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Frequncy and etiology of lymphadenopathy in Iranian HIV/AIDS patients

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PEER REVIEW

Peer reviewer

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Comments

This article sheds light on the importance of tuberculosis and lymphoma as the main considerable etiologies of AIDS-associated lymphadenopathy; while pays attention to other less serious conditions. That is why physicians must keep tuberculosis and lymphoma in mind as two rapidly progressive and deadly diseases need immediate attention. Various aspects of these two serious conditions are well-contoured and discussed in the article.

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ABSTRACT

Objective: To estimate and outline the frequency and etiology of lymphadenopathy in HIV/AIDS patients.

Methods: This study was conducted on 178 consecutive HIV/AIDS patient files for etiologies (categorized into three sub-groups: definite, probable and possible) and associated factors of local and generalized lymphadenopathy.

Results: Seventy-two (40.45%) patients including 63 male patients (87.5%) developed lymphadenopathy. HIV in lymphadenopathy(+) patients was most commonly transmitted intravenously (n=49). Generalized and localized lymphadenopathy respectively occurred in 27 (37.50%) and 45 (62.50%) patients, mainly in the cervical region (28.9% for local and 63% for generalized lymphadenopathy). The most common causes of lymphadenopathy were tuberculosis (n=24, 33.3%) and lymphoma (n=12, 16.6%). The frequency of lymphadenopathy was non-significantly higher in patients with AIDS (CD4 count <200 cell/μL) *vs.* HIV(+) patients (CD4 count >200 cell/μL).

Conclusions: Lymphadenopathy in HIV/AIDS patients may reflect a serious condition, most likely tuberculosis and lymphoma. Since patients might underestimate lymphadenopathy, physicians would rather list these entities for diagnosis.

KEYWORDS
Lymphadenopathy, HIV, AIDS, Etiology

1. Introduction

Although the number of newly infected people with human immunodeficiency virus (HIV) and the related deaths have been steadily declining since the late 1990s, HIV, as a pandemic infection, still affects more than 33 million people per year with 1.8 million annual deaths worldwide[1]. The statistics have strongly shown that the prevalence of HIV/AIDS and the related mortality has been increasing in Iran since the past decade. According to Iran's latest HIV statistics, there were 23 125 HIV(+) and/or confirmed acquired immunodeficiency syndrome (AIDS) patients in Iran in 2011[2], while Iran's HIV statistics for the year 2009 stated that the number of HIV/AIDS patients reached 20 130 with an annual mortality of 3 409[3]. A report by the United Nations AIDS group (UNAIDS) had even estimated an

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increasing average of 100 000 HIV(+) patients in Iran in 2008 and concluded the average number of annual deaths due to HIV/AIDS has increased beyond 5 000 in 2008[4].

Lymphadenopathy (LAP) is one of the most common manifestations at any stage of HIV/AIDS with different underlying pathogenesis[5]. The most common causes of severe immunodeficiency (*i.e.* severely decreased CD4(+) count) are opportunistic infections and malignancy. This study was to estimate the lymphadenopathy frequency and outline its etiology in HIV-infected and AIDS patients in a referral center in Iran.

2. Materials and methods

2.1. Study population

This retrospective survey was conducted on 178 consecutive HIV(+)/AIDS patients hospitalized in Infectious Diseases Department of Imam Khomeini Hospital (Tehran University of Medical Sciences, Tehran, Iran) and outpatient referrals of Behavioral Diseases Consultation Center supervised by Iranian Research Center for HIV/AIDS at Imam Khomeini Hospital between 2006 to 2009. The participants' age, gender, transmission routes and duration of HIV infection, existence/site/duration/etiology of lymphadenopathy, history of tuberculosis, clinical and paraclinical manifestations, history and duration of anti-retroviral therapy, mean CD4(+) and mean CD8(+) counts were recorded as number per microliter (μL, equals to cubic millimeter). Patients with missing data were excluded. All participants signed an informed consent form at admission enabling authors to use their data on condition of anonymity.

2.2. Definitions

Lymphadenopathy, described as a lymph node with a diameter >1 cm at any site except for inguinal region, was diagnosed through clinical examination or imaging of lymph node(s), and the relevant etiology was confirmed through lymph node cytopathology (excisional biopsy and/or fine needle aspiration), otherwise stated (bacteriologic or serologic studies). This approach was accepted and administered in the literature[5,6]. Lymph node involvement in one site represented local lymphadenopathy; while the involvement of at least two lymph nodes in two non-adjacent regions represented generalized lymphadenopathy. Certainty of lymphadenopathy etiologies were categorized into three different groups: definite, probable and possible.

2.2.1. Tuberculosis lymphadenitis

a) Definite diagnosis: positive culture and/or positive polymerase chain reaction (PCR) of cytopathological samples.

b) Probable diagnosis: acid-fast staining of cytopathology samples of lymph node(s), or positive culture/PCR or acid-fast staining of other organs or fluids (*e.g.* sputum), or existence of a granuloma with caseous necrosis in biopsy of lymph node(s), or miliary pattern of chest X-ray.

c) Possible diagnosis: existence of a granuloma with non-caseous necrosis in biopsy of lymph node(s) plus a positive tuberculin skin test (PPD test), or existence of a granuloma with caseous necrosis in other organs, or existence of a granuloma with non-caseous necrosis in other organs responsive to anti-tuberculosis therapy[7].

2.2.2. Lymphoma

a) Definite diagnosis: specific pathology in biopsy of lymph node(s).

b) Probable diagnosis: specific pathology in biopsy of other organs.

c) Possible diagnosis: clinical, laboratory and imaging findings corresponding to lymphoma.

2.2.3. Toxoplasmosis

a) Definite diagnosis: specific pathology in biopsy of lymph node(s).

b) Probable diagnosis: corresponding brain imaging and positive serologic test(s) with response to anti-toxoplasmosis therapy[8].

2.2.4. Cytomegalovirus

a) Definite diagnosis: positive PCR in biopsy of lymph node(s).

b) Probable diagnosis: a compatible clinical presentation, evidence of cytomegalovirus antigenemia, and clinical and/or virological response to specific treatment[9].

2.3. Statistical analysis

Taking a 36% prevalence of lymphadenopathy in HIV/AIDS patients as the lowest prevalence into account[10], and a confidence interval of 95% and error of 7%, the calculated sample size was 178 participants for the present study. The authors assessed and showed the frequency of variables in numbers (percentage), and quantitative results as mean±SD. We applied *Chi*-square test for qualitative characteristics and Student's *t*-test for comparison of quantitative characteristics with normal distribution between the two groups; quantitative characteristics without normal distribution, albeit were analyzed with Mann-Whitney test. All statistical calculations were done with SPSS ver. 17 (IBM, USA). $P<0.05$ was considered significant.

3. Results

3.1. Demographic findings

A total of 72 (40.45%) patients including 63 (87.5%) male patients developed lymphadenopathy. Among

lymphadenopathy patients, 44 (61.11%) participants were afflicted by AIDS (CD4 count<200 cell/μL). The mean age of lymphadenopathy patients was (37.2±8.9) years, and lymphadenopathy was accordingly the most common in ages of 31-40. At least, 50% of lymphadenopathy patients had been suffering from HIV infection within the past 15 months. The authors found out that the most common route of HIV transmission in lymphadenopathy patients was intravenous drug abuse (*n*=49) (Figure 1).

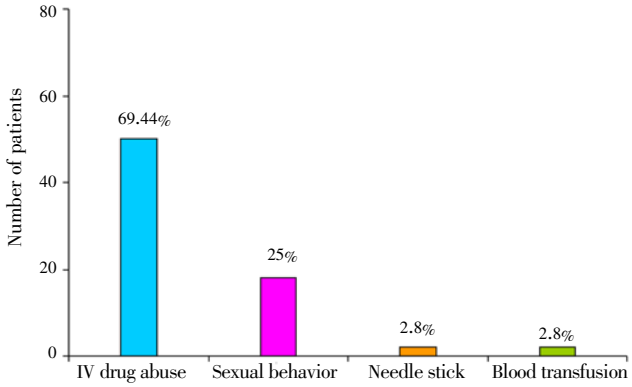

Figure 1. Frequency and proportion of routes of HIV transmission in patients with lymphadenopathy.

3.2. Site and duration of lymphadenopathy

In the majority of lymphadenopathy patients (94%), lymphadenopathy had emerged in the past 3 months. Generalized and localized lymphadenopathy were observed in 27 (37.50%) and 45 (62.5%) patients, respectively. The cervical region was the most common site of lymphadenopathy not only in local (28.9%) but also in generalized lymphadenopathy (63%). The other most common sites in descending order were axillary (*n*=10, 22.2%), intra-thoracic (*n*=11, 24.5%), intra-abdominal (*n*=6, 13.3%), inguinal (*n*=4) and sub-maxillary (*n*=1).

3.3. Etiologies

We have conducted excision biopsy (30 patients), fine needle aspiration (7 patients) and the other diagnostic methods (35 participants) for determining the underlying causes. Those procedures led to the diagnoses represented in Table 1. The etiologies in 59 (81.9%) patients were eventually confirmed. Accordingly, the most common causes of lymphadenopathy in HIV/AIDS patients were tuberculosis (*n*=24, 33.3%) and lymphoma (*n*=12, 16.6%). Tuberculosis was diagnosed and confirmed by means of culture (among 24 cultures, 3 cultures were positive) and/or acid-fast staining (among 12 smears, 3 samples were positive). At the same time, lymphoma was the second most common etiology with 8 (19.5%) and 4 (12.9%) patients in AIDS and HIV (+) subgroups, respectively.

Fifteen patients underwent chest X-ray, and clichés of 13 conformed to tuberculosis manifestations, while chest CT scan results of 17 participants were exposed multiple lymphadenopathy and metastatic lymphoma lesions (*n*=4), tuberculosis (*n*=10) and pericardial effusion (*n*=1).

In accordance with our findings, lymphadenopathy was accompanied by pathologies other than tuberculosis and lymphoma as well. Local lymphadenopathy was associated with toxoplasmosis, cytomegalovirus-induced retinitis/splenomegaly whereas generalized lymphadenopathy was connected by toxoplasmosis and abdominal/pelvic manifestations of lymphoma.

3.4. Paraclinical features

The frequency of lymphadenopathy was 45.5% (*n*=32) in patients with AIDS (CD4 count<200 cell/μL) *vs*. 54.1% (*n*=39) in HIV-positive patients (CD4 count>200 cell/μL). This difference was, however, statistically non-significant. Tuberculosis was responsible in 17 AIDS (41.4%) and 7 HIV (+) patients (22.5%). Besides, the difference of paraclinical features between

Table 1

Frequency and proportion of etiologies of lymphadenopathy in HIV/AIDS patients.

Etiology	Diagnosis (*n*)	Study patients (*n*=72)	Localized LAP (*n*=45)	Generalized LAP (*n*=27)
Tuberculosis	Definite (8) Probable (16)	24 (33.3%)	15 (33.3%)	9 (33.3%)
Lymphoma	Definite (6) Probable (6)	12 (16.6%)	3 (6.6%)	9 (33.3%)
Toxoplasmosis	Definite (4) Probable (1)	5 (6.9%)	1	4 (14.8%)
Cytomegalovirus	Definite (1) Probable (2)	3	2	1
Kaposi's sarcoma	Lymph node pathology (1) Palatine lesion pathology (1)	2	1	1
Leishmaniosis	Skin pathology (1) Bone marrow culture+serology (1)	2	1	1
Streptococcus pyogen	Lymph node smear+culture (1) Lymph ulcer smear+culture (1)	2	2	0
Staphylococcus aureus	Blood/lymph node culture+pathology (1) Lymph node smear+culture (1)	2	2	0
Varicella	Lymph node pathology+skin rash+response to treatment (2)	2	2	0
Herpes simplex	Serology+clinical+response to treatment (2)	2	2	0
Oral cavity infection	Clinical infection+response to treatment (1)	1	1	0
Unknown	N/A	13 (18.0%)	11 (24.4%)	2

All values are shown as number (percent), except for diagnosis that is shown as numbers only. LAP: lymphadenopathy; N/A: not available.

LAP(+) and LAP(−) patients is shown in Table 2.

Table 2

Associated paraclinical and clinical features in HIV/AIDS patients with and without lymphadenopathy.

Features	LAP(+) patients (n=72)	LAP(−) patients (n=106)	P
History of tuberculosis (PPD test)	27 (37.5%)	9 (8.4%)	<0.001
Fever (oral temperature>37.7 °C)	58 (80.5%)	33 (31.1%)	<0.001
Organomegaly	30 (41.6%)	12 (11.3%)	<0.001
Mean Hgb (mg/dL)	10.8±2.8	11.6±2.7	0.040
Mean WBC count (cell/μL)	5725±2743	5625±3173	0.820
Mean ESR (mm/h)	71.9±45.1	49.7±39.9	0.001
Mean lymphocyte count (cell/μL)	1346±871	1381±871	0.790
Mean CD4(+) count (cell/μL)	241±245	264±231	0.460
Mean CD8(+) count (cell/μL)	671.8±437.6	773.2±486.4	0.150
CD4(+) <200 (cell/μL)	41 (56.9%)	49 (46.2%)	0.690

Values are shown in number (percent), unless otherwise stated. LAP: lymphadenopathy; PPD: tuberculin skin test; Hgb: hemoglobin; WBC: white blood cell; ESR: erythrocyte sedimentation rate.

3.5. Clinical characteristics

Upon admission, lymphadenopathy was the origin of chief complaints in 10 (13.8%) patients. The other common clinical manifestations or concerns at admission are presented in Figure 2. General manifestations included fever, fatigue and weight loss. Moreover, authors have compared the difference of clinical characteristics between LAP(+) and LAP(−) patients in Table 2. Sixty-seven (37.64%) out of all 178 study patients received anti-retroviral medications and the mean duration of anti-retroviral therapy was (651.63±151.1) d.

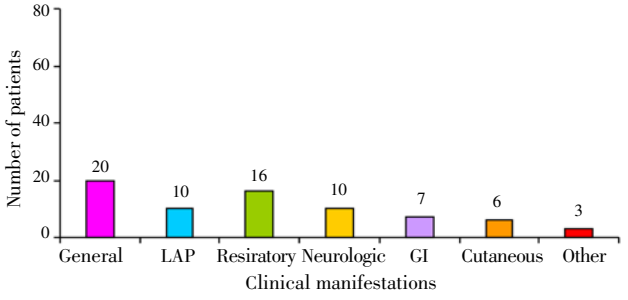

Figure 2. Frequency number of chief complaints in patients with lymphadenopathy at the time of admission.

4. Discussion

Although lymphadenopathy is one of the most common manifestations at any stage of HIV/AIDS, it probably reflects a serious underlying pathology that requires immediate attention. Tuberculosis, malignant lymphoma (Hodgkin/non-Hodgkin), reactive hyperplasia, Kaposi sarcoma and opportunistic infections are among the many causes resulting in lymphadenopathy in HIV/AIDS[11].

In the present study, the frequency of lymphadenopathy was 40.45%, which is close to that of the other studies, *i.e.* 42% in India[12] and 41.6% in Thailand[13]. Risk factors and demographic characteristics of those countries are somehow similar to those of Iran.

In regard to the age group of lymphadenopathy, our finding is comparable to another study by Vansiri *et al*[14]. In their work, 31-40 and 21-30 years of age were the first and second most common groups, respectively. The patients were mostly 25-30 years of age according to Devi *et al*[15]. The results of all these studies emphasize that lymphadenopathy is more common in younger HIV(+) patients.

In the present study, intravenous drug abuse and unprotected sexual contact were the first and second common causes of HIV infection, respectively while other studies have mentioned that sexual contact has been the main route[15-17]. A probable explanation for this discrepancy is cultural obligations in Iran that persuades people to conceal their sexual behavior.

The authors of the present study concluded that the cervical region was the most common site of local lymphadenopathy. This finding is in agreement with the others[13,18-20]. The axillary region, which was the second most prevalently involved region in our study, was the most common place in another research[21].

Reactive hyperplasia and atypical lymphocyte infiltration were the most common pathology findings in our study. In three studies by Martin-Bates *et al.*[19], Bottles *et al.*[20] and Iacovou *et al.*[22]. reactive hyperplasia was reported as the most frequent pathologic finding but with a higher percentage. Granulomas (with or without caseous necrosis) were two times more frequent in another survey in India[14]. Wannakrairot *et al.* reported that granuloma with caseous necrosis and reactive hyperplasia were the two most common pathologies found in HIV(+) patients[6].

When it comes to etiologies, the authors discovered that tuberculosis and lymphoma were the leading causes of lymphadenopathy. This conclusion conforms to some studies; in contrast, some other studies emphasize reactive hyperplasia and opportunistic infections. Ramos *et al.* in Brazil[23] and Vansiri *et al.* in India[14] made a conclusion that tuberculosis and lymphoma were the most frequent causes of lymphadenopathy in HIV-infected patients. Four further studies accomplished in India (which resembles Iran's demography) emphasized the same result[13,15,21,24]. Jamser *et al.* led a research on 318 HIV(+) patients suggesting that mycobacterial infections, bacterial pneumonia and lymphoma were the most common etiologies of intrathoracic lymphadenopathy (diagnosed by chest CT scan)[11]. An investigation in Brazil (the frequency of lymphadenopathy was 32%) described that the most common causes of lymphadenopathy in descending order were tuberculosis, lymphoma and histoplasmosis Kaposi sarcoma, benign reactive hyperplasia, cryptococcal infection and disseminated infection with mycobacterium avium[10].

There are some discrepancies between mycobacterium culture and staining in ours and the other studies. The reported positive mycobacterial culture from lymph node extract is 18%-62%[15] *vs.* 12.5% in our research. Acid-fast bacilli's staining observed in other studies[5] was similarly different: 43.3% *vs.* 25% for the present study.

Comparing chest X-ray clichés with another study suggests that tuberculosis was detectable in 70% of the clichés[24]. The most common findings in the chest CT scans resembles the finding of Fishman *et al*. indicating tuberculosis and lymphoma as the leading causes of chest lymphadenopathy[25].

As the leading reason for lymph node involvement in HIV/AIDS patients, some articles pointed out lymphatic tuberculosis[19,20,26]; while some paid attention to reactive hyperplasia[16,27,28]. Another research by means of fine needle aspiration proposed tuberculosis (54%), reactive hyperplasia (23%) and lymphoma (2%) as the most frequent causes of lymphadenopathy in AIDS patients[28]. One study reported AIDS-related generalized LAP (50%), infections (22%) and malignancies (18%) as the most frequent etiologies according to fine needle aspiration[26]. It seems that the endemicity of tuberculosis makes it show up as the leading reason in some articles including the present study.

Toxoplasmosis, the third most frequent cause of lymphadenopathy in our study, has been an uncommon entity in other assessments. It is probably because of higher prevalence of toxoplasmosis in Iran. A rare case of syphilitic lymphadenopathy was observed in our study. Other works have not mentioned opportunistic fungal infections[14], nor have we found such opportunistic infections.

When it comes to clinical manifestations associated with HIV infection, Knollmann *et al*. have suggested that splenomegaly, hepatomegaly and lymphadenopathy were significantly higher in HIV(+) compared to HIV(−) patients[29]. We dare add fever to this list which is significantly more frequent in lymphadenopathy patients.

In some cases, many clinical and para-clinical findings were taken into account for diagnosing lymphadenopathy etiology. A uniform diagnostic approach with uniform criteria improves the standardization of study patients.

Lymphadenopathy, a common manifestation in HIV/AIDS patients, may reflect the presence of a serious underlying condition, most likely tuberculosis and lymphoma. The most prominent clinical characteristics associated with lymphadenopathy in HIV/AIDS patients are fever, organomegaly and anemia. Patients rarely seek medical assessment for lymphadenopathy by themselves because they are unable either to detect the condition or to realize its importance. Physicians would rather keep those serious entities in mind for differential diagnosis.

Conflict of interest statement

We declare that we have no conflict of interest.

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Comments

Background

Along with increasing number of HIV/AIDS patients in Iran, the number of cases with lymphadenopathy is incrementing. The etiologies for this common sort of lymphadenopathy, however, could be too serious to be ignored, including malignant neoplasms and pulmonary tuberculosis.

Research frontiers

Prioritization of possible etiologies of HIV-associated lymphadenopathy in terms of their fatality enables physicians to diagnose life-threatening conditions as soon as they consider any abnormality in routine physical and paraclinical tests.

Related reports

The number of reports published on AIDS-related lymphadenopathy is not a lot, which leaves a wide gap for clinical suspicion to, proper approaches to and differential diagnosis of this type of lymphadenopathy. Lack of such data makes it necessary to publish an comprehensive article-such as the present manuscript.

Innovations and breakthroughs

Through reading of this article, one can reach to a bigger scheme when facing a HIV/AIDS patient with lymphadenopathy. In this big picture, neoplasms and tuberculosis are better to be considered first; while the treating physician can deal with some entities might not be memorable at a time.

Applications

The present study might better the diagnostic care of AIDS-related lymphadenopathy in Iran because physicians have a warning list of possible causes-in descending order of fatality-in hand and diagnostic approaches in mind.

Peer review

This article sheds light on the importance of tuberculosis and lymphoma as the main considerable etiologies of AIDS-associated lymphadenopathy; while pays attention to other less serious conditions. That is why physicians must keep tuberculosis and lymphoma in mind as two rapidly progressive and deadly diseases need immediate attention. Various aspects of these two serious conditions are well-contoured and discussed in the article.

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