Review

Infection with the Human Immunodeficiency Virus type 1 and vascular inflammatory disease

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ABSTRACT

Since the beginning of the HIV epidemic a wide variety of vascular inflammatory diseases have been described in HIV infected patients. In terms of the primary forms of systemic necrotizing vasculitis, there are no convincing data suggesting HIV infection increases the risk of development of any form of these diseases, but it is possible – though yet unproven – that HIV may lessen the chance of developing other forms (i.e. ANCA-associated disease and HBV-associated PAN). Secondary vasculitis resulting from unusual pathologic expressions of opportunistic infections has been reported and has important clinical significance. Finally, there does appear to be growing clinical, epidemiologic and pathologic evidence that several distinctive forms of vascular inflammatory disease occur in certain settings. These include aneurysmal disease of the large arteries of the brain occurring in children and a large vessel aneurysmal disease primarily affecting the aorta and its branches in young HIV-infected patients from sub-Saharan Africa. Further study of these disorders is necessary to identify specific epidemiologic features and pathogenesis.

Since the beginning of the HIV era in the early 1980s much has been written about rheumatic and immunologic complications observed in this patient population, including the co-occurrence of systemic vascular inflammatory diseases (1). Over this time there have been remarkable changes in our understanding and management of HIV infection and the dramatic attendant changes in patterns of morbidity and mortality. With regard to the associated spectrum of vasculitis, despite literally hundreds of reported cases many questions persist regarding their etiology, clinical expression and management. In particular there has been little clear consensus as to whether any distinct forms of vasculitis exist in the setting of HIV infection similar to those distinctive forms described with hepatitis B and hepatitis C infections. This review will attempt to clarify some of these uncertainties and present a synthesis of data from the more recent clinical and pathologic literature suggesting that there indeed exist one or more forms of vascular inflammatory disease in the setting of HIV infection that are deserving of nosologic distinction.

Vascular inflammatory disease for the purpose of this review will be separated into three categories. For each of these categories a basic review will be cited together with selected references of seminal articles and reports. In addition, commentary with the author's view of clinically important or unique aspects of each disease category will be provided. Methodologically, a search of OVID from 1985 through 2004 was undertaken using the search terms HIV, AIDS combined with vasculitis, vascular disease, and aneurysms. Category I refers primarily to vasculitides generally conforming to the Chapel Hill or American College of Rheumatology classification schemes (2, 3) that have been reported in the setting of HIV infection. Category II refers to secondary forms of vasculitis (e.g. where a precipitin or mechanism can be identified such as a specific infection or drug-induced hypersensitivity). Finally Category III describes those vascular disorders that appear to be unique and for which strong consideration should be given to nosologic distinctions.

I. Primary forms of vasculitis in HIV infection

Since the earliest beginnings of the epidemic there have been numerous case reports and small series of HIV infected patients with primary forms of systemic necrotizing vasculitis (Table I). In addition, the literature abounds with examples of isolated case reports of HIV infected patients with a myriad of disorders not considered among the primary systemic vasculitides *per se*, but also characterized by a component of vascular inflammatory disease (Table II). These data have been summarized in numerous reviews spanning the past 15 years (1,4-6). Given the fact that HIV has infected an estimated 75 million people worldwide over the past 25 years (7), it should not be surprising to find documented accounts of just about any form of vascular inflammatory disease reported on a chance association basis. Furthermore it should readily be appreciated that by its very nature (i.e. a state of progressive immunodeficiency), HIV infection is associated with a wide variety of pathogens such as HCV, HBV, CMV and others, which themselves are associated with vasculitic conditions, which further complicates the epidemiological study of the issue.

With these data in mind, there are two important questions that need to be addressed regarding the relationship between HIV infection and the primary forms of systemic necrotizing vasculitis. Epidemiologically, does HIV infection itself impart the risk of developing one or more forms of systemic vasculitis and clinically does HIV infection alter the clinical expression of systemic vasculitis occurring in this setting? Unfortunately, at present robust epidemiologic and clinical data do not exist to answer these questions definitively, but we suggest that some important inferences and preliminary conclusions may be possible.

To appropriately assess this risk, studies employing a case-control or prospective cohort designs can be employed (8). No such studies with appropriate controls addressing the association of HIVinfection and vasculitis have yet been performed. To do so would require an extremely large study population given the relative rarity of systemic vasculitis in the general population. Limited data however, do exist.

Among the several epidemiologic investigations that have addressed this is the study of Gherardi *et al*. (9) who found evidence of vascular inflammatory disease in 34 of 148 (23%) pathologic specimens, including 11 of which met the American College of Rheumatology criteria for a distinct form of vasculitis. Unfortunately it is unclear how the patients were selected for examination, the denominator from which they were drawn, and there were no controls. In the only on-going longitudinal cohort study of an HIV-infected population that specifically tracks rheumatic complications, Calabrese and colleagues have identified vasculitis in approximately 1% of a cohort of approximately 400 patients followed for a mean period of 53 months with inception in 1989 (data unpublished). Those cases meeting the classification criteria have generally been of the isolated coetaneous vasculitis and poly-

Table I. Primary forms of systemic vasculitis associated with HIVinfection.

	Reported in HIV	Ref.	Comment
Small vessel vascultis			
Wegener's granulomatosis	no		
Churg Strauss syndrome	yes	51	Single case
Microscopic polyangiits	yes*	52	Atypical pulmonary limited,
ANCAnegative			
Henoch Schölein purpura	yes	5+	No distinguishing features
Essential cryoglobulinemia	yes	53, 54	
Cutaneous leukocytoclastic vasculitis	yes	4, 55, 56+	Non-HCV, non-hypersensitivity
Large vessel vasculitis			
Giant cell arteritis	no		
Takayasu's arteritis	no		Large vessel vasculitis of non-granulomatous pathology reported (17) and a single case of angiographically documented disease reported in a 12-year-old (57)
Medium-sized vessel disease			
Polyarteritis nodosa (PAN)	yes	1, 4, 6, 15, 17+	Most numerous category of reported cases, all HBV- and HCV-negative
Kawasaki disease	yes	6+	Numerous cases of children and adults, some with atypical features

+Cases cited in reviews.

Table II. Miscellaneous disorders with vascular inflammation as a feature reported in HIV infection+.

Cutaneous PAN [58]
Behcet's syndrome [4, 59]+
Primary angiitis of the central nervous system [1]+
Erythema nodosum [60]
Rheumatic fever [61]
Erythema elivatinum diutinum [62]
Degos disease [63]
Angiocentric lymphoproliferative disorders [1, 4, 64]+
Coronary arteritis [65]
Eaosinophilic vasculitis [66]
Leukocytoclastic vasculitis with follicular accentuation [67]

+ individual references or cited in reviews as multiple cases

arteritis types, with several cases representing atypical forms of vascular inflammatory disease. More recently Marquez and colleagues (10) have reviewed their experience with referrals in one university rheumatology clinic for HIV infected patients with rheumatic complications. This study, performed in the era of combined antiretroviral therapy (i.e., highly active anti-retroviral therapy or HAART) from 1999 to 2002, failed to report a single case of systemic vasculitis. Again, strong conclusions cannot be drawn from these studies given their design and the absence of controls.

Clinically there appear to be some distinctive features of the reported cases that are at least unusual if not clinically characteristic of systemic vasculitis in the setting of HIV infection. In those patients with PAN-like presentations, there clearly appears to be an unusual frequency of digital necrosis (11-16). Otherwise most cases have lacked any other clinically distinctive features and widespread organ involvement has been reported (15, 17). Therapy for HIV-associated vasculitis remains controversial and problematic, with the largest reported experience being that of Guillevin and colleagues who advocate a combination of glucocorticoids, apheresis and antiviral therapy (13).

The pathophysiology of these reported cases is also unclear (as it is for similar cases in the uninfected population), but given the data on the capacity for other chronic persistent viral infections (i.e. HBV and HCV) to cause vasculitis, much interest has centered on a direct or an indirect role for HIV itself. Despite several reports of the identification of HIV within inflamed tissues (1, 9), evidence for the ability of HIV to infect the endothelium has not been universal, with some tissue being susceptible to infection such as those from liver and glomeruli (18, 19) while saphenous vein and aortic endothelial cells are not (20). Other potential mechanisms include an indirect effect of HIV infection by way of uncontrolled immune activation with attendant cytokine release, which characterizes the underlying infection (21).

At this juncture we would suggest the following assumptions regarding the epidemiology and clinical features of primary systemic forms of vasculitis occurring in the setting of HIV infection.

1. Even in the absence of appropriately designed epidemiologic investigations, the occurrence of any form of systemic vasculitis in the setting of HIV infection is clinically rare. The strength of this conclusion is based on the clinical drama of systemic vasculitis with probable positive reporting bias, the scarcity of reported cases and our own longitudinal cohort investigation revealing a cumulative incidence of no more than 1%.
2. Certain forms of vasculitis appear to be under-represented, in particular those vasculitic conditions associated with antineutrophil cytoplasmic antibodies (ANCA). We are currently unaware of a single documented case of systemic vasculitis that would fit the Chapel Hill classification criteria for Wegener's or microscopic polyangiitis in the setting of ANCA. While ANCA have been reported in HIV infection, they are primarily of the non-proteinase 3 or myeloperoxidase variety (22, 23).
3. In patients with documented medium size vessel vasculitis of the PAN type there appears to be an over-representation of patients with digital necrosis and isolated disease of the muscle and nerves compared to non-infected patient populations, although careful case control studies have not been performed.

Given the rarity of these conditions and the gravity of the underlying HIV infection with its attendant complications, as well as the profound public health implications of the epidemic, it is unlikely that appropriately controlled studies to answer these questions will be carried out in the near future. We would encourage the continued reporting of individual cases with careful pathophysiologic investigations when possible.

II. Secondary forms of vascultis

Given the immunopathology of progressive immunodeficiency, it is understandable that HIV infected patients are susceptible to virtually any pathogen and that unusual clinical expressions of these opportunistic infections have been commonplace. It is well known that vasculitis may arise in the course of virtually any type of infection (i.e., bacterial, fungal, mycobacterial, viral parasitic) and that such pathologic lesions may come about by way of direct angioinvasion or via aberrantly directed host-mediated immune defenses (24). In the setting of HIV associated immunodeficiency, numerous examples of 'infective' vasculitis have been reported (Table III). In most of these infections, direct vascular invasion is an unusual manifestation of their clinical and pathologic course, but in the absence of a normal integrated immune response, atypical pathologic expression may be observed. From a clinical perspective, HIV infected patients with vascular inflammatory disease need careful assessment for the presence of treatable pathogens that mediate direct vascular inflammation and damage.

A striking feature of the literature on infection-associated vasculitis is that despite the strong epidemiologic association between HBV and HIV, with an estimated 10% or more of patients being dually infected (25), we are not aware of a single case of well-documented HBV-associated PAN with evidence of ongoing viral replication. In addition, despite the estimates that HCV exists as a co-infection in up to 30% of HIV infected patients, case reports of HCV-associated cryoglobulinemic vasculitis are extremely rare (13, 26). In prospective studies examining the prevalence of circulating cryoglobulins in the setting of HIV infection, several groups have actually found them to be more common than those

Table III. Secondary forms of vasculitis.

Infectious arteritis
Cytomegalovirus [68, 69]
Pneumocytstis carimii [70, 71]
Toxoplamosis [72]
Herpes zoster associated [45, 46]
Hepatitis C associated [13, 26]
Drug-induced vasculitis
Vasculitis associated with antiretrovirals [29-31]

occurring in HIV-negative patients, but associated with less in the way of extrahepatic immune manifestations (26-28). The reasons for these observations are not known but probably reflect damage of some critical aspect of host defenses required for the expression of vasculitis.

Finally, hypersensitivity may account for some case of vasculitis (29-31) (Table III), which is not surprising given the number and amount of drugs HIV infected patients are exposed to and their underlying predisposition to adverse drug reactions (32).

III. Vascular inflammatory disorders possibly unique to HIV infection

In order to ascribe a nosologic distinction to a vascular inflammatory syndrome or syndromes in the setting of HIV infection, there need to be some distinctive clinical epidemiological and/or pathologic features not observed in the HIV-negative population. We believe that one or more disorders meeting these requirements do exist in HIV infection and their existence is supported by data from two areas. These are: (1) cerebral vasculopathy with aneursymal dilatation in HIV infected children, and (2) large vessel aneurysmal disease in HIV infected patients largely from the third world.

A) Cerebral vasculopathy with aneursymal dilatation in HIV-infected children

Cerebrovascular disease complications are quite common in children, with post mortem studies demonstrating vascular abnormalities in about 50% of patients (33). Both ischemic and hemorrhagic infarcts are observed and are multi-factorial in their etiology, including infective, immunologic and thromboembolic causes.

In addition to the more common forms of vascular disease observed in this population, there are now numerous reports (34-40) of a peculiar aneurysmal dilatation of large arteries primarily of the circle of Willis that has been referred to as HIV associated vasculopathy (33,41). As opposed to aneurysms in children without HIV infection, which tend to be singular in 98%, multiple aneurysms have been found in 57% of patients examined in one study (39). The age of the reported cases in these series range from 6-18 years and the detection of the CNS disease occurred an average of 2.5 years after the diagnosis of AIDS. In several reported cases there was documentation of normal neuroimmaging prior to detection strongly suggesting this is an acquired disorder (34). A common denominator in most patients was an advanced state of disease, with relatively few patients being treated with HAART at the time of diagnosis, and in those who were, there was evidence of ongoing viral replication. Clinical manifestations may be delayed but eventually most demonstrate progressive neurologic deterioration with infarction and fatal hemorrhage.

Histologically these lesions share certain common features and some differing features as well. Most report impressive and at times massive intimal thickening, primarily related to subintimal fibrosis. The internal elastic lamina is generally damaged and there the medial may demonstrate thinning or thickening and fibrosis. The adventitia at times shows some degree of lymphocytic infiltration. Interestingly the smaller vessels of the parenchyma and leptomeningies vary in morphology, from descriptions of sparing (34) to the presence of a striking panarteritis (42). In some specimens multi-nucleated giant cells have been observed in intimal lesions, but most cases such as this have been confounded by mycobacterial infections as well (43).

The pathogenesis of these lesions is unclear but several theories have some supportive data. The brain is a well-known reservoir for HIV infection and some groups have identified HIV by *in situ* techniques in the involved arteries (43), while others have not (35). The observation that these aneurysms appear to form during periods of advancing disease and uncontrolled viral proliferation is also supportive of such a role. Finally Mazzoni and colleagues (37) suggested an arrest of progression of arteriopathy after initiating HAART. While cerebral aneurysms have occasionally been reported in the CNS of HIV infected adults (44), these have been singular lesions and more typical of berry aneurysms as opposed to the multiple lesions described in children. Why children are predisposed to this complication is unclear though some age-related phenomenon of vascular

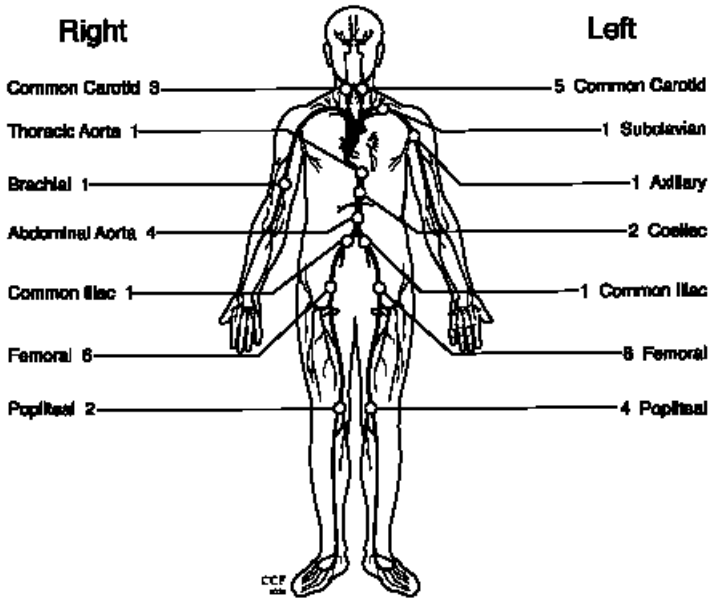

Fig. 1. A diagram representing the distribution and number of aneurysms encountered in the study of Chetty and colleagues (reprinted from CHETTYR, BATITANG S, NAIRR: Large artery vasculopathy in HIV-positive patients: another vasculitic enigma. *Hum Pathol* 2000; 31: 374-9, with permission of Elsevier).

development and biologic expression resulting in altered vascular targeting would be the best explanation.

A number of investigators have suggested other pathogens, especially that other viruses may be acting alone or in concert with HIV in the pathogenesis of the vascular lesions. In particular, varicella zoster (VZV) has been implicated in a spectrum of CNS arteriopathy (45). While not systematically examined for, several groups have identified clinical, serologic or *in situ* evidence of VZVin pediatric patients with aneurysms or unexplained infarction (34,35,39,46). We believe that a vigorous search for VZV by both molecular and serologic techniques is warranted in all cases of possible CNS vasculitides occurring in compromised hosts. VZV can occur without cutaneous manifestations and may be associated with neurologic sequelae (45). Collectively, we believe that based on epidemiologic, clinical, radiographic and histologic data this form of vasculopathy occurring in the setting of HIV infection in children appears unique.

B) Large vessel aneurysmal disease in adults

In 1995 Marks and Kuskov (47) described a small cohort of young patients in Zimbabwe with an unusual pattern of large vessel vascular disease in a subset of their patients. The patients were all HIV-infected indigenous Africans of young age (mean 31 years) with no evidence of atherosclerosis. Their disorder was characterized by the rapid development of focal necrotizing arteriopathy with aneurysm formation and rupture and what was described as a slow, progressive granulomatous vasculitis with vascular occlusion. The sites of vascular involvement were widespread, but were primarily located throughout the aorta and its major branches, and two patients had myocardial aneurysm formation. In none of these patients was there evidence of mycotic aneurysm from opportunistic pathogens, thus leaving them unexplained. Data regarding the underlying HIV infection were scant, but it is assumed that these individuals were largely untreated. Unfortunately there were no detailed pathologic descriptions provided.

Subsequently in a series of articles Nair, Chetty and co-workers (48-50) have described a similar phenomenon in a young HIV-infected patient population in South Africa. Again the aneurysms appeared at multiple sites (Figs. 1 and 2) and tended to multiplicity. In a pathologic study of these lesions (50) in 16 patients (9 men and 7 women), none had obvious infected vascular lesions. The seminal histologic features were found within the adventitia, with marked leukocytoclastic vasculitis of the vaso vasora and periadventitial vessels with proliferation of slit-like vascular channels, chronic inflammation and fibrosis (Fig. 3). In the media there was evidence of some fibrosis and fragmentation of the elastic tissue. In the intima there was duplication and fragmentation of the internal elastic lamina, but the marked intimal proliferation that characterized the aneurysmal lesions in the brains of children was not seen. A search for HIV within the lesions detected occasional p24 positive lymphocytes and macrophages within the inflammatory infiltrates. There were no features of atherosclerosis in this young patient population, which would be the most common etiology for large vessel aneurysm formation.

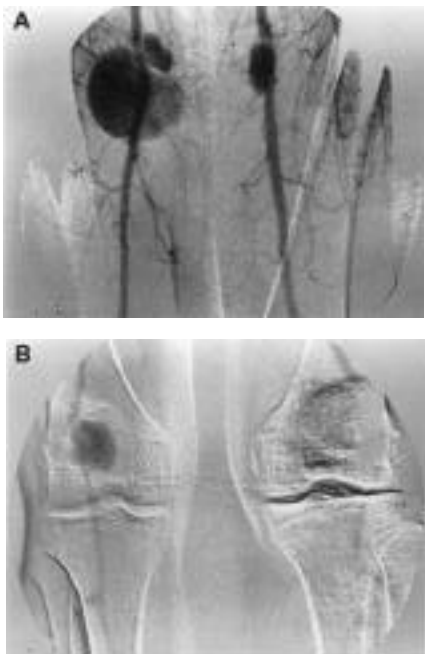

Fig. 2. Arteriograms of an HIV-infected patient showing: (**A**) right popliteal, and (**B**) right axillary aneurysms (reprinted from NAIR R, ABDOOL-CARRIM A, CHETTYR, ROBBS J: Arterial aneurysms in patients infected with human immunodeficiency virus: a distinct clinicopathology entity ? *J Vasc Surg* 1999; 29: 600-7, with the permission of The Society of Vascular Surgery and International Society of Cardiovascular Surgery, North American Chapter).

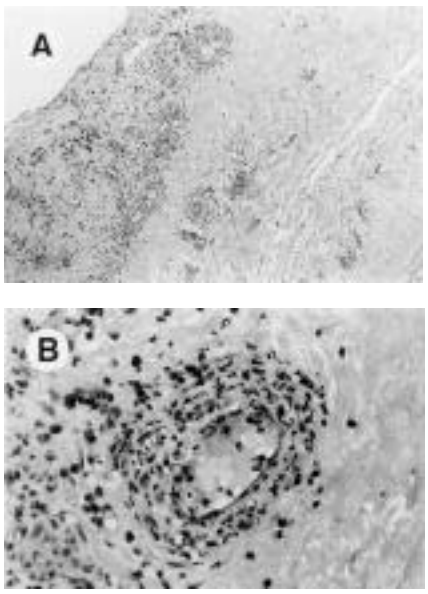

Fig. 3. (**A**) Low power magnification demondtrating the leukocytoclastic vasculitis of the vasa vasora. (**B**) Higher power view demonstrating the leukocytoclastic vasculitis characterized by neutrophils and nuclear debris. (reprinted from CHETTY R, BATITANG S, NAIR R: Large artery vasculopathy in HIV-positive patients: another vasculitic enigma. *Hum Pathol* 2000; 31: 374-9, with the permission of Elsevier).

In the presence of inflammatory large vessel disease with aneurysm formation in a young patient population, the question of whether this represents Takayasu's arteritis or a variant needs to be addressed. Clinically the age of the patients, the presence of multiple aneurysms and evidence of a temporal sequence (active and healing) bear similarity to Takayasu's disease. The lack of female preponderance, the absence of giant cells and the striking leukocytoclastic arteritis in the vaso vasora with slit-like channel proliferation are quite distinctive, however. Given the distinctive features of this disorder the question is begged as to why this form of vascular disease has only been observed in HIV-infected patients in sub-Saharan Africa. While clearly this geographic area has the largest number of

infected cases on earth and the vast majority of its infected patient population is largely untreated, resulting in a disproportionate number of patients with uncontrolled infection compared to the industrialized West, this does not provide a satisfactory explanation. If uncontrolled infection were the common denominator then this distinctive form of vascular inflammatory disease would most certainly have been seen in untreated Western patients in the pre-antiretroviral era. It is possible that some other co-factor indigenous to the sub-Saharan region (i.e. parasitic infection) may be contributing to the pathogenesis of this unique vascular syndrome.

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