Occlusive Arterial Disease in HIV-infected Patients: a Preliminary Report

R. Nair∗1, J. V. Robbs1, R. Chetty2, N. G. Naidoo1 and J. Woolgar1

1Metropolitan Vascular Service, Department of Surgery, and 2Department of Pathology, University of Natal, South Africa

Objectives: to preliminarily describe the clinical features and management of arterial occlusive disease in human immunodeficiency virus (HIV) infected patients.

Materials: twenty HIV positive patients with symptomatic large-vessel arterial occlusion treated by a tertiary vascular unit in a 3-year period.

Methods: retrospective review of clinical case records.

Results: patients were noted to be young (median age 37 years), with preponderance of males. Twelve patients had evidence of advanced HIV infection. All patients had critical ischaemia, involving the upper limbs in four and the lower limbs in 16. Coagulation abnormalities were noted in two cases. Operative intervention in 18 patients included revascularisation in seven. Thrombotic occlusion of normal-looking arteries was noted. Arterial biopsy revealed leucocytoclastic vasculitis indicative of HIV arteritis in three of five cases examined.

Conclusions: initial experience with large-vessel occlusive disease in HIV positive patients suggests an underlying arteritic aetiology, with clinical and pathological features distinct from atherosclerosis. Further in-depth study is necessary to clarify the pathophysiological basis thereof.

Key Words: Arteritis; Large vessel occlusion; HIV.

Introduction

The HIV epidemic poses the foremost challenge currently facing health care providers. The developing world is particularly affected, with intervention aimed at curbing the spread of the disease having been largely ineffective. Sub-Saharan Africa has accounted for the majority of cases, with the rate of seroprevalence increase in South Africa being amongst the highest. Screening for HIV at the antenatal clinic at the King Edward VIII Hospital in Durban has indicated that seroprevalence rates in this cohort have increased from 1.6% in 1990 to 33.7% in 1999 (personal communication: Professor A. N. Smith, Head of Department of Virology, University of Natal). While numerous vasculitic pathologies have been associated with HIV, the peripheral vasculature has been relatively spared. Thus far, description of large vessel involvement has been confined to reports of arteritic aneurysms. A series thought to be the first associating HIV arteriopathy with large-vessel occlusive disease is presented.

Patients and Methods

The Durban Metropolitan Vascular Service offers a tertiary vascular referral service to the province of Kwa-Zulu Natal’s nine million inhabitants. Data from patients treated by the unit at two academic hospitals in Durban (King Edward VIII and Addington Hospitals) are recorded on a dedicated vascular computerised database. A data search identified patients with occlusive arterial disease treated between 1997 and 1999 that tested positive for HIV and their clinical case records were retrospectively reviewed. Since 1996, the unit has offered voluntary HIV screening to patients with atypical arterial disease or where clinical suspicion of HIV infection existed. All patients tested gave informed consent, and were offered pre- and post-test counselling. The proportion of patients who were tested and the number who declined to be tested is not known. Management of presenting vascular pathology was individualised for each patient and followed conventional practice. The Ethics Committee of the University of Natal approved the review of patients’ clinical records for the purpose of this report.

Of the 20 patients who tested positive for HIV, 18 were male. The median age was 37 (range 17–53) years.
Table 1. Presenting features.

<table>
<thead>
<tr>
<th>Location</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower limb</td>
<td>16</td>
</tr>
<tr>
<td>Rest pain</td>
<td>3</td>
</tr>
<tr>
<td>Painless tissue necrosis*</td>
<td>3</td>
</tr>
<tr>
<td>Rest pain + tissue necrosis*</td>
<td>10</td>
</tr>
<tr>
<td>Upper limb</td>
<td>4</td>
</tr>
<tr>
<td>Rest pain</td>
<td>2</td>
</tr>
<tr>
<td>Painless tissue necrosis#</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
</tr>
</tbody>
</table>

* Necrosis of toes and forefoot in six, whole foot in four, leg in three. (Wet gangrene in three cases).  
# Dry gangrene up to forearm.

Nineteen patients were Negro and one of Asiatic descent. Twelve patients (60%) had clinical evidence of advanced HIV infection, with marked weight loss, opportunistic infection and generalised lymphadenopathy being prominent features. Four patients gave a history of previous pulmonary tuberculosis (TB), and another four had active pulmonary TB at the time of presentation. Three of the patients with active pulmonary TB were considered to have advanced HIV infection on the basis of clinical and laboratory evidence. No patient demonstrated the typical mucocutaneous, ocular or rheumatologic features of Behçet’s disease.

All patients presented with Fontaine III-IV ischaemia. As encountered frequently in the authors’ practice, patients presented late, with the average duration of symptoms being 9 weeks (range 2 days–7 months). Presenting clinical features are summarised in Table 1.

Of the 16 patients with lower-limb ischaemia, seven had unilateral disease, with normal pulses in the contralateral limb. Clinical examination localised the level of occlusion in the limbs of patients with diminished or absent pulses as follows: aorto-iliac segment 10, femoral and popliteal arteries 12, tibio-peroneal disease seven. Ankle-brachial indices were measured for all but one of the 16 patients with lower-limb ischaemia. Of the 30 limbs, 15 had indices of 0.3 or less. Eight had indices that ranged between 0.3 and 0.9, and the remainder had indices of 0.9 or greater.

Blood tests revealed a median haemoglobin of 12 (range 8–17) g/dl, a median white cell count of 7.6 (range 4–20) × 10^9/litre, and a median platelet count of 289 (range 76–758) × 10^9/litre. Abnormal findings on liver function testing were hypoalbuminaemia (median 20, range 16–33 g/l) and hyperglobulinaemia (median 55, range 34–83 g/l). Assessment of coagulation including disseminated intravascular coagulation screen and assay of protein-C, protein-S and antithrombin III levels was performed in 11 patients and returned positive results in two. Both patients demonstrated hyperfibrinogenaemia, with one having elevated fibrin degradation products and a positive protamine sulphate test in addition. Lymphocyte flow-cytometry was performed on seven patients, with CD4 counts being depressed below normal in all (average 254, range 157–401). The average CD4/CD8 count ratio was 0.2 (range 0.1–0.3) further indicating advanced immunosuppression.

Angiography was performed in 16 cases, and confirmed the clinical distribution of occlusive disease. A striking feature was the focal involvement of affected vessels, with pristine proximal and distal, and contralateral vessels (Fig. 1). Extensive collateral development was noted, in keeping with the chronic presentation of most patients. Apart from a patient who demonstrated an isolated common iliac stenosis, no other lesions amenable to balloon angioplasty were identified, as other patients had long-segment arterial occlusions. In an attempt to identify a cardiac source of arterial emboli, trans-thoracic echocardiography (TTE) was performed on eight patients, and was negative in all cases. The superiority of transoesophageal echocardiography over TTE in the identification of cardiac sources of emboli is well recognised, however, due to limited resources, TOE is performed only in highly selected cases, and was not offered to the patients in this cohort.

Results

Eighteen patients were treated surgically, and two were offered non-operative treatment. A 43-year-old patient who presented with focal dry digital necrosis and tibio-peroneal occlusion was treated non-operatively in view of his having full-blown AIDS, with associated renal and congestive cardiac failure. A second patient who presented with ischaemic rest pain of the arm due to brachial artery occlusion had symptomatic relief from simple analgesics and pentoxifylline.

Procedures performed are listed in Table 2. Extensive tissue necrosis due to late presentation was the indication for major amputation in eight patients. A constant finding at arterial exposure was macroscopically normal arterial walls with no evidence of atherosclerotic plaque. Vessels were noted to be occluded by organised thrombus in seven cases, of which four were successfully cleared by balloon-cather embolectomy. Bypass procedures utilised reversed saphenous vein grafts in two cases (popliteal-posterior tibial, popliteal-peroneal bypasses) and polytetrafluoroethylene (Gore-Tex™, Flagstaff, Ariz.,
Occlusive Arterial Disease in HIV Infected Patients

Fig. 1. Intra-arterial digital subtraction angiogram illustrating sparing of the proximal arterial tree in a 17-year-old male who presented with dry gangrene of the left foot and treated by femoral thrombo-embolectomy and below-knee amputation. No cardiac source of emboli was found on TTE. (a) Flush aortogram showing normal aorta, iliac and visceral vessels. (b) Left superficial femoral artery occluded at origin (arrow). No reconstitution of distal vessels noted on delayed angiography.

Table 2. Surgical procedures performed.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolectomy†</td>
<td>4</td>
</tr>
<tr>
<td>Bypass</td>
<td>3</td>
</tr>
<tr>
<td>Percutaneous transluminal angioplasty</td>
<td>1</td>
</tr>
<tr>
<td>Major amputation</td>
<td>8</td>
</tr>
<tr>
<td>Above-knee</td>
<td>4</td>
</tr>
<tr>
<td>Below-knee</td>
<td>2</td>
</tr>
<tr>
<td>Above-elbow</td>
<td>2</td>
</tr>
<tr>
<td>Minor amputation#</td>
<td>5</td>
</tr>
<tr>
<td>Lumbar sympathectomy†</td>
<td>1</td>
</tr>
</tbody>
</table>

* Bilateral in two.
# Combined with revascularisation in three.
† Combined with below-knee amputation.

Five patients had arterial biopsies taken from arteriotomy sites (two) or from amputated limbs (three), and these were subjected to histological examination. Normal arterial wall architecture was noted the two arteriotomy margin biopsies, with similar pathological features present all sections of specimens from the occluded vessels of amputated limbs. The vessel lumen was occluded by bland organising thrombus. Special stains for micro-organisms were negative in every case. The intima did not have any evidence of atherosclerosis, whilst the media and adventitia contained variable numbers of chronic inflammatory cells. Significantly, there was focal loss of medial muscle and elastic fibres, but no caseative necrosis or features of Takayasu’s arteritis. The major changes were present in the adventitia and peri-adventitial area. A prominent proliferation of slit-like vascular channels, many of which dissected between adventitial collagen, and a leucocytoclastic vasculitis of the vasa vasora were constant features (Fig. 2).

U.S.A.) in the last (external iliac-common femoral bypass). Aspirin (150 mg/day) was empirically prescribed for all patients, and anti-tuberculous therapy for those with active TB.
While the exact mechanism of occlusive disease remains unclear, several possibilities merit consideration. With the high community HIV seroprevalence levels in the province served by the authors’ unit, a coincidental association may have arisen as a result of atypical atherosclerotic degeneration in HIV-positive individuals. However, the focal nature of disease, angiographic findings, and macroscopic and histological appearances militate against this argument. In addition, the young age of patients in this cohort provides circumstantial evidence against a coincidental association.

Short-term outcome was favourable, with no perioperative deaths or morbidity. Follow-up was poor, with all but five patients defaulting planned review. Mean follow-up duration was 5 months. The two patients treated by popliteal-crural bypass were seen at 3 and 6 months after surgery, and found to have patent functioning grafts. Only two patients initially subjected to major amputation returned for review, one of whom had experienced disease progression leading to superficial femoral artery occlusion of the contralateral limb. As symptoms were limited to claudication, this was treated conservatively. The second amputee was seen 2 months after surgery, having a well-healed stump and being ambulant with a prosthetic limb. The last patient was seen 12 months following bilateral groin embolectomies, and was well, with palpable pedal pulses.

Discussion

As the HIV epidemic continues its rampant advance, numerous associated pathological conditions are being recognized. In the main, these are neoplastic or opportunistic infective conditions secondary to systemic immunosuppression. Despite the wide variation of HIV-vasculitis, most pathology arises from involvement of one or a small number of visceral vessels. Organs frequently affected include skin, peripheral nerve and skeletal muscle, and the central nervous system. Large-vessel involvement has been reported, with HIV-related aneurysms and arteriovenous fistula having been described. Based on the initial experience reported in this paper, it would appear that a specific form of large-vessel occlusive arterial disease might also result from HIV infection.

While coagulation abnormalities were identified in only two of the patients reported in this series, haematological testing was neither extensive enough nor uniformly applied to exclude their presence in the remainder. Aberrations of coagulation in association with HIV infection have been well documented, with thrombocytopenia, acquired protein-S deficiency and elevated antiphospholipid antibody titres being frequently described, and an increased risk of thrombotic events recognised. The frequency and significance of hyper-coagulable states in HIV-related arterial disease needs to be clarified by further investigation.

The distinct histological findings in some patients raise the possibility of an underlying vasculitic aetiology. Specific vasculitic features have been described in association with HIV-related aneurysms and arteriovenous fistula. The microscopic similarity between HIV-related aneurysmal and occlusive disease suggests a common initial pathological response, with a variable clinical expression. It is felt that leucocytoclastic vasculitis of the vasa vasora and peri-adventitial vessels is the common pathogenetic event. Leucocytoclastic vasculitis is a well-described phenomenon in the HIV setting, and the resultant vessel wall damage may lead to either aneurysmal dilatation or occlusive disease. This is akin to Takayasu’s arteritis, where vessels affected by stenosing or aneurysmal degeneration share common histological features. The normal histological findings from the remaining arterial biopsies are thought to reflect the non-representative nature of these specimens. Where specimens were obtained at the time of arterial reconstruction, these were taken from the margins of arteriotomy sites of patent vessels. Thus, the opportunity to perform representative biopsy of occluded segments of affected vessels was not always available.

The presence of histological features of a vasculitic nature common to patients presenting with both occlusive and aneurysmal arterial disease suggests a
similarity with Behçet’s disease. This rare condition has been associated with HIV infection in two case reports describing HIV seropositive patients who demonstrated the typical mucocutaneous, ocular, and articlular manifestations of Behçet’s vasculitis. \textsuperscript{18,19} In neither of these cases was any large vessel arterial pathology demonstrated. Whilst there were obvious similarities between the arterial manifestation of Behçet’s disease and those described in the current cohort of HIV-infected patients, the latter group failed to meet the diagnostic criteria proposed by the International Study Group for Behçet’s Disease. \textsuperscript{20}

While little evidence is available as to the natural history of HIV-related occlusive arterial disease, it would appear appropriate for basic vascular surgical principles to determine management of affected patients. In the authors’ opinion, patients with full-blown pre-terminal AIDS should be offered the least intervention required to achieve symptom relief. In our experience, patients frequently present with advanced tissue necrosis that precludes limb salvage and necessitates major amputation. Although the universally low CD4 counts indicate that arterial occlusive disease is a late manifestation of HIV infection, it is proposed that attempts be made to achieve revascularisation of critically ischaemic limbs where tissue necrosis is absent or minimal, and significant co-morbidity is absent.

As this report describes the results of a retrospective analysis of patients treated outside a standardised protocol, several deficiencies in data regarding investigations and follow-up are present. While these shortcomings are acknowledged, attention needs to be drawn to what is considered to be an emerging problem, likely to assume greater significance as the HIV epidemic progresses. It is intended that this experience provide the basis for a prospective study of consecutive patients subjected to HIV screening and a comparison of HIV-infected patients with matched seronegative controls. An in-depth analysis of coagulation function, routine histological examination of representative arterial biopsies and a detailed description of natural history are required to determine whether HIV-related arterial occlusion constitutes a distinct entity, or is simply an epiphenomenon reflecting a chance association of arterial occlusive disease with HIV seropositivity in an area of high HIV seroprevalence.

References


Accepted 15 August 2000