

Vasculitides associated with HIV infection

R Chetty

Abstract

The manifestations of human immunodeficiency virus (HIV) infection are protean and vasculitides are one of the less common but nonetheless important consequences. A wide range of vasculitides can be encountered, ranging from vasculitis resulting from specific infective agents to a non-specific vasculitis. Among the infective causes, cytomegalovirus and tuberculosis are probably the most common. A polyarteritis nodosa-like vasculitis with important differences to classic polyarteritis nodosa is also described. Hypersensitivity vasculitis resulting in several patterns of vasculitis and angiocentric immunoproliferative vasculitis are well recognised. As part of the immunocompromise caused by HIV, a granulomatous inflammation involving small arteries and veins of the brain surface and leptomeninges, termed a primary angiitis of the central nervous system, is a rare vasculitis associated with high mortality. A recently described large vessel (aorta, femorals, carotids) vasculopathy resulting in either multiple aneurysm formation or occlusive disease is seen in young adults. An infective agent is not found but aetiologically some of these lesions might be the result of a leucocytoclastic vasculitis of vasa vasora or periadventitial vessels. A final group of non-specific vasculitides not fitting into any of the characteristic patterns described accounts for the residue of vasculitides associated with HIV.

(*J Clin Pathol* 2001;54:275-278)

Keywords: human immunodeficiency virus; vasculitis; immunocompromise

Viral infections have been implicated in the pathogenesis of systemic vasculitides, and many viruses, including human immunodeficiency virus (HIV), are associated with vasculitis. One of the first viruses that was found to have a causal relation with vasculitis was hepatitis B

virus (HBV), which was associated with polyarteritis nodosa (PAN).¹ It has been said that the association between HIV and vasculitis, although well described, remains rare.² Certain viruses preferentially affect a particular size of vessel—for example, HBV causes a vasculitis of medium sized vessels, whereas hepatitis C virus (HCV) can involve vessels of any size but has a predilection for small vessels.^{2,3}

According to Mandell and Calabrese, there are three scenarios that can occur with regard to viruses and vasculitis.⁴ First, in immunocompetent hosts, endogenous host defence mechanisms clear viral pathogens without producing clinically evident vascular inflammation. However, when the immune system is compromised, even ubiquitous viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella zoster virus (VZV), and herpes simplex virus (HSV) can cause vasculitis.⁴ Third, viral pathogens characterised by persistent replication or absence of latency have a strong association with systemic necrotising vasculitic syndromes.

The purpose of this overview is to highlight the spectrum of vasculitides seen in HIV infection.

Types of vasculitis seen in HIV

As can be seen in table 1, almost every pattern and type of vasculitis of small, medium and large vessels has been encountered in the HIV setting. An important caveat to the understanding of the relation between vasculitis and HIV involves epidemiological, clinical, and pathophysiological considerations.³ From an epidemiological point of view, it is not clear whether HIV and vasculitis are causally or coincidentally related. Clinically, other presenting conditions related to different systems and organs may well mask the vasculitis. In terms of pathophysiology, the concurrence of other pathogens, in particular viruses such as EBV, HBV, and CMV, which are all associated with vasculitis, complicates the issue. Thus, it can be concluded that HIV associated vasculitis might be associated with a known pathogen or triggering factor, or may occur in the absence of an obviously identifiable agent or aetio-pathogenesis. This means that almost all causes of vasculitis can be seen in HIV positive patients. Given this background, it is not surprising that the literature abounds with case reports and series of the various entities associated with vasculitis. Most of these examples have been categorised according to well known and recognised vasculitides that are also seen in patients without HIV infection. As can be seen from table 1, an extremely diverse array of vasculitides is encountered. Despite this somewhat exhaustive list, it must be borne in mind that the real incidence of vasculitis in HIV

Department of Anatomical Pathology, School of Pathology and Laboratory Medicine, Nelson R Mandela Medical School, University of Natal, Private Bag 7, Congella 4013, Durban, South Africa
R Chetty

Correspondence to: Professor Chetty chettyr@med.und.ac.za

Accepted for publication 30 August 2000

Table 1 Vasculitic processes encountered in human immunodeficiency virus (HIV) positive patients

<i>I Infective</i>	Cytomegalovirus, herpes zoster virus, toxoplasma, pneumocystis, salmonella, tuberculosis, direct HIV infection
<i>II Necrotising systemic</i>	Polyarteritis nodosa-like, non-specific necrotising
<i>III Hypersensitivity</i>	Leucocytoclastic, eosinophilic, Churg-Strauss, Henoch-Schonlein, Behcet's, drug induced, cryoglobulinaemia, relapsing polychondritis, erythema nodosum, erythema elevatum diutinum
<i>IV Angiocentric immunoproliferative lesions</i>	Benign lymphocytic angiitis, lymphomatoid granulomatosis, angiocentric lymphoma
<i>V Primary angiitis of the central nervous system</i>	
<i>VI Large vessel vasculopathy</i>	Related to infection or leucocytoclastic vasculitis of vasa vasora
<i>VII Miscellaneous</i>	Non-specific vasculitides not fitting into the above categories

positive patients is low and in the order of 1%.⁵ However, Gherardi *et al* encountered vasculitis in 34 of 148 (23%) HIV positive patients.⁶ Despite the wide spectrum and pattern of vasculitis, the pathology is invariably restricted to one or a small number of visceral vessels.⁶ The organs that are usually involved include: skin,⁷⁻⁹ peripheral nerve and skeletal muscle,¹⁰ and the central nervous system^{11,12}; in addition, the lung,¹³ gastrointestinal tract,¹⁴ oropharynx, and kidney⁶ can also be affected, although less commonly. The pre-eminent sites are the brain, skin, and neuromuscular tissues. As far as I am aware, there has been no correlation between HIV vasculitides and Kaposi's sarcoma.

Major patterns of vasculitis

Seminal work on elucidating the patterns of vasculitis seen in the HIV context was done by Calabrese.³ As more diverse types of vasculitis have been described, an expanded subdivision of the various categories is warranted. This breakdown is not meant to be a classification but an "aide de memoir" for ease of diagnosis.

INFECTIVE VASCULITIDES

As in any immunocompromised state, opportunistic infections are likely in patients with HIV infection and vasculitis may be a manifestation of this infection. Infectious agents of all types and classes can cause vasculitis of arteries and veins of all sizes and in all organs.¹⁵ CMV, HZV, toxoplasmosis, pneumocystis, salmonella, and *Mycobacterium tuberculosis* have all been associated with vasculitis in patients with HIV infection. The diagnosis is dependent on one or more diagnostic modalities including serology, culture, light microscopy, immunohistochemistry, and in situ hybridisation. There are cases of vasculitis in HIV positive patients in which a causative agent is not found despite the use of the abovementioned techniques. It is this residue of cases of vasculitis that can be regarded as the result of direct infection by HIV.¹⁶

Infected false aneurysms of large vessels have been described in HIV positive drug addicts, especially in large arteries such as the femoral artery.

The two major mechanisms by which infection is thought to induce a vasculitis are direct microbial invasion, with resultant damage of the vessel wall, and immune mediated injury (both humoral and cellular).

POLYARTERITIS NODOSA-LIKE SYNDROME AND OTHER SYSTEMIC NECROTISING VASCULITIDES

Several cases of PAN-like vasculitis have been described in the literature.^{6,17-19} The target organs that are usually involved are muscles and nerves, although skin and the gastrointestinal tract can also be involved.³ In general, there are two modes of presentation: either as a peripheral neuropathy or with digital ischaemia. The clinical spectrum of the neuropathy ranges from mononeuritis multiplex and symmetrical sensorimotor polyneuropathy, to distal sensory neuropathy and ascending myelodysplasia.^{6,18} The neurological deficit

develops either insidiously or rapidly over a period of weeks. General constitutional symptoms such as fever, malaise, and weight loss are also encountered and are related to the vasculitic process. There are several important differences between PAN seen in the HIV setting and so called classic or idiopathic PAN. First, the waxing and waning clinical course of classic PAN is not seen in patients with HIV infection. Second, it is well recognised that classic PAN can be associated with viral infections, especially HBV, but in HIV associated cases serology for HBV is invariably negative.^{3,18} Third, multisystem organ involvement, particularly renal involvement, is not seen in HIV associated cases. When the disease is systemic, skin involvement, arthritis, and rectal disease have all been documented.⁶ Lastly, Gherardi and colleagues observed that the affected arteries in HIV associated PAN tend to be smaller than that seen in classic PAN. In their series, there was consistent and pronounced involvement of the microcirculation.⁶ This would implicate immune complex deposition as the probable pathogenesis.

HYPERSENSITIVITY VASCULITIS

Within the rubric of hypersensitivity vasculitis, are several vasculitides that manifest in the skin and display a small vessel involvement with leucocytoclasia. Palpable purpura and sometimes neurological deficit are usual modes of presentation. Henoch-Schonlein purpura, drug induced hypersensitivity vasculitis, and cryoglobulinaemia have all been encountered in the HIV setting.^{3,6} Hypersensitivity vasculitis is also seen with other viruses such as CMV, EBV, and HBV in patients with HIV.²⁰⁻²² Because these viruses can cause a vasculitis without coexistent HIV infection, it is best to regard the vasculitis in the presence of these other viruses as the result of the virus and not of HIV infection. In those cases without identifiable viruses, then hypersensitivity induced by HIV is deemed causative.

LYMPHOMATOID GRANULOMATOSIS AND ANGIOCENTRIC IMMUNOPROLIFERATIVE LESIONS

Angiocentric immunoproliferative lesion is probably the preferred term because within this broad definition both benign and malignant proliferations are included. There are several reports of these lesions in patients with HIV infection ranging from lymphomas to benign lymphocytic angiitis of T cell lineage.³ The mechanism that has been suggested is based on HIV induced immune dysregulation leading to proliferation of T cells with an angiocentric proclivity.

PRIMARY ANGIITIS OF THE CENTRAL NERVOUS SYSTEM

This is a rare condition associated with a high mortality.³ It is characterised by a granulomatous inflammatory infiltrate, often with multinucleated giant cells. It is, of course, mandatory to exclude tuberculosis in this setting. Any part of the central nervous system can be affected but small arteries and veins on the

brain surface and associated with the leptomeninges are usually involved. Primary angiitis of the central nervous system is not specific to HIV and can be seen when the immune system is compromised for any reason.

The association between HIV infection and strokes is slightly controversial. Some authors have suggested that the increased risk of stroke, in particular cerebral infarction in young patients, is related to HIV infection, susceptibility to meningitis, and protein-S deficiency.²³ However, a case controlled study found that the rate of stroke in HIV positive patients was no higher than that seen in seronegative patients.²⁴ This study did demonstrate that the incidence of large vessel cryptogenic stroke in HIV positive patients suggested a prothrombotic state.

One of the effects of cerebral vasculitis as a result of HIV infection is a putative opening up of the blood-brain barrier. This can lead to HIV infected and uninfected cells passing into the central nervous system, resulting in HIV encephalitis.²⁵

LARGE VESSEL VASCULOPATHY

Large elastic artery involvement in HIV is uncommon and not well documented. Aneurysm formation or occlusive disease of large elastic arteries (aorta, femoral, popliteal, carotid, and subclavian) has been seen only rarely and most cases have an infective aetiology.²⁶⁻³¹ Direct involvement of the vessel wall results in these mycotic aneurysms. However, large vessel involvement has been encountered in the absence of overt infection by bacteria or fungi.^{30,31} Affected patients tend to be young and present with multiple aneurysms or occlusions of the carotid, femoral, and popliteal arteries. There was no evidence of atherosclerosis, and microbiological cultures of blood, aneurysm wall, and thrombus were negative. Several of the patients did, however, show a leucocytoclastic vasculitis of the vasa vasora and periadventitial vessels. It is felt that this leads to damage of the vessel wall, culminating either in aneurysm formation or occlusive disease. Other intriguing histopathological features seen include proliferation of slit-like vascular channels in the adventitia and fragmentation of adventitial collagen. The media shows minimal chronic inflammation and calcification of the internal elastic lamina is also present. Although leucocytoclastic vasculitis is not seen histologically in every case, aneurysm formation and/or sampling might explain this absence. Alternatively, an episode of leucocytoclastic vasculitis may have been mild but enough to cause ischaemia and consequent weakening of the wall.

MISCELLANEOUS VASCULITIDES

There are several reports in the literature of unusual forms of vasculitis that usually coexist with infections. These include so called non-specific or mononuclear inflammatory vascular disease.⁶ In other words, the histological picture does not fit with any of the characteristic vasculitic entities and appears to be rather nondescript.

Actiopathogenesis

The exact mechanisms by which the vasculitic processes described above occur in the HIV setting are still somewhat conjectural. The most obvious ones are the infective vasculitides. Although the vasculitides encountered in the HIV positive patient are highly heterogeneous, they are underpinned by a common histopathological tenet: inflammation of the vessel wall. This basic pathological process is probably multifactorial. Mandell and Calabrese have speculated on the pathogenesis of HIV vasculopathy.⁴ These patients, being immunocompromised, frequently have other infections or cofactors that might be responsible for the vasculitis. Clearly, there is a large number of cases where no obvious aetiological agent is apparent. In these cases, an indirect effect of HIV infection via an immune complex mediated mechanism or a direct infection of vascular or perivascular tissue has also been suggested.⁴ In fact, Gherardi and colleagues identified HIV particles by electron microscopy and in situ hybridisation in the perivascular tissues of patients with PAN-like vasculitides. Although not conclusive, this is circumstantial evidence pointing towards HIV being the causative agent. The lymphocytes seen in the adventitia and periadventitial tissue are almost exclusively of the T cell lineage. T cell mediated vascular injury has been demonstrated in several vasculitides including PAN, Takayasu's and Wegener's arteritis, and leucocytoclastic vasculitis.³² It is known that in HIV there is an oligoclonal expansion of T cells, especially CD8 positive cells. An interaction of these lymphocytes (which might release growth factors), superantigens, adhesion molecules, immune complexes, cytokines, and growth factors is likely.

Conclusion

Vasculitis in an HIV positive patient is an uncommon but important disease that might manifest as an organ based disease process. Many types of vasculitis have been reported, mainly of small and medium sized vessels. Large vessels can also be involved; usually as part of a leucocytoclastic vasculitis of the vasa vasora or periadventitial vessels. From the point of view of nomenclature, a descriptive name for the vasculitis is best. An infective aetiology should always be sought so that appropriate treatment can be instituted. Once an obvious infectious agent has been excluded, then the vasculitis can be described according to the major histopathological pattern that is the closest fit.

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Presented to you by the BMJ Publishing Group (London, UK) and Institute for Healthcare Improvement (Boston, USA), with the support of the the Commonwealth Department of Health and Aged Care (Australia), Safety and Quality Council (Australia), NSW Health (Australia), and the Ministry of Health (New Zealand).

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