Accuracy of Fine Needle Aspiration Cytology in the Evaluation of Peripheral Lymphadenopathy

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Abstract

We conducted an audit of the lymph node aspirates received from January 1996 to December 1996 of 541 patients sent to the Cytology Division, Department of Pathology, Ramathibodi Hospital by their clinicians. The aim of this retrospective study was to determine the pattern of diseases that commonly present with peripheral lymphadenopathy and to evaluate the accuracy of Fine Needle Aspiration Cytology (FNAC) in the diagnosis of lymph node diseases. An excisional biopsy sample of lymph node was available in 233 (43%) cases for comparison to the histopathology. The predominant lesion was benign which included necrotizing granulomatous lymphadenitis (NGL), reactive changes (RC) and suppurative lymphadenitis (SL). The predominant malignant lesion was metastatic squamous cell carcinoma. The accuracy for NGL, SL and RC were 69 per cent, 75 per cent and 95 per cent, respectively. The accuracy for metastatic disease was 97 per cent. The specificity and sensitivity of FNAC were 99 per cent and 94 per cent, respectively. An excisional biopsy should be done in case of doubt to clarify the pattern of RC.

Lymphadenopathy is a very common clinical problem having a wide range of etiology from reactive process to malignant neoplasm. Therefore a definite diagnosis is very crucial for management of the patient. When malignancy is suspected or if a patient does not respond to antibiotic therapy, nodal biopsy or cytology should be undertaken to establish a definite diagnosis(1). The Fine Needle Aspiration Cytology (FNAC) technique was introduced to be a routine procedure for diagnosis of peripheral lymphadenopathy. It became very popular in worldwide use because of its simplicity, rapidity and inexpense compared to excisional biopsy(2). Its reliability varies from place to place and still there is some reluctance among clinicians and pathologists to recommend FNAC for investigating lymphadenopathy. The key of success of FNAC depends upon proper aspiration,

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fixation, staining and most importantly experience of the interpreting pathologist[3]. In Ramathibodi Hospital, FNAC has been practiced for more than a decade. It is worthwhile to testify the reliability and accuracy of FNAC in this hospital. The aim of this retrospective study was to determine the pattern of diseases that commonly present with peripheral lymphadenopathy and to evaluate the accuracy of FNAC in the diagnosis of lymph node diseases.

MATERIAL AND METHOD

Percutaneous fine needle aspirates of 628 lymph nodes from 541 patients were received in the cytology division of the Department of Pathology of Ramathibodi Hospital, Bangkok, Thailand, during a one year period (January - December 1996). A subsequent H&E-stained slide from excisional biopsy sample of lymph node was available in 233 cases. In some cases special-stained (AFB, GMS, Immunocytochemistry) histopathological slides were also available to support the histologic diagnosis.

FNA had been performed by the clinicians using a 22 to 24 gauge needle mounted on a 10 ml syringe. Smears prepared from the aspirated material were fixed in 95 per cent ethyl alcohol and stained by Papanicolaou's method.

The Papanicolaou's stained cytology slides and the available histopathology slides were reviewed by 3 pathologists before consensus diagnosis was made for every case. The outcomes were reviewed and correlated with the histologic diagnosis. Only slides with adequate cellularity, well-spread and good fixation underwent pathologic interpretation. In cases of unsatisfactory smears such as blood containing from traumatic aspiration, extensive drying artifacts from delayed fixation or inconsistent scanty material from lesion aspirated, repeated aspirations had been done.

The diagnostic smears were classified into benign, malignant and atypical groups. In the benign group, there were 4 pathologic patterns of lymphadenopathy, i.e., necrotizing granulomatous lymphadenitis (NGL, tuberculosis possible), reactive changes (RC), suppurative lymphadenitis (SL), and unremarkable (UR). NGL addresses where there was either collection of epithelioid cells along with variable number of lymphocytes with or without accompanying Langhans' giant cells or clumps of amorphous eosinophilic acellular material along with diffuse lymphoid cell necrosis with infiltration of polymorphs and fibroblast like cells. A combination of both features was also present in many cases. RC was diagnosed by the presence of polymorphic population of cells, i.e., lymphocytes with various degrees of maturation, plasma cells and histiocytes containing tingible body in their cytoplasm[4]. In addition, infiltration of polymorphs and increased fragility of the cells as judged by the presence of strands and tangles of twisted basophilic chromatin material was seen in a good number of cases indicating lymphadenitis. SL was diagnosed by the presence of extensive, both well preserved and degenerated neutrophilic infiltration, cell debris along with a few lymphocytes and histiocytes without any granuloma. No remarkable pathologic process could be identified in an otherwise diagnostic material in UR.

In the malignant group, there were 5 pathologic patterns of lymphadenopathy, i.e., squamous cell carcinoma (SCC), nasopharyngeal carcinoma (NPC), adenocarcinoma (ADC), non-Hodgkin's lymphoma (NHL), and undifferentiated carcinoma (UDC). For SCC, the pathologic change showed a spectrum of differentiation ranging from poorly differentiated spindle element to well differentiated keratinizing squamous cells exhibiting a remarkable tendency to form sheets and cohesive clusters. The NPC showed the presence of very cohesive groups of small undifferentiated cells with definite malignant nuclei. The ADC presented in sheets or cohesive groups of large to small sized cells having malignant nuclei surrounded by cytoplasm showing secretory activity. Sometimes these cells showed attempted gland formation. For NHL, a monotonous population of atypical lymphoid cells were presented. The UDC was diagnosed by the presence of nuclei with malignant feature while cytoplasm does not present any functional differentiation.

The smear was considered as atypical when a diagnostic smear presented in such an atypical borderline fashion that a definite diagnosis cannot be rendered safely.

RESULTS

Of the 628 aspirates, 206 (33%) were unsatisfactory. The second- and third-aspiration were possible in 41 and 23 patients, respectively. Final aspirates from 541 patients (benign 57%, malignant 18%, atypical 3% and unsatisfactory 22%) were evaluated. 43 per cent of our patients were male and 57 per cent were female. The age ranged

from 2-89 years. For benign diseases, the mean age was 35.19±13.64 years. For malignant diseases, the mean age was higher than the benign group. The mean ages of different types of malignancy were as follows : SCC = 61.48±14.23 yrs; ADC = 55.71±17.99 yrs; UDC = 51.21±16.63 yrs; and NHL = 44.21±21.59 yrs. Only 233 cases were available for cytohistologic comparison including 41 (11%) cases with unsatisfactory FNAC smears. Cytohistologic comparison of 192 satisfactory smears are presented in Table 1. Table 2 and Table 3 show the cyto-histologic comparison of benign and malignant cases, respectively. The accuracy of FNAC of this study is shown in Table 4 whereas the histologic diagnosis of 41 unsatisfactory samples is shown in Table 5.

Table 1. Cyto-histologic diagnosis of 192 satisfactory smears.

Cytologic Diagnosis	Histologic diagnosis				
	Benign	Metastatic	Lymphoma	Atypical	Total
Benign	101	-	5	1	107
Metastatic	-	66	2	1	69
Lymphoma	-	-	9	-	9
Atypical	2	2	-	3	7
Total	103	68	16	5	192

Table 2. Histo-cytologic correlation of 107 benign cases.

Cytologic Diagnosis	Histologic diagnosis							
	NGL	RC	SL	Kikuchi	UR	NHL	ALH	Total
NGL	47	-	2	-	-	-	-	49
RC	18	20	-	1	1	4	1	45
SL	1	1	6	-	-	1	-	9
UR	2	-	-	-	2	-	-	4
Total	68	21	8	1	3	5	1	107

NGL = necrotizing granulomatous lymphadenitis
RC = reactive changes
SL = suppurative lymphadenitis
UR = unremarkable
NHL = non-Hodgkin's lymphoma
ALH = atypical lymphoid hyperplasia

Table 3. Histo-cytologic correlation of 78 malignant cases.

Cytologic Diagnosis	Histologic Diagnosis					
	SCC	NPC	ADC	NHL	ALH	Total
SCC	32	-	-	1	-	33
NPC	-	19	-	1	1	21
ADC	-	-	13	-	-	13
UDC	2	-	-	-	-	2
NHL	-	-	-	9	-	9
Total	34	19	13	11	1	78

SCC = squamous cell carcinoma
NPC = nasopharyngeal carcinoma
ADC = adenocarcinoma
NHL = non-Hodgkin's lymphoma
ALH = atypical lymphoid hyperplasia
UDC = undifferentiated carcinoma

Table 4. Evaluation of the accuracy of FNAC.

Parameter	Calculation	Percentage
Sensitivity	77/77+5	94%
Specificity	102/102+1	99%
False Positive Rate	1/1+102	0.9%
False Negative Rate	5/5+77	6%
Positive Predictive Value	77/77+1	98%
Negative Predictive Value	102/102+5	95%

True Positive= 77, True Negative= 102, False Positive= 1 False Negative =5

Table 5. Histologic diagnoses of 41 unsatisfactory patients.

Lesion	No	Percentage
Necrotizing granulomatous lymphadenitis (NGL)	10	28%
Reactive changes (RC)	3	7%
Squamous cell carcinoma (SCC)	6	14%
Undifferentiated carcinoma (UDC)	6	14%
Adenocarcinoma (ADC)	2	5%
Soft tissue lesion (Benign)	9	21%
Suppurative lymphadenitis (SL)	1	2%
Unremarkable (UR)	3	7%
Atypical lymphoid hyperplasia (ALH)	1	2%

DISCUSSION

The false positive rate in our study is quite low (0.9%) which matches the rates previously quoted in the literature[5,6]. Avoidance of false positive diagnosis is of obvious importance since therapeutic and surgical decisions are based increasingly on the cytology results only. The false positive case involved the interpretation of atypical lymphoid cells in cluster as malignant epithelial cells. On biopsy it was turned out as atypical lymphoid hyperplasia.

In the present study, benign lymph node disorders constituted the commonest lymph node disorder diagnosed by FNAC (Table 1). Necrotizing granulomatous lymphadenitis was the commonest among the benign disorders (Table 2). The diagnosis of NGL was made at 69 per cent (47 of 68) accuracy. In NGL the lesion usually is focal rather than diffuse[7]. The background is usually reactive. So if the needle does not penetrate the representative area, aspirate should not present the characteristic findings, rather it shows reactive changes. In this study 18 patients of necrotizing granulomatous lymphadenitis were interpreted as reactive changes. So adequate and multiple sampling from different areas are recommended to reduce this inadequate diagnosis.

RC was diagnosed by cytology with 95 per cent (20 of 21) accuracy. However, reactive process may be associated with many specific lymph node disorders such as Hodgkin's disease, tuberculosis and even metastatic lesions. In the present study, 25 cases of different lesions were falsely interpreted as reactive process (Table 2).

Of the 16 cases of NHL, 9 (56%) were diagnosed by cytology correctly. Four cases of NHL were misdiagnosed as reactive changes in our series. Previous studies have noted the difficulty in distinguishing reactive changes from low grade lymphomas by cytologic criteria[8]. Sometimes a NHL, especially the mixed cellularity type is impossible to separate with certainty from the

reactive process[9]. On review we found the smears were not really monotonous but the appearance of the majority of the lymphoid cells was atypical with hypochromatic nuclei that was overlooked initially. In addition, these smears present diffuse stretching of the nuclear material of the lymphocytes which we usually find in the reactive process. Another case of NHL had a false negative diagnosis of suppurative lymphadenitis because the central area of the lymph node contained frank suppuration surrounded by a narrow rim of immature lymphoid cells. These immature cells were not represented in the smear. One case of NHL was interpreted as SCC and another as NPC. On review these specimens were found to be inadequate and not representative.

In Kikuchi's disease the smear contains karyorrhectic and granular debris mixed with phagocytic histiocytes with peripherally placed cresentic nuclei and abundant cytoplasm containing phagocytosed karyorrhectic or eosinophilic granular debris and medium sized plasmacytoid monocytes[10]. The smear of our case does not present the typical features of Kikuchi's disease. The diagnosis of Kikuchi's disease is difficult on cytologic samples. Klinger and his coworkers reported two cases from Germany where Kikuchi's disease was diagnosed as NHL on FNA[11].

For the metastatic lesion FNAC is the most rewarding. In this study we could make the diagnosis of metastatic lesion with 97 per cent (66 of 68) accuracy. Subtyping of the metastatic lesion could be done with a very high degree of accuracy (Table 3). Out of 34 cases of SCC, 32 were diagnosed by cytology (accuracy 94%), for NPC and ADC the accuracy was 100 per cent. Two cases of SCC were categorized as UDC. One case of atypical lymphoid hyperplasia was falsely interpreted as NPC by cytology.

In the present series seven cases were diagnosed by FNAC as atypical lesion. Three of these were diagnosed as atypical lesion and the other four as SCC, adenocarcinoma, NGL and normal lymph node (one each) on histologic examination. So, any atypical lesion should be followed by lymph node biopsy. However, FNAC should be done at least after 2-3 weeks of lymphadenopathy to allow the cytologic changes become full blown and to decrease false positive results in highly reactive atypical lymphoid cells. Sometimes the lesion may be self limiting.

In this series out of 628 aspirates 206 (33%) were unsatisfactory. The second and third aspirations were done in quite a good number of the cases and thereafter the unsatisfactory rate came down to 22 per cent. It reflects the level of experience of the aspirator. Several studies have shown a direct effect of aspirator experience upon the unsatisfactory rate[12]. Lee et al noted that the failure rate for 82 breast cases performed by a single operator was 9.8 per cent compared to a 45.9 per cent failure rate for 37 cases performed by many different operators[13]. Nine (21% of the unsatisfactory group) cases turned out to be soft tissue lesions instead of lymph node in our study. To alleviate this problem recently some workers have advocated on-site evaluation of FNA by Pathologists. In Saleh and Khatib' study showed that on-site evaluation by a pathologists greatly increased the diagnostic yield[14].

In conclusion, FNAC of enlarged lymph node is a reliable procedure that can be used as a first line diagnostic tool with 94 per cent sensitivity and 99 per cent specificity (Table 4) in the diagnosis of most of the lymph node diseases and often can obviate the need for an excisional biopsy. If satisfactory explanation for nonspecific reactive change is not evident, an excisional biopsy should be performed.

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ความแม่นยำของการตรวจทางเซลล์วิทยาในภาวะต่อมน้ำเหลืองโตโดยวิธีเอฟ.เอ็น.เอ

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วิธีใช้เข็มเล็กเจาะดูดเอาเซลล์จากต่อมน้ำเหลืองที่โตมาตรวจทางเซลล์วิทยา (เอฟ เอ็น เอ) เป็นกรรมวิธีวินิจฉัยโรคที่ทำได้ง่าย, ประหยัด และสามารถวินิจฉัยโรคได้รวดเร็วและแม่นยำพอสมควร รายงานนี้เป็นผลการศึกษาย้อนหลังผู้ป่วย 541 ราย ที่มีตัวอย่างเซลล์ต่อมน้ำเหลืองที่ถูกเจาะดูดโดยใช้เข็มเล็กส่งตรวจที่หน่วยเซลล์วิทยา ภาควิชาพยาธิวิทยา คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี ระหว่างเดือนมกราคม–ธันวาคม 2539 โดยเปรียบเทียบการวินิจฉัยโรคที่ได้จากการตรวจทางเซลล์วิทยากับการตัดต่อมน้ำเหลืองส่งตรวจทางพยาธิวิทยา จำนวน 233 ราย ปรากฏว่าการวินิจฉัยโรคที่พบบ่อยในกลุ่มที่เป็นโรคไม่ร้ายแรงได้แก่ การอักเสบแบบแกรนนูโลมา; การเปลี่ยนแปลงแบบรีแอคทีฟทั่วไป และการอักเสบเป็นหนองเรื้อรัง ส่วนโรคมะเร็งที่พบบ่อยคือมะเร็งสแควมัสเซลล์ที่กระจายมาจากแหล่งอื่น ความแม่นยำของการตรวจเอฟเอ็นเอ ในกลุ่มการอักเสบแบบแกรนนูโลมา, การอักเสบเป็นหนองอย่างเรื้อรัง กับการเปลี่ยนแบบรีแอคทีฟทั่วไป พบเป็นอัตราร้อยละ 69; 75 และ 95 ตามลำดับ ส่วนในกลุ่มโรคมะเร็งมีความแม่นยำสูงร้อยละ 97 จะเห็นว่าความไว (Sensitivity) และความจำเพาะ (Specificity) ของการตรวจวิธีนี้มีอัตราร้อยละ 94 และ 99 ตามลำดับ ในกรณีที่การวินิจฉัยทางเอฟเอ็นเอเป็นการเปลี่ยนแปลงแบบรีแอคทีฟ ถ้ายังอธิบายปัญหาทางคลินิกได้ไม่สมบูรณ์ สมควรต้องตัดต่อมน้ำเหลืองส่งตรวจทางพยาธิวิทยา

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