INTRACRANIAL MASS LESIONS IN HIV-POSITIVE PATIENTS — THE KWAZULU/NATAL EXPERIENCE

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Background. Neurological disease heralds the development of AIDS in 10 - 20% of HIV-seropositive individuals. In over half of these cases the presentation will be that of an intracranial mass lesion (IML). In developed countries toxoplasmosis is the most frequent cause of IML in a positive patient, followed by primary central nervous system lymphoma. Less common causes include tuberculomas, cryptococcomas, abscesses and gummas. As a result of these observations, the algorithm adopted in developed countries calls for initial empirical treatment for toxoplasmosis. Biopsy of the IML is only considered if there is no response to treatment after 10 - 14 days. Whether such an algorithm would be applicable to the local population is unknown.

Objective. We undertook a prospective study to determine the type and frequency of IML in local HIV-seropositive patients. A secondary objective, based on the findings, was to develop a local algorithm of management.

Patients and Methods. Over a 17-month period HIV-seropositive individuals with an IML were entered into the study. Biopsy or aspiration of the lesion was performed either stereotactically or free-hand. Tissue obtained was processed for routine and special histological studies.

Results. In the 38 cases where tissue was obtained, the most frequent cause of the IML was toxoplasmosis followed by 'encephalitis of obscure origin', brain abscess and tuberculoma/mycobacterial infection.

Conclusion. This study demonstrated that the spectrum of IML seen locally was similar to that in developed countries. The management protocol used elsewhere was therefore adopted for local patients.

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Up to 70% of HIV-seropositive individuals will develop clinically relevant neurological disease at some stage of their lives.[1] The neurological disease heralds the development of AIDS in 10 - 20% of cases; over half of these cases will involve intracranial mass lesions (IML).

Studies of IML in HIV-positive patients emanate primarily from the developed countries. There the most frequent causes are toxoplasmosis, occurring in up to 10 - 20% of patients, and primary CNS lymphoma (PCNSL), occurring in up to 2% of patients.[2] Less common causes include tuberculomas, cryptococcomas, abscesses, gummas, metastatic tumours and cerebral infarcts. Although progressive multifocal leuco-encephalopathy (PML) does not present with a mass lesion, this condition is often included in the differential diagnosis. Cytomegalovirus infection may occasionally present as a mass lesion.[3]

As a result of their experience, some groups have developed decision analytic models of proposed management.[4,5] More recently the Quality Standards Subcommittee of the American Academy of Neurology published its report on the evaluation and management of IML in AIDS.[6] In essence, the consensus is that HIV-seropositive patients presenting with mass lesions be given treatment for toxoplasmosis first. Biopsy should be considered only if there has been no improvement after 10 - 14 days of treatment.

In KwaZulu-Natal (KZN), an HIV-hyperendemic area, there were no data on the nature of intracranial masses in HIV-positive individuals. Whether an algorithm developed elsewhere would be applicable locally was unknown. Consequently the Neuroscience AIDS Group, with members of the departments of Neurology, Neurosurgery, Neuroradiology and Pathology at the University of Natal Medical School, undertook a prospective study to determine the nature of IML in the local population and to develop its own algorithm.

Patients and methods

Over a 17-month period, patients who had intracranial masses were tested for antibodies to HIV enzyme-linked immunosorbent assay (ELISA) AXYSM test (Abbot Diagnostics, Wiesbaden, Germany). A ratio of greater than 6 was regarded as positive. Those patients who tested positive were entered into the study. Each patient underwent a clinical examination and neuro-imaging. The latter usually consisted of a computed tomography (CT) brain scan as most patients were admitted on an emergency basis. Where possible, CD4 counts were measured. Baseline blood tests were done as required.

Biopsy or aspiration was performed both stereotactically and free-hand. For the stereotaxis, a graphite Codman-Roberts-Wells (CRW) stereotactic frame was applied to the head and secured by means of four pins screwed into the outer table of the cranial vault. A localiser framer was then fitted onto this frame. The patient was scanned and the lesion was localised using standard techniques. In theatre, a burr-hole was made and up to eight biopsies were taken from the edge and centre of the lesion. The biopsies were small, approximately 1 - 2 mm.[3] Histological sections were subjected to routine and special stains. These included haematoxylin and eosin, periodic acid-Schiff reaction, Gram's stain, silver methenamine, Giemsa's stain and Ziehl-Neelsen stains. Immunohistochemical stains were undertaken to detect cytomegalovirus (CMV) (Dako, Carpinteria, Calif.), HIVp24 (Dako A/S, Glastrup, Denmark), and *Toxoplasma* (Biogenex, San Ramon, Calif.) antigens using monoclonal antibodies.

Results

The demographic data and main clinical features are summarised in Table I. A total of 45 patients were entered into the study. Focal signs were present in over 90% of the patients. Seizures occurred in approximately half the patients.

Table I. Demographic features and main clinical findings in 45 patients

Gender	
Male	22
Female	23
Age of male patients (yrs)	
Mean	33.8
Range	18 - 56
Age of female patients (yrs)	
Mean	25.3
Range	20 - 43
Clinical features	
Headache	30/39 (76.9%)
Seizures	20/44 (45.5%)
Focal signs	41/44 (93.5%)

CT scanning rather than magnetic resonance imaging (MRI) was done in the majority of patients. Apart from cerebral abscesses (Fig. 1), prediction of histology from radiological appearance was not reliable. (Figs 2 and 3).

Biopsy was not possible in 7 patients because of logistical problems, no consent for surgery, or death. In this group no diagnosis was possible in 4 patients. Of the remainder, 1 patient was thought to have a tuberculoma and 2 were thought to have toxoplasmosis on the basis of response to specific anti-microbial agents.

The diagnoses in the remaining 38 cases are listed in Table II. If one includes the 'encephalitis' group (Table II), positive biopsies were obtained in 89.5% of cases. This figure drops to 71% if the encephalitis group is excluded. Toxoplasmosis was the most frequent diagnosis. Two patients had double infections, namely toxoplasmosis and cryptococcosis.

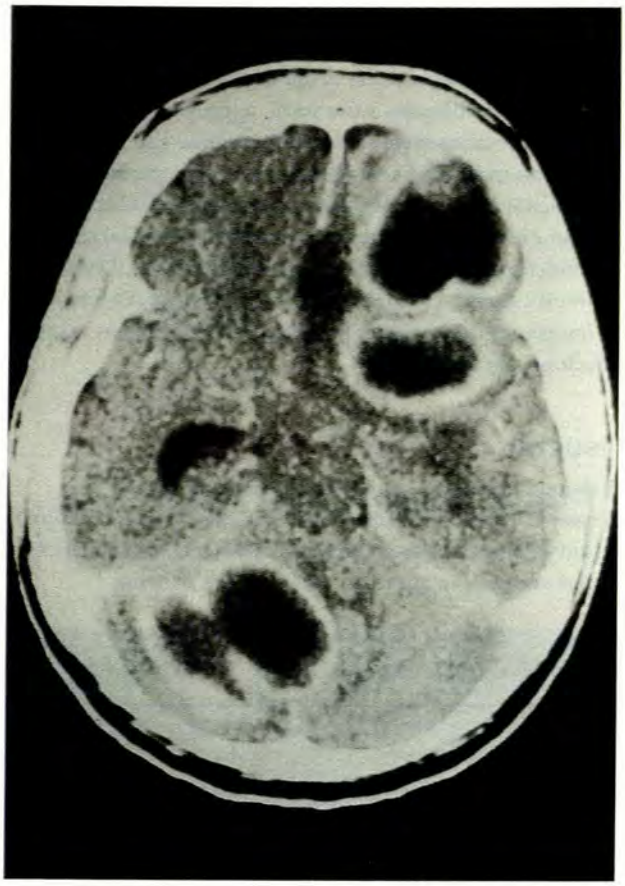

Fig. 1. CT scan showing both supra- and infratentorial abscesses.

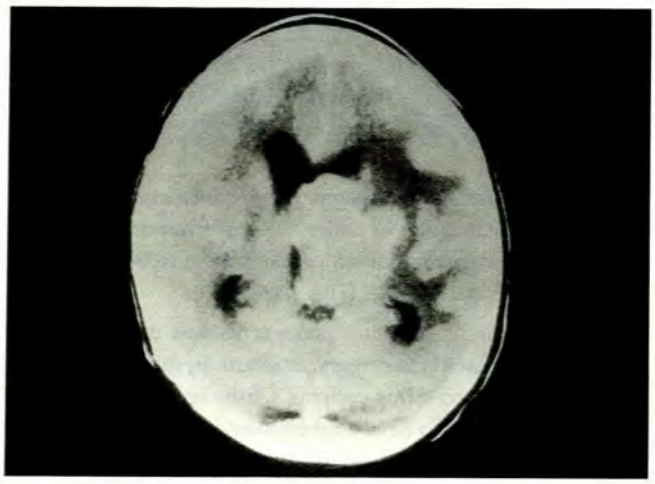

Fig. 2. Mass on this CT scan found to be a tuberculoma.

Encephalitis patients formed a large group. The main histological features were perivascular and parenchymatous inflammation. The inflammatory infiltrate consisted of lymphocytes, plasma cells and monocytes, and in one case eosinophils. Six patients had cerebral abscesses, 5 of which have been reported on elsewhere.[7] The abscesses tended to be multiple and in unusual sites (Fig. 1). Multiple organisms were isolated from single abscess cavities and often no primary source was identified. There were no cases of PCNSL.

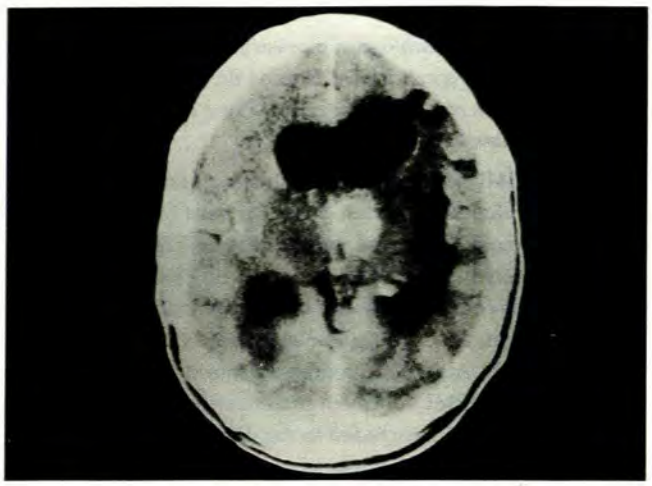

Fig. 3. Mass on this CT scan found to be due to toxoplasmosis.

Table II. Histological findings in the operated cases

Total biopsied/operated	38*
Diagnosis	No
Toxoplasmosis	15†
Brain abscess	6
Tuberculoma/mycobacterial infections	4
Encephalitis	7
Cryptococcoma/cryptococcal meningitis	2
Infarct	1
No diagnosis	3

* Four were postmortem biopsies.
† The 2 patients with cryptococcal infection had toxoplasmosis as well.

The CD4 count was measured in 27 patients. For statistical purposes those patients who had CD4 counts were divided into two groups: toxoplasmosis ($N = 10$), and non-toxoplasmosis ($N = 17$). The median (range) in the toxoplasmosis group was 40.5 (16 - 183) and in the non-toxoplasmosis group, 79 (26 - 487). The P-value was 0.083. Three of the 4 patients with tuberculomas had CD4 counts of 142, 170 and 341 respectively.

Of 37 patient samples tested for CMV antigen, all were negative. Twenty-six of 29 samples tested positive for the p24 HIV antigen. Thirteen of the 15 cases of toxoplasmosis were confirmed by immunohistochemistry. In 2 cases there was insufficient tissue for analysis. No new cases of toxoplasmosis were diagnosed by immunohistochemistry.

Only 9 (20%) of the 45 patients improved. Sixteen (36%) remained static for the duration of their hospitalisation, while 20 (44%) died. Of the 9 who improved, 5 had toxoplasmosis, 1 cryptococcoma, 1 infarct and 2 had no diagnosis. There were no complications relating to the surgical procedure.

DISCUSSION

The advent of HIV has necessitated a reassessment of the differential diagnosis of IML in the local population. For example, in the past toxoplasmosis was never considered a diagnostic possibility.

The clinical presentation of IML in HIV-seropositive patients is nonspecific and does not assist in the differential diagnosis. CT and MRI findings too are not diagnostic. Both toxoplasmosis and PCNSL may exhibit multiple deep enhancing lesions.[8-10] Equally, a single lesion does not exclude toxoplasmosis.[8-10] This was also demonstrated in our cases (Figs 2 and 3). Steinmetz *et al.*[11] hold an opposing view. They found a 100% positive predictive value for toxoplasmosis if there were multiple lesions with mass effect or contrast enhancement. While it is conceded that MRI is more sensitive than CT in picking up multiplicity of lesions, MRI is neither widely available nor easily accessible in emergency situations.

As in all cases of IML, histological examination remains the gold standard. Open biopsy constitutes major surgery, with significant morbidity. A much safer alternative is stereotactic biopsy. In a study of 500 non-HIV patients, Apuzzo *et al.*[12] found a mortality rate of 0.2% and a morbidity rate of 1%. The main complication was haemorrhage. Morbidity and mortality have been reported to be higher in HIV-positive patients in some studies,[13,14] but not in others.[15] Further considerations, especially in HIV-positive patients, are the rates of non-diagnostic biopsies, treatability of the lesions, the subsequent quality of life and length of survival. In a review of nine retrospective studies, Holloway and Mushlin[5] noted that biopsies were non-diagnostic in 10.4% of patients. The mean duration of survival ranges from 40 to 120 days. Despite these reservations, histological confirmation does allow for rational therapy where this is available.

As the pattern of IML in the local population was unknown, we undertook a prospective study. There was no operative morbidity or mortality. A definite diagnosis was possible in 71% of the patients.

As elsewhere in the world,[1] toxoplasmosis was found to be the most frequent cause of IML in our series. The clinical and radiological features were nonspecific. Since specific therapy is available, it was not surprising that most of these patients improved. We did not test the sera of our patients for *Toxoplasma* antibodies. This may be regarded as a shortcoming of the study as negative *Toxoplasma* serology in a patient with a single lesion makes toxoplasmosis less likely. However, negative serology alone does not have sufficient negative predictive value to exclude the diagnosis of toxoplasmosis.[6,16] With advancing HIV disease, detection of the antibodies may become more difficult. Similarly, only 25 - 50% of patients who are seropositive for toxoplasmosis will develop central nervous system (CNS) toxoplasmosis.[6] This observation must be assessed further against the local background *Toxoplasma* seroprevalence of 12 - 46%.[17]

A more useful test would be CD4 count, as the toxoplasmosis group showed a trend towards lower CD4 counts than the non-toxoplasmosis group. A CD4 count of over 200 virtually excludes toxoplasmosis.

Pyogenic cerebral abscesses (PCA) constituted an important cause of IML in our study. These data have been published previously.[7] PCA does not rank high in many other series. One possible reason is that our study was a combined neurology and neurosurgery study. However, 3 of the 7 patients were first referred to the neurology department. PCAs are probably the only IML that have a sufficiently characteristic CT or MRI appearance.

Four of the patients had tuberculomas. While there were no characteristic clinical or radiological features, the CD4 counts in the 3 patients in whom this was measured were greater than 100 cells/mm^3. Tuberculomas tend not to occur in patients with very low CD4 counts (this study and personal observation), presumably because there are insufficient numbers of memory cells to form a discrete granuloma.

In 7 cases the histological sections showed nonspecific perivascular and parenchymatous inflammation. The obvious reason for this is sampling error. In an attempt to address this problem we tested the tissue section for specific infectious agents using a panel of monoclonal antibodies. There were no cases of CMV infection. HIV antigen was, not surprisingly, present in most patients. Immunohistochemical detection of *Toxoplasma* antigen was not helpful in identifying a cause in the encephalitis group. It is possible that other infections were being missed.

There was not a single case of PCNSL in this series, nor has a case been seen locally outside this study (personal observation). This observation contrasts strikingly with those reported from the USA and Europe.[2,10,14,15] In fact, in the developed world PCNSL is not only the second most common cause of HIV-related IML, but it appears to be increasing in incidence.[2,18] The reason for our observation is not clear. One possible reason is that patients in developing countries do not live long enough. It does not appear to be due to a local lack of exposure to Epstein-Barr virus (A Smith — personal communication), which has been closely linked to PCNSL.[19] More recently, human herpesvirus 8 (HHV8), the aetiological agent linked to Kaposi's sarcoma, has also been shown to be associated with the development of PCNSL irrespective of HIV status.[20] Although there are no sero-epidemiological data for HHV8 in KZN, Kaposi's sarcoma occurs in both HIV-positive and negative patients. It can therefore be reasonably assumed that HHV8 is present in the local population. Consequently the absence of PCNSL remains an enigma.

CONCLUSION

This study confirmed that toxoplasmosis is the most frequent cause of ICM in local HIV-positive patients. As a result we

recommend a management algorithm similar to that adopted in developed countries, i.e. to first treat empirically for toxoplasmosis. If there is no improvement after 7 - 10 days, a stereotactic biopsy should be performed. In the one exception, namely where neuro-imaging is suggestive of a brain abscess, initial management should be surgical.

Notwithstanding the above recommendations, the treatment options should be tailored to the individual patient. Factors that need to be considered are the general condition of the patient, the level of consciousness, the suspected diagnosis, the natural history of HIV disease at this stage of illness, and the resources available.

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