HIV and the necropsy

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Introduction

In mid-1981 reports from the USA documented clusters of homosexual men with *Pneumocystis carinii* pneumonia and disseminated Kaposi's sarcoma, until then both rare conditions. These and other early accounts of the disease complex that was subsequently labelled AIDS were supported by diagnoses from necropsy, which also emphasised the presence of multiple opportunistic infections in these patients.¹⁻⁴ Within two years the first of an everlengthening list of necropsy series of patients with AIDS (in this case 10 patients) emphasised that there was underdiagnosis during life of many opportunistic infections and neoplasms. Ten years on, the peroration that pathologists "are in a unique position to facilitate research efforts by distributing blood, biopsy and necropsy tissues of AIDS patients . . . by complete autopsy examinations pathologists will not only assist with patient care but will continue to increase understanding of this new syndrome" remains true.⁵

At the same time, regular necropsies conducted in a hospital in Miami, USA, showed that among immigrants from Haiti who died between 1979-82, a high proportion had opportunistic infections⁶: eight of 23 patients had AIDS defining conditions by existing criteria (most frequently cerebral toxoplasmosis), though in retrospect, with broadening of the surveillance criteria for AIDS, the true figure was 13 of 23. Not only were these proportions significantly higher compared with necropsy figures for African-Americans, but none of the Haitian patients had the then accepted risk factors for AIDS—haemophilia, homosexual behaviour, intravenous drug misuse. The fact that women were affected and that the incidence of tuberculosis among these patients was high, these observations from the mortuary presaged three of the major features of AIDS in developing countries: heterosexual spread; women affected as well as men; and the importance of tuberculosis as an opportunistic infection. A year later, the main viral agent of AIDS was discovered. Human immunodeficiency virus type 1 (HIV-1) is the major virus, prevalent in virtually all countries of the world; HIV-2, identified subsequently, is restricted mainly to West Africa.

The present value of the necropsy in HIV disease

There are six major reasons for performing necropsies on HIV positive patients, in addition to any forensic requirement:

CLINICOPATHOLOGICAL FOLLOW UP

Clinicopathological follow up is the traditional role of the necropsy. As many reports have iterated, necropsies reveal major discrepancies with premortem diagnoses which are of potential therapeutic relevance.⁷ The situation is no different with AIDS, in which cytomegalovirus infection, tuberculosis, systemic Kaposi's sarcoma and *Mycobacterium avium* complex infection may be missed before death on a substantial scale.⁸ The prevalence of cerebral lesions such as primary cerebral lymphoma, progressive multifocal leucoencephalopathy, and HIV encephalitis may be doubled by necropsy compared with those suggested by premortem diagnoses.⁹ There are, of course, certain lesions which necropsy does not detect well, particularly intestinal infections with *Cryptosporidium* and the microsporidian *Enterocytozoon bieneusi* (because of autolysis) and bacteraemia.

DESCRIPTIVE CLINICAL PATHOLOGY AND EPIDEMIOLOGY OF HIV DISEASE

The pathology of AIDS is now well described in industrialised countries. In the Third World—where the major current and, especially, future burdens of HIV infection will fall—the patterns of disease are not well defined; and they are not predictable from the First World's experience. To supplement clinical studies of HIV disease (logistically difficult in the tropics), systematic post mortem examination of seropositive adults and children dying in hospitals provides representative data on the main infections and tumours that characterise AIDS in that community. This has been done in Africa,¹⁰ and could provide a short-cut to the understanding of the clinical pathology of HIV disease in regions such as India and South-East Asia, where HIV is now spreading rapidly. In Thailand and Hong Kong, for example, disseminated *Penicillium marneffei* infection will probably be a major opportunist disease in HIV positive people,^{11 12} as necropsies will readily show.

In industrialised countries the HIV necropsy can still reveal hitherto unknown infections. A recent example is a new microsporidian parasite which, unlike intestinal *Enterocytozoon* infection, spreads to the kidney, respiratory tract, and liver parenchyma.^{13 14}

In addition to cross-sectional studies, long term comparisons of findings at necropsy of HIV positive patients can indicate very important changes in the pattern of HIV disease. These may reflect the use of specific prophylaxis—for example, reducing the over-

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Accepted for publication
29 July 1993

all prevalence of *P carinii* pneumonia at necropsy while increasing the proportion who have extra-pulmonary pneumocystosis.¹⁵ On the basis of point prevalences over several years, it has been suggested that use of the antiretroviral agent azidothymidine (AZT) is associated with a reduction in the proportion of patients with AIDS whose brains had multinucleate giant cell encephalitis (a marker of productive HIV infection in the brain).¹⁶ As HIV positive people in industrialised countries live longer due to better medical care while severely immunocompromised, it is predicted that more of them will develop non-Hodgkin's lymphoma¹⁷; again, the necropsy will be the most sensitive means of detecting this. Finally, tuberculosis is globally the most important opportunistic infection associated with AIDS.¹⁸ At present it is a relative rarity at necropsy in patients with AIDS in the United Kingdom. But given the difficulties in the premortem diagnosis of disseminated tuberculosis and the likelihood of mortality if untreated, a high necropsy rate of HIV positive patients could provide an early indication of increasing coinfection of HIV and *M tuberculosis*, which would have important public health implications.

Finally, necropsies on HIV positive people who do not have clinical AIDS and who have died from unnatural causes (such as intravenous drug misuse, and trauma) provide useful data on the early stages and pathogenesis of HIV disease, particularly in the central nervous system.¹⁹

ENDPOINTS IN CLINICAL TRIALS

Studies of antiretroviral agents and drugs directed against opportunistic infections and tumours in cohorts of HIV positive patients require the validation of endpoints. Once HIV disease has progressed to AIDS it is probably always fatal; the necropsy will indicate whether the patient died with an AIDS-defining illness or from an incidental event.²⁰

DRUG EFFICACY AND TOXICITY

There is no antiretroviral drug that has been proved to have sustained efficacy, so the management of patients with HIV disease depends to a large extent on optimising the prophylactic and therapeutic range of treatment against infections and tumours. Clinical response provides data on drug efficacy, but the necropsy will give information on the ultimate response of many specific lesions. The activity of *M avium* complex infection, the resolution or not of lymphoma, and the extent of *P carinii* pneumonia are instances of this. In our hospital, for example, we encounter patients with known pulmonary Kaposi's sarcoma who worsen and die because of undiagnosed *P carinii* pneumonia. Similarly, patients have presented with confirmed or suspected *P carinii* pneumonia and died rapidly, despite maximal appropriate chemotherapy. Necropsy showed that they died with severe *P carinii* pneumonia: all this reminds us that although the management of

P carinii pneumonia has been very thoroughly studied, not all patients are successfully treated for it. Drug reactions in HIV positive patients are of increasing concern. Many are cutaneous and readily evaluated in life²¹ but necropsy material is needed for the study of damage of deep organs such as the pancreas: antimicrobial and antiretroviral agents are associated with pancreatitis.²²

SPECIFIC ORGAN BANKS

Davies *et al*²³ document the benefits of accumulating tissue banks of brain specimens. Studies on the epidemiology and pathology of HIV related brain disease are done optimally in such special centres using uniform methodologies. These tissue banks are also a resource for basic scientists wishing to study the mechanisms of damage in the central nervous system associated with HIV. Similar collections of spinal cords and eyes from HIV positive patients will greatly aid the evaluation of myelopathies and retinopathies in infected patients.²⁴

EDUCATION

The wealth of macroscopic pathology found at necropsy in most patients with AIDS provides excellent material for teaching medical students and postgraduates. With histology, these necropsies make valuable clinicopathological conferences, emphasising the pathologist's role in the management of HIV disease. The proceedings of several such conferences at our hospital have been published which highlight specific diagnostic and therapeutic problems.²⁵⁻²⁹

The quantity of HIV related diagnostic material arriving at histopathology laboratories varies regionally, so that pathologists have a wide range of experience of the lesions associated with HIV. The study of necropsy histology helps greatly in learning—for example, the variations in the patterns of Kaposi's sarcoma and the various types of intracerebral lesions that may be biopsied.

Risks of performing necropsies on HIV positive cadavers

Among pathologists and anatomical pathology technicians, globally, there is a good deal of concern over the likelihood of becoming infected with HIV by performing necropsies on HIV positive cadavers. It is important to be aware of the real risks. Infection might arise: (1) from contact of infected blood or body fluids on skin, eyes, mouth or nose; (2) from penetrating percutaneous injuries from infected bone spicules, scalpel blades, syringe needles, and sewing-up needles; or (3) inhaled aerosols of infected fluids or sawn bone dust.

The quantities of HIV present in blood peak at the time of seroconversion, are then low for years, and rise again during the final illness of AIDS.³⁰ HIV-1 virus is recoverable from cadaveric blood and tissue samples. The largest study to date found virus in 21 of 41 (51%) serum specimens or blood

mononuclear cell fractions from cadavers.³¹ The longest post mortem time tested was 37.5 hours, but virus was found only up to 21.5 hours. In other smaller investigations, HIV-1 virus has been recovered 18 hours to 11 days after death.^{32–34} Skull bone contained HIV six days after death, but no samples of sawn bone dust did. HIV was recovered from spleen specimens stored for up to 14 days.³⁴ Refrigeration of cadavers did not seem to diminish the recovery of virus. HIV-2 has been cultured from cadaveric blood 16.5 days after death.³⁵

Necropsies are usually performed within a few days of death, so for practical purposes, all HIV positive cadavers must be assumed to contain viable infectious HIV. None the less many thousands of necropsies have been performed on HIV positive adults, children, and on cases of perinatal death. There are no reports of a pathologist acquiring HIV infection from a necropsy.³⁶ Three "morgue technicians/embalmers" in the USA are stated to have possible occupation-related HIV-1 infection, but no further details are available.³⁷

Global data up to December 1992, on the risk of occupational transmission of HIV, indicate that 52 health care workers have HIV seroconversion documented after a specific exposure. Most of these occurred after needle-stick injuries (needles may contain 1 µl of blood), and the estimated HIV transmission rate after a single percutaneous exposure is 0.27% (95% confidence interval 0.12–0.42%). For a single mucocutaneous exposure, the HIV transmission rate is estimated to be 0.04%.³⁸ Transmission by aerosol inhalation has not been documented.

It is arguable whether a scalpel injury incurred whilst dissecting a cadaver carries a greater or lesser risk of HIV transmission than a needle-stick injury.³⁹ The incidence of cuts during necropsy does depend on the experience of the operator. One study found that pathology trainees sustained a cut or needle-stick injury once out of every 11 necropsies; for the more experienced consultant pathologists, the rate was one out of 53 necropsies.⁴⁰ Although there is evidence that the rate of cuts to the hands among surgeons is not affected by prior knowledge of the patient's HIV infection status,⁴¹ there are no data on this point regarding pathologists. Anecdotal and personal observations, however, indicate that pathologists performing necropsies on HIV positive cadavers, in the United Kingdom at least, rarely if ever cut themselves as they take great care not to. It is most unlikely that statistically useful data on the occupational risk of HIV infection for pathologists will accumulate. We should therefore accept the theoretical risk and proceed using sensible and appropriate practices.

Other risks of infections

The emphasis hitherto has been on HIV infection, but HIV infected cadavers often have multiple opportunistic and other infec-

tions with the attendant potential for transmission to staff in the mortuary. *Cryptococcus neoformans*, *P. carinii*, *Candida*, *M. avium* and other non-tuberculous mycobacteria may be inhaled during the necropsy. But as they are ubiquitous, they will not cause disease unless the pathologist or technician is already immunosuppressed (and therefore should not be working in a mortuary). Hepatitis B virus (HBV) infection is common in HIV positive patients, and far more transmissible than HIV, but with vaccination against HBV, infection is minimised. More worrying is the possibility of infection with hepatitis C virus, particularly from the cadavers of intravenous drug misusers. We need studies on the prevalences of this infection among HIV positive and HIV negative cadavers, and on the risk of acquisition by prosectors.

Tuberculosis is a special concern. As yet, the proportion of HIV positive patients (and, implicitly, cadavers) in the United Kingdom with *M. tuberculosis* infection is low. However, it is likely that the prevalence of tuberculosis in HIV positive cadavers is greater than that in HIV negative cadavers. This is certainly true in sub-Saharan Africa where about 50% of cadavers with AIDS may have active tuberculosis, and the lesions contain vast numbers of bacilli with the concomitant potential of inhalation. Because of international travel, several other virulent infections that are prevalent outside the United Kingdom may be encountered in HIV positive cadavers, such as *Histoplasma capsulatum* and *Coccidioides immitis*.

Mortuary practices

The principles of safe practice for working with HIV positive cadavers are no different from those that should be used for all cases. They are appropriate training and experience, good work practices, the use of safe implements, and a safe working environment.³⁹

In addition to standard guidelines on necropsy and mortuary practice,^{42,43} there are specific recommendations for HIV necropsies.^{44–46} Although in principle a policy of adopting such special precautions may be advocated for all necropsy work, in the United Kingdom, where the prevalence of HIV infection is currently low,⁴⁷ this is unrealistic. The Health Services Advisory Committee guidelines adopt a two-tier approach on safety measures with regard to HIV and other high risk infections.⁴² A similar approach is advocated by the Clinical Pathology Accreditation Scheme. This stratification may seem to be illogical and unsatisfactory, but with the current very low prevalence of previously unknown HIV infection in cadavers for necropsy, there is no consensus among pathologists for advocating special precautions for all necropsies. In the United Kingdom at present, the only group of cadavers with a substantial likelihood of unknown HIV infection is intravenous drug misusers coming to medicolegal necropsy; 15–38% of such cadavers are HIV positive

(Dr I West, personal communication),⁴⁶⁻⁴⁸ but the numbers studied have been small. In a study in London and Cardiff of cadavers for medicolegal necropsy, which excluded the "high risk" categories of homosexual men, prisoners, and intravenous drug misusers, only one in 264 was found to be HIV positive (Drs P Vanezis and S Leadbeater, personal communication).

The recommendations for performing HIV necropsies include: wearing a face mask and glasses to protect mucosal surfaces; wearing a water-impermeable gown or body suit to cover the arms, and a plastic over-apron; and wearing two pairs of gloves (latex inner gloves and outer thicker household rubber gloves); some pathologists also opt for cut-resistant glove liners. The instruments used should be kept to a minimum, and blunt-ended implements used in preference to sharp-pointed—for example, round-ended scissors, and non-pointed body-opening knife blades and organ-slicing knives. It is ideal to have a separate "infectious disease" suite available within a mortuary, but it is not essential.

Final note

In November 1992, 30 pathologists from Great Britain and Ireland, representing most of those interested in necropsy work on HIV disease, met at the Royal College of Pathologists. They included forensic pathologists and neuropathologists in addition to general histopathologists. The issues discussed included fears among pathologists and technical staff in general; screening before necropsy for HIV positivity; the problems in obtaining consents for necropsy (in many units, the major limiting factor for HIV necropsies); the cost of HIV necropsies, which are more expensive than non-HIV cases as they occupy more of the pathologists' time and generate more tissue blocks; and pathologists' actual practices for performing HIV necropsies. The latter showed a wide range of safety measures adopted, but as in other fields of histopathology uniformity is not a notable behavioral characteristic. But all agreed that HIV necropsy work was safe when carried out sensibly, and that special precautions over and above those required for non-infectious cases should be taken, as outlined earlier.

The aim of this editorial is emphatically to encourage pathologists to perform necropsies on patients with AIDS. In addition to the arguments about clinico-epidemiological usefulness, it is the experience of those who have done many HIV necropsies that they provide very interesting cases. It is the pathologist's privilege to take aesthetic and intellectual pleasure in the material he or she studies. The multiplicity of hitherto unusual gross and microscopic diseases that is encountered in such cadavers usually provides more satisfaction than the usual "routine" necropsy.

As Davies *et al* note, in only 28% of United Kingdom health districts were pathologists knowingly performing necropsies on HIV

positive patients in 1990/91.²³ The major reason cited for not doing so was lack of requests. However, AIDS is not going to go away in industrialised countries like the United Kingdom,⁴⁹ and the amount of HIV necropsy work will increase over the decades to come.

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