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SHORT COMMUNICATION

Clinical predictors for the aetiology of peripheral lymphadenopathy in HIV-infected adults

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Objectives

The aim of the study was to determine the aetiology and clinical predictors of peripheral lymphadenopathy in HIV-infected individuals during the antiretroviral (ARV) era in a nontuberculosis endemic setting.

Methods

A multicentred, retrospective cohort study of peripheral lymph node biopsies in HIV-positive adults was carried out. A total of 107 charts were identified and reviewed for clinical features, lymphadenopathy size, and ARV use and duration. Biopsy results were categorized, and multivariate logistic regression determined independent predictors of lymphadenopathy aetiology.

Results

Evaluation of 107 peripheral lymph node biopsies revealed that 42.9% of peripheral lymphadenopathy was attributable to malignancy, 49.5% to reactive changes, and 7.5% to infections, with only 2.8% of all cases secondary to tuberculosis. Fevers, weight loss, ARV use, and lower viral loads are significantly associated with nonreactive lymphadenopathy.

Conclusions

Lymphadenopathy is likely to be reactive or malignant in nontuberculosis endemic regions. Readily available clinical features can aid clinicians in predicting the underlying aetiology, those at risk for malignancy, and who to biopsy.

Keywords: biopsy, HIV, lymphadenopathy, opportunistic infection, tuberculosis

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Introduction

Peripheral lymphadenopathy is a common clinical finding among HIV-infected individuals [1]. The differential diagnosis of peripheral lymphadenopathy in the HIV-infected population typically falls into one of three major categories: infection, malignancy, or reactive changes. It is vital to distinguish between these entities because treatments differ and adverse events may arise from delayed diagnosis of infectious or malignant aetiologies. Because it is often challenging to determine the cause of enlarged peripheral lymph nodes on clinical examination, clinicians are often faced with the decision to biopsy enlarged lymph nodes and the urgency of this procedure.

Several studies have assessed the aetiology of lymphadenopathy in HIV-infected individuals prior to the widespread use of antiretroviral therapy (ART) [1–3]. In the ART era, studies reporting the aetiology of peripheral lymphadenopathy in HIV-positive patients have been primarily based on fine needle aspiration (FNA) and were carried out in highly endemic regions for tuberculosis (TB) [4–9], which accounts for 20–60% of diagnoses in these locations.

Little is known about the aetiology of peripheral lymphadenopathy in HIV-positive individuals in regions of low TB prevalence during the ART era. We retrospectively analysed lymph node biopsy data from four Boston-area

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hospitals for the period in which ART had become widely used. We examined the aetiology of lymphadenopathy among these biopsies and determined clinical factors that may serve as predictive markers for diagnosis.

Methods

Institutional Review Board permission was granted by Partners Healthcare (Massachusetts General Hospital, Brigham and Women's General Hospital), Tufts Medical Center, and the Lemuel Shattuck Hospital. In this multicentred retrospective cohort study, we searched pathology records and electronic medical records from these institutions for peripheral lymph node biopsies from HIV-infected individuals between 1996 and 2011. We included only individuals over the age of 18 years with lymph node biopsies of the head and neck region (cervical, supraclavicular, submandibular and submental), axillary, and inguinal region. All other sites of lymph node biopsy, including sentinel axillary lymph node dissection in the setting of breast cancer, were excluded. Patients presenting with diffuse lymphadenopathy who underwent peripheral lymph node dissection were included. Basic demographic data, purified protein derivative (PPD) status, medical history, use of ART, and location of lymphadenopathy was abstracted from the electronic medical record and paper charts. The size of lymph nodes was determined based on the following measurements, in descending order of priority: radiographic measurements, pathological measurements from whole biopsy dissection, and physical examination (for example, if a lymph node measured 3 cm on computed tomography scan and 2 cm on physical examination, the value assigned was 3 cm). Clinical symptoms, such as painful lymphadenopathy, documented fever > 100 degrees Fahrenheit, and unintentional weight loss of $\geq$ 10% of total body weight within 1 year, and patient laboratory information including complete blood counts, CD4 T-cell count, CD4 T-cell nadir, and HIV RNA levels were recorded. Type of biopsy (FNA or surgical excision) and pathological and microbiological diagnoses were documented.

We classified lymphadenopathy aetiologies into two groups for comparison: reactive and nonreactive. Nonreactive aetiologies were defined as infections and malignancies. Lymphadenopathy was considered infectious only if an infectious aetiology was diagnosed directly from the lymph node. Reactive aetiologies included nonspecific inflammation in the absence of infectious, malignant, granulomatous or other diagnoses. We followed up on all pathological and microbiological studies in initial and repeat biopsies to ensure that reactive adenopathy was not misclassified.

Clinical features of the patients with reactive and nonreactive lymphadenopathy were evaluated. We used Fisher's exact test for categorical variables and Student's *t*-test or the Wilcoxon test for continuous variables, as guided by the normality of the data. We calculated odds ratios (ORs) for bivariate predictors of aetiology. We performed multivariate logistic regression to determine independent predictors of lymphadenopathy aetiology and summarized these results with adjusted odds ratios (AORs). CD4 cell count was log-transformed to normalize the distribution. A cut-off criterion of $P < 0.2$ on bivariate analysis was used to select variables for imputation into the multivariate model. We performed an Allen–Cady modified, backward selection procedure with age, sex, viral load detectability and CD4 cell count nadir included by default. Bivariate and multivariate analyses were carried out using R (R Foundation for Statistical Computing) [10].

Results

A total of 109 HIV-infected patients with peripheral lymph node biopsies were reviewed, of whom 107 were included in the initial analysis. Two patients were excluded because a diagnosis could not be reliably identified from existing pathology or microbiology reports. Patient demographics and characteristics are summarized in Table 1. In addition to undergoing biopsy, 98.2% of patients had radiographic imaging to investigate their lymphadenopathy. Excisional biopsy was performed in 82% of patients, FNA in 8.3% and both procedures in 11%. At the time of lymph node biopsy, 53 patients (46.7%) were on ART (median ART duration 3 years; range 0.25–17 years). The median CD4 T-cell count was 256 cells/μL and 31 patients (29%) had an undetectable viral load (Table 1). Lymphadenopathy was documented as being present in the head or neck in 20 patients (18.7%), in the axillary region in 12 patients (11.2%), in the inguinal region in 16 patients (15.0%), in two out of three locations in 39 patients (36.4%), and in all three locations in 20 patients (18.7%). Based on the lymph node biopsy, malignancy was diagnosed in 46 patients (42.9%), infection in eight patients (7.5%), and reactive changes in 53 patients (49.5%).

Non-Hodgkin's lymphoma (NHL) was the most common malignancy, occurring in 25 patients and accounting for 54.3% of all malignancies. Biopsies were consistent with diffuse large B-cell lymphoma in 11 patients, Burkitt's lymphoma in six patients, and B-cell lymphoma that was not further defined in the medical record in eight patients. The two cases of squamous cell carcinoma both originated from metastatic anal cancer, and the two cases of adenocarcinoma originated from lung and cervix primary malignancies (Table 2).

Table 1 Demographic and clinical characteristics according to aetiology of lymphadenopathy, with crude odds ratios (ORs) and adjusted odds ratios (AORs) for a nonreactive aetiology

Predictor	Nonreactive		Reactive		OR	CI	AOR	CI
Age (years) [median (IQR)]	45	(40–50)	42	(35–47)	1.07	(1.02–1.13)	1.08	(1.01–1.16)
Female sex [*n* (%)]	8	14.8%	21	39.6%	0.27	(0.10–0.67)	0.45	(0.12–1.53)
North America born [*n* (%)]	39	72.2%	30	56.6%	1.97	(0.88–4.52)	–	–
CD4 count nadir (cells/μl) [median (IQR)]	137.5	(32–226)	193	(81–381)	0.49	(0.24–0.93)	0.73	(0.52–2.10)
Current CD4 count (cells/μl) [median (IQR)]	222	(82–488)	289	(105–444)	0.75	(0.36–1.54)	–	–
On ART [*n* (%)]	34	63.0%	19	35.8%	3.00	(1.37–6.74)	11.66	(2.37–82.51)
VL nondetectable* [*n* (%)]	21	63.6%	6	31.6%	3.65	(1.12–13.14)	2.87	(0.57–15.10)
Fevers [*n* (%)]	32	59.3%	13	24.5%	4.38	(1.94–10.38)	6.35	(1.69–28.25)
Weight loss [*n* (%)]	30	55.6%	16	30.2%	2.85	(1.30–6.46)	5.22	(1.19–31.66)
LN size (cm) [median (IQR)]	2.35	(2.0–3.3)	2	(1.6–2.5)	2.19	(1.38–3.83)	2.01	(1.32–3.71)

Odds ratios for CD4 counts represent log cell counts.
ART, antiretroviral therapy; IQR, interquartile range; LN, lymph node; VL, viral load.
*Nondetectable viral load among individuals on antiretroviral therapy.

Table 2 Aetiology of peripheral lymphadenopathy in 107 HIV-positive patients undergoing lymph node biopsy

Aetiology	*n* (%)
Malignancy	**46 (42.9)**
Non-Hodgkin's lymphoma	25 (23.4)
Hodgkin's lymphoma	6 (5.6)
Kaposi's sarcoma	7 (6.5)
Castleman's disease	3 (2.8)
Squamous cell carcinoma	2 (1.9)
Adenocarcinoma	2 (1.9)
Hemangiopericytoma	1 (0.9)
Infectious	**8 (7.5)**
Mycobacterium avium complex	4 (3.7)
Tuberculosis	3 (2.8)
Syphilis	1 (0.9)
Reactive	**53 (49.5)**

Mycobacterium avium complex was the most common infectious cause of lymphadenopathy, identified in four patients. Three patients were diagnosed with tuberculosis, and one with syphilis.

Demographic variables that were predictive of nonreactive lymphadenopathy included increasing age [OR 1.07; 95% confidence interval (CI) 1.02–1.13] and female sex (OR 0.27; 95% CI 0.10–0.67) (Table 1). Fevers and weight loss were both positively associated with a nonreactive aetiology (OR 4.38; 95% CI 1.94–10.38 for fevers; OR 2.85; 95% CI 1.30–6.46 for weight loss). The odds of nonreactive aetiology also increased with lymph node size (OR 2.19; 95% CI 1.38–3.83). ART was predictive of nonreactive aetiology (OR 3.00; 95% CI 1.37–6.74), and the odds were higher among those with a nondetectable viral load on ART (OR 3.65; 95% CI 1.12–13.14).

In multivariate analysis, increasing age (AOR 1.08; 95% CI 1.01–1.16), current use of ART (AOR 11.66; 95% CI 2.37–82.51), presence of fevers (AOR 6.35; 95% CI 1.69–28.25), weight loss (AOR 5.22; 95% CI 1.19–31.66) and lymph node size (AOR 2.01; 95% CI 1.32–3.71) were independently associated with a nonreactive aetiology. CD4 cell count was not associated with aetiology in crude or adjusted analysis.

Discussion

In the ART era, the aetiology of peripheral lymphadenopathy among HIV-infected individuals living in low TB prevalence settings has not been well described. We reviewed the records of 107 HIV-infected patients with lymphadenopathy presenting to Boston hospitals over a 15-year period to determine the prevalence of various aetiologies of lymphadenopathy. We found that readily available clinical characteristics could help distinguish patients at high risk for malignant or infectious aetiologies from those with reactive lymphadenopathy. These results may aid clinicians in deciding the need and urgency for lymph node biopsy in patients with HIV infection.

The majority of studies assessing peripheral lymphadenopathy in HIV-infected individuals during the ART era are from India and Brazil, where TB is highly endemic [4–9]. In these studies, over 90% of biopsies were obtained from cervical and axillary sites, with a small percentage (0–6%) of patients undergoing mediastinal or intraabdominal lymph node biopsies. Among peripheral biopsies, TB infection represented between 20 and 60% of FNA diagnoses; in contrast, in our study, only 2.7% of patients who underwent lymph node biopsy were diagnosed with TB. The low rate of TB in Massachusetts probably accounts for this difference. As of 2009, the incidence of TB in Massachusetts was 3.84 cases per 100 000 individuals and has remained relatively constant since 1996 [11]; in contrast, the incidence of TB is

much higher in countries where recent lymph node studies were performed (168 and 60 cases per 100 000 individuals in India and Brazil, respectively [12]). Although there were only three cases of TB in this study, 20% of patients had a positive PPD documented, most of whom were treated for latent TB infections after this diagnosis was made. Other infections that were diagnosed, such as *Mycobacterium avium* complex and syphilis, are frequently diagnosed by methods other than peripheral lymph node biopsy.

The proportion of malignancy was greater in our series compared with other studies conducted in the post-ART era. A total of 42.9% of lymph node biopsies were malignant, far greater than the 2.5–14% reported in TB-endemic regions [4,6,9]. In all series, most malignancies were categorized as NHL; however, malignancies may have been under-diagnosed in these series because FNA was the primary diagnostic tool rather than excisional biopsy. Some patients with NHL who underwent FNA may have been misclassified as 'reactive' or 'inconclusive'.

Reactive lymphadenopathy accounted for 53% of biopsies in our study, similar to the 30–50% in other case series [4,5,9]. It is likely that the proportion of reactive lymphadenopathy was underestimated here, as many patients never undergo biopsy as a result of resolution of symptoms following the initiation of ART. One prospective study found that reactive changes were diagnosed in 32% of biopsied lymph nodes among 280 HIV-positive patients in India [4], although TB accounted for roughly 62% of cases in that study. The underlying cause of reactive hyperplasia in lymph nodes may be attributable to multiple factors such as direct HIV involvement, Epstein Barr virus (EBV) reactivation, or occasionally both. Histological features of hyperplastic germinal centres are more commonly seen in EBV-infected, and follicular fragmentation in HIV-infected lymph nodes [13].

Several clinical features were strongly predictive for a nonreactive diagnosis of peripheral lymphadenopathy. These included ART use at the time of biopsy, fevers, unintended weight loss, and larger lymph node diameter. Given that reactive lymphadenopathy is common among patients with uncontrolled viral replication, it is not surprising that ART use was strongly associated with nonreactive pathology.

A limitation to this study is that it included retrospective data collection, which probably underestimated the proportion of reactive lymphadenopathy. Additional clinical features of lymphadenopathy such as duration and texture may have contributed valuable data to a prediction tool; however, they could not be reliably documented from charts.

In summary, peripheral lymphadenopathy in HIV-infected individuals in non-TB endemic areas is likely to be reactive or malignant, and readily available clinical factors – such as ART use, larger size, presence of fevers or weight loss – may direct clinicians in deciding about the urgency of lymph node biopsy in this setting.

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