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HIV-associated primary CNS lymorbidity and utility of brain biopsy

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Abstract

Introduction: Human immunodeficiency virus (HIV) infection is associated with several central nervous system (CNS) infections and neoplasms. These opportunistic processes generally occur with advanced immunosuppression, but if an accurate diagnosis is made, effective treatment can frequently be initiated. **Methods**: In an attempt to assess the safety, diagnostic yield, and utility of stereotactic brain biopsy in the clinical management of suspected HIV-associated primary CNS lymphoma, we retrospectively studied the performance of biopsy in HIV-seropositive patients presenting with focal intracranial lesions. This analysis included 435 patients undergoing brain biopsy, identified through a local case series ($n=47$) combined with all published cases ($n=388$). The years of analysis for this study were 1984 and 1997. We also assessed the survival of HIV-associated intracranial mass lesions and of PCNSL patients treated at JHU. **Results:** Definitive histopathological diagnoses were established in eighty-eight percent of biopsied cases: primary CNS lymphoma (PCNSL) (30%), CNS toxoplasmosis (CNS TOXO) (16%), progressive multifocal leukoencephalopathy (PML) (25%), and other specific diagnoses (17%). Post-biopsy morbidity within thirty days was 8.4% and mortality was 2.9%. PCNSL was the most common diagnosis among cases biopsied after failure of anti-toxoplasmosis therapy, 134/205 (65%). In the local case series, biopsy-related morbidity was associated with poor functional status, decreased platelet count, and number of lesions at presentation. The median survival of irradiated PCNSL cases was 29 days longer than untreated cases (median survival 50 days versus 21 days, respectively, Chi-square=6.73, $P<0.01$). **Discussion:** Stereotactic brain biopsy had a high diagnostic yield for HIV-associated focal intracranial lesions, however, the biopsy complication rate in this patient population was relatively high. PCNSL was diagnosed in the majority of patients failing anti-toxoplasmosis therapy. Survival after irradiation for PCNSL remains very poor.

Keywords: HIV infection; Primary CNS lymphoma; Brain biopsy; Morbidity (mortality)

1. Introduction

Human immunodeficiency virus (HIV) infection is associated with several central nervous system (CNS) opportunistic infections and neoplasms, some of which are AIDS defining illnesses [7]. These include CNS toxoplasmosis (CNS TOXO), primary CNS lymphoma (PCNSL), progressive multifocal leukoencephalopathy (PML), CNS cryptococcal infection, cytomegalovirus (CMV) encephalitis and tuberculosis. As improvements are made in the clinical management of HIV infection and the prevention and treatment of systemic opportunistic infections, it is conceivable that the prevalence of HIV-associated neurological diseases will increase [4]. The expected rise in prevalence requires an effective strategy for the management of patients presenting with these diseases. This strategy should provide a means to confirm a diagnosis

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early in clinical course and to provide effective treatments. Current standard therapy for HIV-seropositive patients presenting with CNS mass lesions is to initiate empiric anti-toxoplasmosis therapy, as CNS TOXO is a commonly occurring and treatable cause of HIV-associated intracranial lesions (ICL) [25]. If no clinical or radiological response is evident after up to two–four weeks of empiric therapy, primary CNS lymphoma is the likeliest alternative process and represents the major reason for considering brain biopsy [25].

In published case series of the utility of stereotactic brain biopsy in the diagnosis of HIV-associated ICL, there are differences in the diagnostic yield and in the associated morbidity and mortality of stereotactic brain biopsy. Much of this variation may be explained by: (1) small sample size in these studies, (2) lack of standardization in patient selection criteria, (3) the biopsy procedure, and (4) the processing of the specimen. For example, results from one group, which has optimized patient selection and technique of stereotactic brain biopsy, established a diagnosis in 95% of cases with a morbidity rate of only 2.0% and no procedure-associated mortality. The biopsy procedure and the histopathological examination were performed by a highly specialized team [24]. Procedure-associated morbidity is defined as complications, such as hemorrhage or infection, occurring within thirty-days of biopsy, for which disease progression is not implicated. To reduce procedure-associated morbidity and mortality by obviating the need for stereotactic brain biopsy, less invasive techniques have been developed, including neuroimaging techniques and CSF detection of EBV DNA. Neither of these neurodiagnostic techniques is readily available in all centers and CSF analysis may be unsafe due to the risk of herniation with large mass lesions.

Once an accurate diagnosis has been determined, biopsy may alter the clinical management of a patient. In a decision analysis model of patients presenting with ICL, Holloway demonstrated a thirty-one day survival advantage for patients undergoing stereotactic brain biopsy. This advantage was dependent on a number of variables: likelihood of PCNSL, diagnostic sensitivity of the pathological staining, procedure-associated mortality, and the life expectancy of the patient [21]. Another study examined patient factors in an attempt to predict outcome of radiation therapy in patients with PCNSL to improve survival. In a multivariate analysis, pre-biopsy functional status (Karnofsky Performance Scale (KPS)$\geq$70 versus KPS$\leq$60) and biologically available dose of radiation were significantly associated with a better outcome [12]. These results suggest that biopsy should be performed in HIV-seropositive patients with suspected PCNSL. We attempt to address the diagnostic yield and associated morbidity and mortality of stereotactic brain biopsy in this situation and the impact of radiation therapy on survival. To accomplish this, we examined patients undergoing stereotactic brain biopsy or thallium-spectroscopy and then compared survival in those patients diagnosed with PCNSL and receiving radiation therapy versus those patients diagnosed with PCNSL and not receiving radiation therapy.

2. Methods

2.1.1. Case definition

A case was defined by either an HIV-seropositive patient presenting failing at least one week of empiric anti-toxoplasmosis therapy with either (a) neurological signs and symptoms suggesting an HIV-associated ICL or (b) Computer-assisted tomography (CT)/magnetic resonance (MR) scans uncharacteristic for CNS toxoplasmosis. Scans were considered uncharacteristic for CNS toxoplasmosis if lesions were either $>$2.5 cm or had heterogenous enhancement rather than the typical ring-enhancement. This case definition was used to screen published reports of stereotactic brain biopsy in the target population for use in our review [2,3,9–11,14,16,19,22,24,27,28,30,32,33]. We identified a total of 435 cases meeting this definition from the literature review (n=388) and from our Johns Hopkins case series (n=47), which were then stratified based on histopathological examination of the resultant biopsy tissue.

2.1.2. Literature review

A review of published experience with stereotactic brain biopsy in HIV-associated ICL between 1984 and 1996 was conducted using the medical literature database MEDLINE. A paper was included for the literature review if stated patient selection criteria met the above case definition, detailed histopathological outcomes from the biopsy were reported, and follow-up data with respect to survival and biopsy-related morbidity and mortality were available. Fifteen articles were identified yielding 388 cases of biopsied intracranial lesions in HIV-seropositive patients.

2.1.3. Local case series

The Johns Hopkins Hospital was the setting of our local case series. The patients identified were followed by the AIDS Neurology Service and underwent brain biopsy between 1984 and 1997. These patients were initially identified using a large clinical database containing patients' descriptive and diagnostic histories. The medical record of each patient was reviewed retrospectively for relevant clinical, radiological, and laboratory data. Forty-seven patients were identified.

The distributions of demographic characteristics, where available, of age, gender, and risk factors of the subjects from both sources were deemed similar. In this analysis, data from the two sources were pooled to examine the safety, diagnostic yield, and utility of the stereotactic brain biopsy procedure in HIV-related ICL. Safety of the brain

biopsy procedure was assessed using two measures: post-biopsy morbidity (the rate of significant complications. such as hemorrhage or infection, within thirty days after procedure) and post-biopsy mortality (the rate of death within thirty days after procedure). Morbidity and mortality were attributed to the procedure if they are clue directly to complications arising from the biopsy itself, such as intracranial hemorrhage or post-operative infection.

2.1.4. Local PCNSL cases

To examine the effect radiation therapy (RT) has on survival after diagnosis of PCNSL. we conducted an observational analysis of survival and post-biopsy morbidity and mortality on patients with confirmed PCNSL who either received or did not receive RT. Since this was not a controlled clinical trial, the decision not to receive radiation was based upon the severity of the neurological deficits, physician judgement, and patient wishes. There were thirty-six patients in the confirmed PCNSL group (nineteen biopsy-confirmed and seventeen T-SPECT confirmed) with twenty (fifteen biopsy-confirmed and five T-SPECT confirmed) having received radiation therapy. The sixteen patients who received no specific treatment for PCNSL served as a concurrent control group in this analysis.

To compare the demographic characteristics of the patients from the literature review and from the local case series, frequencies of categorical variables, such as gender and risk factor, were compared using chi-square tests. To compare these groups on the distribution of continuous variables, such as age. Student's *t*-test was used. Survival analysis between the irradiated PCNSL cases and the untreated PCNSL cases was performance using Kaplan Meier methods. In reporting survival statistics, median values were used followed by the interquartile range (IQR), which is the difference between the 75^{th} and 25^{th} percentiles of the distribution. The IQR approximates the spread of the data without assuming normality of distribution.

3. Results

3.1. Diagnostic yield of stereotactic brain biopsy for HIV-associated ICL

Of 435 cases, a definitive diagnosis was established in 88% of the cases, with a wide range of diagnoses made upon histopathological examination (Table 1). There were 205 patients undergoing biopsy due to apparent failure of anti-toxoplasmosis therapy (the cases of biopsied CNS toxoplasmosis are assumed to have had slow responses or may have been unable to tolerate empiric anti-toxoplasmosis therapy). There were 134 cases of PCNSL, sixty-nine cases of CNS toxoplasmosis and 2 additional cases with both PCNSL and CNS toxoplasmosis found. There were 134 (65%) cases with biopsy-confirmed PCNSL, in which either radiation therapy and/or chemotherapy might have been used. There were 108 cases of PML and 73 cases with other specific diagnoses. Those labeled with other diagnoses included patients with other infectious agents (such as atypical mycobacterial infection and cryptococcoma) and neoplasms. For the purposes of this analysis, these patients were included in calculating the overall diagnostic yield of the stereotactic brain biopsy procedure but were subsequently excluded from any survival analyses.

3.2. Morbidity and mortality of stereotactic brain biopsy for HIV-associated ICL

Cases from the local case series and the literature review were combined in order to examine the safety, diagnostic yield of the stereotactic brain biopsy procedure in HIV-associated ICL. Of the 415 (95.4%) cases where follow-up information was available (forty-seven from the local case series and 368 from the literature review), there were fourteen (3.4%) deaths within thirty days of the procedure. Two of these deaths were attributed to disease progression rather than the procedure, while the remaining twelve (2.9%) were not attributed to disease progression. There

Table 1
Diagnostic yield of stereotactic brain biopsies in HIV infection

Diagnostic category	Total biopsy cases	Cases with survival information	Median days (range)
Primary CNS lymphoma (PCNSL)	134	35	61 (112)
CNS toxoplasmosis/toxoplasma encephalitis	69	12	182 (285)
Progressive multifocal leucoencephalopathy	108	38	80.5 (160)
Non-diagnostic procedures	39	15	56 (82)
Mixed diagnoses [a]	2	N/A	N/A
Procedure aborted [b]	2	N/A	N/A
Other diagnoses [c]	73	N/A	N/A

[a] Mixed diagnoses included one ease each with CNS toxoplasmosis and PCNSL.
[b] Procedure aborted due to complications.
[c] Included two cases of CNS toxoplasmosis, with atypical mycobacterial infection or cryptococcoma which were not included in the CNS toxoplasmosis group.

Table 2
Characteristics and treatment status of Johns Hopkins University HIV Neurology Program PCNSL patients

Category	*N*	Irradiated	Median survival (range)
Stereotactic brain biopsy confirmed	19	15/19	49 (45)
T-SPECT positive	17	5/17	90.0 (135)
Concurrent controls	16	0/16	21.0 (33)

were thirty-five reported post-biopsy complications, with major intracranial hemorrhage being the most common complication, making the overall morbidity rate in this series 35/415 (8.4%). There was considerable variation in the morbidity and mortality of the stereotactic brain biopsy procedure reported in the literature review, ranging from 3.3% to 30.8% for morbidity and 0% to 5.3% for mortality. Data from our site suggests a slightly lower morbidity rate 3/47 cases (6.4%) and a mortality of 2/47 cases (4.3%). Detailed functional status and laboratory information was available only in the local case series. Compared to patients with no post-biopsy morbidity, the group of patients experiencing post-biopsy morbidity had poorer functional status (median Karnofsky Performance Scale score 30 versus 60), decreased platelet count prior to biopsy (117 000 (SD 68 000) versus mean 230 000 (SD 99 000)), and a higher number of intracranial lesions (median number 1.5 versus 1). Because of the small number of patients involved, these differences were not statistically investigated.

3.3. Survival after HIV-associated ICL

There were 116 cases with survival information available. These included the forty-seven patients from the case series and sixty-nine patients from the literature review. Overall, the median survival for patients with PCNSL was 61 days (IQR 112) compared to 182 days (IQR 285) for CNS-TOXO, 80.5 days (IQR 160) for PML, and 56 days (IQR 82) for those with non-diagnostic procedures (Table 1). Of note, there was no consistent mention of post-diagnostic therapy implemented in patients with PCNSL in the literature review, therefore, it is conceivable that this patient group contains both treated and untreated patients in unknown proportions.

To determine the influence of radiation therapy on survival of patients with confirmed PCNSL (following brain biopsy or thallium spectroscopy) from the local case series, we examined the survival of irradiated patients versus the untreated concurrent controls (Table 2). Twenty irradiated patients had a median survival of 50 days (IQR 113) [fifteen with biopsy-confirmed median survival of 49 days (range 31–76 days) and 5 positive T-SPECT median survival of 90 days (range 0–278 days)]. The sixteen untreated concurrent controls had a median survival of 21.0 days (IQR 33). The difference in median survival between the two groups was approximately 29 days (Chi-square 6.73, $P<0.01$) (Fig. 1). The median time between initial presentation and diagnostic procedure in the irradiated patients was 3.5 weeks (range 0–16). Among the patients with a time interval less than the median, survival tended to be higher (56.3 days (range 4–278 days) versus 43.8 days (range 0–92 days)), though the numbers were too small to test rigorously. Using CD4 cell count as an

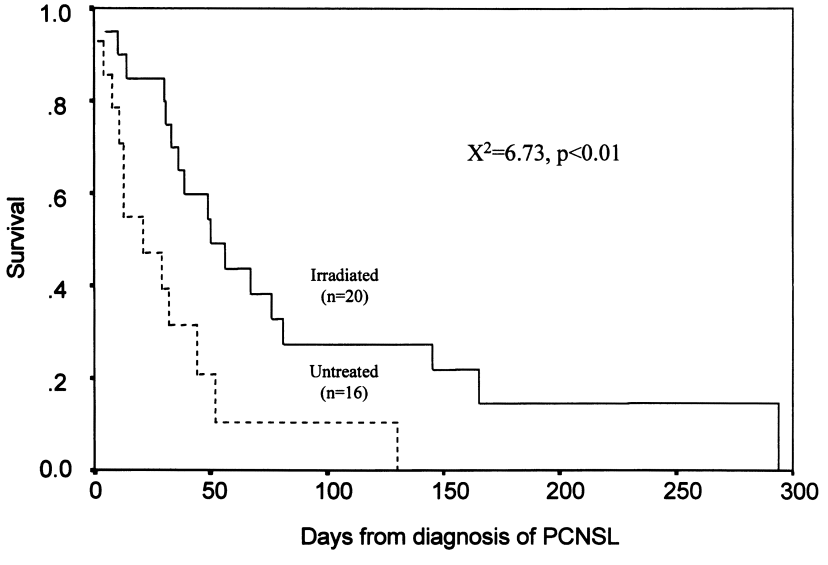

Fig. 1. Survival alier diagnosis of PCNSL for treated and untreated patients. Patients included those undergoing both brain biopsy and T-SPECT and either receiving radiation therapy (median 50, IQR 113) or remaining untreated (median 21.0, IQR 33) (Chi-square=6.73, $P<0.01$).

indicator of HIV disease stage, there was no significant difference between the irradiated patients (mean 17.00, SD 37.76) and the untreated concurrent controls (mean 40.64, SD 66.42) at the time of stereotactic procedure ($t_{34}=1.35$, $P=0.19$).

4. Discussion

Overall, the diagnostic yield from stereotactic brain biopsy was high, 88%, establishing that biopsy remains a sensitive and specific method of establishing diagnoses in cases of HIV-associated ICL. To determine whether stereotactic brain biopsy was a safe diagnostic tool, our study examined thirty-day post-biopsy morbidity and mortality across several institutions. We found a relatively high morbidity rate of 8.4% and a mortality rate of 2.9%. which is comparable to the mortality rate seen in coronary artery bypass graft surgery [17]. There was considerable variance in both morbidity and mortality associated with the stereotactic biopsy procedure. As suggested by Levy, a number of factors contribute to this variation [24]. These factors include, but are not limited to, lesion characteristics (etiology, size and location) and center characteristics (available facilities and experience with HIV-associated focal intracranial lesions). There was insufficient information to allow us to identify risk factors for heightened surgical morbidity in the entire sample: however, our local case series suggests that decreased functional status and platelet count and higher number of lesions were associated with a greater risk of post-biopsy morbidity.

Because neurological involvement usually occurs in severely immunocompromised patients (CD4 cell counts $\leq 200/mm^3$), there has been much discussion as to the utility and safety of brain biopsy in this population. The risk of significant complications is quite high in this population [13]. Our diagnostic yield of 88% was slightly lower than that reported by Levy, where a 96% diagnostic yield was established. Of note, our study includes results pooled from a wide range of institutions that may have had different degrees of experience with the procedure and the cytological interpretation. In the report by Levy, a single neurosurgeon and neuropathologist worked to maximize the efficacy of the brain biopsy procedure. In addition to multiple sampling from both the core and the periphery of a suspected lesion, the neuropathologist performed an extensive panel of assays. Additionally, in their study, there was no biopsy-associated mortality and only one patient experienced hemorrhage post-operatively (biopsy-associated morbidity 2.0%) [24].

Examination of survival of patients with confirmed PCNSL receiving radiation therapy compared to untreated concurrent controls and showed a modest but statistically significant survival benefit for irradiated patients. Though the numbers are small in our observational series, median survival tended to be better for patients diagnosed by T-SPECT rather than biopsy. Additionally, a trend toward improved survival was noted among patients that had a shorter interval between initial presentation and biopsy procedure. These findings may suggest a survival benefit from early assessment using a non-invasive technique, such as T-SPECT. As with any non-controlled study, the issue of selection bias must be confronted when discussing clinical outcomes, such as survival or response to treatment. Because the patients were not selected to undergo the stereotactic brain biopsy or the radiation therapy using a randomized design, there exists the possibility that the patients with a better clinical prognosis were selected. If this were true, then these patients would tend to have a higher survival than their untreated counterparts even without clinical intervention. In our study, we attempted to assess this by comparing baseline stage of HIV disease between the treated and untreated groups to show no difference.

New neuroimaging techniques for the diagnosis of PCNSL include positron-emission tomography (PET), MR spectroscopy, and thallium spectroscopy (T-SPECT). PET has been shown to differentiate between infectious mass lesions, such as CNS TOXO and PCNSL [20,29]. In twenty patients with AIDS who had contrast-enhancing mass lesions, PET provided an accurate diagnosis in 18/20 (90%) patients [29]. In a study of twenty-six HIV-seropositive patients with intracranial lesions, proton MR spectroscopy showed significantly different biochemical profiles for each diagnostic group and correctly diagnosed 94% of cases with no overlap between CNS TOXO and PCNSL [8]. Barker showed that T-SPECT was capable of excluding PCNSL in a population of 24 patients with AIDS who had intracranial lesions when read in conjunction with neuroanatomical scans, such as MRI or CT. Of 19 patients presenting with a differential diagnosis of PCNSL versus CNS TOXO, T-SPECT correctly identified 9/9 PCNSL cases and 7/10 CNS TOXO cases [5]. A recently completed examination of the experience with T-SPECT in HIV-associated PCNSL at our site has demonstrated a sensitivity of 83%, a specificity of 93%, and a diagnostic efficiency of 88% [31]. Based on the ability of PET and T-SPECT to differentiate between cases of PCNSL and CNS-TOXO, recent recommendations for algorithms of evaluation and treatment of HIV-seropositive patients presenting with focal intracranial lesions includes these neuroimaging techniques as diagnostic tools [1].

CSF assays have also been developed for diagnosis of PCNSL. De Luca has shown that the detection of EBVDNA in the cerebrospinal fluid is a sensitive and specific diagnostic tool for AIDS-related PCNSL. EBV–DNA was found using nested PCR in 7/8 biopsy proven cases of PCNSL and in 0/11 patients with other ICL, demonstrating a specificity of 100% and a sensitivity of 87.5% [15]. In a study of twenty patients with HIV-associated ICL undergoing both stereotactic brain biopsy

and CSF analysis, PCR was shown to have a sensitivity of 100% in detecting EBV–DNA [26].

Once a definitive diagnosis of PCNSL is established, there is a lack of effective and tolerable treatments. While no controlled clinical trials of radiation therapy for PCNSL have been completed, retrospective studies have suggested a survival benefit with whole-brain RT [23]. However, recently, the Eastern Cooperative Oncology Group (ECOG) and the AIDS Clinical Trials Group (ACTG) completed a trial of a single cycle CHOP chemotherapy followed by RT for biopsy-proven PCNSL with a median survival of 83 days (personal communication R. Ambinder). In a recent uncontrolled study of intravenous methotrexate as a treatment for PCNSL, 7/15 patients showed a complete resolution with a median survival of 19 months. The most common side effect was neutropenia, occurring in six patients, but these side effects were not treatment limiting. Unlike radiation therapy, no decline in functional, or cognitivc status was seen in this patient group [6]. Prolonged median survival of 7 months was witnessed in 8/10 patients with PCNSL with combined chemotherapy and radiotherapy (with two patients surviving more than one year) [18]. Prognostic factors associated with increased survival have been identified. Survival benefits have also been attributed to patient characteristics at the time of presentation with symptoms. In an analysis of 163 patients with PCNSL, performance status (Karnofsky Performance Score $\geq$70), female gender, age ($\leq$35 years), and higher biologically available dose of radiation therapy (Gy10$>$ 39) was associated with complete response rates following cranial irradiation [12].

In summary, brain biopsy for HIV-associated PCNSL has a high diagnostic yield, but also a relatively high morbidity and mortality. There is an urgent need to refine and broaden the use of non-invasive techniques for diagnosis of HIV-associated PCNSL, which might include the combined use of thallium SPECT and CSF EBV PCR. While the overall survival statistics for PCNSL associated with HIV infection remains poor, there is a continued effort to improve treatments, both radiation therapy and novel strategies including radiosensitizers.

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