ACQUIRED IMMUNEDEFICIENCY SYNDROME IN MALAWI

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Introduction

In 1976 a Danish surgeon who had worked in Zaire for several years died in Denmark of a mysterious illness characterised by recurrent opportunist infections due to a inexplicable failure of her immune defences. In 1983 this illness was recognised to fulfil the diagnostic criteria of the acquired immunedeficiency syndrome (AIDS) and as such remains the earliest generally accepted case in the world literature[1]. Further studies in Zaire[2], Rwanda[3] and Uganda[4] have shown that the disease is frequent in this part of central Africa and has probably been present there since the early 1970's[5]. Reports from Zambia however suggest that the disease is new there the first cases appearing in 1983[6]. The first recognised case in Malawi presented in February, 1985 and further 12 cases were recognised during that year.

Infection with the Human T-lymphotropic virus type III (HTLV III) is now recognised to be closely associated with AIDS[7]. While the majority of people infected with the agent remain completely well in a small proportion the virus causes a catastrophic derangement of immune function which results in AIDS. A further small proportion encures a less severe derangment of their immunity resulting in the AIDS related complex (ARC), characterised by prolonged fever, weight loss, persistant lymphadenopathy and often non life threatening opportunistic infection. This paper summarises experience with HTLV III related diseases seen at Kamuzu Central Hospital, Lilongwe (KCH) and Queen Elizabeth Central Hospital, Blantyre (QECH) during 1985.

AIDS is defined as i) The presence of a reliably diagnosed disease at least moderately predictive of cellular immune deficiency such as atypical Kaposi's Sarcoma and ii) the absence of an underlying cause for the immune deficiency or of any defined cause for reduced resistance to disease.

AIDS related complex is defined as a condition in which a person must have two or more symptoms or signs of specific chronic unexplained conditions for three months or longer, together with two or more abnormal laboratory values. The symptoms and signs include non-inguinal lymphadenopathy, weight loss, fever, diarrhoea, fatigue-malaise, and night sweats and the laboratory studies include measurements of lymphocyte count, increased immunoglobulins, cutaneous energy and serum antibodies to HTLV-III.

Since diagnostic facilities in Malawi are inadequate for the positive diagnosis of many opportunistic infections these case definitions cannot be rigorously applied in this report. However the use of the clinical criteria alone in the presence of antibodies to HTLV III gives accurate case definitions providing follow up is adequate.

All Sera were positive for anti-HTLV-III antibodies by both ELISA and an immunoflouresent assay performed in the Republic of South Africa.

Case 1

A 23 years old self employed man was admitted at the beginning of April 1985, with a month's history of fever, wasting, cough, general malaise and swelling of the legs. He had attended private practitioners in town and received treatment for malaria (chloroquine) and chest infection (ampicillin). He was delirious, had a temperature of 40°C and oral candidiasis. He was anaemic, with bilateral basal crepitations and moderate splenomegaly. Fundoscopy showed a crop of haemorrhages. The working diagnosis was Typhoid fever with lymphoma and tuberculosis as alternatives.

Laboratory investigations showed:-Hb was 5.0 g/dl, WCC 2.7×10^3/cc (with 69% polymorphs, 31% lymphocytes), platelets 36×10^3/cc, ESR 95mm/hr. Sputum for AAFB, blood culture, Widal test and test for Brucella agglutinins were all negative. He received chloramphenicol and Nystatin for 2 weeks with some clinical improvement; the sedimentation rate remained high at 75mm/hr.

He was re-admitted five days after discharge with a recurrence of symptoms. He had now developed cervical, axillary and epitrochlear lymphadenopathy and a pleural rub. The CXR showed bilateral patchy infiltrates. The blood count showed anaemia, 5.0g/dl, and lymphopaenia (13%). A lymph node biopsy showed non-specific reactive changes with marked

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increase of plasma cells in the cortex and medulla.

He received Bactrim for 2 weeks with some symptomatic improvement but relapsed two weeks later. A trial of TB treatment was stopped because of a drug reaction. He was treated with antibiotics and nystatin. A suspected diagnosis of AIDS was confirmed by positive antibody test to HTLV III (ELISA and FTA).

He was discharged soon afterwards when his father felt that a second opinion in the manner of a traditional healer had to be consulted. The patient died at the traditional healer. A post-mortem was not possible.

Case 2

AIDS related complex with recurrent fever, lymphadenopathy and pneumonia.

A 45 year old female began to feel unwell in February, 1985 with a non-specific febrile illness clinically diagnosed as malaria. There was no response to anti-malarial treatment and she developed lower abdominal pain suggesting a diagnosis of salpingitis. Her fever settled on antibiotics over seven days and the abdominal pain resolved. She was noted to have oral candidiasis which was attributed to the antibiotics; this cleared rapidly on nystatin suspension. All investigations were normal except the total W.B.C. was only 2.4×10^3/cc.

She remained well until early June when an intermittent fever recurred associated with night sweats and weight loss. A few moderately enlarged lymphnodes were found in the neck. After three weeks of fever she developed a sore throat and a cough. There was no response to penicillin or tetracyline. By this time she was running a sustained high fever and was clearly toxic. The throat was injected but free of candida. There was symetrical firm lymphadenopathy in the neck and both axillae. Bilateral coarse crackles were present in the chest, and there was tender spleenomegaly. Her fever continued despite ampicillin and gentamicin and a trial of anti-T.B. treatment was given.

Investigations revealed a haemoglobin of 13.5 G/dl and a W.B.C. of 5.5×10^3/cc with a normal differential. A blood culture was negative, Mantoux non-reactive. The chest X-ray showed hazy perihilar shadows. A lymphnode biopsy showed non-specific reactive changes. Further investigations after referal revealed a reversed helper to suppressor T-lymphocyte ratio and antibodies to HTLV-III. In view of this a diagnosis of ARC was made. Her chest infection improved on antibiotics and no pathogen was isolated despite bronchoscopy for suspected pneumocystis carinii pneumonia.

Progress since then has been one of steady improvement with some weight gain although there is still persistent lymphadenopathy.

Case 5

Atypical Kaposi's sarcoma, restricted to lymphoid tissue at presentation.

A 23 year old teacher was admitted in August, 1985 with a two week history of progressive generalised lymphadenopathy associated with cough and night sweats. On examination he had gross generalised symmetrical lymphadenopathy and was febrile. Investigations revealed a normochromic aneamia of 8.4 G/dl with a normal W.B.C. and differential. Chest X-ray showed bilateral hilar lymphadenopathy but clear lung fields. A lymph node biopsy showed Kaposi's scarcoma.

He was unmarried and had spent three months in France in early 1985, but had otherwise always lived in Malawi.

His condition deteriorated with a high fever which settled rapidly with cytotoxic drugs and steroids. Although he stabilised and there was some regression of the lymphadenopathy on repeated courses of this treatment he eventually relapsed with increasing anaemia, lymphopenia, weight loss and recurrence of the lymphadenopathy. He died at home three and a half months after presentation.

Case 9

AIDS related complex with miliary T.B., focal neurological deficit, progressive weight loss, severe oral candidiasis and necrotising perianal leisons.

A 22 year old sales assistant presented in July, 1985 with a one month history of fever weight loss and progressive confusion with loss of speech and power in the right limbs. On admission she was critically ill with a fever of 40°C, severe bilateral pneumonia and a right hemipariesis with aphasia. Investigations releaved a normal full blood count and chest X-ray with bilateral infiltrates. Blood cultures were sterile but a lymphnode biopsy showed granulomata with numerous acid fast bacilli. The fever did not respond to antibiotics but resolved rapidly on anti T.B. treatment and dexamethasone. Despite the initial improvement in conscious level she continued to loose weight and developed severe oral candidiasis and ulcerative perianal leisions. There was no improvement in her neurological deficit and her Mantoux test was still negative after three months of anti-tuberculous treatment. A repeat differential white blood cell count revealed a profound lymphopenia. She continued to deteriorate finally dying in January, 1986.

Her only child died in June, 1985 aged one year after six months of illness characterised by failure to thrive, lymphadenopathy, oral candidasis and relapsing diarrohea. Investigation at another hospital could find no cause and there was no response to a trial of anti-tuberculous treatment.

Her husband who is in good health has also been found to have antibodies to HTLV-III.

Case 11

Atypical Kaposi's sarcoma, with widespread cutaneous nodules and lymphadenopathy.

A 32 year old fish farm operative began to notice swelling of both legs with cutaneous nodules on the feet in August, 1985. The swelling increased despite diuretics and nodules appeared on the arms and trunk.

He divorced in 1983 and had contracted both syphilis and gonorrhea once. He had received a full course of i.m. penicillin for each disease. He also had scarifications recently for the leg swelling. He had never travelled outside Malawi or received any blood transfusions.

On examination he had widespread rubbery deep purple nodules of Kaposi's searcoma in the skin and on the palate. He had an intermittent low fever. Lymphnodes were enlarged in both axillae and groins. The F.B.C. showed a lympopenia.

He remains unwell with ulcerating nodules of K.S. on both feet which have not improved on chemotherapy.

Summary of HTLV-III related syndromes seen in Malawi in 1985

Case No.	Age	Sex M/F	Paying/ non paying	Date of initial symptoms	Date of final diagnosis	Clinical Manifestations.	Progress
1*	21	M	P	FEB.	AUG. (stored serum)	Lymphadenopathy, sore throat recurrent fever, oral candida splenomegaly and fits.	death, April 1985
2	45	F	P	FEB.	JUL.	Lymphadenopathy, weight loss recurrent fever, pneumonia	symptomatic recovery with persistant lymphadenopathy
3	36	M	NP	MAY	AUG.	Atypical pneumonia and lymphadenopathy.	Continued weight loss and persistant lymphadenopathy
4	45	M	P	MAY	AUG.	Ulcerative oesophagitis, Oral candida, Lymphadenopathy Hepatosplenomegaly.	Progressive weight loss and terminally severe heamaturia ? renal tumour. Death, Jan., 1986
5*	23	M	P	AUG.	AUG.	AKS L.N. only with very rapidly progressive disease	Death, Nov., 1985
6	39	M	NP	NOV., '84	AUG.	AKS Skin + L.N.	Relatively slowly progressive AKS with severe bilateral foot involvement and visceral spread.
7	34	M	P	JUN.	SEP.	AKS SKIN + L.N. Oral candida with fever	Death, Dec., 1985
8	34	M	P	MAR.	SEP.	AKS Skin + L.N.	Slowly progressive AKS.
9*	22	F	NP	JUN.	SEP.	Fever, weight loss, hemiparesis. Pneumonia and lymphadenopathy due to T.B. ? intracrainial T.B.	Progressive deterioration with oral candida, gross weight loss. Death, Jan., 1986.
10	21	F	NP	AUG.	OCT.	Recurrent fever, Diarrohea sore throat, lymphadenopathy and abdominal pain ? P.I.D.	Severe bilateral pneumonia ? Pneumocystis carinii. Death, Dec., 1985
11*	32	M	NP	AUG.	NOV.	AKS Skin + L.N.	Slow deterioration.
12	33	M	P	JUL.	DEC.	AKS L.N. only causing a right lower motor neurone VII nerve palsy.	Progressive deterioration with skin and visceral K.S. leisons.
13	27	F	P	MAY	DEC.	Lymphadenopathy, sore throat, weight loss. Radiological T.B. No sputum available.	Continued illhealth but able to work. No weight gain on T.B. treatment, Mantoux negative after 4 months R

***Case history given in detail.**

Results

Of the 13 cases, ten fulfiled the definition of AIDS and the remaining three ARC. The demographic features are summarised below: the most stricking aspect is the preponderance of cases among the relatively affluent in middle life. Eight of the thirteen patients held either professional or administrative posts and were seen in the paying wards or clinics. This is unlikely to be a selection artifact; both paying and non paying patients are seen by the same medical specialists and the figures are even more stricking since there is approximately one paying for every ten non-paying patients in both central hospitals. Even those patients on the non-paying wards were of above average socio-economic achievement with three of the five speaking fluent English.

Demographic features

Sex ratio M:F	9:4
Age- median (range)	33 (21-45) years
Paying ward: non-paying ward	8:5
Fluent English: non fluent	11:2

Clinical features

Presenting feature	Number of patients (%)
Fever	9 (69)
Weight loss	8 (62)
Diarrohea	2 (15)
Lymphadenopathy	13 (100)
Hepatosplenomegaly	3 (23)
Oesophagitis	1 (8)
Opportunistic disease	
AKS Skin and Lymphnode	5 (38)
Lymphnode only.	1 (8)
Oral Candida.	5 (38)
Tuberculosis: Definite.	1 (8)
Suspected.	1 (8)
Case: fatality ratio	13:6
Mean duration of illness in fatal cases	5.7 months

The eventual cases fatality ratio will almost certainly rise further with continued follow up, the figures represent the situation on 1st of February, 1986.

Lymphadenopathy was a universal finding. A biopsy was taken in every case; in six the patients this revealed Kaposi's Scarcoma and in one tuberculosis. The remaining biopsies showed prominent reactive changes only.

Discussion

Atypical Kaposi's sarcoma (AKS) in adults is almost exclusively associated with HTLV-III infection and as such may provide a useful marker for the arrival of this virus in a community[8]. The distinctive cutaneous lesions which are prominent in many cases of AKS and their association with progressive weight loss resulting in death within a few months of presentation is a stricking and easily recognisable syndrome which is likely to reach medical attention. Assuming a constant proportion of the cases of AKS in Malawi are diagnosed the dramatic increase in its incidence in 1985 suggests that AIDS is a genuinely new disease in Malawi.

While the clinical features of AIDS and ARC in Malawi are broadly similar to those observed in other countries the demographic features contrast sharply with those seen in North America and Europe where the disease is predominately one of men, reflecting the major role that homosexual intercourse plays in its transmission there. The virtually equal involvement of both sexes in all African countries with AIDS and the peak age of onset in the late twenties to thirties suggest that heterosexual intercourse is the major route of infection in Africa[2-4]. This belief is supported by the finding of both a very high prevalence of anti-HTLV-III and clinical and immunological features of AIDS/ARC among prostitutes in studies performed in Rwanda[9]. Our observations in Malawi fit in with this picture. The only cases in which other risk factors are apparent are one in which blood transfusion may have been responsible and one probable case of vertical transimission from mother to child. (case 9)

Other risk factors which may play a relatively minor role include transmission by accidental needle injury among medical staff and transmission between patients if needles and syringes are inadequately sterilised. The risk to medical staff following needle injury appears to be low[10] but cases have been documented and there is a suggestion that African HTLV-III may be more easily spread than North American HTLV-III by this route although this requires further investigation[11]. The evidence from i.v. drug abusers leaves no doubt that dirty syringes and needles present a very real hazard. Scarification, a very widespread practise in Malawi, may be a further mode of transmission although no conclusive information exists. The role of insect vectors is uncertain. While the demographic features of the cases so far observed here suggests that this mode of transmission does not occur, an association between the age specific prevalence of anti-malarial antibodies and anti-HTLV-III has been observed. These data are open to a wide number of interpretations and may indeed be due to cross reactions in the assay[12].

The apparent predisposition of relatively affluent city dwellers which has also been observed in Zambia may be a reflection of several factors: This may simply be a selection artifact although this is unlikely in Malawi which has a good infrastructure of rural hospitals and dispensaries. This may be due to the wider opportunities for travel among this group and

acquisition of disease abroad. The greater use of medical facilities and hence exposure to potentially infected needless is a further possibility. Finally their greater disposable income may facilitate a more promiscuous lifestyle.

The median incubation period of AIDS is approximately two and a half years[13] so it seems probable that HTLV-III was introduced into Malawi around 1982. The emergence of AKS in Zambia in 1983, the recognition of cases further north in Central Africa in the late seventies and the detection of antibodies to HTLV-III in sera collected in Uganda in the early seventies all suggest that the disease is progressively spreading from a central African focus into southern Africa. This notion is supported by seroepidemiological studies which reveal a gradient of prevalence from between 10-20% in Zaire, Rwanda and Uganda to only 2% in Zambia. As yet antibodies to HTLV-III are extremely rare in the black population of the Republic of South Africa (the few cases of AIDS that have been seen there almost all are among white homosexuals some of whom had probably contracted it in the U.S.A.)[4].

The ultimate origin of HTLV-III remains uncertain but the isolation of an immunologically indistinguishable virus from monkeys in central Africa raises the possibility of a mutant strain capable of replicating in man arising there. This remains very speculative as similar viruses have been found in asian primates where as yet AIDS is vertually unknown[15]. Recently antibodies to HTLV-III have been found among very isolated Amerindian populations in Venezula although no cases of clinical AIDS have been observed there[16]. It is possible that there may be a number of very closely related variants of HTLV-III of differing pathogenic potential (for humans) found in different parts of the world which are not distinguished in most of the currently available assays. It does however seem most likely that virus responsible for the current world AIDS epidemic arose at a single focus and then spread rapidly among certain at risk groups. Where this focus was remains uncertain and the virtually simultaneous appearence of AIDS in both Africa and the U.S.A. gives no clear lead.

The emergence of HTLV-III related diseases in Malawi presents new challenges. It is inevitable that the number of cases will increase rapidly over the next few years. It is important that our resources are deployed so that appropriate steps are taken not only to combat it but also to avoid unnecessary fear among both medical staff and general public and prevent the regretable stigmatisation of known carriers which has been witnessed occasionally in other countries. Information which will assist medical staff to recognise cases, confirm the diagnosis and minimize the hazard such patients pose to others is in the accompanying centre pages article. So that the potential number of future cases can be better assessed it is essential that studies should be undertaken soon to determine the prevalence of the virus in Malawi particularly among high risk groups such as prostitutes and develop policies to attempt to control its spread. While AIDS will never emerge as a major cause of death comparable to diarrhoea, Malaria or Measles in childhood it seems probable that it will account for a substantial number of deaths in early middle life an age at which the patient may have a young family to support or may have just completed a long period of training and be about to embark on their carreer. Clearly excess death among this age group is both tragic for the dependants and an additional burden in a developing country still short of skilled personnel in a wide number of fields.

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