

Cytomorphological profile of lymphadenopathy in HIV-infected persons

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Abstract

Objective: To assess the role of fine needle aspiration cytology (FNAC) and to determine the cytomorphological profile in persons infected with human immunodeficiency virus presenting with lymphadenopathy.

Materials and Methods: This was a five year (2010-2015) analysis of 54 HIV positive cases who presented with lymphadenopathy. Archival FNAC smears stained with Papanicolaou, Giemsa and Ziehl-Neelsen stains were reviewed for their cytological features.

Results: Lymph nodes from 54 HIV-positive patients in the age range of 11-61 years were reviewed. The most common FNA diagnosis was tubercular lymphadenitis (n=24). The other diagnoses were: reactive lymphadenitis (n=11), suppurative lymphadenitis (n=6), lymphoma (n=9), metastases (n=3) and cryptococcal lymphadenitis (n=1). Of the 24 cases of tubercular lymphadenitis, seven showed epithelioid granulomas with Langhan's giant cells and caseous necrosis. Numerous clusters of epithelioid cells in reactive background were noted in one case which was AFB positive. There were five cases which showed mostly caseous necrotic material with few epithelioid cells. Our study found that three cases showed only presence of acellular caseous necrosis. Caseous necrotic material with few lymphocytes and histiocytes and no epithelioid cells were reported in four cases. The remaining four cases showed tubercular abscess showing predominantly neutrophils along with epithelioid cells and semi fluid necrosis. These cases were AFB positive.

Conclusion: FNAC is a cost-effective technique in patients of HIV lymphadenopathy to segregate lymph nodes that need to be biopsied from infective lymphadenopathy.

Introduction

Human immunodeficiency virus infection/ acquired immunodeficiency syndrome (HIV/AIDS) is a disease caused by human immunodeficiency virus and it mainly involves the immune system of the body. Lymph nodes form the main bulk of lymphoid tissue and are the major anatomic sites for the beginning and spread of HIV infection. Hence, HIV positive patients often present with lymphadenopathy. HIV-induced lymphadenopathy can be classified into four histological patterns: follicular hyperplasia, follicular fragmentation, follicular atrophy and follicular depletion.¹ This study was conducted to determine the cytological pattern of lymphadenopathy seen in patients infected with HIV in India. We analyzed the cytological profile of HIV-positive cases who presented with lymphadenopathy in the last five years at our hospital.

Material and Methods

Setting

The Mahatma Gandhi Institute of Medical Sciences (MGIMS) is a medical school located in Sevagram in Central

India. It is attached to Kasturba Hospital which is a 934 bedded tertiary care rural hospital. Around 500000 patients attend the outpatient department annually, while around 40000 patients receive care as inpatients. The Cytology section of the Department of Pathology receives approximately 8500 specimens each year.

Cases

This study has received approval from the Institutional Ethics Committee. The current study was conducted retrospectively in the Cytology section of the Department of Pathology. Over a five-year duration (2010-2015), 36,417 patients were screened for HIV at our hospital, and 569 turned out to be positive for HIV which was confirmed by ELISA positivity for HIV-1 antibodies using a commercial kit. Of 569 HIV positive cases, 54 presented with significant lymphadenopathy and were sent to the cytology section for FNAC. The study involved analysis of de-identified patient data.

FNAC of the lymph nodes was performed with help of 22-26 gauge disposable needles and 10 ml syringe with a Cameco syringe holder using standard precautions. Smears

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made from the aspirates were air dried as well as fixed in 95% ethyl alcohol. We reviewed the archival FNA smears which were stained with Papanicolaou and Giemsa stains. Ziehl-Neelsen stain for AFB was done for all cases which showed caseous or granulomatous lymphadenitis. Special stains for fungi had been used wherever necessary.

Results

The ages of the 54 HIV seropositive cases ranged from 11-61 years and their male: female ratio was noted to be 1.7: 1. Maximum cases belonged to the age group of 21-40 years. Of the 54 HIV positive cases, 28 (51.8%) showed involvement of the cervical lymph nodes. Twelve (22.2%) patients had enlargement of the axillary lymph nodes, while in four (7.4%) cases inguinal lymph nodes were involved. There were three (5.6%) cases of supraclavicular lymph node involvement. One case each showed involvement of submandibular (1.8%), submental (1.8%) and para-aortic (1.8%) group of lymph nodes. Four (7.4%) cases showed multiple sites of involvement.

Table 1 shows the distribution of these cases based on their cytological diagnosis. Tubercular lymphadenitis was found to be the most common lesion (n=24, 44.4%). Reactive lymphadenitis, where smears comprised of neutrophils, mature and transformed lymphocytes and monocytoïd cells, constituted 20.4% of cases. Smears from six cases showed acute suppurative lymphadenitis (11.1%). All these were negative for AFB. This series included three cases of Hodgkin's lymphoma as well as six patients with Non-Hodgkin's lymphoma. All three cases of Hodgkin's lymphoma were of the mixed cellularity subtype. The cases with Non-Hodgkin's lymphoma included five cases of diffuse large B cell lymphoma and a single case of anaplastic large cell lymphoma. Smears from the diffuse large cell lymphomas showed a diffuse infiltrate of large cells with irregular nuclear contours, large nuclei, prominent nucleoli and vesicular chromatin. There were three cases of metastatic carcinoma. Of these two were metastatic nasopharyngeal carcinoma and one showed metastases from a duct carcinoma of breast. Cryptococcal lymphadenitis was reported in one case. This patient did not have disseminated disease. Smears showed presence of large number of intracellular and extracellular round to oval organisms of varying sizes. These were round, empty looking structures with clear halos. (Fig.1).

We reviewed the smears of the 24 tubercular cases and classified them on the basis of their cytomorphological features into one of six patterns as described by Gangane et al² (Table 2). Seven cases showed presence of epithelioid granulomas, Langhan's giant cells and caseous necrosis (Fig. 2). One case showed plenty of epithelioid cell clusters in a reactive background and this case was AFB positive. Five cases showed few epithelioid cells within predominantly caseous necrotic material. In our study we encountered three cases which showed only caseous necrosis without presence of other cell types. Four cases showed caseation with few lymphocytes and histiocytes and no epithelioid cells. The remaining four cases presented with tubercular abscess

showing mostly neutrophils with semi-fluid necrosis. Occasional epithelioid cells were scattered and these cases were AFB positive (Fig. 3).

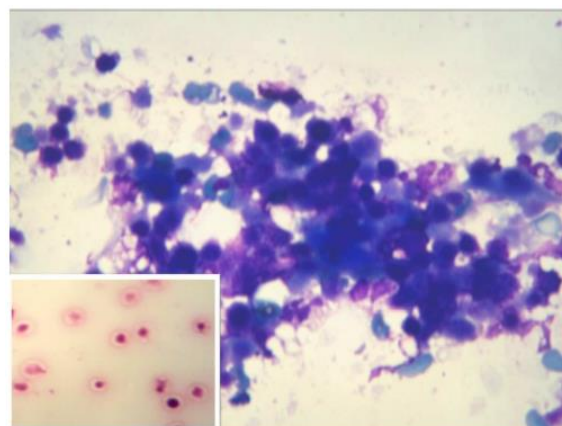


Fig. 1: Smear from a case of cryptococcal lymphadenitis showing large number of organisms (Giemsa, 200X). Inset shows PAS positive cryptococci

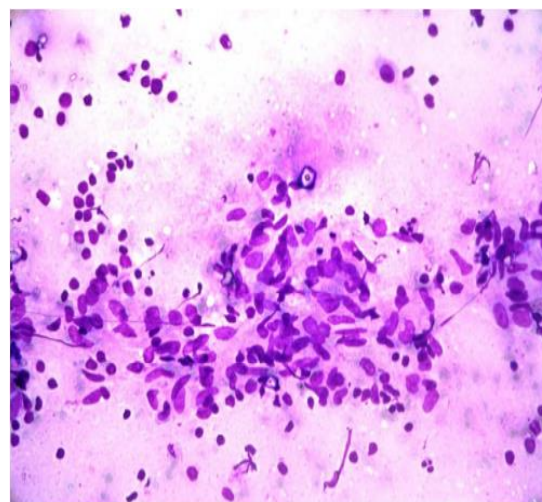


Fig. 2: Smear showing well-formed granulomas in tubercular lymphadenitis (Giemsa, 400 X)

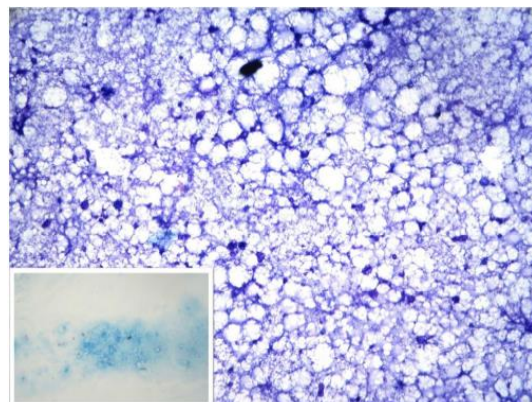


Fig. 3: Smear showing large number of foamy macrophages in a tubercular abscess (Giemsa, 200 X). Inset shows acid fast bacilli on Ziehl Neelsen stain

Table 1: Distribution of cases according to cytological diagnosis in HIV positive patients

Diagnosis	No. of cases	Percentage (%)
Tubercular lymphadenitis	24	44.4%
Reactive lymphadenitis	11	20.4%
Acute suppurative lymphadenitis	6	11.1%
Lymphoma		
Hodgkin's lymphoma	3	5.5%
Non- Hodgkin's lymphoma	6	11.6%
Metastatic lymphadenopathy	3	5.5%
Cryptococcal lymphadenitis	1	1.8%
Total	54	100%

Table 2: Cytomorphological features of cases of tubercular lymphadenitis

S. No.	Features	No. of cases	AFB positive cases
1	Epithelioid granuloma with Langhan's giant cells and caseous necrosis	7	0
2	Numerous clusters of epithelioid cells in reactive background.	1	1
3	Mostly caseous necrotic material with few epithelioid cells	5	0
4	Caseous necrotic material with few lymphocytes and histiocytes. No epithelioid cells.	4	0
5	Only caseous necrosis without other cell types	3	0
6	Tubercular abscess showing predominantly neutrophils along with epithelioid cells and semi fluid necrosis.	4	4
Total		24	5

Discussion

The most common presentation of HIV-infected patients is enlarged lymph nodes and these are readily amenable to FNAC. Persistent generalized lymphadenopathy (PGL) is defined as enlargement of two or more extra-inguinal lymph nodes for at least three months duration in an individual at risk for AIDS. In developing countries, HIV is most commonly associated with infection or lymphoma, unlike the West where follicular hyperplasias are more commonly encountered.³

Cervical lymph node involvement was the most common in our study (51.8%). Approximately 300 lymph nodes in the body are situated in the neck.⁴ The neck nodes are easily accessible, visible and are the most frequently reported site of enlarged lymph nodes. Similar findings have been reported by several other authors.⁵⁻⁸

The most common finding in our study was tubercular lymphadenitis. AFB positivity or caseous necrosis was taken

as the criteria for diagnosis of tuberculosis. Our findings correlated with those of Parikh et al,⁵ Deshmukh et al,⁶ Vanisri et al⁹ and Gupta et al.¹⁰ Our observations show that presence of tuberculosis is rather common (44.4%) in HIV seropositive patients due to decreased immunity. Tubercular infection occurs relatively sooner in the course of this infection in Indian patients as compared to other AIDS related opportunistic infections.¹¹

The cause of lymphadenitis in HIV-positive patients is usually tuberculosis. Tubercular infection occurs by airborne mode of transmission in immunocompetent and immunosuppressed individuals.¹² There is a dramatic fall in interferon- γ during HIV infection, in parallel with decrease in CD4+ T lymphocytes. This leads to increased susceptibility of developing reactivation or re-infection with M. tuberculosis in infected patients.^{13,14} As immunosuppression progresses, the risk of extra pulmonary tuberculosis and mycobacteremia increases. Tuberculosis may also accelerate immunosuppression in HIV by inducing proinflammatory cytokines. These have been found to be associated with increased HIV viraemia.¹⁵ Patients suffering from HIV have a higher rate of progression from latent tuberculosis to active tuberculosis as compared to those without HIV infection. Immunocompetent individuals who are infected with M. tuberculosis harbor an approximately 10% lifetime risk of developing tubercular infection¹⁶ while this risk is increased 20-30 times more in HIV-infected individuals with latent tuberculosis at a rate of 8-20% per year.¹⁷

Eleven (20.4%) of our cases showed features of reactive lymphadenitis. Reactive lymphadenitis was the commonest finding in studies of Kumarguru et al¹⁸ Baghel et al⁷ and Ratan et al.⁸ Six (11.1%) of our cases showed suppurative lymphadenitis. Our reporting were similar to those of Gupta et al¹⁰ and Baghel et al⁷ who observed 10.8% and 9.5% patients of acute suppurative lymphadenitis respectively. Acute suppurative lymphadenitis is diagnosed in patients where the aspirate contains purulent material. Such patients when left untreated eventually tend to develop full blown discharging sinuses. Hence, it is crucial to do Ziehl-Neelsen (ZN) staining for AFB in cases where purulent material is aspirated. Detection of AFB was carried out by routine ZN staining. We had difficulty in arriving at a definitive diagnosis in some of our cases of tubercular lymphadenitis when aspirates did not show classical cytological features of tubercular infection. When aspirates had scant AFB positivity, searching for them was both tedious as well as time-consuming. Gangane et al² demonstrated that AFB could be more easily visible and detectable with use of modified bleach method, due to better preserved AFB morphology in lymph node aspirates.

We found one case (1.8%) of cryptococcal lymphadenitis. Srinivasan et al¹⁹ reported that FNAC is a good method to accurately diagnose cryptococcal lymphadenitis in the setting of immunosuppression as it helps in prompt initiation of treatment. Cryptococcal lymphadenitis usually presents in disseminated form in immunosuppressed patients. However, as can be seen in our study, occasional

cases do present with disease localized to lymph nodes.²⁰ We found a higher percentage (16.6%) of lymphoma cases compared to findings of other Indian studies. In their studies Parikh et al⁵ and Vanisri et al⁹ reported 2.7% of lymphoma cases. Kumarguru et al¹⁸ reported 1.7% of lymphoma cases and found that the incidence of lymphoma in HIV seropositive patients greatly outnumbered that of the normal population. The relative risk of developing non-Hodgkin lymphoma in HIV patients increases to 60–200 times^{21,22} while, that of developing classical Hodgkin's lymphoma increases to 8–10 times²³ when compared to the general population. This raised susceptibility for lymphoma is thought to occur due to multiple reasons. Some of these are: the transforming properties of the retrovirus-like immunosuppression as well as cytokine dysregulation as a result of the disease.²⁴ Further, susceptibility to opportunistic infections such as human herpes virus 8 (HHV8) and Epstein–Barr virus (EBV) appear to play a role in causing heightened risk of disease.²⁴

Three cases of metastatic carcinoma (two nasopharyngeal carcinomas and one duct carcinoma of the breast) were seen in our study. Gupta et al¹⁰ and Ratan et al⁸ reported 0.8% and 1.3% cases of metastatic carcinoma respectively in their studies. Melbye et al²⁵ in their study did not observe an elevated risk of nasopharyngeal carcinoma in HIV-infected persons. They found only four cases of nasopharyngeal carcinoma amongst 50,050 subjects. In contrast, a study conducted by Frisch et al²⁶ in 2001, found elevated risk for nasopharyngeal cancer. Shebl et al²⁷ in their study found an increased risk of salivary gland and nasopharyngeal carcinoma in HIV-infected people. They proposed that immunosuppression or oncogenic viral infections play a role in their etiology.

Conclusion

Diagnosis of tuberculosis or other opportunistic infections, commonly encountered at FNAC, enables early initiation of treatment, in developing countries, where there are economic constraints. This procedure may spare the patient unnecessary excision and enable immediate treatment of early infection. FNAC is a cost-effective technique in HIV patients with lymphadenopathy to segregate infective lymph nodes from those that need to be biopsied to arrive at a definitive diagnosis.

Conflict of Interest: None.

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