

# Pathogenesis and pathology of HIV-related large-vessel disease

J. V. ROBBS, CH.M., F.C.S. (S.A.), F.R.C.S. (EDIN.), F.R.C.P.S. (GLASG.)

Professor of Surgery, University of KwaZulu-Natal

The first reported series of large-vessel aneurysms in patients with HIV infection emanated from Zimbabwe.<sup>1,2</sup> A more comprehensive study of the pathology was reported by Nair *et al.* in 1999.<sup>3</sup> More recently there has been some focus on occlusive large-vessel disease, with separate reports by Nair *et al.*<sup>4</sup> and Mulaudzi *et al.*<sup>5</sup> in 2000 and 2005, respectively.

## Aneurysms

These are found in atypical sites with a predilection for the carotid and superficial femoral arteries. The aneurysms are usually multiple and almost invariably saccular in nature. For obscure reasons males predominate, and most patients are young, usually in the 4th decade and predominantly black Africans. The HI virus, however, has no selectivity.

Nair *et al.*<sup>3</sup> considered that HIV arteritis exhibited a unique pathology and reported the histological changes in detail. They established that the inflammation was centred on the vasa vasora of the major vessels. The inflammatory process consisted of neutrophils surrounded by a cuff of plasma cells and lymphocytes. These were accompanied by occasional macrophages containing haemosiderin. There is also marked endothelial swelling with surface fibrin deposits leading to occlusion of the vasa vasora. They noted that within the wall of the large vessels there were active lesions with acute inflammatory infiltrate, and that in the same specimen one would find inactive areas with extensive fibrosis and haemosiderin deposits. This suggested a temporal sequence of events. The inflammation was concentrated in the adventitia, but where there was acute activity trans-mural necrosis occurred. Special stains for bacteria such as acid-fast bacilli and others were negative. HIV protein was found to be present in the lymphocytes within the lesions.

The pathogenesis remains an enigma. The histological features seem to represent a distinct entity compared with other arteritic processes such as Takayusu's disease or tuberculosis.

The first question is whether this is a direct action of the HI virus or of an immune complex mechanism. As stated, HIV protein was present in lymphocytes within the lesions, but this pertains throughout the body in HIV-infected patients. Lang *et al.* performed immunohistochemical studies testing for anti-GP41 and found these to be negative.<sup>6</sup> More extensive investigation is required to look for other viruses that may be superimposed upon this, but current evidence cannot support a specific viral causation.

The other possibility is that the damage is mediated by another infective agent, i.e. an opportunistic bacterial infection. Although bacteria such as mycobacteria, *Salmonella*

and *Haemophilus* have been sporadically isolated by various workers, this is not a consistent finding. Nair *et al.*'s series of 92 aneurysms in 28 patients yielded positive cultures in only 3, which were of mixed organisms including *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus faecalis* and *Salmonella*, all of which were grown from aneurysm clot.<sup>7</sup>

A consistent feature in all patients was a low albumin level (median 22 g/dl) with an increased globulin level (mean 58 g/dl). The CD4 counts were below normal in 94% of patients with a median of 370 cells/ $\mu$ l and a range of 52 - 733. The CD8 count was a median of 780 with a range of 483 - 2 056. The CD4/CD8 ratio was uniformly reversed and ranged from 0.1 to 0.9. This indicates advanced immunosuppression.

## Occlusive disease

Occlusive disease is less well studied, and preliminary reports were published by Nair *et al.*<sup>4</sup> and Mulaudzi *et al.*<sup>5</sup> independently. The pathology is characterised by pristine proximal as well as contralateral vessels with patchy segmental occlusion, which may affect the upper or the lower limbs. There is also poor distal runoff due to thrombosis into the small vessels.

Histological examination of thrombosed vessels in the amputation stumps showed bland organising thrombus, and on special staining for micro-organisms none were found. There was no atheroma in the intima and media and in the adventitia chronic inflammatory cells were noted. The major changes were concentrated in the adventitia. The picture was identical to that found in aneurysms, with a leucocytoclastic vasculitis involving the vasa vasora. It is postulated that this is a different expression of the pathological process, analogous to what one finds, for example, in Takayusu's disease.

The obvious conclusion must be that there are aberrations in the coagulation process. These are well documented in HIV, with thrombocytopenia or thrombocytosis, protein S deficiency, increased phospholipid antibody titres and a definite increased risk of thrombotic events.

Nair *et al.*<sup>4</sup> noted an increased fibrinogen level in 2 of 10 patients investigated.

Mulaudzi *et al.*<sup>5</sup> comprehensively investigated 10 patients for thrombophilia with protein C and protein S levels, platelet counts, fibrinogen levels, antiphospholipid antibody levels and antithrombin III levels. They found no abnormalities at all in this cohort.

These patients also were shown to have low CD4 counts, indicating severe immunocompromise universally.

In relation to large-vessel vasculopathy in HIV-infected patients, although the pathology has been well described,

it would appear that occlusive disease and aneurysmal disease share a similar basic pathological process. Further investigation is required in order to elucidate the pathogenesis.

## REFERENCES

1. Sinzobahamya N, Kalangu K, Hamel-Kalinowski W. Arterial aneurysms associated with human immunodeficiency virus (HIV) infection. *Acta Chir Belg* 1989; 89: 185-188.
2. Marks C, Kuskov S. Patterns of arterial aneurysms in acquired immunodeficiency disease. *World J Surg* 1995; 19: 127-132.
3. Nair R, Abdool-Carrim ATO, Chetty R, Robbs JV. Arterial aneurysms in patients infected with human immunodeficiency virus: A distinct clinicopathological entity? *J Vasc Surg* 1999; 29: 600-607.
4. Nair R, Robbs JV, Chetty R, Naidoo NG, Woolgar J. Occlusive arterial disease in HIV-infected patients: a preliminary report. *Eur J Vasc Endovasc Surg* 2000; 20: 353-357.
5. Mulaudzi TV, Robbs JV, Pillay W, et al. Thrombectomy in HIV-related peripheral arterial thrombosis: A preliminary report. *Eur J Vasc Endovasc Surg* 2005; 30: 102-106.
6. Lang C, Jacobi G, Krenz W, et al. Rapid development of giant aneurysm at the base of the brain in an 8 year old boy with HIV infection. *Acta Histochem Suppl* 1992; 42: 83-90.
7. Nair R, Robbs JV, Naidoo NG, Woolgar J. Clinical profile of HIV-related aneurysms. *Eur J Vasc Endovasc Surg* 2000; 20: 235-240.