIV/AIDS-infected persons are the Sub-Saharan regions of Africa. More than 72% of the world's population with HIV live in Africa. According to the 2007 report on HIV/AIDS, the world's total population living with this infection is about 33 million [3]. The burden of the worldwide epidemic of HIV infection continues to increase, especially in the developing world. Third World countries experience a vast financial burden of managing and treating HIV-infected and affected persons with scarce resources. The new advancement of potent antiretroviral therapies has, however, made it possible for more patients to live longer, allowing healthcare providers to witness new clinical manifestations of the chronic HIV infection.

There have been major improvements in novel clinical management in a bid to manage HIV [2]. For instance in 1987, HIV was for the first time linked to vasculopathy, impulsive arteriovenous fistula and arterial occlusive disease or aneurysmal infection [4]. The prevalence of symptomatic vasculitis in HIV patients is about 1% according to recent studies [5]. The chief objective of this review will be to describe the HIV-associated vasculopathies in various parts of the body.

Pathogenecity of HIV, which is associated with vasculopathy, is rather complex and hence not fully comprehended. The complexity is a result of several factors such as inflammatory and immunological response to HIV infections. These factors lead to deleterious and dynamic effects on the endothelial and smooth muscle cells of the blood vessels.

HIV infection results in several interleukins and tumor necrosis factor-α (TNF-α) in response to production of viral proteins by the virus. The HIV-transactivator of transcription protein (*tat*) and viral envelope glycoprotein component (gp120) are believed to induce and mediate the inflammatory responses to vessels. This inflammation consequently results in the production of cytokines and adhesion molecules that interfere with endothelial function. In essence, the viral protein accesses the smooth muscle component of the media layer through CD4 surface receptor. Ultimately, this results into abnormal proliferation of the smooth muscle, and abnormal activation of the coagulation cascade [6–10].

Histological studies show an infiltration of the large vessels surrounded by different inflammatory cells including neutrophils, lymphocytes, monocytes and plasma cells in HIV-infected persons. The infiltration of those cells results in obliterate endarteritis, which is an occlusion of the vessels supplying the vasa vasorum, and leads to ischemia, and necrotic changes of the vessel wall are induced [7–11]. Studies of the biopsy and culture of those aneurysms, however, fail to reveal infectious pathogens.

A murine AIDS model has helped investigate pathogenesis of acquired AIDS. In this model the murine leukemia virus (MuLV) is injected into mice. The mice characteristically develop hypergammaglobulinemia, splenomegaly, lymphadenopathy, T-cell and B-cell functional abnormality. The mice also become highly susceptible to opportunistic infections. The murine AIDS and human AIDS have a lot of similarities regarding immune function alterations. Further clinical progression based on this model and vessel wall animal models has suggested a link between endothelial dysfunction and vasculopathy. It has been found that aortas from infected mice have increased concentrations of ICAM-1 and VCAM-1. Moreover, decrease in their contractile responses and impairment in the endothelium-dependent relaxation are observed.

Pathological findings, conversely, have indicated the thinning of the media layer as a result of the viral infection. In addition, they have indicated a direct viral invasion of the aortic fibroblasts at the level of the adventitia. It has therefore been postulated that an autoimmune destructive process can happen as a result of the similarity in the DNA sequence of the viral glycoprotein and a component of the matrix of the vessel wall. Important to note is that, no strong evidence has been found to support this theory.

It has been postulated that an autoimmune destructive process is possible where there is a DNA sequence of the viral glycoprotein, and a component of the matrix of the vessel wall. This, however, is not fully agreeable as there is lack of strong evidence to support the theory [8–12].

To diagnose HIV-associated vasculopathy, other causes of arterial occlusions and aneurysms have to be eliminated. These are mycotic aneurysms caused by syphilis and tuberculosis. Second, arterial occlusions caused by Takayasu's arteritis, vasculitis, and systemic lupus erythematosus (SLE) and Behcet's disease. Finally, elimination of antiphospholipid antibody syndrome-related aneurysms which make close differentials [13–15].

Recent studies indicate that various symptoms of HIV disease have been affecting almost all body organs. For example, studies in radiological, clinical and postmortem indicated cerebral, cardiac, renal and peripheral vascular pathologies in HIV-infected persons. This chapter will look at different HIV-associated vasculopathies affecting the main organ systems in a body.

2. HIV-associated large vessel aneurysm

The large arteries' condition in HIV-infected persons is not very researched, as it is a rare occurrence. Its pathology is different from atherosclerosis and mycotic aneurysm. It is considered a distinct clinical and pathological entity. It is non-infective vasculopathy, where the microbiological cultures of blood, aneurysm wall and thrombus are negative. Furthermore, the patients with atherosclerotic aneurismal disease are older in comparison to patients with aneurysms related to HIV. HIV-related aneurysm is commonly found in young patients in their 30s [10–14].

While the condition stands to affect any large artery, aneurysms typically affect superficial femoral, carotid and popliteal artery. Aneurysms are not uncommonly found to be multiple and have primarily pseudoaneurysm-like focal saccular transformations. Medical practitioners are therefore advised to screen patients for multiplicity using ultrasound or CT scan with contrast. Leukocytoclastic vasculitis of the vasa vasorum and periadventitial vessels is an important mechanism which weakens the wall of the vessel, and leads to focal disruption of the wall at the position of transmural necrosis. This mainly causes the false impression of aneurysm [9, 10, 13, 14]. The symptoms associated with the aneurysm depend on its location and size. It might be that compressive symptoms in an adjacent organ or structure result in life-threatening hemodynamic instability in case of a rupture. Thromboembolic and venous thrombosis are also likely complications of the aneurysm which have often been reported.

Majority of HIV-infected persons with associated aneurysm have advanced immunosuppressed state. This is usually indicated by abnormally reversed CD4:CD8 ratio. Such patients illustrate an abnormally low CD4 count (a median of about 400 cells/μl only). In addition, if such patients have high globulin level, they exhibit low serum albumin consistently [9–13].

While deciding the management approach of HIV-infected persons with asymptomatic aneurysm, it's important to take into consideration their clinical condition and nutrition status. With this in mind, symptomatic aneurysm lesions should be treated according to the standard guidelines, rules and open surgery standard therapy. The use of endovascular therapy has also gained popularity over the past years. HIV-infected patients should be optimized according to standard practice such as an earlier intervention. Conservative treatment on the other hand would be the best option for patients with advanced HIV/ AIDS. Low albumin (<35 g/l) and CD4 count are both indicators of poor operative outcome. Clinical management

should, however, maintain a consistency in administering antiretroviral therapy regardless of CD4 level. This is because such prevalence is indicator of an advanced phase of the condition [8–11, 13, 14].

3. Cerebral vasculopathy

Cerebral vasculopathy in HIV-infected patients is infrequently observed. The disease is believed to be under-diagnosed in most cases according to recent reports. HIV vasculopathy of the central nervous system affects small- to medium-sized blood vessels. The HIV-associated aneurysmal disease is frequently of a fusiform type, and occurs in young adults. This type of aneurysm affects carotids and extracranial vessels mainly. On the other hand, the intracranial aneurysm is a rare discovery and is often observed in children. Some reports have linked the low CD4 counts to increased chances of intracerebral vasculopathy occurrence [11, 12, 15, 16].

The primary pathogenesis of intracerebral vasculopathy is not known. However, various studies have shown that postmortem histological examination indicates damage of the interior elastic lamina and fibrosis. This histological examination has also shown interference of the media along with intimal hyperplasia. The resulting aneurysmal and occlusive patterns of this disease tend to lead to ischemic and/or hemorrhagic complications [10–14].

The pathogenesis of HIV-associated cerebral aneurysms has also been postulated to be a result of immune response to the HIV protein. This occurs, according to various researches, inside the endothelial cell. It has been suggested that the use of antiretroviral therapy may exacerbate the vasculopathy because it can lead to immune reconstitution inflammatory syndrome (IRIS) [15, 16].

A similar theory suggested that an abnormal and significant change in the vascular response to blood flow, which occurs due to changes in circulating cytokines and growth factors, can lead to vascular remodeling. These changes are thought to play a main role in aneurismal dilatation. The production of cytokines and growth factors is believed to be caused by opportunistic infections, which involve the blood vessel endothelial wall, allowing it to abnormally increase. Such repeated infections contribute to an amplified production of elastase, which increases the thickness and fragmentation of the internal elastic lamina. Such changes in the lamina are associated with development of fusiform aneurysms. Because of this suggested association, patients with cerebral aneurysm should be investigated for underlying opportunistic infections [11–13].

4. Carotid disease in HIV patients

Carotid intima-media thickness (IMT) measurement by B-mode high-resolution ultrasound is a noninvasive method of assessing atherosclerosis. It is also a strong predictor of cardiovascular events. IMT is considered in HIV persons to evaluate cardiovascular risk.

The prevalence of carotid atherosclerosis in HIV population varies, and correlates with Framingham risk score (FRS). The higher the FRS, the higher the prevalence. The prevalence is estimated to be 26.6% in the very low-risk group and 76.5% in high-risk group. The carotid IMT of individuals with HIV infection was, on average, 0.04 mm thicker (95% confidence interval; and 0.02–0.06 mm, $p < 0.001$) than that of individuals without HIV infection. Carotid plaque also has been found to be 1.5-fold more frequent in HIV patients in comparison to non-infected persons.

It is believed that the traditional CVD risk factors, in addition to HIV infection factors, play a role in this pathology. However, the role of ART is still not clearly confirmed. There are several studies that have suggested the use of ART as a significant and an independent risk associated with carotid atherosclerosis in HIV-infected patients. Moreover, it has been found that there is a moderate independent association between HIV immunological marker and increased carotid IMT and plaque presence [16, 17].

5. HIV-associated vascular thrombosis

Even though women comprise the highest population of HIV-infected persons in Africa, their male counterparts are said to be more likely to have primary arterial thrombosis. In addition, they are likely to present with late advanced limb ischemia. The pathophysiology of this disease is not well comprehended. Several causes of primary HIV infection-associated thrombosis have been documented. The levels of total proteins and the von Willebrand factor have been found to be increased in such patients. This suggested that endothelial cell dysfunction may play a role, as a predisposing factor for primary thrombosis. Hypercoagulable states associated with the HIV infection, including antiphospholipid antibody syndrome, deficiencies in free protein S, protein C, and antithrombin III, could predispose patients to arterial thrombosis [18, 19].

What is unique about HIV-associated vascular thrombosis is the normality of the arterial tree proximal to the thrombosed arteries by duplex ultrasonography, angiography and macroscopic appearance. Second is the thrombosis of all distal vessels with no demonstrable runoff. Duplex ultrasonography also showed hyperechoic 'spotting' in the arterial wall, the 'string of pearls sign', which has also been observed in patients with HIV-associated arterial aneurysms. Both endothelial dysfunction and coagulation abnormality of the HIV patients were found to correlate with the state of immunosuppression [19, 20].

When managing HIV-associated occlusive vasculopathy, the vascular surgical rules should be followed. Patients having less CD4 count should not be excluded from surgical intervention, since surgical findings show that its success does not depend on CD4 levels. The treatment for primary arterial thrombosis includes surgical thrombectomy with or without thrombolysis. The use of corticosteroid post thrombectomy has been considered previously, although it did not decrease the rethrombosis rate. The treatment modality available unfortunately did not significantly alter the level of amputation. The rate of limb salvage in such cases is about 27%. According to therapy researches, it is clear that therapies do not address the underlying ongoing processes. It's important to note that such studies are only but a few; they are sporadic and reflect individual experiences [19–24].

Venous thrombosis is reported as a complication in HIV-infected patients. It is believed to be a result of disturbance of coagulation process. It is estimated that deep vein thrombosis in HIV-infected patients of up to 5% is attributable to a process of thrombophilia. In addition, protein anticardiolipin antibodies and protein C deficiency have been reported in such patients [25–29].

6. HIV-associated peripheral arterial disease

Peripheral arterial disease is a significant clinical management issue in HIV-infected patients. The disease creates a risk of cardiovascular disease, and is associated with increased morbidity and mortality rate. HIV-infected individuals are believed to have higher prevalence and more severe forms of PAD. Measuring ankle-brachial index (ABI) is the initial noninvasive test to diagnose PAD. It usually correlates to obstructive disease and more than 50% stenosis by angiography in the lower extremity arterial system, if abnormal. Moreover, post-exercise ABI measurement could be used to uncover milder diseases.

Low ABI and high ABI readings have been linked to atherosclerosis and increased cardiovascular events. The exact prevalence of PAD in HIV population is still under-studied and not clearly defined. The studies are not numerous and the existing ones show contradicting results. However, the prevalence is believed to be higher than in normal population and in the range of 9.8–13.9%. High ABI prevalence in HIV patients has risen and is estimated to be in the range of 13.3–19.7%. However, none of the classical vascular risk factors were associated with ABI measurements.

Post-exercise ABI measurement change is suggestive of PAD in HIV-infected patients. It has been reported to range from 10.9% to 26.5%, depending on the criteria used. The exercise test was performed to symptomatic versus asymptomatic HIV-patients. Interestingly, the post-exercise changes in ABI are not associated with traditional atherosclerosis risk factors such as diabetes mellitus, hypertensive disorder and dyslipidemia. Screening for subclinical PAD using post-exercise measurement is encouraged in HIV-infected patients, even when they do not depict symptoms of PAD. PAD has a frequent occurrence in young HIV population and coexists with critical limb ischemia. In HIV-infected patients, there is growing evidence suggesting a high prevalence of PAD and a higher risk of developing severe and accelerated atherosclerosis. PAD in HIV patients is six-fold more than in HIV-negative patients [30–33].

The antiretroviral protease inhibitor induces dyslipidemia, making HIV infection a risk factor for atherosclerosis. HIV causes direct injury to the arterial wall, resulting in the initiation of the inflammatory process. Such inflammations contribute to the development of premature atherosclerosis. Endothelial dysfunction in HIV-infected patients is associated with increasing levels of soluble adhesion molecules, cytokines and procoagulant proteins. The effect of the HIV-associated proteins gp(120)on endothelium have been suggested to cause endothelial dysfunction [25–28, 32, 33]. In addition, PAD in HIV-infected patients can occur even in undetectable viral levels or in absence of severely suppressed immune system. This can be explained by the chronic inflammatory state in HIV patients. PAD, in addition, does not correlate to Framingham risk score in the HIV-infected population [34].

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7. HIV and atherosclerotic coronary artery disease

HIV-infected patients live longer since the introduction of ART. It is believed that the risk of atherosclerosis in HIV patients is increased because of associated metabolic disturbances. The coronary disease in such infected individuals is considered distinctive. It is usually more diffuse and is associated with circumferential-intimal thickening, atherosclerotic plaques and abnormal proliferation of the smooth muscle. The muscles with luminal protrusions share several similarities with cardiac transplant vasculopathy [34–38]. Reports have suggested that the most common initial presentation of the HIV patient with CAD is acute myocardial infarction and its mortality can go as high as 24%. In addition, more than 40% test positive to triple vessel disease [39–41].

Coronary artery disease (CAD) is commonly observed in patients who are on ART. During a study conducted on this, HIV-infected patients who were not using ART showed a slight risk of ischemic heart disease. The risk was slightly higher in HIV-infected persons who were on ART. However, during the post-ART period there was a significant increase in the risk of ischemic cardiac disease in the HIV-infected population. The 3-year risk for myocardial infarction was 3.6-fold higher in patients on ART in comparison to those who were not [34, 38–43].

There are numerous metabolic changes that are associated with ART (protease inhibitor in particular). They include impaired glucose metabolism and lipodystrophy as a result of increased insulin insensitivity, and they tend to accelerate the atherosclerosis process. The data regarding nucleoside reverse transcriptase inhibitors, as a risk for CAD, are not very clear. In a D.A.D study, abacavir and didanosine were found to be associated with increased risk of myocardial infarction. Consequently, abacavir has been linked to higher cardiovascular events in first 6 months of the infection. Conversely, other studies could not establish a similar relationship, especially after controlling the traditional cardiovascular risk factors. Furthermore, no link was established in non-nucleoside reverse transcriptase inhibitors and integrase inhibitors as an association with cardiovascular events [20, 44–47].

On one hand, HIV infection has been postulated to independently increase the risk of premature CAD. The mechanism by which the virus can accelerate atherosclerosis is multifactorial and complex. This mechanism involves the activation of inflammatory cells, which changes the immune response in HIV patients. This leads to exposure to a variety of xenoantigens from HIV infection and other viral and bacterial infections. These infections result in the ignition of a continuous inflammatory condition that speeds up atherosclerosis [21, 30, 34].

Endothelial dysfunction is an early marker of atherosclerosis. Endothelial dysfunction has been found in young HIV-infected individuals and has been attributed to increased viral load. HIV affects directly the endothelium function and results in increased levels of prothrombotic plasma markers such as von Willebrand factor, b2 microglobulin and thrombomodulin. In addition, it leads to increased levels of the circulating inflammatory molecules, interleukin 6 and D-dimer.

Prevention of CAD is a cornerstone in clinically managing HIV-infected patients. Careful cardiac screening of individuals who are receiving ART is important. Patients with a history in cardiovascular risk factors stand to benefit from such screening as they are at a higher risk.

Identification of asymptomatic atherosclerotic diseases of the coronaries would help to maximize patients' therapy. By the use of risk stratification tests such as coronary artery calcium score, high sensitivity C-reactive protein and carotid intima-medial thickness, HIV patients with higher risk of cardiovascular events can be identified. This will protect such patients from aggressive risk factors through modification and preventive measures.

Interruption of chronic ART therapy is highly discouraged as it could lead to increase in cardiovascular-associated morbidity and mortality. The SMART study has shown that the risk of cardiovascular morbidity and mortality has increased significantly. This is in patients who were assigned to a CD4 cell count guided therapy arm, as compared to their counter parts with continuous therapy arm. However, no studies or theories support an association of CD4 count and CAD [34, 43].

The conventional cardiovascular risk factors are found to be higher in HIV patients. Patients with smoking habits particularly, experience increased risk of atherosclerosis and increase the prothrombotic state [38, 39]. Controlling and modifying the risk factors and comorbidities is important in managing atherosclerosis. The fasting lipids should be checked before starting ART, and followed up to adjust therapy according to the lipids' value changes. If statin therapy is needed to treat high low-density lipoprotein (LDL) levels, the dose to be used should be identified carefully. This is because the risk of statin drug interaction and possible rhabdomyolysis is higher in HIV patients. PI, ritonavir and some antimicrobial agents inhibit specific cytochrome P450 enzymes, which are important in metabolizing several statins. This is because such agents could increase the toxicity of those drugs. Pravastatin (20–40 mg), low-dose atorvastatin (10 mg) and rosuvastatin (5–10 mg) have been suggested as safe if used with protease inhibitors. Ezetimibe can also be added to statin therapy to achieve target levels of LDL. Fibrates are used to control hypertriglyceridemia, if the concentration is above 500 mg/dL.

8. Pulmonary arterial hypertension

HIV-related pulmonary arterial hypertension (PHT) is estimated to occur in 0.5% of the HIV population. It is usually present with nonspecific symptoms such as dyspnea on exertion, lower extremity edema and fatigue. PHT is considered a poor prognostic finding and it is said to lead to right ventricular dysfunction, therefore significantly increasing the mortality rate.

The pathogenesis of HIV-related PHT is complex and still not very well understood. Factors that are believed to participate in the pathogenesis are related to the viral infection in patients. It is believed that the HIV virus stimulates an immune response, which leads to the release of different cytokines and growth factors. This may include the potent vasoconstrictors, endothelin-1, interleukin 6, tumor necrosis factor and platelet-derived growth factor. These immunological responses result in endothelial damage, intimal fibrosis, and stimulate the proliferation of the smooth muscle and fibroblast of the arterioles. Eventually, the pathological structural changes lead to the formation of plexiform lesion. The lesion is quite similar to those found in PaHTN caused by other factors. More recent evidence suggests that the patient's immunologic response, virus HIV-negative factor (Nef), HIV-transactivator of tran-

scription (Tat) accessory proteins and human herpes virus-8 coinfection, may play an important role to cascade events.

Its prognosis is poor and the reported mortality rate is said to be high. PaHTN in HIV population is an independent predictor of mortality with 1-year survival rate reported to range from 51% to 88%. The severity of HIV infection and CD4 cell count has no apparent correlation with this complication. The effect of highly active antiretroviral therapy regimens on the clinical course is still not well defined and is presently being investigated. However, it has been suggested that long-duration treatment with HAART might reduce mortality rate. Currently the treatment of HIV-PaHTN is similar to that of idiopathic pulmonary arterial hypertension patients. There have been reports of the use of diuretics, anticoagulation, phosphodiesterase V inhibitors and calcium channel blockers to treat HIV-PaHTN. HAART prostacyclin analogs (e.g.epoprostenol and endothelin) and receptor inhibitors (such as bosentan) were found to be effective in reducing the pulmonary arterial pressure in HIV patients. Heart-lung transplantation is the last treatment option in this subgroup of patients [21, 22, 34].

9. Conclusion

HIV-associated vascular diseases is not a common occurrence, even though it is considered to be of significant clinical importance. A comprehensive screening for possible etiology such as co-infections, lymphoproliferative disease, and autoimmune disorders, before other pathological attributions to HIV infection is important for appropriate patients' management. HIV-associated vascular disease can be manifested either as aneurysms or occlusive forms. The two forms of diseases can lead to hemorrhagic or ischemic life-threatening complications, respectively.

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