# Original Papers

# The emerging AIDS epidemic in Ireland – clinicopathological findings in 23 early cases

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## Abstract

**A longitudinal study with follow up to the end of 1989 was carried out on 23 patients with AIDS who had attended St. James's Hospital, Dublin, by the end of 1987. Until then only 33 cases of AIDS had been reported in Ireland. The patients, all of whom had antibodies to human immunodeficiency virus (HIV). were predominantly male, young (mean age 31.3 years) and belonged about equally to three major risk groups: homosexuals, intravenous drug abusers (IVDA) and haemophiliacs. AIDS was diagnosed because of oesophageal candidiasis (8 cases), Kaposi's sarcoma (4), mycobacterial infection (4), pneumocystis carinii pneumonia (3), toxoplasmosis (2) or encephalopathy (2). Malignant lymphoma and a variety of infections occurred in the course of illness, and neurological involvement developed in 11 patients (48%). Mortality following diagnosis of AIDS was 39% at one year and 64% after two years. Autopsy in 10 of the 16 deaths contributed much to defining the extent and nature of the disease. The demographic pattern, risk group status, survival and range of complications were broadly similar to the pattern of AIDS as seen elsewhere in developed countries. However, compared to the profile of disease reported from the United States, oesophageal candidiasis (52%) and *Mycobacterium tuberculosis* (22%) were more prominent, pneumocystis carinii pneumonia (39%), Kaposi's sarcoma (22%) and *Mycobacterium avium intraceUulare* (13%) were less frequent and cryptococcal infection was not identified. These regional variations in the frequency of the various complications and particularly the prominence of tuberculosis, probably reflect the interaction of the immunocompromised patient with the local environment and may have important diagnostic and therapeutic implications.**

## Introduction

The first reported case of the acquired immunodeficiency syndrome (AIDS) in Ireland[1] was diagnosed in September 1980 by the finding of Kaposi's sarcoma in an Irish male homosexual. This was very early in the AIDS pandemic; only 20 cases of AIDS retrospectively recognised as occurring before 1981 have been reported from Europe (mainly from France)[2] and the first published report of the acquired immunodeficiency syndrome[3] did not appear until the following year. In Ireland the number of cases increased slowly, only three cases had occurred by the end of 1983 and in the following four years three, three, five and 19 cases respectively were reported giving a cumulative total of 33 cases in the Republic by the end of 1987.[4] A large proportion of these have attended St. James's Hospital, Dublin. By December 1987 we had seen a sufficiently large number of patients to begin to define the pattern of the disease as it was emerging in Ireland and to determine if any local factors influenced the expression of the syndrome.

## Materials and Methods

A pattern of referral has developed so that the majority of adult AIDS cases in the Dublin area have been seen at St. James's Hospital. We reviewed the clinical records and pathology material of all cases of AIDS who had attended the hospital by December 1987 and obtained follow up information to the end of December 1989. All cases were HIV positive by both enzyme linked immuneassay and western blot techniques and all fulfilled the definitive criteria for AIDS.[5]

## Results

There were 23 cases of AIDS seen between 1985-87 - 22 men and one woman. The mean age at diagnosis was 31.3 years (range 14 to 59). The risk groups were haemophiliacs (8) intravenous drug abusers (9) and homosexuals (8), (One haemophiliac and one homosexual were also IVDA), Three patients presented in 1985, four in 1986 and 16 in 1987. AIDS was diagnosed in the presence of positive HIV serology, by oesophageal candidiasis (8 cases), Koposi's sarcoma (4), mycobacterial infection (4), pneumocystis carinii infection (3), toxoplasmosis (2) and encepholopathy (2). At one year following diagnosis nine (39%) had died and 14 of 22 (64%) had died at two years. Two patients emigrated and were lost to follow up at 22 and 29 months respectively. The longest survival was 42 months. Aspects of two cases have been published elsewhere.[6,7]

## Neoplastic complications

*Kaposi's Sarcoma* occurred in five patients and was confirmed histologically in each. In four it was the presenting manifestation of AIDS and involved the skin (2), the palate or the gastroduodenal mucosa where it was the source of severe upper gastrointestinal haemorrhage. Cutaneous and extensive pulmonary Kaposi's sarcoma developed during the course of AIDS in the fifth patient.

*Malignant Lymphoma* occurred in three patients all of whom were homosexual and had Kaposi's sarcoma. In each case it was a large cell immunoblastic lymphoma of B-cell type and involved the brain in one instance, and in a second the ileocaecal region with spread to regional nodes, liver and

bone marrow. There was generalised disease involving the skin, bone marrow, lungs, pleura and pericardium in the third case.

## Infectious complications

Candida involved the oropharynx in most patients. Oesophageal involvement occurred in 12 patients and was the presenting manifestation of AIDS in eight of these.

*Pneumocystis Carinii Pneumonia,* confirmed mor-phologically, occurred in nine patients. It was the presenting manifestation of AIDS in three, one of whom had multiple subsequent recurrences. Five other patients had episodes of this infection during the course of their illness – it was the cause of death in one and was a significant contributing factor to death in another. In the case of one, it was only identified at autopsy.

*Toxoplasmosis* was diagnosed and histologically confirmed in two patients, it produced a fatal severe generalised systemic and neurological infection in one, and was confined to the nervous system in the other.

*Cytomegalovirus (CMV)* occurred in five cases. In one it produced bilateral blindness due to retinal involvement (with pulmonary, renal and adrenal involvement terminally). Episodes of CMV enteritis (1) or retinitis (2) responded to foscarnet or gancyclovir therapy while adrenal, colon and pulmonary involvement was identified at autopsy in a patient who had multiple additional neoplastic and infectious complications.

*Mycobacterial Infections* were identified in nine patients and confirmed by culture in all. Generalised *Mycobacterium tuberculosis* occurred as a presenting manifestation of AIDS in three patients. Each case showed pulmonary and urinary disease with additional involvement of meninges, lymph nodes and gaslrointestinal tract and all three responded to appropriate antimycobacterial chemotherapy; in one, active meningeal tuberculosis was discovered at autopsy 38 months later. Pulmonary *M tuberculosis* infection was diagnosed during the course of AIDS in another patient and generalised *M tuberculosis* was found at autopsy in one patient who also had extensive malignant lymphoma and Kaposi's sarcoma. Pulmonary *Mycobacterium kansasii* was the presenting feature in a patient who was suspected of having generalised disease because of hepatosplenomegaly and severe anaemia, *Mycobacterium avium intracellulare* involving spleen, liver, lymph nodes and lung was identified at autopsy in one case and in two others, *M avium intracellulare* was grown from a pericardial effusion and from urine respectively.

*Additional Infections:* Oral or genital herpes simplex occurred in four patients, and in three viral papillomas or anal condylomata accuminata were seen. Forms of hepatitis occurred in four patients but probably predated AIDS. Aspergillus involving lungs or brain was found at autopsy in two patients. Other individual infections are listed in table 1.

## Neurological Involvement

Neurological involvement was the dominant clinical manifestation of disease in six patients (26%) who had various combinations of impaired memory or concentration, confusion, dementia, ataxia, paraplegia, quadriplegia and epilepsy. Five additional patients showed lesser degrees of neurological involvement and one patient, who also had chronic schizophrenia, developed a fatal malignant neuroleptic syndrome. Postmortem examination revealed cerebral toxoplasmosis in two and cerebral HIV infection in seven patients (four of whom had additional cerebral pathology; vacuolar myelopathy in one, aspergillus infection and vacuolar myelopathy in the second, malignant lymphoma in the third and tuberculous meningitis in the fourth.

## Other Manifestations

One patient developed a suppurative pericholangitis possibly related to intestinal cryptosporidiosis. Individual episodes of nephrotic syndrome, choledochoduodenal fistula and severe diarrhoea of unknown cause occurred.

*Therapy:* Infectious complications were treated by standard antimicrobial chemotherapeutic agents and patients who had had PCP pneumonia were subsequently placed on prophylactic trimethoprim sulphamethoxazole or pentamidine. Advanced Kaposi's sarcoma was treated by chemotherapy. Lymphomas were diagnosed agonally or at autopsy and thus were not treated. No specific antiretroviral therapy was available before the introduction of zidovudine. This drug was first used in the present series during 1987 by three haemophiliac patients as part of a multicentre trial. All discontinued the drug after a few months because of side effects. When zidovudine became generally available in 1988 it was taken by nine patients. Temporary remission of encephalopathy was observed in two, while two others discontinued the drug because of side effects. Objective assessment of effect was not possible in the remaining patients.

*Autopsies* were performed on 10 of the 16 patients who died. There was marked emaciation in seven and three were of normal or just below normal weight. The range of infections and neoplasms first identified at autopsy is indicated by parentheses in table 1. Autopsy was particularly useful in clarifying neurological involvement. In addition, diseases suspected on clinical or serological grounds (CMV retinitis, positive serology for toxoplasma or CMV) were confirmed. The extent of disease already diagnosed in vivo and any evidence of response to therapy was delineated e.g. known Kaposi's sarcoma was unexpectedly widespread at autopsy in two patients and pneumocystis carinii pneumonia showed no response to therapy in one case. Unusual manifestations such as suppurative cholangitis and toxoplasma colitis or retinitis were identified and the anatomy of a suspected gastroduodenal fistula was delineated.

## Discussion

The pattern of disease in these early cases of AIDS in Ireland broadly resembles that seen elsewhere in Europe and North America.[8] The patients were predominantly male, the mean age was early thirties and they belonged to the major recognised risk groups (IVDA, homosexuals or recipients of parenteral blood products). The principal manifestations of disease included oro-oesophageal candidiasis, pneumocystis carinii pneumonia, and disseminated mycobacterial and cytomegalovirus infection. Severe neurological disease was frequent and Kaposi's sarcoma and malignant lymphoma occurred. At the terminal stage the majority of patients became emaciated. Within a year 39% died and almost two thirds died within two years of diagnosis.

There was some variation in disease manifestation among the different risk groups. Oesophageal candidiasis was the dominant mode of presentation in the haemophiliacs, all of whom were already under medical care and known to be at high risk of AIDS. It is not clear if this group is more susceptible to Candida or if similar infections in the other groups, who were not under such intense medical scrutiny, might have remained undiagnosed. Kaposi's sarcoma was not seen in haemophilia where it is known to be rare,[9] but it was frequent in the homosexual group. Mycobacterial infections were particularly prominent among the IVDA group, as has been recognised elsewhere[10] but also occurred among the other two groups.

Although the patterns of malignancy and infection were

TABLE 1 – **The range of neoplasms and infectious complications in 23 AIDS cases**

| | Case Number | Kaposi's Sarcoma | Malignant Lymphoma | Candida Oesophagus | Candida Oral | PCP | Toxo | CMV | Mycobacterium | Other infections |
|---|---|---|---|---|---|---|---|---|---|---|
| **H** | 1. | | | + | + | | | | | C.difficile, Skin Folliculitis |
| **A** | 2. | | | + | + | + | | | | (Aspergillus) |
| **E** | 3. | | | + | + | | | | | Hepatitis B + Non A Non |
| **M** | | | | | | | | | | B. (Cryptosporidiosis) |
| **I** | | | | | | | | | | (aspiration pneumonia) |
| **O** | 4. | | | + | + | | | | | (Aspergillus), |
| **P** | | | | | | | | | | (pseudomembranous colitis) |
| **H** | | | | | | | | | | (bacterial |
| **I** | | | | | | | | | | broncho-pneumonia) |
| **L** | 5. | | | + | + | + | | | *M avium* | |
| **I** | 6. | | | + | + | + | | | *M tuberculosis* | |
| **A** | 7. | | | + | + | + | | | | |
| | 8. | | | + | + | | | | | Chronic persistent hepatitis |
| | 9. | | | + | + | | | | | (Acute pyelonephritis) |
| | | | | | | | | | | (aspiration pneumonia) |
| | | | | | | | | | | Hepatitis B, viral papilloma skin |
| | 10. | | | + | + | | | | | Bacterial pneumonia |
| **I** | 11. | | | | + | (+) | | + | *M tuberculosis* | Chronic persistent hepatitis, |
| **V** | | | | | | | | | | (Klebsiella pneumnia) |
| **D** | | | | | | | | | | streptococcal septicaemia |
| **A** | 12. | | | + | + | | | | *M tuberculosis* | Hairy leukoplakia, |
| | | | | | | | | | | condyloma accuminatum |
| | 13. | | | | + | | | | *M tuberculosis* | |
| | 14. | | | | + | | | | *M kansasii* | |
| | 15. | + | | | | | | + | | |
| | 16. | | | | + | + | | | | (Bacterial bronchopneumonia) (Acute colitis) |
| **H** | 17. | | | + | | + | | | | Herpes simplex, condyloma |
| **O** | | | | | | | | | | accuminatum |
| **M** | 18. | + | | | | + | + | | + | |
| **O** | 19. | + | (+) | | + | | | | | Campylobacter colitis, viral |
| **S** | | | | | | | | | | lymphadenitis, herpes |
| **E** | | | | | | | | | | simplex (aspiration |
| **X** | | | | | | | | | | pneumonia) |
| **U** | | | | | | | | | | |
| **A** | 20. | + | + | | | | | | (*M tuberculosis*) | |
| **L** | 21. | | | | + | + | | + | *M avium* | Herpes simplex |
| | 22. | | | | | | + | | | Herpes simplex |
| | 23. | + | (+) | | | | + | (+) | (*M avium*) | Varicella zoster |

*IVDA: intravenous drug abuser; PCP: pneumocystics carinii pneumonia; TOXO: toxoplasmosis; CMV: cytomegalovirus; M avium: M avium intracellulare;parentheses indicate lesions first diagnosed at autopsy.*

broadly similar to those reported from North America there were some differences which may reflect either altered diagnostic criteria for AIDS,[5] or the small size of the series but might indicate a true regional variation. Of the 13 most frequently reported infectious diseases in AIDS patients in the United States[11] ten were identified in this study but histoplasmosis, coccidiomycosis and cryptococcosis were not seen. The absence of coccidiomycosis and histoplasmosis is not surprising as these diseases are usually confined to specific endemic areas and have no known reservoir in Ireland. However, cryptococcus is considered to be a ubiquitous organism identified in 7-11% of US cases.[11] We had only once identified cryptococcus in our laboratory (in a leukaemic patient who had recently been abroad) before late 1989 when a cluster of three cases occurred in newly diagnosed AIDS patients not part of the present series. The initial absence and subsequent cluster of infection raises the possibility of nosocomial infection or the emergence of more pathogenic strains of cryptococcus but this can not be confirmed by currently available techniques. Pneumocystis carinii pneumonia which is reported in more than two thirds of American cases[11] was present in less than 40% in this series.

*M tuberculosis* which has been described in approximately four to 21% of AIDS patients depending on the risk group studied" was particularly frequent in this study where it occurred in five cases (22%). It manifested as generalised disease at presentation, or with meningeal involvement which was unexpectedly found at autopsy, or as pulmonary disease during the course of the illness. It is particularly important to recognise the frequency of tuberculosis because it may simulate other complications of AIDS, it is amenable to treatment, and it has serious cross-infection implications both to the healthy and to other immunocompromised patients. Moderate numbers of cases of tuberculosis still occur in the general population in Ireland[12] and in one case in this series the patient's mother developed pulmonary tuberculosis some months before her son who visited her frequently and presumably contracted the infection from her. It was not determined if the other cases represented recent infection or reactivation of old disease. Infections with atypical mycobacteria are rare in Ireland[13] (a finding that has been attributed to the protective effect of the widespread use of BCG vaccination), nevertheless atypical mycobacterial infections (M*kansasii* and *M avium intracellulare)* occurred in this series, although the frequency of *M avium intracellulare* (13%) was much less than the 50% rate at autopsy identified in the US.[11]

The relative risks and benefits of post mortem examination on AIDS patients have been difficult to assess. The risk to the pathologist of accidental infection during autopsy from the potentially high concentrations of HIV has caused

anxiety especially when there are suboptimal facilities and insufficient technical support. Where satisfactory facilities are available the autopsy has proved to be of major importance. The wide range of potential infectious and neoplastic complications associated with AIDS in addition to unfamiliarity with a new disease make AIDS a difficult clinical challenge. In the present series the autopsy has confirmed suspected clinical diagnoses, delineated the extent of known disease and has identified unexpected pathology, as indicated above in the results section. It has thus played a major role both in delineating the natural history of AIDS as it occurs in our population and in increasing clinical diagnostic skills.

Epidemiologically, the historic pattern of spread of AIDS from country to country has been difficult to define due mainly to the long incubation period of the virus. It is likely that the disease became established in Ireland by several routes. The early reported Irish cases[1] and many of the initial cases in this study[7] were homosexuals, some of whom had, from the late 1970s, travelled in Europe and Africa but especially to the seaboard cities of the United States where AIDS first became apparent. The haemophiliac patients appear to have become infected, mainly between 1980 and 1984, principally through infected commercial blood factor concentrates originating in the United States. Infection in the IVDA group may have begun later as only one of our cases from this group presented before 1987. IVDA had become a major problem in Dublin in the early 1980s[14] and the disease may have jumped to and rapidly spread in this population either from the homosexual or haemophiliac population (IVDA from both groups are included in the present study) or from contact with foreign IVDA. Our hospital is not a paediatric referral centre so no neonatal cases are included in this series but two Irish AIDS cases in children of HIV positive IVDA mothers had been reported by 1988.[4] Heterosexual spread of the disease does not yet appear to be a problem in Ireland.

The predominance of the Dublin area in the development of the AIDS epidemic in Ireland is indicated by the relatively large number of patients presenting to our hospital. Haemophiliacs attend the national centre from most areas of the country and several of the cases of AIDS from this risk category came from provincial areas. However, all of the homosexuals and IVDA were based in Dublin. Outside of Dublin social and religious attitudes and migration have probably limited the number of promiscuous homosexuals. Similarly intravenous drug abuse is a much smaller problem in provincial cities and rural areas and consequently the number of AIDS cases from outside the Dublin region has to date been small.

In contrast to the present study from the Republic of Ireland it is of interest that only four cases of AIDS had been reported in Northern Ireland by the end of 1987.[15,16] A further five cases each year occurred in 1988 and 1989.[16] It is likely that factors similar to those discussed for the Republic influenced the epidemiology of the disease in Northern Ireland where, in addition, intravenous drug abuse may have been actively suppressed by paramilitary groups.

This study involved patients who presented by the end of 1987. Since then in the Republic of Ireland 41 new cases have been reported during 1988 and 50 during 1989 and a substantial pool of HIV positive patients has been identified mainly among the IVDA and homosexual population so that despite recent health promotion campaigns[17] it is clear that the disease in Ireland has, as in other countries, entered a rapid growth phase and is likely to become a major health problem.

We have described this group of patients in order to define the clinicopathological spectrum of AIDS as it is now presenting in this country. The patient population and the range of infections and neoplasms identified indicates that the disease here has a broadly similar profile to that reported from major centres of involvement in developed countries. Differences in the frequency of some manifestations in this small series of 23 cases must be viewed with caution and may be partly due to altered diagnostic criteria[5] but may reflect local disease variations associated with genetic, risk group or environmental factors. Many of the complications of AIDS may be reversible so that, especially as anti HIV agents are beginning to appear, it is most important to be aware of the local range and relative frequency of the various manifestations of AIDS in order to devise the best diagnostic strategies.

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